Environmental and Microbial Biotechnology

Inamuddin
Mohd Imran Ahamed
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Advanced Antimicrobial Materials and Applications

Springer

Environmental and Microbial Biotechnology

Series Editor

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Innovative and novel advances in microbial biotechnology are providing great understandings in to the machineries of nature, presenting fascinating prospects to apply principles of biology to different arenas of science. Sustainable elucidations are emerging to address the concerns on improving crop productivity through microbes, depleting natural resources, environmental pollution, microbial degradation of pollutants, nanomaterials, nanotoxicity & safety issues, safety of food & agricultural products etc. Simultaneously, there is an increasing demand for natural bio-products of therapeutic and industrial significance (in the areas of healthcare, environmental remediation, microbial biotechnology). Growing awareness and an increased attention on environmental issues such as climate change, energy use, and loss of non-renewable resources have carried out a superior quality for research that provides potential solutions to these problems. Emerging microbiome approaches potentially can significantly increase agriculture productivity & human healthcare and henceforth can contribute to meet several sustainable development goals.

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Antimicrobial Polymers

L. A. Camacho-Cruz, M. A. Velazco-Medel, A. Cruz-Gómez, and E. Bucio

Abstract The development of new antimicrobial substances has been a topic of prime importance in recent years because of the growing appearance of antimicrobial resistant pathogens, which have become one of the most worrying threats for public health in recent years. Polymeric antimicrobials are a good alternative for the development of new medicines since they have non-specific antimicrobial mechanisms and unique characteristics as materials which allow for the production of robust substrates for therapeutic uses. In recent years, many examples of antimicrobial polymeric materials have been produced with a great variety of morphologies, functionalities, and specific applications. Since this topic continues to be relevant, this chapter deals with the most fundamental aspects of antimicrobial polymeric materials as well as describing recent advances in the field to provide the reader with a reference on the most general aspects of this area.

Keywords Bacteria growth inhibition · Polymers · Antimicrobial polymers · Drug delivery systems · Cationic polymers · Peptide mimics · Zwitterionic polymers

1 Introduction

Antimicrobial substances have been one of the most influential advances in human development because of the substantial improvement in the quality of life that was derived from their uses. Currently, humans take for granted having a life which is devoid of any serious illness derived from pathogens such as bacteria, viruses, and fungi; however, life before the twentieth century was often plagued with mortality rates (due to infections) that would be unthinkable in the modern world. Due to this usefulness, antibiotics, antifungal substances, antivirals, and antiseptics have been

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widely overused by medical practitioners and by the public in general. This, combined with the persistence of these substances on medical waste, has caused the development of an increasing amount of antimicrobial resistant pathogens. These types of organisms would be uncurable with current medicines, fact that will inevitably cause a serious health problem if the current trends continue (World Health Organization n.d.). Therefore, the development of new antimicrobial substances is of prime importance, especially if these new substances contribute poorly to the increase of antimicrobial resistance. In this sense, antimicrobial polymeric materials are good alternatives to conventional molecular antimicrobial substances because of their unique characteristics.

Antimicrobial polymers may be advantageous in many ways compared to discrete molecular antibiotics. For instance, antimicrobial polymers have non-specific mechanisms to stop pathogen growth; for example, the lysis of bacteria by the disruption of cell membranes due to opposing charges (Muñoz-Bonilla and Fernández-García 2012). This is in stark contrast to molecular antibiotics which normally have very specific mechanisms of action; for example, the prevention of DNA synthesis by binding to determinate receptor sites (Neu 1989). Since the mechanisms of action of antimicrobial polymers are much more general, the development of antibiotic resistance against these polymers is harder. Although this may be regarded as one of the most relevant characteristics of antimicrobial polymers, some other advantages include the ability to form solid substrates for application on medical devices and implants and the combination with other polymeric materials to add properties such as pH or thermal responses. Additional to intrinsically antimicrobial materials, polymers which are not naturally antimicrobial (i.e. most polymers) may also be used for the controlled and localized release of discrete antimicrobial substances, which may also be beneficial in many scenarios. This not only allows for better treatment of certain diseases, but also allows for the fabrication of existing polymeric implants and medical devices which are also antibacterial (Pino-Ramos et al. 2016).

Because of the relevant characteristics of these systems and the growing interest to produce new antimicrobial substances, it is relevant to compile the most common characteristics of antimicrobial polymers and the advances this field has achieved. Therefore, this chapter will deal with the general characteristics of three major groups of antimicrobial polymers; polymeric materials with intrinsic bactericidal properties, antifouling or pathogen repellant polymers, and polymeric substrates enhanced with discrete antimicrobials. Since most of the advancements in this field have been achieved to produce antibacterial substrates, most of this chapter will deal with these materials; however, antifungal, antialgal, and antiviral materials will be also briefly considered.

2 Fundamentals

To better understand the relevance of antimicrobial substances, it is important to firstly correctly identify some terms which are often used interchangeably even when there are crucial differences between them: Antimicrobial, antibacterial, biocidal, bactericidal, and antifouling substances.

Firstly, an antimicrobial substance is a chemical compound that may inhibit the development of pathogens such as bacteria, fungi, yeasts, algae, etc. For an antimicrobial substance to be useful it also must be relatively biocompatible, namely by not being harmful to mammal cells. An antibacterial substance is, in contrast, only stops bacteria from developing. These lasts substances are sometimes also wrongly called bactericidal substances (which means that they kill bacteria). In addition, antimicrobial substances may also inhibit the development of bacteria by not allowing the formation of antibacterial colonies on their surfaces (antifouling behavior). Finally, biocidal substances not only kill pathogens, but also kill mammal cells; these substances are still useful for general disinfection; however they do not present the same biocompatibilities as true antimicrobial substances (Ergene et al. 2018). As a reference for the reader, Fig. 1 illustrates the differences between these kinds of behaviors.

The verification of antimicrobial properties is normally conducted by in vitro or in vivo assays that test the effectiveness of the material in either inhibiting the growth of a certain pathogen, or the effectiveness of the material in killing a certain pathogen. The most common quantification parameter for antimicrobial growth inhibition is the minimum inhibitory concentration (MIC) which is the concentration of an antimicrobial needed to inhibit visible growth of a pathogen. Another quantification parameter is the minimum bactericidal concentration (MBC) which is defined as the concentration needed to kill at least 99.9% of the pathogen in a culture medium (Andrews 2001).[1] Additional to these parameters, another way to quantify the antimicrobial effect is to measure the circular zone of inhibition when the material is placed on a petri dish culture containing ~10^6 CFU/mL of a given pathogen (Fig. 2), additionally, Petri dish cultures may be used to visually count the CFU that are formed in presence of the microorganism. This test is also known as the Kirby–Bauer method (Drew et al. 1972).

As mentioned above, another important characteristic of antibacterial substrates is that they are not toxic to mammal cells (or human cells if their applications are limited to human use); therefore, additional parameters exist to quantify the toxicity of these materials. HC_{50} is the most common parameter to compare the toxicities of different polymeric substrates, this parameter is defined as the concentration in

[1] Although these parameters were originally defined for bacterial assays, they have been used to describe the effects on growth and death of other pathogens.

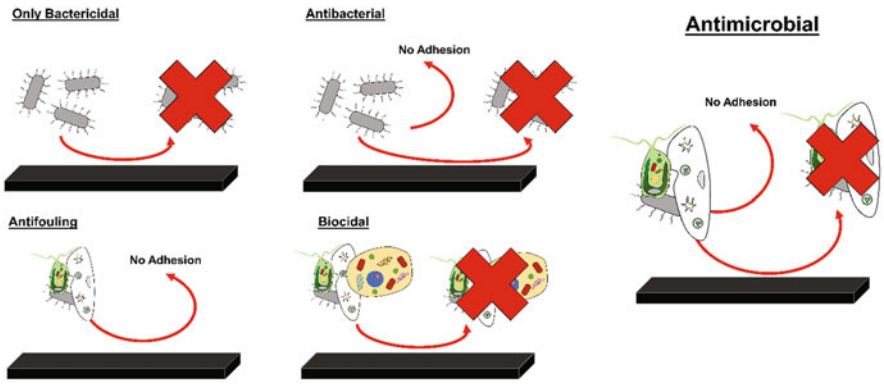


Fig. 1 Definition of various terms used to describe antimicrobial substances

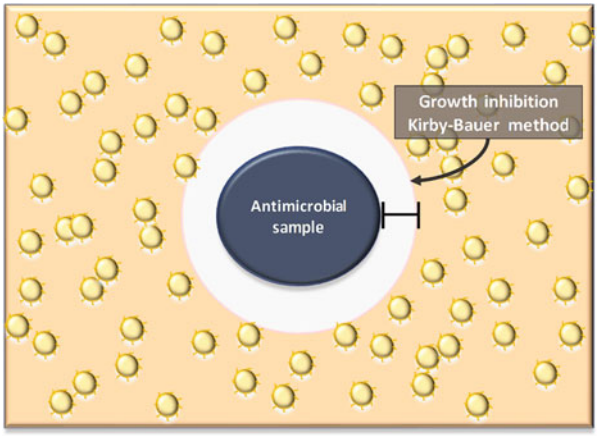


Fig. 2 Zone of inhibition test for antimicrobial performance

which a tested substance produces a release lysis on 50% of the red blood cells in buffer media given a certain incubation period (Punia et al. 2015).

3 Polymeric Materials with Intrinsic Antimicrobial Properties

Polymers and polymeric derivatives with intrinsic antimicrobial properties are of great interest for the development of novel antibiotics both to fight the growing trend of antimicrobial resistant organisms, and to find materials useful for the treatment of pathogenic infections with more specific characteristics. Derived from the fact that polymeric chains do not enter as easily within cells (in contrast to smaller molecules), many of the current antimicrobial polymers target the cell membranes (or cell

walls) of pathogens. In this sense, most polymeric antimicrobials destabilize the cell membranes by electrostatic interactions; specifically, since many bacteria and other pathogens have an overall negative charge in their cell membranes, many polymeric antimicrobials tend to be positively charged (Xue et al. 2015; Ergene et al. 2018). Even when this is the most common mechanism of antimicrobial behavior for polymers, many other polymers act through other mechanisms; therefore, there exist other antimicrobial polymeric systems without a net charge which even mimic other natural antimicrobial peptides (Brogden 2005). Due to this variety, in this section, an overview of the most common types of antimicrobial polymers with intrinsically activity will be presented and some representative and recent examples of each group will be discussed.

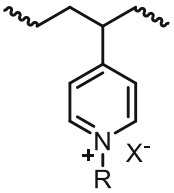
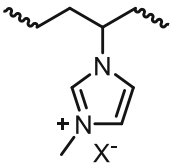
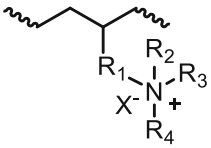
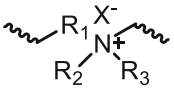
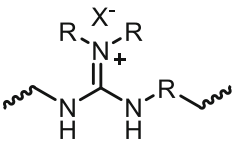
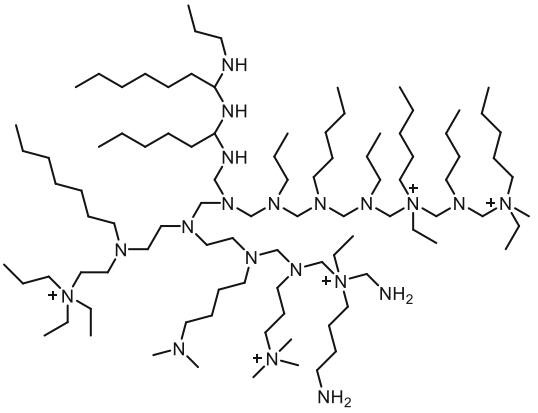
3.1 Polymers with Ammonium Groups

Arguably, polymers that contain quaternary ammonium ions are the most often researched variety of antimicrobial materials. This family of polymers is so interesting for the research community because it is relatively easy to produce poly(quaternary ammonium) salts through alkylation of polymers containing amine groups or by the polymerization of ammonium-containing monomers (Arora and Mishra 2018). Additional to this, there exist many biocompatible heterocycles containing amine groups that may be used as a basis for these kinds of polymers (Anderson and Long 2010; Almeida et al. 2012). Finally, this functional group is also important because monomers containing amines and ammonium salts may be synthesized from other monomeric bases such as acrylate and methacrylate monomers and these monomers may be further copolymerized to form materials with great assortment of characteristics (Muñoz-Bonilla and Fernández-García 2012; Xue et al. 2014). As a result of this range of features, antimicrobial polymers containing ammonium groups may be further subdivided into many categories which are shown in Table 1. This classification is by no means exhaustive, but it allows for an easier identification of antimicrobial polymers despite their different structures.

Although these kinds of polymers have clear differences, most studies have focused in finding the relationship between specific structural characteristics and the antimicrobial behavior of the polymers. Firstly, something that is definitive is that ammonium-containing polymers have an antibacterial behavior because of their positive charges; however, the potential of these polymers to be antibacterial depends on the density of this positive charge. In general, a greater density of positive charge promotes greater bacterial inhibition because of a greater potential to disrupt cell membranes. As a result, dendrimers and hyperbranched polymers containing many ammonium groups tend to have lower MIC for bacteria (Ergene et al. 2018).

Another important parameter is the length of an alkyl chain that is supported by an ammonium nitrogen because this is directly related to the hydrophobic/hydrophilic balance of the polymeric material. It has been shown that the optimal chain

Table 1 Classification of antimicrobial polymers containing quaternary ammonium ions

Polymer family	Base structure (R = alkyl/aryl, X^- = counterion)
Polymers containing pyridinium rings	
Polymers containing imidazolium rings	
Polymers with pendant ammonium groups	
Polymers with amines on the main chain (ammonium ionenes)	
Polymers derived from guanidine	
Hyperbranched and dendritic ammonium polymers	

size to fulfill this objective and decrease MIC for these substances are alkyl chains between 6 and 8 carbons which vary depending on the structure of the polymer. On the one hand, shorter chains (between 1 and 5 carbons) may not function optimally because proteins tend to adhere to hydrophilic substrates, covering the substrate and neutralizing its positive charge. On the other hand, longer chains (more than 8 carbons) may promote bacterial adhesion, they may be difficult to solubilize, and may be toxic to the host cells (Muñoz-Bonilla and Fernández-García 2012; Xue et al. 2014; Ergene et al. 2018).

A third parameter that affects the antimicrobial effect of many polymeric systems is the average molecular weight of the system. This parameter is important because it influences the capacity of the polymer to interact with the cell membranes of pathogens and also influences the net charge density (Kenawy et al. 2007).

Finally, the identity of the counterion may also be influential in the antibacterial activity. A very important factor for the effect of this counterion is it size which influences the hydrophobic/hydrophilic balance of a substrate; however, many other factors are involved when determining if a counterion will change the antimicrobial activity. Firstly, the dissociation of the polymeric salt is very important for the antimicrobial effect. Therefore, these polyelectrolytes should be preferably strong electrolytes, a factor which may be determined by the identity of the counterion. Additionally, some polymers may not only disrupt the cell walls, but also replace Ca^{2+} or Mg^{2+}, effectively disrupting the electrolytic balance within the cells. This is also dependent on the counterion's mobility within the cell environment. Since these factors may all influence the counterion's role on the antimicrobial activity, it is not as easy to find general trends, so the effect of a counterion is better evaluated for each antimicrobial substrate (Xue et al. 2014; Ergene et al. 2018). As a final note, Fig. 3 summarizes the characteristics that may define the antimicrobial characteristics of ammonium-containing polymers mentioned within this section.

As an additional consideration, although the mechanisms of microbial inhibition for these polymers are similar, the effectiveness of the growth inhibition depends on the type of pathogen involved. Since most of the pathogens which have negatively charged membranes are bacteria, ammonium-containing polymers are much more used as antibacterials rather than antimicrobials. The antibacterial behavior further depends on the type of bacteria involved. For instance, the outer layers of the cell walls of Gram-negative bacteria possess a membrane of lipopolysaccharide, which prevents the charged polymeric chains to interact with the negatively charged peptidoglycan cell wall; in contrast, Gram-positive bacteria have their loose peptidoglycan membranes exposed (Beeby et al. 2013). A diagram depicting the differences in membranes of these types of bacteria is presented in Fig. 4. Due to these differences, Gram-positive bacteria often need lower antibacterial concentrations to be inhibited.

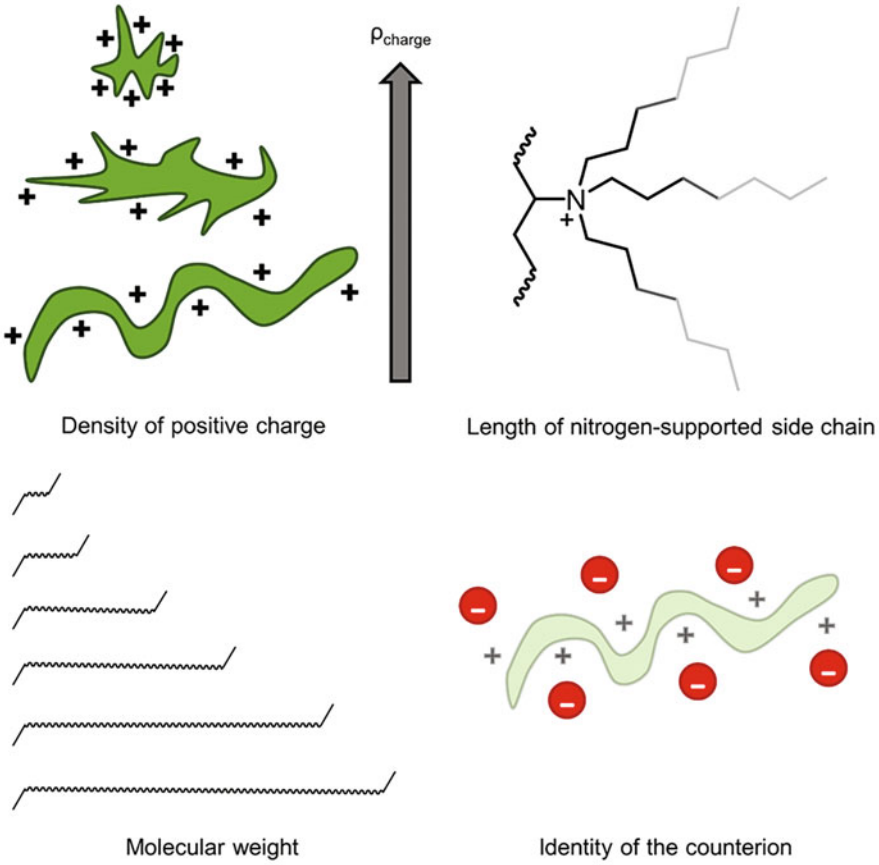


Fig. 3 Factors determining the antimicrobial characteristics of amine salts

3.1.1 Polymers Containing Pyridinium or Imidazolium Rings

Pyridine and imidazole rings are very resourceful bases for antimicrobial polymers since both heterocycles are biocompatible because they are present in compounds such as DNA bases and other biologically relevant substances such as histamine (Muñoz-Bonilla and Fernández-García 2012). The formation of polymers containing such heterocycles is achieved by the previous synthesis of vinyl containing heterocyclic monomers such as *N*-vinylimidazole, or 4-vinylpyridine (4VP). The corresponding vinylic monomer is then polymerized by a radical polymerization by any conventional method of initiation to form the antimicrobial polymers. This methodology, although simple, if combined with finer methods of polymer synthesis such as controlled living polymerizations, allows for the development of polymers and copolymers with very specific microstructures. Since these materials have been researched extensively, many reviews already cover many of the developments on

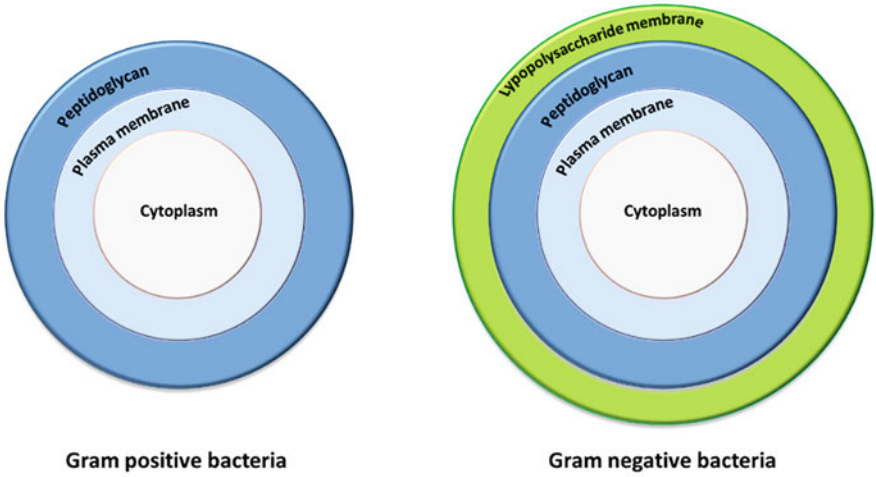


Fig. 4 Difference between Gram-positive and Gram-negative bacteria. Gram-negative bacteria possess an external extra lipopolysaccharide membrane

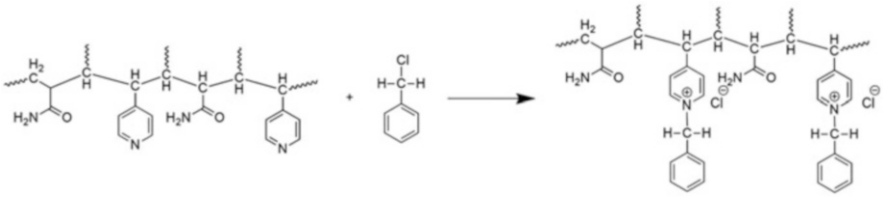


Fig. 5 Production of pyridinium-containing polymers quaternized with chloromethyl benzene

this area; therefore, in this chapter, only recent and relevant advances will be exemplified (Anderson and Long 2010; Jain et al. 2014; Xue et al. 2014; Arora and Mishra 2018; Ergene et al. 2018).

Pyridine may be readily quaternized because of the nucleophilicity of its nitrogen, even when the ring is already within a polymer; therefore, the most common route for obtaining pyridinium polymers is to first obtain a polymer with pyridine group and then performing the quaternization. One recent example of this is the formation of a copolymer of acrylamide (AAm) and 4VP initiated with γ-radiation for the development of cross-linked hydrogels which were later quaternized with chloromethyl benzene (Fig. 5). The MBC and pathogen killing kinetics of these substrates were tested against *S. aureus*, *E. coli*, *P. aeruginosa*, and *C. albicans*. It was found that this substrate was effective in inhibiting against the bacteria, but not the fungi, suggesting that the killing mechanism of the polymer is indeed the disruption of the charged membranes. Although no hemolysis data is reported, the material has potential to function as wound dressings (Arslan et al. 2017).

Ammonium-containing polymers have gained such importance that they have been combined with other substrates to include functionalities beyond pure

antibacterial activities. For example, by using ATRP poly(4-vinylpiridine) (P4VP) has been grafted onto graphene oxide (GO) for intrinsic antibacterial applications and drug delivery for therapeutic effects against cancer. In this work, Kavitha et al. (2015) measured the antibacterial effect in vitro of GO-*g*-P4VP, showing slight bacterial inhibition at concentrations at low as 100 μg/mL and a considerable growth inhibition effect (>80%) at 1000 μg/mL. Additional to the antibacterial properties, these materials were also verified to have low cytotoxicity (for NIH3T3 cells, MTT assay); for instance, the materials maintained high cell viability (~90%) at concentrations of 10 mg/mL after 5 day incubation, behavior which is similar to the one reported for GO. Finally, the load and release of camptothecin onto the materials allow for a considerable reduction on the cell viability of cancerous cells at concentrations as low as 10 nM (Kavitha et al. 2015).

As a final example, pyridinium polymers [poly(pyridinium-1,4-diyliminocarbonyl-1,4-phenylene-methylene chloride)] have also been combined with poly(3,4-ethylenedioxythiophene) (PEDOT) which allowed for the production of biocompatible and antibacterial n-doped conducting films for their use as electrochemical electrodes and sensors (Sánchez-Jiménez et al. 2019).

The imidazole group has also been thoroughly used as an antibacterial substrate because even when it is not quaternized, it shows antibacterial and antifungal properties (Anderson and Long 2010; López-Saucedo et al. 2017). Nevertheless, quaternized polymers tend to be more effective than their non-quaternized counterparts. Polymeric imidazolium compounds are also interesting because they commonly are ionic liquids; therefore, solubility issues are not as common. Recent advancements on the antibacterial activities of antibacterial imidazolium compounds include the synthesis of *N*-alkylated derivatives of many different *N*-vinylimidazole polymers, the grafting of quaternized *N*-vinylimidazole onto existing polymeric substrates, and the formation of different polymeric microstructures and morphologies of quaternized polyimidazoles. In 2016, for example, Zheng et al. synthesized a series of quaternized monomers of *N*-vinylimidazole (Fig. 6a), and their subsequent polymerization using AIBN, obtaining MICs as low as 0.009 μmol/mL for *S. aureus* and 0.018 μmol/mL for *E. coli.* In this work, the quaternized monomers were also copolymerized with styrene and acrylonitrile in presence of divinylbenzene as a crosslinking agent and benzoin ethyl ether as photoinitiator (Fig. 6b), these membranes not only were better substrates for solid polymeric membrane formation, but also retained good antibacterial activities (Zheng et al. 2016).

Another recent example of imidazolium-containing polymers was the formation of nanoparticles from *N*-alkylated poly(*N*-vinylimidazole) with bromine as a counterion. In this work, spherical nanoparticles of sizes below 100 nm were synthesized through radical polymerization initiated with AIBN. MICs were measured to be around 0.003 μmol/mL against *S. aureus* and 0.002 μmol/mL against *E. coli*, while also having relatively low cytotoxicity when cell viability was evaluated for mouse fibroblasts 3T3(A) and L929(B) (Fang et al. 2019).

Imidazolium polymers have also been grafted onto other polymeric substrates to produce antibacterial alternatives of these materials. For example, in 2016,

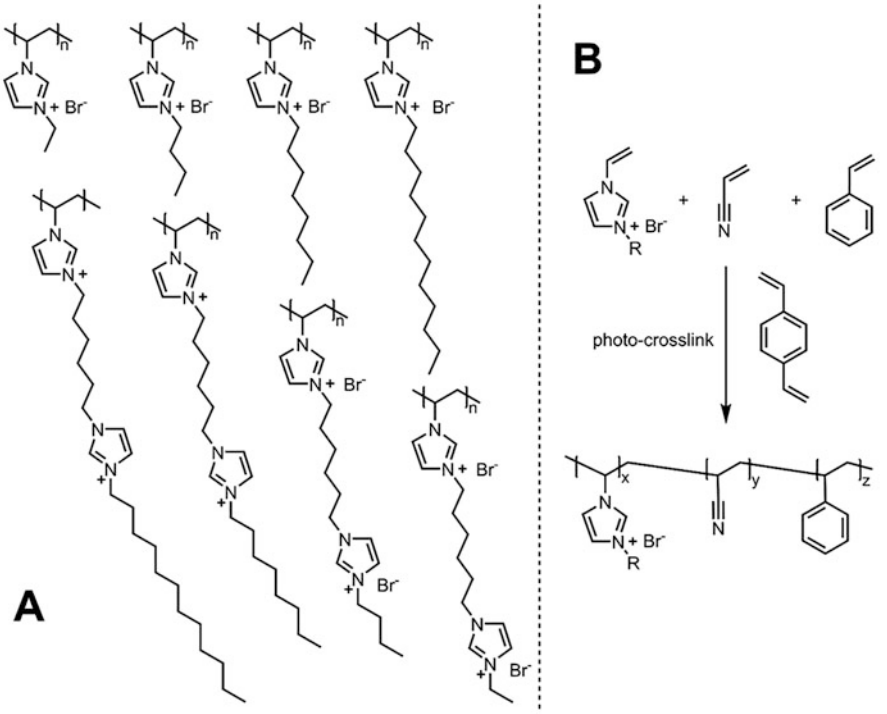


Fig. 6 Synthesis of derivatives of poly(*N*-vinylimidazole) for antibacterial purposes

N-vinylimidazole was grafted onto polyvinylchloride (PVC) using radiation as a clean initiator method. After the grafting procedure, the imidazole was quaternized with CH_3I through a nucleophilic substitution reaction. The synthesized materials were proven to be slightly antibacterial against *S. aureus* (Meléndez-Ortiz et al. 2016).

3.1.2 Polymers with Pendant Ammonium Chains

Polymers with ammonium chains are also a very common group of antimicrobial materials because they may be synthesized through many methods (Froidevaux et al. 2016). However, the most common examples of these polymers use amine containing vinyl monomers which are later polymerized through conventional methods. A recent example of this type of polymers was the UV-initiated synthesis of copolymers of 2-hydroxyethyl methacrylate and acryloyloxyalkyltriethylammonium bromides derivatives for the formation of antibacterial films, these polymeric materials were effective antibacterials against *E. coli* and *S. aureus* (Galiano et al. 2019). Another interesting example of polymeric materials containing pendant ammonium groups is the synthesis of amino acid-based polymers through RAFT polymerization (Fig. 7). These polymers were also verified

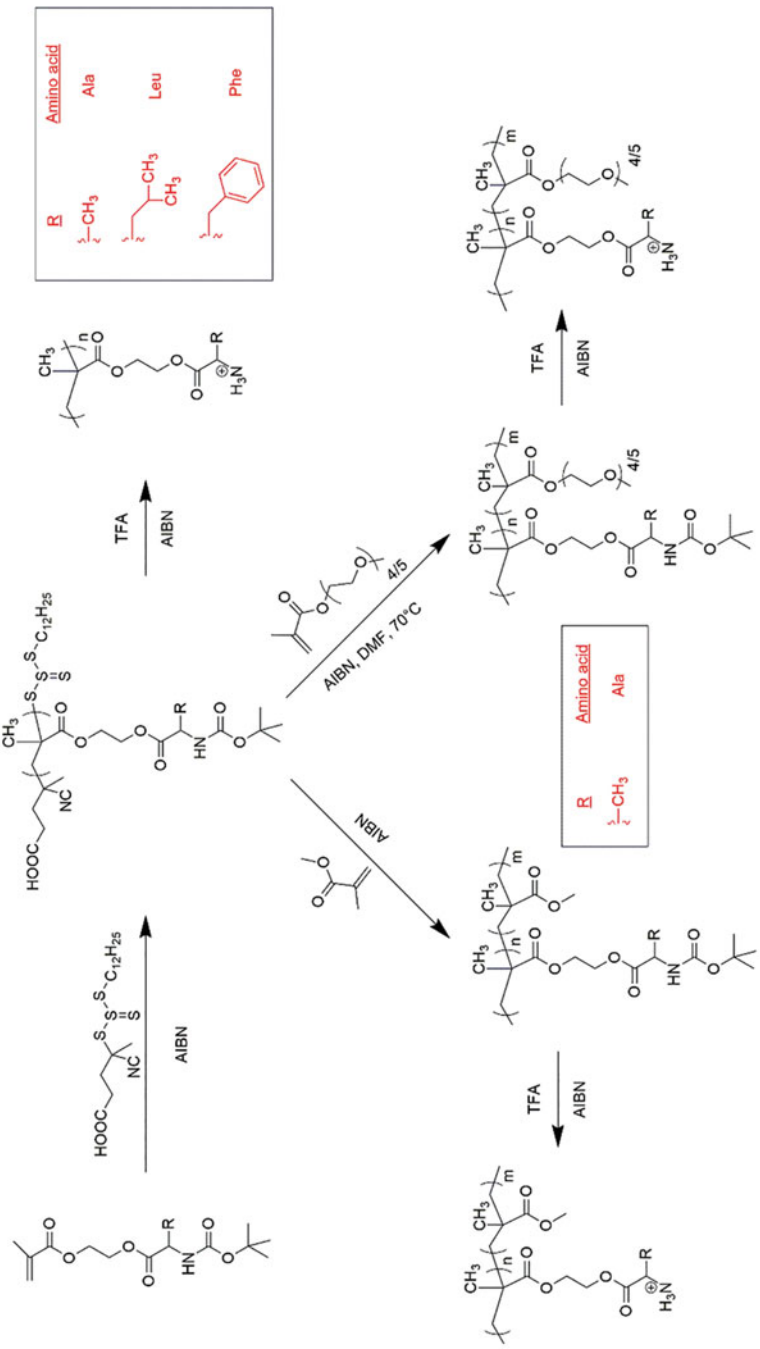


Fig. 7 Amino acid-containing polymers as an example of pendant ammonium groups

to be antibacterial against *E. coli* by measuring the zone of inhibition on Lysogeny broth (LB) agar after incubation for 12 h, and by quantifying the absorbance of LB culture medium containing *E. coli* and a polymeric sample against culture time (Mukherjee et al. 2017).

3.1.3 Polymers with Amines on the Main Chain

Another important variety of polymers which have been used as antimicrobial agents are polymers with ammonium groups on the main polymeric chain. These types of compounds are also called ammonium ionenes and are usually synthesized through polycondensation reactions, either by reaction of dicarbonyl groups and amines, or by the reaction of carbon dichlorides and amines (Fig. 8).

Some recent developments involve the formation of novel microstructures and composites of ionene materials with other solid substances. For example, Ding et al. (2015) synthesized a polyurethane (PU) derivative through the condensation of polyethylene glycol (PEG), butylene glycol, and an ammonium-containing diol with methylene diphenyl diisocyanate (MDI) as seen in Fig. 9. Afterward, $ZnCl_2$

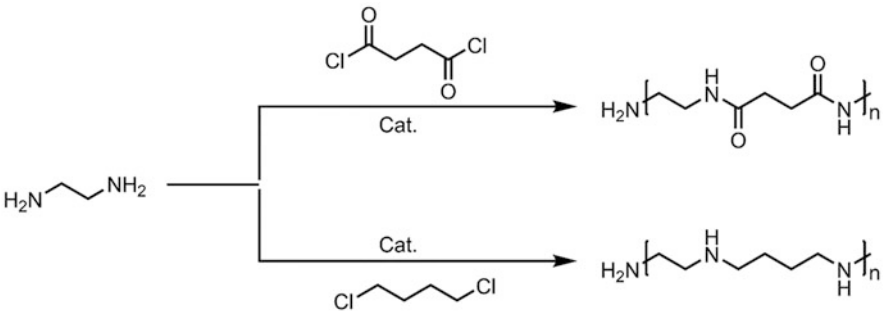


Fig. 8 Synthesis of polymers containing amine or amide groups on the main chain

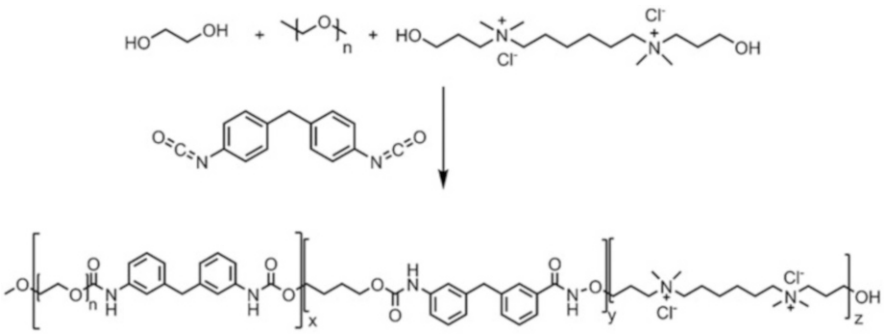


Fig. 9 Synthesis of PU ionenes

was added to the PU system to enhance the antimicrobial properties of the system against *E. coli*. Through this work it was found that the antibacterial effect of the ammonium ionene and $ZnCl_2$ caused a synergistic effect that provided the films with bacterial growth inhibition at least in vitro (zone of inhibition test) (Ding et al. 2015).

In another work, the effect of the topology of the ammonium ionenes in the antibacterial and hemolysis properties of the materials was investigated. For this, Mayr et al. (2017) synthesized a series of polyamide derivatives through a two steps procedure. First, they reacted one equivalent of either *o*-, *m*-, or *p*-phenylenediamine with 4-(Chloromethyl)benzoyl chloride to form dichloride derivatives which were later polycondensed with quaternized diamines. When evaluating MICs against *E. coli*, it was found that the *m*-derivative of the polyamides was not significatively antibacterial, while the other derivatives were (MICs ~2 μmol/mL). This indicated that the topology does affect in the interactions between the polymers and the bacteria. Additionally, these materials showed overall low cytotoxicity (hemolysis below 15%) at concentrations 2 μmol/mL of with no relevant trends found between topology and hemolysis caused by the ionenes (Mayr et al. 2017).

As a final example of ammonium-containing ionenes, in 2018 polymeric materials derived from lithocholic acid and tertiary amine linkers were synthesized by polycondensation reactions. In this work the MICs of the materials against *S. aureus* and *E. coli* was measured, showing that these materials are indeed effective in inhibiting the growth of this pathogens (Ganewatta et al. 2018).

3.1.4 Polymers Derived from Guanidine

Guanidine polymers are one of the most important groups among ammonium polymers because these substrates have been proven successful and have been readily used as antiseptics because of their antibacterial, antiviral, antifungal, and antiamoebic activities. The most common guanidine polymeric derivative is poly (hexamethylene biguanide) (PHMB) (Fig. 10) which has been already used commercially as antiseptic in wound dressings, topical agents for wound treatment, gloves, cleaning solutions for contact lenses, and general antiseptic solutions for both human and veterinary use (Lee et al. 2004; Lim et al. 2008; Kariduraganavar et al. 2014; Ali and Wilson 2017; Niu et al. 2017). This polymeric system has been demonstrated to be effective against many pathogens; however, it is important to mention that it may be slightly toxic to human cells at higher concentrations than it is normally used for therapeutic effects; therefore, its use must be taken with care (Asiedu-Gyekye et al. 2015).

Recently, even when most of the developments have focused on improving pharmaceutical formulations of PHMB, some other polymeric analogs have been

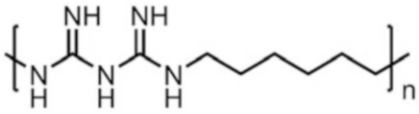


Fig. 10 Structure of poly (hexamethylene biguanide)

produced. For instance, in 2017, Grace and collaborators synthesized different varieties of acrylic polymers containing a guanidine pendant group through Cu (0) mediated polymerization of amide containing acrylate monomers with different chain lengths on the pendant groups followed with a guanylation with 1H-pyrazole-1-carboxamidine hydrochloride. The antibacterial effects of this polymer were tested against *P. aeruginosa*, *K. pneumonia*, *St. pneumoniae*, *S. aureus*, and *E. coli*, with low MICs (<8 g/mL) against *S. pneumoniae*, *S. aureus*, and *E. coli.* Additionally, hemolysis testing was performed within the concentrations around the MIC, showing low cytotoxicity for materials with longer alkyl chains, suggesting that the hydrophilic/hydrophobic balance importantly influences the hemolysis of the materials (Grace et al. 2017).

3.1.5 Hyperbranched and Dendritic Ammonium Polymers

The final classification of antimicrobial polymers is hyperbranched and dendritic ammonium polymers. This type of polymers has also shown to be very effective antibacterial substances because of their big positive charge densities. Even when they show very promising antibacterial application, the use of these polymers is often limited by their biocompatibilities, because they tend to interact more strongly with mammal cells. However, recent advances have achieved better biocompatibility.

One recent example of antimicrobial activity of dendritic polymers was the synthesis of silane dendrimers containing pendant amine groups which have been shown to be effective against ram-positive *S. aureus* and Gram-negative *E. coli*. In this study the MBCs and MICs for different dendritic systems and values as low as 1 ppm were found to be effective against both bacteria. Additionally, toxicity assays suggest that some of the dendritic materials represent useful systems with hemolysis below 20% at therapeutic concentrations (Fuentes-Paniagua et al. 2016). Another example in this area includes the formation of polyamide dendrimers with quaternized amine groups with antibacterial activity and low toxicity (Zainul Abid et al. 2016).

3.2 Polymers with Phosphonium Groups

Analogous to ammonium-containing polymers, phosphonium derived polymers are an important variety of antimicrobials which mainly function by destabilizing the cell walls or membranes of pathogens, especially those of bacteria. Therefore, many of the characteristics which are representative of ammonium-containing polymeric materials are also valid for phosphonium containing polymers, namely the effect of the charge density on polymer chains, the length of pendant alkyl chains, the effect of the average molecular weight, and the effect of counterions.

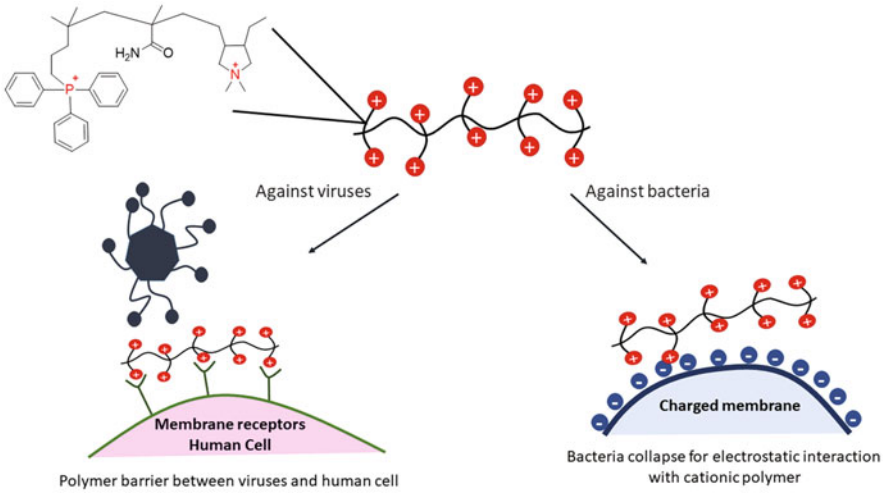


Fig. 11 Mechanisms of action of phosphonium and ammonium-containing polymers against bacteria and viruses (Xue et al. 2014)

Recent examples of phosphonium antimicrobial polymers are much more limited than those containing quaternary ammonium ions; therefore, in this section some representative examples of these systems will be presented briefly. It is important to note that these polymeric materials have historically been also very important, thus many reviews already cover many classical and important examples (Kenawy et al. 2007; Xue et al. 2015; Cuthbert et al. 2018).

As a first example of these types of systems, copolymers of acrylamide and (4-penten-1-yl)triphenylphosphonium bromide (PTPB) were produced by conventional radical polymerization with 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AIBA) as an initiator. As an addition, they formed terpolymers of acrylamide, PTPB, and diallyldimethylammonium chloride (DADMAC) to form a system containing both ammonium and phosphonium groups. After obtaining the polymers the authors evaluated both the antibacterial and antiviral activities of the materials against *E. coli* and adenovirus through viability of infected HEK 293 cells. The antibacterial activity of the materials was directly correlated with the content of phosphonium groups, with the lowest MICs reported for the copolymer only containing phosphonium groups (~20 ppm). According to AFM imaging, the lysis of *E. coli* is achieved at around 30 min. At MIC concentrations, the compounds also showed good antiviral activities that were due to cytotoxicity on host cells for viruses. The authors theorized that the mechanism of action for antibacterial properties is due to bacterial membrane disruption, while antiviral properties are present due to blocking of the passage of viruses onto endocytosis receptors of host cells. An illustration of these mechanisms is present in Fig. 11 (Xue et al. 2014).

In another example, carbohydrate-containing polymers which also contained pendant phosphonium groups were produced. To get these polymers, first,

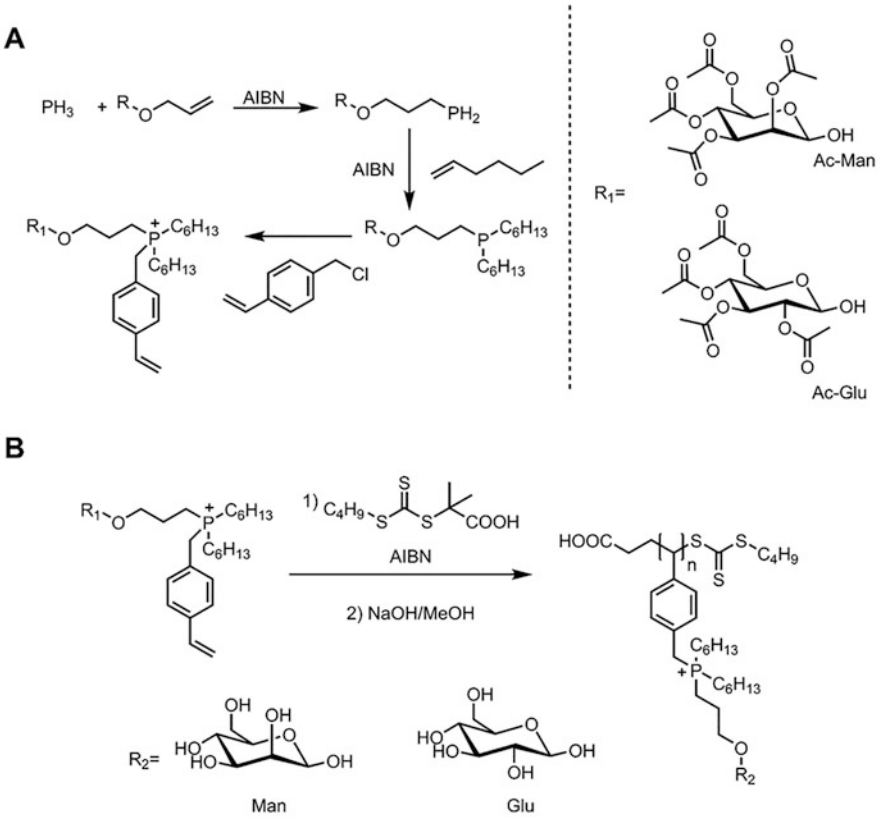


Fig. 12 Synthetic route for carbohydrate-containing phosphonium polymer

monomers containing phosphonium groups and hexoses were synthesized as shown in Fig. 12. This step was followed by the polymerization of said monomers through RAFT (Fig. 12). The inclusion of carbohydrates was intended as a mean for better absorption of the polymeric antibacterials onto bacterial pili with mannose receptors (*E. coli*); additionally, glucose was also used to compare the effect of this moieties. Counterintuitively, the MIC for the material containing mannose was not as low as others in the series, which indicates that charge is the prime factor which renders the materials antibacterials. Additionally, the antibacterial activity and hemolysis were correlated with the hydrophilicity of the substrates since the most hydrophilic polymer presented the lowest values MIC and the highest values for concentration at HC_{50} (Cuthbert et al. 2018).

As a final recent example of this material, temperature resistant polyphosphonium polymers were added to the extrusion process of common ABS as a mean to provide antibacterial properties to the final plastics. These materials were successfully extruded into the polymer without changing the mechanical properties of ABS polymer and without leaking when in solution. The polymers showed good

antibacterial activities against *E. coli* and *S. aureus* with MICs as low as 4 g/mL for *E. coli* and 1 g/mL for *S. aureus* (Zeng et al. 2019).

4 Halogen-Containing Antimicrobial Polymers: N-halamine Polymers

It is well-known that some antibiotics present halogens in their structure, which confer part of the antimicrobial properties. The antimicrobial activity of the halogen-containing polymers is mainly associated with their poor hydrophilicity. In some studies, it has been demonstrated that the halogen group is the leader in the growth inhibition process, and when the halogen is removed, the antimicrobial activity decreases considerably.

In 1996, Worley and Sun developed this functional group to stabilize the antimicrobial properties of free halogens. The chemical structure of *N*-halamines contains at least one nitrogen–halogen covalent bond which provides stability and slow release of free active halogen species into the environment. The general structure of these compounds is represented on structure 1 in Fig. 13. The main biocidal impact of the *N*-halamines is because they can be a protector group for active oxidative halogen species (Cl^+ or Br^+), which can be transferred to the cell

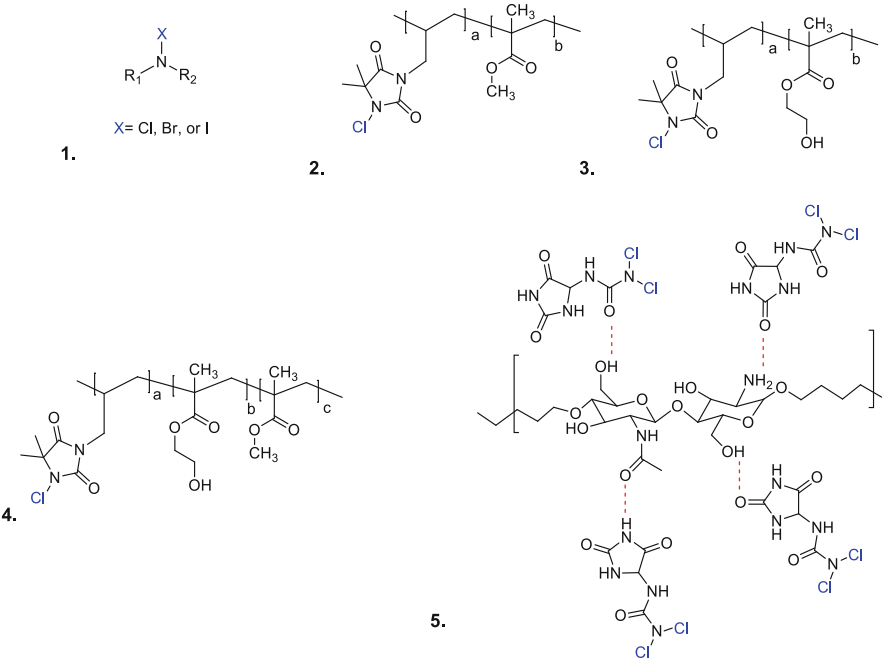


Fig. 13 *N*-halamine functional group and polymers containing it

membrane and have it oxidized. Thus, these types of polymers are considered as oxidant polymers. For that reason, these groups have been used in the elaboration of antimicrobial additives for polymers (Chen and Sun 2006). For instance, they have both been only loaded into polymeric matrixes and particles (Dong et al. 2015), and attached covalently to preformed polymers (Dong et al. 2014).

Gao's group in 2018 made copolymers and a terpolymer with pendant *N*-halamine group (see Fig. 13). With this work they demonstrated the impact of the morphology of the polymer in its antimicrobial properties. The terpolymer (structure 4 in Fig. 13) showed growth inhibition against *E. coli* and *S. aureus*, with better biocompatibility compared with that of the copolymers. They attributed this to the aggregation state of the polymers (Chang et al. 2018).

As another example, Chylinska et al. immobilized *N*-halamine groups in carboxymethyl chitosan films via hydrogen bonds (see structure 5 in Fig. 13). The resulting material showed good antimicrobial performance against *E. coli* and *S. aureus*. Besides, the modification with the *N*-halamine groups did not modify the thermal, mechanical, or chemical properties of the initial chitosan (Chylińska et al. 2019).

The incorporation of this functional group into the polymer structure has provided antimicrobial properties to polymers used for food packaging and drug excipients. Finally, it is of interest to mention some of the systems in which *N*-halamines have been incorporated; for instance, polyethylene terephthalate (PET) (Chien et al. 2019), polyurethane (Qiao et al. 2017; Xiu et al. 2017), and natural polysaccharides (Lan et al. 2019) have all been modified with these types of compounds.

5 Antimicrobial Peptides

Antimicrobial peptides (AMPs) are molecules composed, generally, from 12 up to 50 amino acids that are present in practically all kinds of living organisms, from prokaryotic cells to plants, animals, and humans which create a natural self-defense mechanism against pathogens (Brogden 2005). AMPs comprise a gamut of over 2000 compounds that act mostly contra bacteria but also have been useful as antifungal, antiparasitic, and antiviral agents (Lei et al. 2019). Besides, some studies have exposed that AMPs exhibit anticancer and antifouling activities (Wang 2010). The mentioned properties have aroused a special interest in the understanding and developing of these compounds as an alternative treatment versus multidrug-resistance bacteria (Waghu et al. 2018), since some studies have shown that the resistance developed to AMPs is lower compared to the usual prescribed antibiotics.

Regarding their structure, AMPs are amphipathic and, typically, have a polycationic character, though this does not exclude the existence of some neutral and polyanionic peptides (Lei et al. 2019). Thanks to these two main attributes, AMPs are attracted to the characteristic negative charged microbial membranes.

Lysozyme was the first AMP discovered in 1922 by Alexander Fleming, the same that a few years later would open the door to the golden era of antibiotics with the

discovery of penicillin in 1928 (Phoenix et al. 2013). The apparent supremacy and efficiency of antibiotics killing bacteria produced a momentary pause in researching of AMPs and their properties. Nonetheless; when bacteria were capable of evolving multidrug resistance, scientists turned back to AMPs as an alternative to fight the serious health problems arising from abuse and misuse of antibiotics.

Some studies in this respect were done between 1960s and 1970s; however, it was until 1980s that AMPs began to emerge again with the discovery of cecropins isolated from the moth (*Hyalophora cecropia*) (Hultmark et al. 1983), and the posterior identification of magainins from clawed frog *Xenopus laevis* (Zasloff 1987), which currently are still under consideration about their spermicidal and microbicidal activity (Zairi et al. 2009).

As a simple classification, it is possible to talk about four classes of AMPs: the first one is peptides with cationic character without cysteine residues. There compounds are characteristically disordered in water, but in presence of lipid compounds (for example, phospholipid vesicles and liposomes) they adopt a helical form (α-helix), which is presumably the responsible (and proportional to) for the activity against Gram-positive and Gram-negative bacteria. The second one is another group of cationic peptides with no presence of cysteine but instead having proline, phenylalanine, arginine, or tryptophan residues. The third group contains both cationic and anionic peptides, these AMPs possess cysteine residues and adapt to a β-sheet conformation with intramolecular disulfide bonds. An example of these is α-defensins from animals (including humans). Finally, a fourth group is formed by anionic peptides that require zinc to show antimicrobial activity.

5.1 Transmembrane Pore Formation as a Mechanism for Cellular Killing

To understand the mechanism with which AMPs kill bacteria, it is important to start considering the different stages where these peptides initiate to interact with pathogens (Matsuzaki 2019). This process begins with the electrostatic attraction between the bacteria's membrane surface, which is negatively charged, and the positive charge present in peptides. It is important to mention that AMPs do not produce a similar effect in plants' and animals' membranes because the negative electric charge is within the inner leaflet as well as the stability that cholesterol confers to the cells. To continue the process, an attachment to the cytoplasmic membrane must occur, which is commonly hindered by the layers that protect bacteria (polysaccharides in Gram-positive bacteria or pass over polysaccharides, teichoic, and lipoteichoic coat in Gram-negative bacteria). Once these barriers have been overcome and the interaction is established, the pathogen's death is carried out because of pore formation into the membrane that produces the membrane permeation. This pore formation depends on the relation between peptide and lipid composition relation. When there is enough peptide presence, a reorganization into the membrane

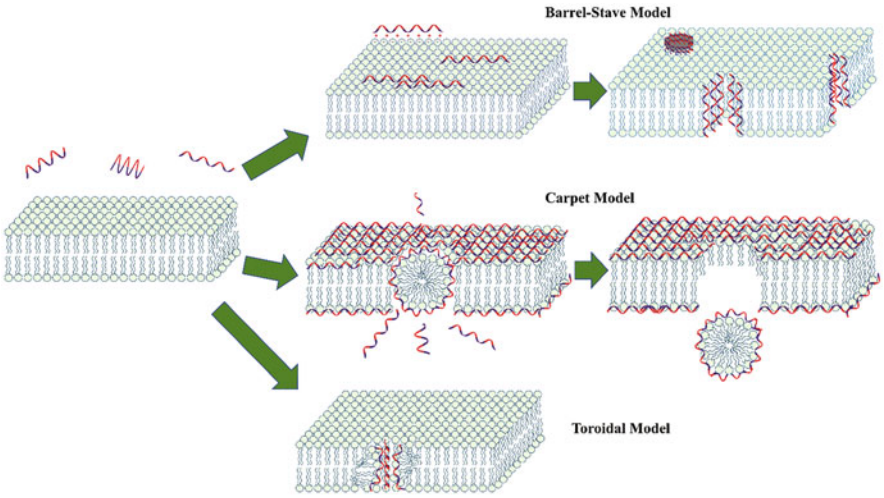


Fig. 14 Proposed models of action for AMPs

structure is accomplished, giving place to its permeabilization. There have been recognized three model lysis membrane mechanisms for α-helical structures: the barrel-stave, the carpet and the toroidal model (Fig. 1).

The "barrel-stave model" (Shai 1999) is proposed to explain the pore formation as a consequence of the shape that a group of α-helices adopts in the middle of the lipid membrane, this is, as the AMPs-lipid ratio increases, the hydrophobic parts of both components are aligned so that the peptides are transversal to the membrane plane forming a channel (pore). Alamethicin is a peptide that illustrates this model in a perfect way.

The "carpet model" (López-Meza and Aguilar 2011) describes the behavior of most of AMPs. In this model, as cationic peptides begin to be attracted to the anionic lipid layer, they stay oriented parallel to the pathogen membrane. When a critical concentration is reached, the peptides act as detergent and, instead of pores, formation of micelles is observed, causing the membrane disruption. This mechanism has been observed in peptides formed up to 23 amino acids, such as insect cecropin and dermaseptin from amphibian skin (biomedical engineering trends).

Finally the "toroidal model" is followed by molecules like magainins and melittins (Sengupta et al. 2008). Toroidal pores are formed when the peptide-lipid ratio is exceeded and instead of staying parallel to the membrane plane, the peptides are reoriented in transversal position so that the lipid head-groups of the membrane are always associated with the AMP hydrophobic moieties. In addition, and simultaneously, the polar faces of the peptides associate themselves with the polar part of the membrane. These two facts force the lysis of the membrane. As a reference for the reader, Fig. 14 shows a diagram of these mechanisms.

5.2 *Antimicrobial Resistance and Viability*

Even when AMPs have demonstrated to be potential candidates to face pathogens due to the wide range of activity and their fast response time versus microorganisms, it is important to considerate that there is a lack of successful and conclusive studies that support their use as commercial drugs. Moreover, for this to happen it is essential that the costs of synthesis and production are reduced and to find a way so that AMPs increase their stability as therapeutic agents (Gordon et al. 2005). Although AMPs have shown almost no resistance to pathogens, some bacteria have developed strategies to annul the peptides action. An illustration is the case of *Staphylococcus aureus* which has exhibited a reduction of its surface net negative charge as a mechanism of inhibition peptide attachment; *S. aureus* also produces a proteolytic enzyme (aureolysin) that gives place to the AMP degradation, nullifying the antimicrobial effect. Some Gram-negative bacteria (*Yersinia enterocolitica*) have transformed the composition of their outer membrane, resulting in resistance to AMPs.

6 Antimicrobial Peptide Mimics

Since AMPs have appeared as an alternative to common antibiotics, the power of emulate the properties of this compounds has attracted the attention of many researchers because it not only offers the possibility to better understand natural AMPs, but also because it offers the ability to more easily control structural their structural parameters (Thaker et al. 2012). The main characteristics to imitate in mimics of AMPs are cationic charge and amphiphilic structure, which, as previously discussed, are thought to be the attributes that grant AMPs their antimicrobial activity. In addition, the mimicked structures must show more resistance to proteases than current AMPs to be of interest in this field (Unubol et al. 2017).

Among the molecules proposed until today are poly-*N*-substituted glycines, where side chains are added to the nitrogen in their structure, thus reducing protease sensibility (Rotem and Mor 2009). Besides, when these groups are incorporated in periodical form, they confer a helical structure to the molecules just as the ones which are typical in α-helix AMPs conformation.

Other molecules that have exhibited some antibacterial activity are β-peptides mimics. These β-amino acid-derived polymers possess both helices and a β-sheet architecture, and have demonstrated the ability to form pores, promote phospholipid transbilayer diffusion (Epand et al. 2004), and have less response to protease activity.

As an additional system, aryl amide oligomers and phenylene ethynylenes studies display promising antimicrobial activity. The first ones present a membrane lysis mechanism with low toxicities, these compounds also resemble magainins and

cecropins (Liu et al. 2004). On the other hand, phenylene ethynylenes produce severe damage to the pathogen lipidic membrane (Wang et al. 2011).

In summary, the synthetic route to mimetic AMPs and its potential as agents with antimicrobial activity has already been explored by several scientists; however, the challenge to control the properties of these designed peptidomimetics is still present and several other studies must be carried out in order to offer new alternatives to present antibiotics.

7 Polymers with Added Antimicrobial Agents

The fabrication of polymers with intrinsic antimicrobial activity depends directly on the polymer structure, molecular weight, solubility, and forms. All of these parameters are very difficult to control if a reproducible and trustworthy synthetic procedure is needed, which has become an issue that has slowed down the development of intrinsic antimicrobial agents. Therefore, to mitigate this issue and to accelerate the development of these kinds of systems, another approach that is often used to provide antimicrobial activity to preformed polymers and polymeric devices is the addition of different well-known agents, such as bactericidal compounds, or AMPs.

The incorporation of these antibiotics inside the polymer chains conducts to a resulting polymer with high bacterial repellence or growth inhibition. These antimicrobial compounds can be coated onto surfaces for several applications such as medical devices, paint additives, water treatment, food packaging, among others (Kumar et al. 2008; Das et al. 2015). The compounds attached to polymers possess intrinsically antibacterial properties by themselves with a mechanism of action which is described in literature.

The nature of the antimicrobial agent can be organic or inorganic, with a notable example being the incorporation of peptides or proteins has been used for the same purpose. A broad number of antimicrobial compounds have been attached or mixed with polymers to avoid microbial growth or adhesion. The addition of these compounds can be achieved by two ways: On the one hand, using conventional synthetic chemistry reactions to covalently bind the active molecule to the substrate. On the other hand, the incorporation may be carried out by mixing the compound and the polymer to form a composite.

A wide range of medical devices (such as catheters, sutures, and valves), membranes, and food wraps are manufactured with polymers like polypropylene (PP), polyethylene (PE), poly(lactic acid) (PLA), poly(vinyl chloride) (PVC), polydimethylsiloxane (PDMS), polyurethane (PU), polyamide, poly (tetrafluoroethylene) (PTFE), etc. In the case of medical instruments and devices, these polymeric devices tend to become contaminated within a few days of contact with the patient, causing risky hospital-acquired infections (HAI). To mitigate this problem, the incorporation of antimicrobial compounds to polymeric materials is very useful even if the material is prone to pathogen contamination.

7.1 Metal-Loaded Polymers

In this section, the addition of inorganic compounds to polymeric matrixes will be studied. There are a lot of reviews that cover the incorporation of these type of compounds to polymeric matrixes to provide antimicrobial capacity to polymers (Muñoz-Bonilla and Fernández-García 2012; Siedenbiedel and Tiller 2012; Jain et al. 2014; Palza 2015). The most common approach is to use elemental metals which organize in nanoclusters or nanoparticles (NPs) since these systems are toxic to bacteria (Ren et al. 2009). Another way to add inorganic compounds is deposition of other inorganic compounds onto the polymeric surfaces. Silver, copper, or zinc NPs are probably the most widely used metal particles as an antimicrobial agent in polymeric composites; however, other compounds such as titanium dioxide (TiO_2) (Felice et al. 2017; Krehula et al. 2017), nitric oxide (NO) (Sadrearhami et al. 2018; Rong et al. 2019), and zinc oxide (ZnO) (Marra et al. 2016) have also been employed too for both biomedical and food applications (Hoseinnejad et al. 2018).

One advantage of these metals is that their MICs are commonly extremely low, but at the same time, they are typically expensive. Although the mechanism of action of these inorganic compounds is not completely described, at least for silver compounds (silver nanoparticles (AgNPs) and silver ions), one of the main pathways that stops bacterial growth is that silver ions (Ag^+) tend to bind to proteins, altering the pathogen cells. AgNPs also interfere with the microorganisms' growth due to the formation of complexes with nitrogenous bases in DNA and RNA (Morones et al. 2005; Petica et al. 2008; Woo et al. 2008; Aziz et al. 2014, 2015, 2016, 2019; Gudikandula and Charya Maringanti 2016; Burdușel et al. 2018).

In addition to the previous mechanisms, metals can participate in redox reactions and can act as a catalyst for some enzymatic reactions. The presence of external metals can increase these reactions, producing an excess of reactive oxygen species (ROS) derivatives which produce oxidative stress in the cell. The cytotoxicity of different metal have been reported against Gram-positive and Gram-negative bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus*, *S. epidermis*, among others (Lemire et al. 2013).

Different metals (reduced and oxidized forms) have been deposited into hydrogels and polymers by different methods. Some of these methods are the following: electrochemistry (Domínguez-Domínguez et al. 2008; Jovanović et al. 2012; Fu et al. 2016; Karimzadeh et al. 2016; Tian et al. 2017), radiation (Son et al. 2006; Pant et al. 2011), or, most commonly, conventional chemistry, such as redox reactions (Payami et al. 2016). Typically for these substrates, antimicrobial activities of the resulting material are measured in many of these studies. The immobilization of these metallic particles and ions is favored by coordinating functional groups onto the polymeric structure (Tylkowski et al. 2017); for example, AgNPs and oxidized silver can coordinate with carboxylate groups of polymer chains, through electrostatic interactions, as seen in Fig. 15a. Additionally, they can interact with positive charged groups such as ammonium salts when the metallic nanoparticles are suspended in a surfactant, forming a micelle-type structure (Agnihotri et al. 2013)

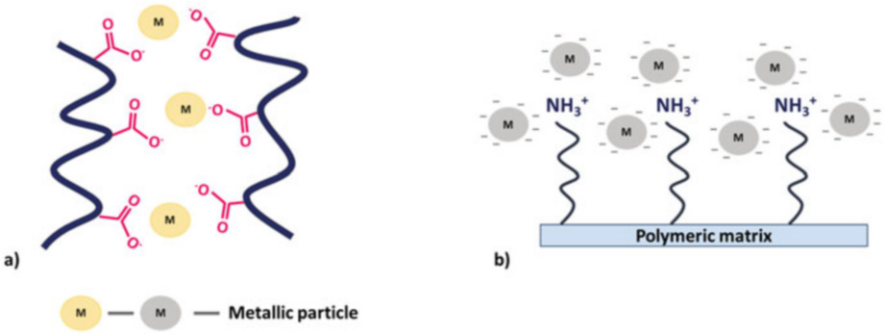


Fig. 15 Metallic particle immobilization via electrostatic interaction with (**a**) carboxylate groups and (**b**) ammonium salts

as it is represented in Fig. 15b. Nevertheless, there exist reports about direct covalent attachment of silver in polymer chains with significant results against *S. aureus* (Akhavan et al. 2018).

Although many metals have shown good antibacterial activities, silver is the most used and studied metal due to its broad-spectrum antimicrobial activity, since it presents high stability, low-cost, and ease of preparation. AgNPs have been embedded and immobilized onto different and relevant polymers used in food industry (Llorens et al. 2012) and biomedical applications (Zare and Shabani 2016), by a variety of methods. Some polymeric matrixes that have been modified with AgNPs are: PTFE (Reznickova et al. 2014; López-Saucedo et al. 2019), PLA (Busolo et al. 2010), PE (Song et al. 2011), PP (López-Saucedo et al. 2018), among others (Mei et al. 2014).

Extensively, there exist a lot of reports about hydrogel/AgNPs composites (Xu and Zhou 2008; Jovanović et al. 2012; Rhim et al. 2013; Fazly Bazzaz et al. 2014) which are vastly used as antimicrobial materials. The NPs deposition and immobilization can be reached by two pathways, one alternative is mixing both components (hydrogel and preformed AgNPs) to form a polymer/metal composite; the other option is in situ formation using any aforementioned method; both techniques result in materials with high capacity to killing bacteria (Cioffi et al. 2005; Araújo et al. 2018). Most reports employ the second way to obtain AgNPs inside a polymer or hydrogel, mainly by chemical reduction of $AgNO_3$ using conventional reducing agents (sodium borohydride ($NaBH_4$), monosaccharides, citrate, polyols, etc.) (Rodríguez Nuñez et al. 2019). For surface immobilization of metal NPs, brush-type polymer grafting is used, this allows for NPs retention when the nanoparticle gets embedded between polymer chains. As a greater enhancement, the use of stimuli-responsive polymers provides controlled retention and release of the metal nanoparticle (Gupta et al. 2008).

As an example, hydrogels used for contact lens manufacturing tend to contaminate easily by common bacteria, and the incorporation of antimicrobial compounds has reduced the risk for microbial-associated infections for lens users. Fazly Bazzaz

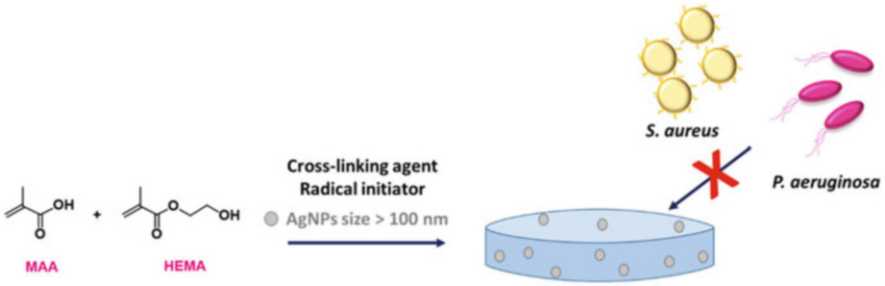


Fig. 16 Synthesis of MAA-*co*-HEMA 3D hydrogel impregnated with high size AgNPs for growth inhibition of bacteria

et al. (2014) added preformed AgNPs (size >100 nm) to a cross-linked hydrogel of methacrylic acid (MAA) and 2-hydroxyethyl methacrylate (HEMA) (similar material to that of soft contact lenses) to avoid bacterial adherence onto the hydrogel surface. They tested the impregnated material against *S. aureus* and *P. aeruginosa*. The hydrogels with different amount of AgNPs demonstrated high antibacterial properties which were not related to AgNPs content (Fazly Bazzaz et al. 2014). A schematic representation of this is shown in Fig. 16.

Since the addition of AgNPs has demonstrated good bactericidal capacity while mixed with some polymers, they have been used in injectable-hydrogel systems showing the same antibacterial activity and good biocompatibility. Niu and coworkers in 2018 achieved AgNPs stabilization with the encapsulation using a poly(ethylene glycol dimethacrylate)/Poly(acrylic acid) (PEGMA/PAAc) copolymer. The formation of silver nanoparticles was conducted by chemical reduction of $AgNO_3$ with $NaBH_4$, while the silver was reducing, the encapsulation with the polymer was occurring. The coating formation is driven by the electrostatic interactions between the carboxylic acids (or their conjugated carboxylate base) and the silver particle. The formation of the micelle-type particle prevents AgNPs aggregation during the reduction process (Ag^+ to Ag^0) as it is represented on Fig. 17a. The antibacterial test results against *S. aureus* and *E. coli* showed growth inhibition for both bacteria with minimal concentration of AgNPs. The biocompatibility studies with HeLa cells showed low cytotoxicity when silver concentrations were kept low (but still in therapeutical ranges for this study) (Niu et al. 2018).

Other hydrogels made of poly(vinyl alcohol) (PVA) (Alcântara et al. 2019), alginate (Ghasemzadeh and Ghanaat 2014; Martins et al. 2015), agar (Rhim et al. 2013), cellulose (El-Shishtawy et al. 2011; Yang et al. 2012; Rouabhia et al. 2014), chitosan (Agnihotri et al. 2012; Nguyen et al. 2019), and gelatin (Xu and Zhou 2008; Kanmani and Rhim 2014). These materials have either been impregnated or mixed with AgNPs and have exhibited good antibacterial capacity against common pathogenic bacteria.

Other hydrogels have been loaded with copper and gold following the same procedures (Ribeiro et al. 2017; Araújo et al. 2018). Some of the materials are useful for burn wound dressings and as wound healing agents (Boonkaew et al. 2014a, b;

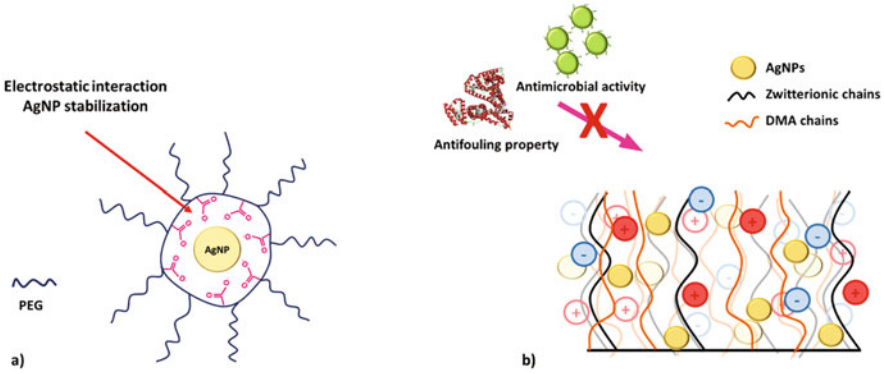


Fig. 17 AgNPs immobilization into a hydrogel structure by the (**a**) AgNPs stabilization by electrostatic interaction with carboxylic groups and by the (**b**) in situ formation with catechol groups as reducing agent with zwitterionic moieties for antifouling properties

Mohamed and Sabaa 2014). Moreover, zwitterionic hydrogels and AgNPs have been mixed to form bifunctional materials. In this case, the zwitterionic moiety provides antifouling properties (avoids protein adhesion and consequently bacterial adhesion) and the silver provides the antimicrobial properties. As it can be seen in Fig. 17b, a copolymer of dopamine methacrylate (DMA) and *N*-(3-Sulfopropyl)-*N*-(methacryloxyethyl)-*N*,*N*-dimethylammonium betaine (DMAPS) was synthesized to immobilize silver nanoparticles, the AgNP formation was conducted by reduction of $AgNO_3$ with the catechol group in the DMA, which is oxidized to the ortho-quinone form while the silver was reduced (GhavamiNejad et al. 2016).

7.2 Polymers with Organic Antimicrobials: Attachment and Immobilization

As we mentioned previously, the antimicrobial activity of a polymeric matrix or of a hydrogel can be attributed to the active molecules embedded on their chains, since not all the polymers present intrinsic antimicrobial properties. Some of them have application in the controlled release of drugs, and others only to avoid bacteria adherence to the surfaces.

The main content of this section is the addition of organic compounds to polymeric matrixes for antimicrobial and antifouling properties. These compounds can be biocides, antibiotics, or active molecules against any type of microorganisms, like fungi, viruses, or bacteria. Several drugs have been introduced to polymers and hydrogels, especially those with broad-spectrum antimicrobial activity, some of the most representative examples are shown in Fig. 18. These antimicrobial compounds have well-known bactericidal activity, and their mechanisms of action are

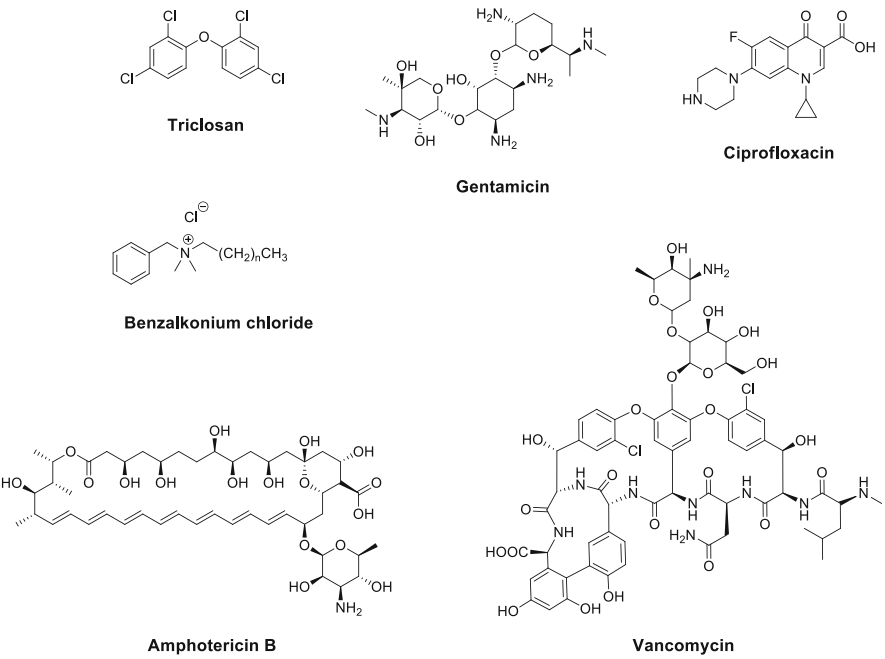


Fig. 18 Antimicrobial agents introduced in polymers

extensively described in the literature (Hancock 2005; Kohanski et al. 2010; Kapoor et al. 2017).

One important aspect is that some polymers used for biomedical applications have been directly modified with other macromolecules under the same purpose, mainly to avoid the bacteria biofilm formation and prevent HAIs. In contrast, some studies suggest that the addition of hydrophilic moieties onto the surfaces only stops bacterial adhesion, for that situation, it is necessary to add other antimicrobial compounds.

The incorporation of the bioactive organic compounds can be attained by two methods. On the one hand, by the immobilization via non-covalent bonds between polymer chains, and on the other hand by the covalent connection of the molecule to the polymer backbone, using different *grafting* techniques.

The first one is the loading of the drug inside the polymer, which allows the controlled retain/release of drugs. The grade of retention depends directly from the chemical structure of both drug and polymer, because they influence the supramolecular (non-covalent) interactions between their functional groups. Other important aspect to consider is the acid-base behavior of the groups and the thermostability of the components, since the usability of the material also depends on them, as well as the capacity of load drugs.

As mentioned before, the immobilization of the bioactive molecules can be reached using different *grafting* techniques, but the main approach used is the

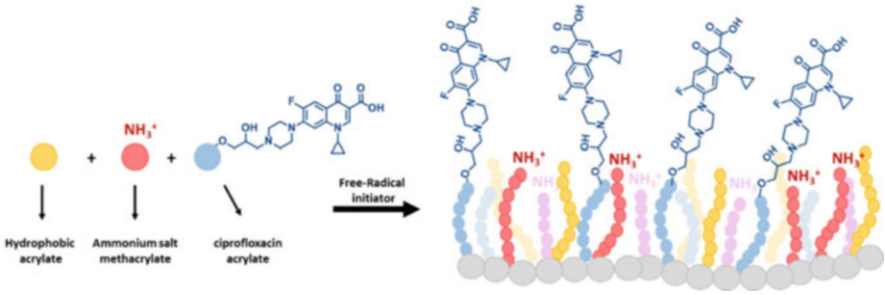


Fig. 19 Amphiphilic copolymer with ciprofloxacin as pendant

synthesis of a monomer containing the antimicrobial group. This strategy has been employed to covalently attach molecules with different properties. The synthesis of a monomer, specially, "drug"—acrylates or—methacrylates is the most used procedure. Ciprofloxacin, AMPs, gentamicin, and other antibiotics have been bound to polymers using this technique to provide or to improve antimicrobial properties (Permyakova et al. 2018; Xiao et al. 2018; Hu et al. 2019).

For example, ciprofloxacin has been loaded and introduced in polymers and hydrogels by the two methods. Some of these polymers have been, for example, cyclodextrin-agar hydrogels (Blanco-Fernandez et al. 2011), chitosan films and nanoparticles (García et al. 2017; Sobhani et al. 2017), alginate and alginate copolymers (Ahmed and Boateng 2018; Patel et al. 2019), PLA/gelatin mixture (Xia et al. 2019), poly(lactic-*co*-glycolic acid) (PLGA) (Liu et al. 2018), etc. The presence of ciprofloxacin confers antimicrobial properties, mainly, against a broad number of Gram-positive and Gram-negative bacteria (Campoli-Richards et al. 1988), such as *S. pneumoniae*, *P. aeruginosa*, *E. coli,* and *S. aureus*.

Although, in most cases, ciprofloxacin has been loaded in the polymer, there are reports about covalent immobilization in the polymer structure, as a pendant group (Xue et al. 2012; He et al. 2018), Man He et al. 2018 synthesized an amphiphilic copolymer with dual antimicrobial effect, first provided by the ammonium salts and second provided by ciprofloxacin covalent attached to the polymer. The polymerization was performed by a conventional free-radical polymerization of the three different components, see Fig. 19. Each component in the polymerization was selected with a specific purpose, the alkyl acrylate (yellow ball) provided hydrophobic character to the final polymer, as well as the amino methacrylate (red ball) fulfilled two functions: first, offering hydrophilicity and second to provide antimicrobial properties, the last component was the ciprofloxacin acrylate (blue ball in Fig. 19) with known antibiotic effect. This amphiphilic polymer showed growth inhibition against *E. coli* (He et al. 2018).

The grafting method has been employed to modify polymers with additional brush-type or stimuli-responsive polymers. In this graft, the drug loading and release can be reached by a stimulus and non-covalent interactions. For example, PVC catheters were modified with poly(methacrylic acid) (PMAA) using ionizing

radiation (PVC-*g*-MAA), loaded with ciprofloxacin and benzalkonium chloride, and their antimicrobial performance was tested (Zuñiga-Zamorano et al. 2018). The pH-sensitivity of the PMAA allowed the diffusion of ciprofloxacin and benzalkonium chloride inside the chains when the pH is above the pKa of the acidic groups. The antimicrobial effect was demonstrated with *P. aeruginosa*, *E. coli,* and *S. aureus*, the ciprofloxacin-loaded catheters showed good bacteria growth inhibition against the three pathogens and those with benzalkonium chloride only affected the *S. aureus*.

Vancomycin has been loaded onto hydrogels and polymeric matrixes, and due to its chemical structure, it can interact through hydrogen bond with the polymer. Drug delivery systems employ vancomycin for its broad-spectrum activity and for providing antifouling properties. This antibiotic has been loaded in chitosan nanoparticles and aerogels for wound dressing applications (Xu et al. 2015; López-Iglesias et al. 2019; Hassan et al. 2020), alginate (Kurczewska et al. 2017), polycarbonate (Zhang et al. 2017), gelatin (Aksoy et al. 2019), and commercial polymeric excipients such as Eudragit RL 100 (Santos Ferreira et al. 2018) and HPMC (Mahmoudian and Ganji 2017).

8 Zwitterionic Polymers as Antifouling Materials

Zwitterionic polymers (Poly(Zw)) are polymers with both positive (cations) and negative (anions) charges incorporated into their structure, these charges can be distributed randomly in all the macromolecule, but always maintaining the stoichiometry 1:1. This class of polymers includes polybetaines and polyampholytes, whose differences can be seen in Fig. 20.

Poly(Zw)s present excellent properties in solution (Blackman et al. 2019), due to the charges in their structure. They are also considered as stimuli-responsive polymers, because some of them respond to changes in temperature, electric field, and pH. Nevertheless, the most important and exploited property is that they can repel and stabilize proteins (Pelegri-O'Day et al. 2017) due to their multi-charges in their structure. This causes a decrease in the cell and bacteria deposition too. Their main application is as surface coatings since they prevent the biofilm formation or present

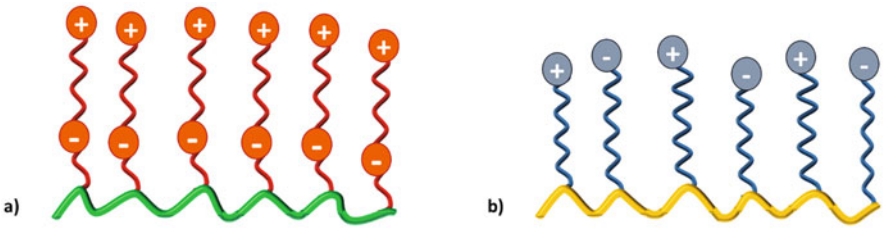


Fig. 20 General charge distribution of zwitterionic polymers, (**a**) polybetaines and (**b**) polyampholytes

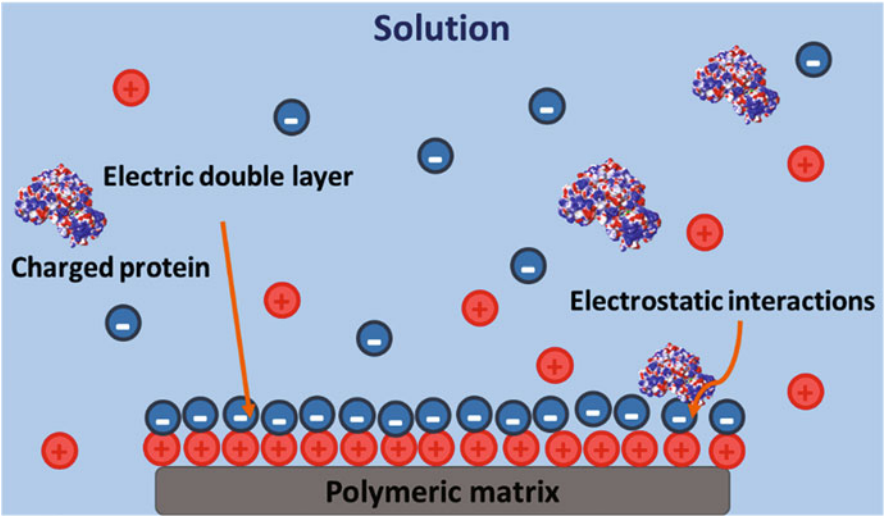


Fig. 21 Electrical double layer formed onto the pristine surfaces that promotes the protein attachment

antifouling properties (He et al. 2016; Zheng et al. 2017; Wang et al. 2018; Zeng et al. 2018; Zhang et al. 2018a, b, 2019a, b; Fu et al. 2019; Van Andel et al. 2019; Sun et al. 2020), but they are also used as polymeric drug delivery systems (Sun et al. 2017).

The difference between the unmodified polymeric matrixes and those modified with poly(Zw)s is that the former tend to form an electrical double layer (see Fig. 21) and this favors the attachment of charged proteins (Lubarsky et al. 2005), which trigger the migration and stabilization of microbes and cells onto the surface; while the modified surfaces for the well distributed charges do not polarize the charges, hence they do not allow the protein attachment.

Several polyampholytes and polybetaines have demonstrated high repellence to proteins, and have been employed to modified surfaces for marine and biomedical applications (Haag and Bernards 2017; Kardela et al. 2019), for the improvement of membranes (Zhang et al. 2018a, b; Yang et al. 2020), and even the synthesis of multi-charged containing hydrogels is also explored (Shen et al. 2019; Vales et al. 2020). The synthesis methods to obtain this kind of macromolecules involve controlled living radical polymerizations (CLRP), controlling living ionic polymerizations (CLIP), free-radical polymerizations (FRP), and ring-opening metathesis polymerizations (ROMP) (Kudaibergenov 1996; Bernards and He 2014; Laschewsky 2014; Tao et al. 2018; Morimoto et al. 2020). In addition, these polymers can be grafted onto surfaces by different techniques, such as grafting from and grafting to approaches (Wu et al. 2019a, b).

For example, Zhang et al. (2018a, b) made a functionalization of membranes with a polyampholyte polymer to provide it with antibacterial and antifouling properties. Additionally, they loaded graphene oxide sheets (GO) into the polymer chains using vacuum filtration (see Fig. 22). The immobilization of GO in the polymer was

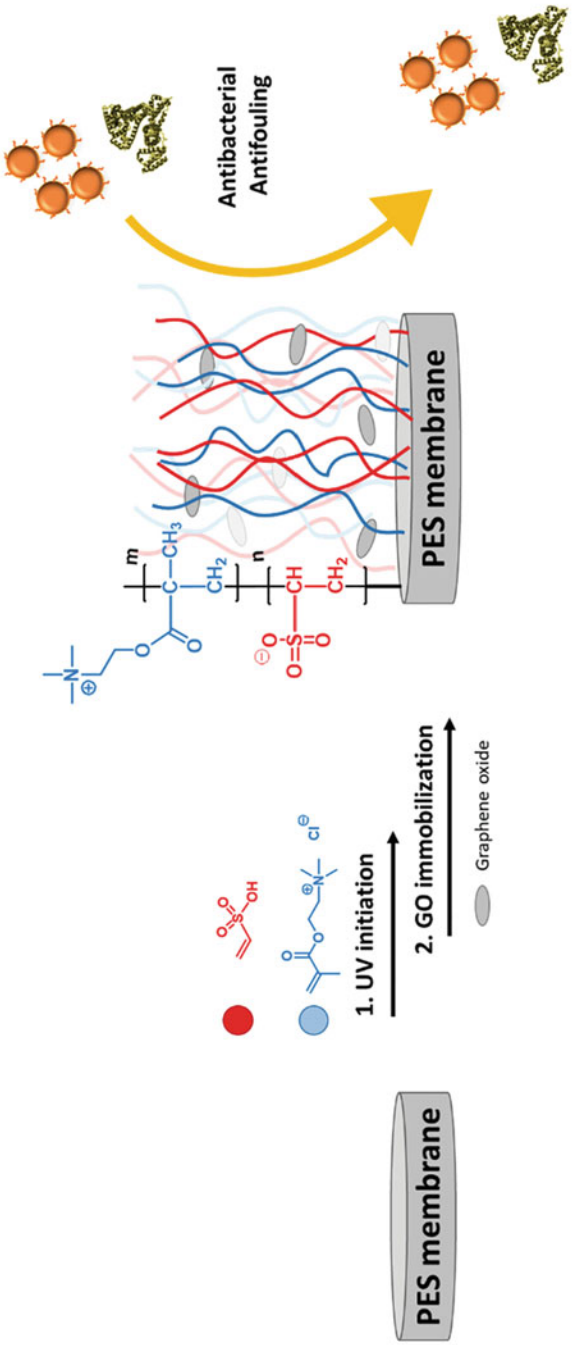


Fig. 22 UV-photoinitiated polyampholyte grafting onto PES membranes and GO for antifouling and antimicrobial properties

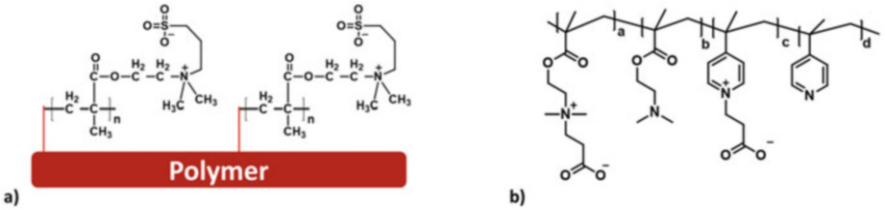


Fig. 23 (**a**) Modification of polymeric matrixes with DMAPS and (**b**) Synthesis of zwitterionic copolymers for antimicrobial and antifouling properties

because GO prevents the bacteria growth. The protein absorption and antimicrobial tests were performed to the final modified dual membrane, and they demonstrated that the functionalization with GO and zwitterion hydrogel is a promising strategy to prevent biofouling and protein adhesion in ultra-filtration membranes. Similar work was carried out by Zhang and Yang group in 2019 on graphene oxide carbon nanofibers for the development of aptasensors (Zhang et al. 2019a, b).

Another example is the modification and manufacturing of surface coatings with polybetaine-type polymers. In 2018, Lee et al. and Wu et al. grafted *N*-(3-Sulfopropyl)-*N*-(methacryloxyethyl)-*N*,*N*-dimethylammonium betaine (DMAPS) onto polyurethane (PU) and polydimethylsiloxane (PDMS), respectively, by different grafting techniques, obtaining good antifouling materials, Fig. 23a.

As a final example, polymers derived from 4-vinyl pyridine (4VP) and dimethyl amino ethyl methacrylate (DMAEMA) were *N*-substituted with an ethyl carboxylate to form the zwitterionic copolymer, see Fig. 23b. The resulting polymer was further characterized and tested for protein adsorption and cell adhesion. With these experiments, they found that the polymers displayed non-fouling activity against Bovine Serum Albumin (BSA), lysozyme proteins, and human kidney cells (Wu et al. 2019a, b).

9 Conclusions

As pictured in the sections above, antimicrobial polymers have many varieties and have been already shown effective for many applications. Although this field had huge advancements, better and more applicable polymeric materials are expected to appear in the following years. These materials present an alternative to classical molecular antibiotics and are expected to improve the odds against the rise of antimicrobial resistant pathogens in order to improve healthcare conditions and have alternative therapies for all types of pathogens.

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References

Agnihotri S, Mukherji S, Mukherji S (2012) Antimicrobial chitosan–PVA hydrogel as a nanoreactor and immobilizing matrix for silver nanoparticles. Appl Nanosci 2(3):179–188. https://doi.org/10.1007/s13204-012-0080-1

Agnihotri S, Mukherji S, Mukherji S (2013) Immobilized silver nanoparticles enhance contact killing and show highest efficacy: elucidation of the mechanism of bactericidal action of silver. Nanoscale 5(16):7328. https://doi.org/10.1039/c3nr00024a

Ahmed A, Boateng J (2018) Calcium alginate-based antimicrobial film dressings for potential healing of infected foot ulcers. Ther Deliv 9(3):185–204. https://doi.org/10.4155/tde-2017-0104

Akhavan B et al (2018) Direct covalent attachment of silver nanoparticles on radical-rich plasma polymer films for antibacterial applications. J Mater Chem B 6(37):5845–5853. https://doi.org/10.1039/C8TB01363B

Aksoy EA et al (2019) Vancomycin loaded gelatin microspheres containing wet spun poly (ε-caprolactone) fibers and films for osteomyelitis treatment. Fibers Polym 20(11):2236–2246. https://doi.org/10.1007/s12221-019-9271-7

Alcântara MTS et al (2019) Simultaneous hydrogel crosslinking and silver nanoparticle formation by using ionizing radiation to obtain antimicrobial hydrogels. Radiat Phys Chem 165:108369. https://doi.org/10.1016/j.radphyschem.2019.108369

Ali S, Wilson APR (2017) Effect of poly-hexamethylene biguanide hydrochloride (PHMB) treated non-sterile medical gloves upon the transmission of Streptococcus pyogenes, carbapenem-resistant E. coli, MRSA and Klebsiella pneumoniae from contact surfaces. BMC Infect Dis 17(1):1–8. https://doi.org/10.1186/s12879-017-2661-9

Almeida H, Amaral MH, Lobão P (2012) Temperature and pH stimuli-responsive polymers and their applications in controlled and selfregulated drug delivery. J Appl Pharm Sci 2(6):1–10. https://doi.org/10.7324/JAPS.2012.2609

Anderson EB, Long TE (2010) Imidazole- and imidazolium-containing polymers for biology and material science applications. Polymer 51(12):2447–2454. https://doi.org/10.1016/j.polymer.2010.02.006

Andrews JM (2001) Determination of minimum inhibitory concentrations. J Antimicrob Chemother 48(suppl_1):5–16. https://doi.org/10.1093/jac/48.suppl_1.5

Araújo IMS et al (2018) Hydrothermal synthesis of bacterial cellulose–copper oxide nanocomposites and evaluation of their antimicrobial activity. Carbohydr Polym 179(May 2017):341–349. https://doi.org/10.1016/j.carbpol.2017.09.081

Arora A, Mishra A (2018) Antibacterial polymers - a mini review. Mater Today Proc 5 (9):17156–17161. https://doi.org/10.1016/j.matpr.2018.04.124

Arslan M et al (2017) Radiation-induced acrylamide/4-vinyl pyridine biocidal hydrogels: synthesis, characterization, and antimicrobial activities. Polymer 56(12):1295–1306. https://doi.org/10.1080/03602559.2016.1275683

Asiedu-Gyekye IJ et al (2015) Toxicological assessment of polyhexamethylene biguanide for water treatment. Interdiscip Toxicol 8(4):193–202. https://doi.org/10.1515/intox-2015-0029

Aziz N, Fatma T, Varma A, Prasad R (2014) Biogenic synthesis of silver nanoparticles using *Scenedesmus abundans* and evaluation of their antibacterial activity. J Nanopart, Article ID: 689419. https://doi.org/10.1155/2014/689419

Aziz N, Faraz M, Pandey R, Sakir M, Fatma T, Varma A, Barman I, Prasad R (2015) Facile algae-derived route to biogenic silver nanoparticles: synthesis, antibacterial and photocatalytic properties. Langmuir 31:11605–11612. https://doi.org/10.1021/acs.langmuir.5b03081

Aziz N, Pandey R, Barman I, Prasad R (2016) Leveraging the attributes of *Mucor hiemalis*-derived silver nanoparticles for a synergistic broad-spectrum antimicrobial platform. Front Microbiol 7:1984. https://doi.org/10.3389/fmicb.2016.01984

Aziz N, Faraz M, Sherwani MA, Fatma T, Prasad R (2019) Illuminating the anticancerous efficacy of a new fungal chassis for silver nanoparticle synthesis. Front Chem 7:65. https://doi.org/10.3389/fchem.2019.00065

Beeby M et al (2013) Architecture and assembly of the Gram-positive cell wall. Mol Microbiol 88 (4):664–672. https://doi.org/10.1111/mmi.12203

Bernards M, He Y (2014) Polyampholyte polymers as a versatile zwitterionic biomaterial platform. J Biomater Sci 25(14–15):1479–1488. https://doi.org/10.1080/09205063.2014.938976

Blackman LD et al (2019) An introduction to zwitterionic polymer behavior and applications in solution and at surfaces. Chem Soc Rev 48(3):757–770. https://doi.org/10.1039/C8CS00508G

Blanco-Fernandez B et al (2011) Synergistic performance of cyclodextrin–agar hydrogels for ciprofloxacin delivery and antimicrobial effect. Carbohydr Polym 85(4):765–774. https://doi.org/10.1016/j.carbpol.2011.03.042

Boonkaew B, Kempf M et al (2014a) Antimicrobial efficacy of a novel silver hydrogel dressing compared to two common silver burn wound dressings: Acticoat™ and PolyMem Silver®. Burns 40(1):89–96. https://doi.org/10.1016/j.burns.2013.05.011

Boonkaew B, Suwanpreuksa P et al (2014b) Hydrogels containing silver nanoparticles for burn wounds show antimicrobial activity without cytotoxicity. J Appl Polym Sci 131(9):40215. https://doi.org/10.1002/app.40215

Brogden KA (2005) Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat Rev Microbiol 3(3):238–250. https://doi.org/10.1038/nrmicro1098

Burdușel AC et al (2018) Biomedical applications of silver nanoparticles: an up-to-date overview. Nanomaterials 8(9):1–25. https://doi.org/10.3390/nano8090681

Busolo MA et al (2010) Novel silver-based nanoclay as an antimicrobial in polylactic acid food packaging coatings. Food Addit Contam 27(11):1617–1626. https://doi.org/10.1080/19440049.2010.506601

Campoli-Richards DM et al (1988) Ciprofloxacin. Drugs 35(4):373–447. https://doi.org/10.2165/00003495-198835040-00003

Chang D et al (2018) N-Halamine polymer from bipolymer to amphiphilic terpolymer with enhancement in antibacterial activity. Colloids Surf B: Biointerfaces 163:402–411. https://doi.org/10.1016/j.colsurfb.2018.01.013

Chen Z, Sun Y (2006) N-Halamine-based antimicrobial additives for polymers: preparation, characterization, and antimicrobial activity. Ind Eng Chem Res 45(8):2634–2640. https://doi.org/10.1021/ie060088a

Chien H-W et al (2019) Studies of PET nonwovens modified by novel antimicrobials configured with both N -halamine and dual quaternary ammonium with different alkyl chain length. RSC Adv 9(13):7257–7265. https://doi.org/10.1039/C9RA00094A

Chylińska M, Kaczmarek H, Burkowska-But A (2019) Preparation and characteristics of antibacterial chitosan films modified with N-halamine for biomedical application. Colloids Surf B: Biointerfaces 176:379–386. https://doi.org/10.1016/j.colsurfb.2019.01.013

Cioffi N et al (2005) Copper nanoparticle/polymer composites with antifungal and bacteriostatic properties. Chem Mater 17(21):5255–5262. https://doi.org/10.1021/cm0505244

Cuthbert TJ et al (2018) Surprising antibacterial activity and selectivity of hydrophilic polyphosphoniums featuring sugar and hydroxy substituents. Angew Chem Int Ed 57 (39):12707–12710. https://doi.org/10.1002/anie.201806412

Das A et al (2015) Preparation and characterization of silver nanoparticle loaded amorphous hydrogel of carboxymethylcellulose for infected wounds. Carbohydr Polym 130:254–261. https://doi.org/10.1016/j.carbpol.2015.03.082

Ding BP et al (2015) Synthesis and characterization of a polyurethane ionene/zinc chloride complex with antibacterial properties. RSC Adv 5(16):12423–12433. https://doi.org/10.1039/c4ra15480k

Domínguez-Domínguez S et al (2008) Electrochemical deposition of platinum nanoparticles on different carbon supports and conducting polymers. J Appl Electrochem 38(2):259–268. https://doi.org/10.1007/s10800-007-9435-9

Dong A et al (2014) N-halamine-decorated polystyrene nanoparticles based on 5-allylbarbituric acid: from controllable fabrication to bactericidal evaluation. J Colloid Interface Sci 413:92–99. https://doi.org/10.1016/j.jcis.2013.09.036

Dong Q et al (2015) Synthesis and bactericidal evaluation of imide N-halamine-loaded PMMA nanoparticles. New J Chem 39(3):1783–1791. https://doi.org/10.1039/C4NJ01806K

Drew WL et al (1972) Reliability of the Kirby-Bauer disc diffusion method for detecting methicillin-resistant strains of Staphylococcus aureus. Appl Microbiol 24(2):240–247. https://doi.org/10.1128/aem.24.2.240-247.1972

El-Shishtawy RM et al (2011) In situ production of silver nanoparticle on cotton fabric and its antimicrobial evaluation. Cellulose 18(1):75–82. https://doi.org/10.1007/s10570-010-9455-1

Epand RF et al (2004) Antimicrobial 14-helical β-peptides: potent bilayer disrupting agents. Biochemistry 43(29):9527–9535. https://doi.org/10.1021/bi049414l

Ergene C, Yasuhara K, Palermo EF (2018) Biomimetic antimicrobial polymers: recent advances in molecular design. Polym Chem 9(18):2407–2427. https://doi.org/10.1039/c8py00012c

Fang C et al (2019) Antibacterial activities of N-alkyl imidazolium-based poly(ionic liquid) nanoparticles. Polym Chem 10(2):209–218. https://doi.org/10.1039/c8py01290c

Fazly Bazzaz BS et al (2014) Preparation, characterization and antimicrobial study of a hydrogel (soft contact lens) material impregnated with silver nanoparticles. Cont Lens Anterior Eye 37 (3):149–152. https://doi.org/10.1016/j.clae.2013.09.008

Felice B et al (2017) Antimicrobial polymers: antibacterial efficacy of silicone rubber–titanium dioxide composites. J Compos Mater 51(16):2253–2262. https://doi.org/10.1177/0021998316668984

Froidevaux V et al (2016) Biobased amines: from synthesis to polymers; present and future. Chem Rev 116(22):14181–14224. https://doi.org/10.1021/acs.chemrev.6b00486

Fu C et al (2016) Antimicrobial silver-hydroxyapatite composite coatings through two-stage electrochemical synthesis. Surf Coat Technol 301:13–19. https://doi.org/10.1016/j.surfcoat.2016.03.010

Fu Y et al (2019) Mixed polymer brushes with integrated antibacterial and antifouling properties. Prog Org Coat 130:75–82. https://doi.org/10.1016/j.porgcoat.2019.01.038

Fuentes-Paniagua E et al (2016) Structure-activity relationship study of cationic carbosilane dendritic systems as antibacterial agents. RSC Adv 6(9):7022–7033. https://doi.org/10.1039/c5ra25901k

Galiano F et al (2019) New polymeric films with antibacterial activity obtained by UV-induced copolymerization of acryloyloxyalkyltriethylammonium salts with 2-hydroethyl methacrylate. Int J Mol Sci 20(11):1–11. https://doi.org/10.3390/ijms20112696

Ganewatta MS et al (2018) Facially amphiphilic polyionene biocidal polymers derived from lithocholic acid. Bioactive Mater 3(2):186–193. https://doi.org/10.1016/j.bioactmat.2018.02.001

García MC et al (2017) Bioadhesive and biocompatible films as wound dressing materials based on a novel dendronized chitosan loaded with ciprofloxacin. Carbohydr Polym 175:75–86. https://doi.org/10.1016/j.carbpol.2017.07.053

Ghasemzadeh H, Ghanaat F (2014) Antimicrobial alginate/PVA silver nanocomposite hydrogel, synthesis and characterization. J Polym Res 21(3):355. https://doi.org/10.1007/s10965-014-0355-1

GhavamiNejad A, Park CH, Kim CS (2016) In situ synthesis of antimicrobial silver nanoparticles within antifouling zwitterionic hydrogels by catecholic redox chemistry for wound healing application. Biomacromolecules 17(3):1213–1223. https://doi.org/10.1021/acs.biomac.6b00039

Gordon YJ, Romanowski EG, McDermott AM (2005) A review of antimicrobial peptides and their therapeutic potential as anti-infective drugs. Curr Eye Res 30(7):505–515. https://doi.org/10.1080/02713680590968637

Grace JL et al (2017) Cationic acrylate oligomers comprising amino acid mimic moieties demonstrate improved antibacterial killing efficiency. J Mater Chem B 5(3):531–536. https://doi.org/10.1039/C6TB02787C

Gudikandula K, Charya Maringanti S (2016) Synthesis of silver nanoparticles by chemical and biological methods and their antimicrobial properties. J Exp Nanosci 11(9):714–721. https://doi.org/10.1080/17458080.2016.1139196

Gupta S et al (2008) Immobilization of silver nanoparticles on responsive polymer brushes. Macromolecules 41(8):2874–2879. https://doi.org/10.1021/ma800204h

Haag SL, Bernards M (2017) Polyampholyte hydrogels in biomedical applications. Gels 3(4):41. https://doi.org/10.3390/gels3040041

Hancock RE (2005) Mechanisms of action of newer antibiotics for Gram-positive pathogens. Lancet Infect Dis 5(4):209–218. https://doi.org/10.1016/S1473-3099(05)70051-7

Hassan D et al (2020) Novel chitosan-based pH-responsive lipid-polymer hybrid nanovesicles (OLA-LPHVs) for delivery of vancomycin against methicillin-resistant Staphylococcus aureus infections. Int J Biol Macromol 147:385–398. https://doi.org/10.1016/j.ijbiomac.2020.01.019

He M et al (2016) Zwitterionic materials for antifouling membrane surface construction. Acta Biomater 40(92):142–152. https://doi.org/10.1016/j.actbio.2016.03.038

He M et al (2018) Synthesis of amphiphilic copolymers containing ciprofloxacin and amine groups and their antimicrobial performances as revealed by confocal laser-scanning microscopy and atomic-force microscopy. J Agric Food Chem 66(31):8406–8414. https://doi.org/10.1021/acs.jafc.8b01759

Hoseinnejad M, Jafari SM, Katouzian I (2018) Inorganic and metal nanoparticles and their antimicrobial activity in food packaging applications. Crit Rev Microbiol 44(2):161–181. https://doi.org/10.1080/1040841X.2017.1332001

Hu S et al (2019) Preparation of biocompatible wound dressings with long-term antimicrobial activity through covalent bonding of antibiotic agents to natural polymers. Int J Biol Macromol 123:1320–1330. https://doi.org/10.1016/j.ijbiomac.2018.09.122

Hultmark D et al (1983) Insect immunity. Attacins, a family of antibacterial proteins from Hyalophora cecropia. EMBO J 2(4):571–576

Jain A et al (2014) Antimicrobial polymers. Adv Healthc Mater 3(12):1969–1985. https://doi.org/10.1002/adhm.201400418

Jovanović Ž et al (2012) Alginate hydrogel microbeads incorporated with Ag nanoparticles obtained by electrochemical method. Mater Chem Phys 133(1):182–189. https://doi.org/10.1016/j.matchemphys.2012.01.005

Kanmani P, Rhim J-W (2014) Physicochemical properties of gelatin/silver nanoparticle antimicrobial composite films. Food Chem 148(2):162–169. https://doi.org/10.1016/j.foodchem.2013.10.047

Kapoor G, Saigal S, Elongavan A (2017) Action and resistance mechanisms of antibiotics: a guide for clinicians. J Anaesthesiol Clin Pharmacol 33(3):300. https://doi.org/10.4103/joacp.JOACP_349_15

Kardela JH et al (2019) Nonfreezable water and polymer swelling control the marine antifouling performance of polymers with limited hydrophilic content. ACS Appl Mater Interfaces 11(33):29477–29489. https://doi.org/10.1021/acsami.9b05893

Kariduraganavar MY, Kittur AA, Kamble RR (2014) Polymer synthesis and processing. In: Natural and synthetic biomedical polymers, 1st edn. Elsevier, London

Karimzadeh I, Dizaji HR, Aghazadeh M (2016) Preparation, characterization and PEGylation of superparamagnetic Fe 3 O 4 nanoparticles from ethanol medium via cathodic electrochemical deposition (CED) method. Mater Res Exp 3(9):095022. https://doi.org/10.1088/2053-1591/3/9/095022

Kavitha T, Kang IK, Park SY (2015) Poly(4-vinyl pyridine)-grafted graphene oxide for drug delivery and antimicrobial applications. Polym Int 64(11):1660–1666. https://doi.org/10.1002/pi.4968

Kenawy E-R, Worley SD, Broughton R (2007) The chemistry and applications of antimicrobial polymers: a state-of-the-art review. Biomacromolecules 8(5):1359–1384. https://doi.org/10.1021/bm061150q

Kohanski MA, Dwyer DJ, Collins JJ (2010) How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol 8(6):423–435. https://doi.org/10.1038/nrmicro2333

Krehula LK et al (2017) Properties of UV protective films of poly(vinyl-chloride)/TiO2 nanocomposites for food packaging. Polym Bull 74(4):1387–1404. https://doi.org/10.1007/s00289-016-1782-4

Kudaibergenov SE (1996) Synthesis and characterization of polyampholyte hydrogels. Ber Bunsenges Phys Chem 100(6):1079–1082. https://doi.org/10.1002/bbpc.19961000662
Kumar A et al (2008) Silver-nanoparticle-embedded antimicrobial paints based on vegetable oil. Nat Mater 7(3):236–241. https://doi.org/10.1038/nmat2099
Kurczewska J et al (2017) Molecularly imprinted polymer as drug delivery carrier in alginate dressing. Mater Lett 201:46–49. https://doi.org/10.1016/j.matlet.2017.05.008
Lan S et al (2019) Electrospun sesbania gum-based polymeric n-halamines for antibacterial applications. Polymers 11(7):1117. https://doi.org/10.3390/polym11071117
Laschewsky A (2014) Structures and synthesis of zwitterionic polymers. Polymers 6 (5):1544–1601. https://doi.org/10.3390/polym6051544
Lee WR et al (2004) In vitro efficacy of a polyhexamethylene biguanide-impregnated gauze dressing against bacteria found in veterinary patients. Vet Surg 33(4):404–411. https://doi.org/10.1111/j.1532-950X.2004.04059.x
Lei J et al (2019) The antimicrobial peptides and their potential clinical applications. Am J Transl Res 11(7):3919–3931
Lemire JA, Harrison JJ, Turner RJ (2013) Antimicrobial activity of metals: mechanisms, molecular targets and applications. Nat Rev Microbiol 11(6):371–384. https://doi.org/10.1038/nrmicro3028
Lim N et al (2008) Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of acanthamoeba keratitis. Am J Ophthalmol 145(1):130–135. https://doi.org/10.1016/j.ajo.2007.08.040
Liu D et al (2004) Nontoxic membrane-active antimicrobial arylamide oligomers. Angew Chem Int Ed 43(9):1158–1162. https://doi.org/10.1002/anie.200352791
Liu X et al (2018) Ciprofloxacin-loaded sodium alginate/poly (lactic-co-glycolic acid) electrospun fibrous mats for wound healing. Eur J Pharm Biopharm 123:42–49. https://doi.org/10.1016/j.ejpb.2017.11.004
Llorens A et al (2012) Metallic-based micro and nanocomposites in food contact materials and active food packaging. Trends Food Sci Technol 24(1):19–29. https://doi.org/10.1016/j.tifs.2011.10.001
López-Iglesias C et al (2019) Vancomycin-loaded chitosan aerogel particles for chronic wound applications. Carbohydr Polym 204:223–231. https://doi.org/10.1016/j.carbpol.2018.10.012
López-Meza JE, Aguilar AO-ZJA, Loeza-Lara PD (2011) Antimicrobial peptides: diversity and perspectives for their biomedical application. In: Biomedical engineering, trends, research and technologies. InTech, London. https://doi.org/10.5772/13058
López-Saucedo F et al (2017) Achieving antimicrobial activity through poly (N-methylvinylimidazolium) iodide brushes on binary-grafted polypropylene suture threads. MRS Commun 7(4):121. https://doi.org/10.1557/mrc.2017.121
López-Saucedo F et al (2018) Antimicrobial silver-loaded polypropylene sutures modified by radiation-grafting. Eur Polym J 100:290–297. https://doi.org/10.1016/j.eurpolymj.2018.02.005
López-Saucedo F et al (2019) Radiation grafting of poly(methyl methacrylate) and poly (vinylimidazole) onto polytetrafluoroethylene films and silver immobilization for antimicrobial performance. Appl Surf Sci 473(November 2018):951–959. https://doi.org/10.1016/j.apsusc.2018.12.229
Lubarsky GV et al (2005) The influence of electrostatic forces on protein adsorption. Colloids Surf B Biointerfaces 44(1):56–63. https://doi.org/10.1016/j.colsurfb.2005.05.010
Mahmoudian M, Ganji F (2017) Vancomycin-loaded HPMC microparticles embedded within injectable thermosensitive chitosan hydrogels. Prog Biomater 6(1–2):49–56. https://doi.org/10.1007/s40204-017-0066-x
Marra A et al (2016) Polylactic acid/zinc oxide biocomposite films for food packaging application. Int J Biol Macromol 88:254–262. https://doi.org/10.1016/j.ijbiomac.2016.03.039
Martins AF et al (2015) Bactericidal activity of hydrogel beads based on N,N,N-trimethyl chitosan/alginate complexes loaded with silver nanoparticles. Chin Chem Lett 26(9):1129–1132. https://doi.org/10.1016/j.cclet.2015.04.032
Matsuzaki K (2019) Antimicrobial peptides. In: Advances in experimental medicine and biology. Springer, Singapore. https://doi.org/10.1007/978-981-13-3588-4

Mayr J et al (2017) Antimicrobial and hemolytic studies of a series of polycations bearing quaternary ammonium moieties: structural and topological effects. Int J Mol Sci 18(2):303. https://doi.org/10.3390/ijms18020303

Mei L et al (2014) Polymer-Ag nanocomposites with enhanced antimicrobial activity against bacterial infection. ACS Appl Mater Interfaces 6(18):15813–15821. https://doi.org/10.1021/am502886m

Meléndez-Ortiz HI et al (2016) Modification of medical grade PVC with N-vinylimidazole to obtain bactericidal surface. Radiat Phys Chem 119:37–43. https://doi.org/10.1016/j.radphyschem.2015.09.014

Mohamed RR, Sabaa MW (2014) Synthesis and characterization of antimicrobial crosslinked carboxymethyl chitosan nanoparticles loaded with silver. Int J Biol Macromol 69:95–99. https://doi.org/10.1016/j.ijbiomac.2014.05.025

Morimoto N, Oishi Y, Yamamoto M (2020) The design of sulfobetaine polymers with thermoresponsiveness under physiological salt conditions. Macromol Chem Phys 221 (5):1900429. https://doi.org/10.1002/macp.201900429

Morones JR et al (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16 (10):2346–2353. https://doi.org/10.1088/0957-4484/16/10/059

Mukherjee I et al (2017) Side-chain amino acid-based cationic antibacterial polymers: investigating the morphological switching of a polymer-treated bacterial cell. ACS Omega 2(4):1633–1644. https://doi.org/10.1021/acsomega.7b00181

Muñoz-Bonilla A, Fernández-García M (2012) Polymeric materials with antimicrobial activity. Prog Polym Sci 37(2):281–339. https://doi.org/10.1016/j.progpolymsci.2011.08.005

Neu HC (1989) Overview of mechanisms of bacterial resistance. Diagn Microbiol Infect Dis 12 (4):109–116. https://doi.org/10.1016/0732-8893(89)90122-3

Nguyen TD et al (2019) In vivo study of the antibacterial chitosan/polyvinyl alcohol loaded with silver nanoparticle hydrogel for wound healing applications. Int J Poly Sci 2019:1–10. https://doi.org/10.1155/2019/7382717

Niu B et al (2017) Fungicidal, corrosive, and mutational effects of polyhexamethylene biguanide combined with 1-bromo-3-chloro-5,5-dimethylimidazolidine-2,4-dione. Biomed Res Int 2017:4357031. https://doi.org/10.1155/2017/4357031

Niu Y et al (2018) An injectable supramolecular hydrogel hybridized with silver nanoparticles for antibacterial application. Soft Matter 14(7):1227–1234. https://doi.org/10.1039/C7SM02251D

Palza H (2015) Antimicrobial polymers with metal nanoparticles. Int J Mol Sci 16(1):2099–2116. https://doi.org/10.3390/ijms16012099

Pant HR et al (2011) Photocatalytic and antibacterial properties of a TiO2/nylon-6 electrospun nanocomposite mat containing silver nanoparticles. J Hazard Mater 189(1–2):465–471. https://doi.org/10.1016/j.jhazmat.2011.02.062

Patel KK et al (2019) Alginate lyase immobilized chitosan nanoparticles of ciprofloxacin for the improved antimicrobial activity against the biofilm associated mucoid P. aeruginosa infection in cystic fibrosis. Int J Pharm 563:30–42. https://doi.org/10.1016/j.ijpharm.2019.03.051

Payami R, Ghorbanpour M, Parchehbaf Jadid A (2016) Antibacterial silver-doped bioactive silica gel production using molten salt method. J Nanostruct Chem 6(3):215–221. https://doi.org/10.1007/s40097-016-0193-2

Pelegri-O'Day EM, Paluck SJ, Maynard HD (2017) Substituted polyesters by thiol-ene modification: rapid diversification for therapeutic protein stabilization. J Am Chem Soc 139 (3):1145–1154. https://doi.org/10.1021/jacs.6b10776

Permyakova ES et al (2018) Antibacterial biocompatible PCL nanofibers modified by COOH-anhydride plasma polymers and gentamicin immobilization. Mater Des 153:60–70. https://doi.org/10.1016/j.matdes.2018.05.002

Petica A et al (2008) Colloidal silver solutions with antimicrobial properties. Mater Sci Eng B 152 (1–3):22–27. https://doi.org/10.1016/j.mseb.2008.06.021

Phoenix DA, Dennison SR, Harris F (2013) Antimicrobial peptides. Wiley, Weinheim. https://doi.org/10.1002/9783527652853

Pino-Ramos VH et al (2016) Radiation grafting for the functionalization and development of smart polymeric materials. Top Curr Chem 374(5):63. https://doi.org/10.1007/s41061-016-0063-x
Punia A et al (2015) Effect of relative arrangement of cationic and lipophilic moieties on hemolytic and antibacterial activities of PEGylated polyacrylates. Int J Mol Sci 16(10):23867–23880. https://doi.org/10.3390/ijms161023867
Qiao M et al (2017) N-Halamine modified thermoplastic polyurethane with rechargeable antimicrobial function for food contact surface. RSC Adv 7(3):1233–1240. https://doi.org/10.1039/C6RA25502G
Ren G et al (2009) Characterisation of copper oxide nanoparticles for antimicrobial applications. Int J Antimicrob Agents 33(6):587–590. https://doi.org/10.1016/j.ijantimicag.2008.12.004
Reznickova A et al (2014) Immobilization of silver nanoparticles on polyethylene terephthalate. Nanoscale Res Lett 9(1):305. https://doi.org/10.1186/1556-276X-9-305
Rhim JW, Wang LF, Hong SI (2013) Preparation and characterization of agar/silver nanoparticles composite films with antimicrobial activity. Food Hydrocoll 33(2):327–335. https://doi.org/10.1016/j.foodhyd.2013.04.002
Ribeiro M et al (2017) Antibacterial silk fibroin/nanohydroxyapatite hydrogels with silver and gold nanoparticles for bone regeneration. Nanomedicine 13(1):231–239. https://doi.org/10.1016/j.nano.2016.08.026
Rodríguez Nuñez Y et al (2019) Preparation of hydrogel/silver nanohybrids mediated by tunable-size silver nanoparticles for potential antibacterial applications. Polymers 11(4):716. https://doi.org/10.3390/polym11040716
Rong F et al (2019) Nitric oxide-releasing polymeric materials for antimicrobial applications: a review. Antioxidants 8(11):556. https://doi.org/10.3390/antiox8110556
Rotem S, Mor A (2009) Antimicrobial peptide mimics for improved therapeutic properties. Biochim Biophys Acta 1788(8):1582–1592. https://doi.org/10.1016/j.bbamem.2008.10.020
Rouabhia M et al (2014) Production of biocompatible and antimicrobial bacterial cellulose polymers functionalized by RGDC grafting groups and gentamicin. ACS Appl Mater Interfaces 6 (3):1439–1446. https://doi.org/10.1021/am4027983
Sadrearhami Z et al (2018) Recent advances in nitric oxide delivery for antimicrobial applications using polymer-based systems. J Mater Chem B 6(19):2945–2959. https://doi.org/10.1039/C8TB00299A
Sánchez-Jiménez M et al (2019) Antimicrobial activity of poly(3,4-ethylenedioxythiophene) n-doped with a pyridinium-containing polyelectrolyte. Soft Matter 15(38):7695–7703. https://doi.org/10.1039/c9sm01491h
Santos Ferreira I et al (2018) Encapsulation in polymeric microparticles improves daptomycin activity against mature staphylococci biofilms—a thermal and imaging study. AAPS PharmSciTech 19(4):1625–1636. https://doi.org/10.1208/s12249-018-0974-7
Sengupta D et al (2008) Toroidal pores formed by antimicrobial peptides show significant disorder. Biochim Biophys Acta 1778(10):2308–2317. https://doi.org/10.1016/j.bbamem.2008.06.007
Shai Y (1999) Mechanism of the binding, insertion and destabilization of phospholipid bilayer membranes by α-helical antimicrobial and cell non-selective membrane-lytic peptides. Biochim Biophys Acta 1462(1–2):55–70. https://doi.org/10.1016/S0005-2736(99)00200-X
Shen J et al (2019) Strategy to construct polyzwitterionic hydrogel coating with antifouling, drag-reducing and weak swelling performance. RSC Adv 9(4):2081–2091. https://doi.org/10.1039/C8RA09358J
Siedenbiedel F, Tiller JC (2012) Antimicrobial polymers in solution and on surfaces: overview and functional principles. Polymers 4(1):46–71. https://doi.org/10.3390/polym4010046
Sobhani Z et al (2017) Nanoparticles of chitosan loaded ciprofloxacin: fabrication and antimicrobial activity. Adv Pharm Bull 7(3):427–432. https://doi.org/10.15171/apb.2017.051
Son WK, Youk JH, Park WH (2006) Antimicrobial cellulose acetate nanofibers containing silver nanoparticles. Carbohydr Polym 65(4):430–434. https://doi.org/10.1016/j.carbpol.2006.01.037
Song H et al (2011) Migration of silver from nanosilver–polyethylene composite packaging into food simulants. Food Addit Contam 74(4):1–5. https://doi.org/10.1080/19440049.2011.603705

Sun H et al (2017) Biodegradable zwitterionic sulfobetaine polymer and its conjugate with paclitaxel for sustained drug delivery. Acta Biomater 64:290–300. https://doi.org/10.1016/j.actbio.2017.10.016

Sun W et al (2020) Chemical surface modification of polymeric biomaterials for biomedical applications. Macromol Rapid Commun 43:1900430. https://doi.org/10.1002/marc.201900430

Tao Y et al (2018) Synthesis and properties of alternating polypeptoids and polyampholytes as protein-resistant polymers. Biomacromolecules 19(3):936–942. https://doi.org/10.1021/acs.biomac.7b01719

Thaker HD et al (2012) Synthetic mimics of antimicrobial peptides with immunomodulatory responses. J Am Chem Soc 134(27):11088–11091. https://doi.org/10.1021/ja303304j

Tian J et al (2017) Electrodeposition of Ag nanoparticles on conductive polyaniline/cellulose aerogels with increased synergistic effect for energy storage. Carbohydr Polym 156:19–25. https://doi.org/10.1016/j.carbpol.2016.09.005

Tylkowski B et al (2017) Applications of silver nanoparticles stabilized and/or immobilized by polymer matrixes. Phys Sci Rev 2(7):24. https://doi.org/10.1515/psr-2017-0024

Unubol N et al (2017) Peptide antibiotics developed by mimicking natural antimicrobial peptides. Clin Microbiol 6(4):1000291. https://doi.org/10.4172/2327-5073.1000291

Vales TP et al (2020) Development of poly(2-methacryloyloxyethyl phosphorylcholine)-functionalized hydrogels for reducing protein and bacterial adsorption. Materials 13(4):943. https://doi.org/10.3390/ma13040943

Van Andel E et al (2019) Systematic comparison of zwitterionic and non-zwitterionic antifouling polymer brushes on a bead-based platform. Langmuir 35(5):1181–1191. https://doi.org/10.1021/acs.langmuir.8b01832

Waghu FH et al (2018) Designing antibacterial peptides with enhanced killing kinetics. Front Microbiol 9:325. https://doi.org/10.3389/fmicb.2018.00325

Wang G (2010) Antimicrobial peptides: discovery, design, and novel therapeutic strategies, 1st edn. CABI Publishing, Nebraska

Wang Y et al (2011) Dark antimicrobial mechanisms of cationic phenylene ethynylene polymers and oligomers against Escherichia coli. Polymers 3(3):1199–1214. https://doi.org/10.3390/polym3031199

Wang Z et al (2018) Dual water-healable zwitterionic polymer coatings for anti-biofouling surfaces. J Mater Chem B 6(43):6930–6935. https://doi.org/10.1039/c8tb01863d

Woo KJ et al (2008) Antibacterial activity and mechanism of action of the silver ion in Staphylococcus aureus and Escherichia coli. Appl Environ Microbiol 74(7):2171–2178. https://doi.org/10.1128/AEM.02001-07

World Health Organization (n.d.) Antimicrobial resistance. Available at https://www.who.int/health-topics/antimicrobial-resistance. Accessed 27 February 2020

Wu C, Zhou Y, Wang H, Hu J et al (2019a) Formation of antifouling functional coating from deposition of a zwitterionic-co-nonionic polymer via "grafting to" approach. J Saudi Chem Soc 23(8):1080–1089. https://doi.org/10.1016/j.jscs.2019.05.011

Wu C, Zhou Y, Wang H, Hu J (2019b) P4VP modified zwitterionic polymer for the preparation of antifouling functionalized surfaces. Nanomaterials 9(5):706. https://doi.org/10.3390/nano9050706

Xia L et al (2019) Fabrication of centrifugally spun prepared poly(lactic acid)/gelatin/ciprofloxacin nanofibers for antimicrobial wound dressing. RSC Adv 9(61):35328–35335. https://doi.org/10.1039/C9RA07826F

Xiao Y et al (2018) A light-weight and high-efficacy antibacterial nanocellulose-based sponge via covalent immobilization of gentamicin. Carbohydr Polym 200:595–601. https://doi.org/10.1016/j.carbpol.2018.07.091

Xiu K et al (2017) Controlling the structure and antimicrobial function of N-halamine-based polyurethane semi-interpenetrating polymer networks. Ind Eng Chem Res 56(42):12032–12037. https://doi.org/10.1021/acs.iecr.7b03302

Xu X, Zhou M (2008) Antimicrobial gelatin nanofibers containing silver nanoparticles. Fibers Polym 9(6):685–690. https://doi.org/10.1007/s12221-008-0108-z

Xu J et al (2015) Preparation and evaluation of vancomycin-loaded N-trimethyl chitosan nanoparticles. Polymers 7(9):1850–1870. https://doi.org/10.3390/polym7091488
Xue Y et al (2012) Synthesis and characterization of ciprofloxacin pendant antibacterial cationic polymers. J Biomater Sci 23(8):1115–1128. https://doi.org/10.1163/092050611X576639
Xue Y et al (2014) Novel quaternary phosphonium-type cationic polyacrylamide and elucidation of dual-functional antibacterial/antiviral activity. RSC Adv 4(87):46887–46895. https://doi.org/10.1039/c4ra08634a
Xue Y, Xiao H, Zhang Y (2015) Antimicrobial polymeric materials with quaternary ammonium and phosphonium salts. Int J Mol Sci 16(2):3626–3655. https://doi.org/10.3390/ijms16023626
Yang G et al (2012) Antimicrobial activity of silver nanoparticle impregnated bacterial cellulose membrane: effect of fermentation carbon sources of bacterial cellulose. Carbohydr Polym 87 (1):839–845. https://doi.org/10.1016/j.carbpol.2011.08.079
Yang Z et al (2020) Improved anti-biofouling performance of polyamide reverse osmosis membranes modified with a polyampholyte with effective carboxyl anion and quaternary ammonium cation ratio. J Membr Sci 595:117529. https://doi.org/10.1016/j.memsci.2019.117529
Zainul Abid CKV et al (2016) Antimicrobial efficacy of synthesized quaternary ammonium polyamidoamine dendrimers and dendritic polymer network. J Nanosci Nanotechnol 16 (1):998–1007. https://doi.org/10.1166/jnn.2016.10656
Zairi A et al (2009) Dermaseptins and magainins: antimicrobial peptides from frogs' skin—new sources for a promising spermicides microbicides—a mini review. J Biomed Biotechnol 2009:1–8. https://doi.org/10.1155/2009/452567
Zare Y, Shabani I (2016) Polymer/metal nanocomposites for biomedical applications. Mater Sci Eng C 60:195–203. https://doi.org/10.1016/j.msec.2015.11.023
Zasloff M (1987) Magainins, a class of antimicrobial peptides from Xenopus skin: isolation, characterization of two active forms, and partial cDNA sequence of a precursor. Proc Natl Acad Sci 84(15):5449–5453. https://doi.org/10.1073/pnas.84.15.5449
Zeng Q et al (2018) Antimicrobial and antifouling polymeric agents for surface functionalization of medical implants. Biomacromolecules 19(7):2805–2811. https://doi.org/10.1021/acs.biomac.8b00399
Zeng W, He J, Liu F (2019) Preparation and properties of antibacterial ABS plastics based on polymeric quaternary phosphonium salts antibacterial agents. Polym Adv Technol 30 (10):2515–2522. https://doi.org/10.1002/pat.4653
Zhang Y et al (2017) Efficient induction of antimicrobial activity with vancomycin nanoparticle-loaded poly(trimethylene carbonate) localized drug delivery system. Int J Nanomedicine 12:1201–1214. https://doi.org/10.2147/IJN.S127715
Zhang W, Cheng W et al (2018a) Functionalization of ultrafiltration membrane with polyampholyte hydrogel and graphene oxide to achieve dual antifouling and antibacterial properties. J Membr Sci 565:293–302. https://doi.org/10.1016/j.memsci.2018.08.017
Zhang W, Yang Z et al (2018b) Surface and anti-fouling properties of a polyampholyte hydrogel grafted onto a polyethersulfone membrane. J Colloid Interface Sci 517:155–165. https://doi.org/10.1016/j.jcis.2018.01.106
Zhang T et al (2019a) A bioinspired antifouling zwitterionic interface based on reduced graphene oxide carbon nanofibers: electrochemical aptasensing of adenosine triphosphate. Microchim Acta 186(4):240. https://doi.org/10.1007/s00604-019-3343-7
Zhang Y et al (2019b) Fundamentals and applications of zwitterionic antifouling polymers. J Phys D Appl Phys 52:40. https://doi.org/10.1088/1361-6463/ab2cbc
Zheng Z et al (2016) Structure-antibacterial activity relationships of imidazolium-type ionic liquid monomers, poly(ionic liquids) and poly(ionic liquid) membranes: effect of alkyl chain length and cations. ACS Appl Mater Interfaces 8(20):12684–12692. https://doi.org/10.1021/acsami.6b03391
Zheng L et al (2017) Applications of zwitterionic polymers. React Funct Polym 118:51–61. https://doi.org/10.1016/j.reactfunctpolym.2017.07.006
Zuñiga-Zamorano I et al (2018) Poly(vinyl chloride) catheters modified with pH-responsive poly (methacrylic acid) with affinity for antimicrobial agents. Radiat Phys Chem 142(October 2016):107–114. https://doi.org/10.1016/j.radphyschem.2017.02.008

Starch-Based Antimicrobial Materials

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Abstract Natural nanocomposites occupy a huge arena in the developing industries related to food and medicine. Nanomaterials are mainly used to strengthen the polymer matrix and their dimensions range from 1 to 100 nm. They also enhance the mechanical, thermal, optical, physical and chemical features of the polymeric materials as compared to their virgin structures. Examples of different nano-based composite materials have been identified in the recent era. Out of those, starch and clay are the most common ones. Other natural materials like chitosan, agar, proteins and their blends are also recognised by the researchers. Nano-based composites, offering antimicrobial properties, have been studied extensively in the recent past due to its applications in food packaging industry, so that the packages can be hygienic in nature and prevent the growth of bacteria causing food borne diseases such as *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative), etc. However, it has limitations like when food is packed in such packages containing such preventive film, needs a high content of the antimicrobial material in the film that leads to the enhancement of the food shelf period and thus there is a scarcity of the main antimicrobial agents. The use of various starch incorporated antimicrobial films can reduce this imitation. This chapter mainly deals with the evaluation of the antimicrobial properties of different starch-based materials containing different nanocomposite films, which have their wide range of applications in the field of biomedicines and food packaging.

Keywords Starch · Antibacterial · Packaging · Nanocomposite

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1 Introduction

As per the reported literature by Parra et al. (2004) almost 150 million tons of synthetic polymeric materials are produced in a year all over the world. The extensive production of synthetic polymeric materials leads to their increase in consumption. These synthetic polymers are generally obtained from petroleum based products. In last few decades, chemically developed synthetic polymers have been used extensively in different applications specifically in food packaging industry. These synthetic polymers are not eco-friendly as well as non-biodegradable which causes environmental pollution and serious health issues to the human beings (Chen et al. 2013). For mitigating problems associated with the synthetic polymers, present generation has tried to find alternative pollution-free and bio-degradable materials. There are different natural polymers which are eco-friendly and bio-degradable in nature and possess easy process ability. For instance, the natural sources can be enlisted as chitin, chitosan, cellulose, protein, lipids, gum and starch-based polysaccharides. Among these starches have drawn a great interest in the different applications due to its large amount of availability, low cost, non-allergic and thermo-processability (Salleh and Muhamad 2010; Bum n.d.). Starch is a biopolymer originated from agricultural sources. Due to the above-mentioned advantages of starch, recently, researchers have tried to develop starch-based materials targeted for manifold industrial applications like in biomedical industries. However, starch has limitations such as lower mechanical properties and higher hydrophilicity. Due to hydrophilic characteristics of starch, it has lower moisture barrier capacity. In order to improve the physical and functional properties of the starch-based biopolymers, other biopolymers have been added with them. For example, chitosan has been blended with the starch to impart their physical and antibacterial properties as chitosan is a good antibacterial natural polymer (Bangyekan et al. 2006). Also, the use of sliver nanoparticles incorporated in starch to produce starch/silver nano-capsules has been reported by a method called addition polymerisation. A very less concentration of such prepared starch-based nano-capsules obstructs the bacterial (*Staphylococcus epidermidis* and *Escherichia coli*) growth (Taheri et al. 2014). Furthermore, the use of both the chitosan and sliver nanoparticles in starch has been illustrated wherein chitosan has been used to reduce sliver nitrate. It has also been observed that starch promotes no antimicrobial properties but when incorporated with chitosan and sliver the composite material shows very effective antimicrobial effect. The inhibition zone of starch-chitosan based film as reported is 28 mm whereas for starch-chitosan-sliver based film is more than 30 mm against *S. aureus*, *B. cereus*, and *E. coli* bacteria (Yoksan and Chirachanchai 2010).

The present chapter is a latest and brief composition of starch-based antimicrobial materials which have promising applications in various segments, especially for packaging food materials and medicines.

2 Source and Structure of Starch

Starch can be obtained in granular form and is found in roots, seeds, stems, and tubers of various plants, like corn, potato, wheat, rice, sago, etc. Starch is made up of anhydro-glucose chains that lead to the formation of two polymers named as amylose and amylopectin. Out of these two polymers, amylose can be found as a well-ordered polymer chain containing 20–30% of starch in granular form. It is available in long chains containing α-(1,4)-linked D-glucose. The other polymer unit amylopectin is a randomly structured polymer including 70–80% of the starch granules. It contains α-(1,4)-linked glucose molecular units, linked with-(1,6)-unit (Torres et al. 2013). As an example, the structure of starch obtained from corn extract is shown in Fig. 1.

3 Antimicrobial Property of Starch-Based Materials

The problems witnessed by using synthetic materials in food packaging lead to pollution in the environment. So, to mitigate the shortcomings various natural polymers have been explored that can be effectively used in packaging industries. Out of various natural polymers identified so far starch is being renowned as the most important one due to its biodegradability, biocompatibility, edible and sustainable properties. But starch has different limitations to be used for food packaging due to its reduced mechanical, barrier and processing characteristics. Therefore, to overcome all such limitations starch is being blended with different natural polymeric materials and their derivatives like carboxy methyl cellulose (CMC), chitosan or by using different nanocomposite based materials consist of nanoparticles of silver, zinc oxide, etc. There are many approaches as explored by the researchers to enhance the properties of starch. Inclusion of starch as nanocomposite film is one so that it can be successfully used in the food industry (Hu et al. 2019).

Ashjari et al. have reported an innovative approach to develop starch-based polyurethane incorporated copper oxide nanocomposite foam to minimise bacterial growth. They have observed that such a fabricated composite shows a promising antimicrobial effect when used in a hospital mattress. They found that copper oxide nanoparticles when synthesised by thermal degradation method at a temperature of

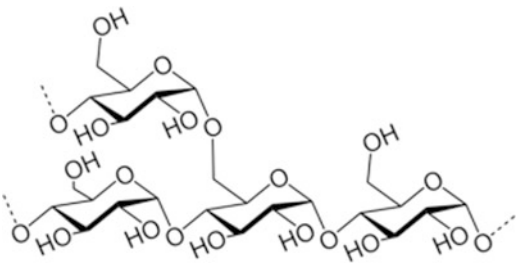

Fig. 1 Structure of starch extracted from corn (Spiridon et al. 2019)

600 °C shows bacterial inhibition against a range of bacteria like *S. aureus*, *E. coli*, *P. aeruginosa*, *E. faecalis and C. albicans.* In this case, copper oxide nanoparticles release Cu^{2+} and show electrostatic interactions between Cu ions and the bacterial membrane which results in rupture of the plasma membrane of the bacteria (Ashjari et al. 2018; Yadav et al. 2017).

Chen et al. have developed an antibacterial film based on tapioca starch/decolorised Hsian-Tsao leaf gum and evaluated its antibacterial activity against *Listeria monocytogenes*. To extract the herb the researchers have used potassium sorbate and thyme. Extracted gum showed a rough texture when potassium sorbate was used whereas, a smooth texture was found when thyme was used. Antimicrobial efficacy of starch along with decolorised Hsian-Tsao leaf gum against *L. monocytogenes* was also revealed. It has also been proved that thyme suspensions show an inhibition zone of diameter ranging from 16 to 19 mm against the above-stated bacteria. On the other hand, as illustrated in the study, potassium sorbate suspension (20%) shows much less microbial obstruction property (a lesser inhibition zone of 10.7–9.7 mm). Therefore, it can be concluded that thyme solution shows better antimicrobial activity when compared to potassium sorbate solution. Antimicrobial activity of potassium sorbate and thyme in film form in combination with starch has also been evaluated. Antimicrobial activity of thyme (with a concentration of 10% showed an inhibition zone of 9 mm) film based material is lower as compared to pure thyme antimicrobial solution (inhibition zone ranging from 16 to 19 mm) due to lower interaction of the active ingredients with bacterial cells as compared to solution (which migrates fast) (Chen et al. 2013).

Vásconez et al. (2009) have studied the antibacterial activity of chitosan and tapioca starch-based film. Potassium sorbate was used with the solution of starch and chitosan coating solution to impart effective antibacterial property of the same. The authors have observed that when chitosan was used as a solution form, antibacterial activity in terms of reduction of bacteria population (*Lactobacillus* spp.) was higher due to direct contact of chitosan biomolecules with the bacteria. Whereas, chitosan in the form of starch/chitosan film shows a lower antibacterial action against *Lactobacillus* spp. This is due to entrapment of antimicrobial chitosan biomolecules firmly in the starch/chitosan film and this the solid form of chitosan in the starch/chitosan film has less chance to get interacted with the bacterial cell surface as compared to the chitosan in the form of solution. As a result the antibacterial property gets reduced.

Abreu et al. (2015) have reported antibacterial property of different starch-based nanocomposites such as starch/nanoclay, starch/silver nanoparticles and starch/nanoclay/silver nanoparticles nanocomposites against *Staphylococcus aureus*, *Escherichia coli and Candida albicans* bacteria. The pure starch-based film shows no inhibition zone against three different bacteria (*S. aureus*, *E. coli and C. albicans*) which confirms that starch has no antibacterial effect. While, starch/nanoclay-based film shows some inhibition of bacterial growth due to the presence of quaternary ammonium compound in nanoclay. However, there is no antibacterial effect of the starch/nanoclay-based film against *C. albicans* bacteria. But all the nanocomposite films based on silver nanoparticles (starch/silver nanoparticles and starch/silver nanoparticles/nanoclay-based nanocomposite films) show substantial antibacterial

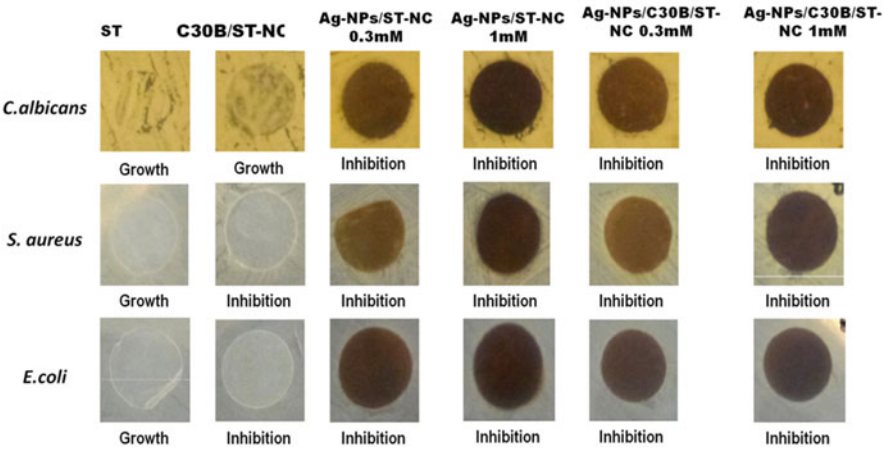

Fig. 2 Antibacterial activity of starch, nanoclay/starch, silver nanoparticles/starch and silver nanoparticles/nanoclay/starch-based nanocomposite films against bacteria of *C. albicans*, *S. aureus* and *E. coli* (Abreu et al. 2015)

action as compared to the starch/nanoclay-based film against all the tested bacteria like *S. aureus*, *E. coli and C. albicans* as shown in Fig. 2. The antibacterial action of silver nanoparticles-based film was due to the interaction of Ag^+ with marcapto group of the bacteria and its controlled release from the nanocomposite film.

In another study, Pyla et al. (2010) have developed tannic acid impregnated starch-based film and tested the antibacterial property of the film. Two differently produced films namely starch/commercially available tannic acid and starch/processed tannic acid have been used to study. It has been found that the starch/processed tannic acid-based film shows the higher inhibition area when compared to the starch/commercially available tannic acid film against *Escherichia coli O157:H7* and *Listeria monocytogenes* bacteria. This study reveals that thermally processed tannic acid is more effective than fresh tannic acid to protect the microbial growth.

Shen et al. (2010) have reported the antibacterial and physical properties of potassium sorbate or chitosan loaded sweet potato starch-based film. They have observed no antibacterial effect in the case of 10% potassium sorbate loaded starch-based films due to strong hydrogen bonding between the hydroxyl groups of starch and carbonyl groups of potassium sorbate. Whereas, antibacterial action was observed for the higher concentration (>10%) of potassium sorbate-based film against *E. coli* bacteria. Conversely, only 5% chitosan loaded starch-based film shows an effective antibacterial action against bacterial growth. This is due to protonation of NH_2 groups of chitosan into the NH_3^+ ions which can interact with the anionic group of microbial cell membranes. The antibacterial activity of potassium or chitosan loaded sweet potato starch-based films against *E. coli* and *S. aureus* bacteria is depicted in Fig. 2. They have also explained the antibacterial properties of sweet potato starch films in the form of solid and semi-solid against *E. coli* and *S. aureus* bacteria. It was found that there is no significant difference in antibacterial

properties of starch films for both the forms (solid and semi-solid). From this finding it can be concluded that the sweet potato starch-based films can be used in food packaging with different water contents. But pH value has significant effects on the antimicrobial action of potassium sorbate and chitosan loaded sweet potato films. When pH value is 4.5, potassium sorbate gets converted into sorbic acid which disturbs the migration of antibacterial agents from the wet film. Whereas, NH_2 groups of the chitosan can be protonated into NH_3^+ ions at 4.5 pH which increase the solubility of chitosan in water and help for easy diffusion of antibacterial agents in wet starch-based film.

Hu et al. (2019) has reported the antibacterial property of the starch-based composite films loaded with ZnO and chitosan nanoparticles. The authors have synthesised ZnO-chitosan nanoparticles by sol-gel method. Then they have evaluated different properties such as mechanical, water vapour permeability and antibacterial properties of the developed starch-based composite films. They have found that microorganism growth was inhibited effectively in the presence of ZnO-chitosan nanoparticles in starch-based films. Antibacterial activity of the developed hybrid film in terms of inhibition area was maximum against Gram-positive (*S. aureus*) bacteria as compared to Gram-negative (*E. coli*) bacteria. They have also reported that antibacterial activity gets increased with increase in the concentration of ZnO-chitosan nanoparticles up to a certain limit after which the mechanical and barrier properties of the developed composite film get hampered. The antibacterial activity of the developed starch-based composite film can be explained by generation of higher amount of superoxide and hydroxyl anions when film is exposed to photocatalytic reaction, which are mainly responsible for killing the different microorganisms.

Clegg et al. (2019) has developed starch-based antibacterial coating by using silver and sodium bentonite as a filler material. They have studied the influence of $AgNO_3$ content along with washed bentonite (for removal of the additional salts). Further, in their studies they have reported the effect of back-exchange procedures, which gives an idea on the form of Ag emitted in the reaction. Various characterisation techniques can be used to measure the quantity of Ag existing in the reaction, which was done in this case by using X-ray fluorescence and a XRD along with TEM. To evaluate the antimicrobial features of the fabricated Ag/Na bentonite material, it was incorporated into a plasticised coating comprising starch along with clay. The developed material showed outstanding antimicrobial properties against a range of bacteria like *Escherichia coli*, *Kocuria rhizophila* and *Aspergillus niger* as shown in Fig. 3. Various concentrations of Ag/Na bentonites were taken into account. 0.03 weight of Ag/Na bentonite with a coat wide of 14 μm was the optimum concentration in this case to show best antimicrobial action.

Arezoo et al. have reported a novel approach to use sago starch, found mainly in the tropical regions, along with cinnamon essential oil and nano-based titanium dioxide. In this study, they have included various weight by weight percentages of nano-based titanium dioxide ranging from 0, 1, 2, 3 and 5 and various volume by weight percentages of cinnamon essential oil ranging from 0, 1 and 3 into the film of sago starch. Evaluations of various properties like physical, chemical, mechanical,

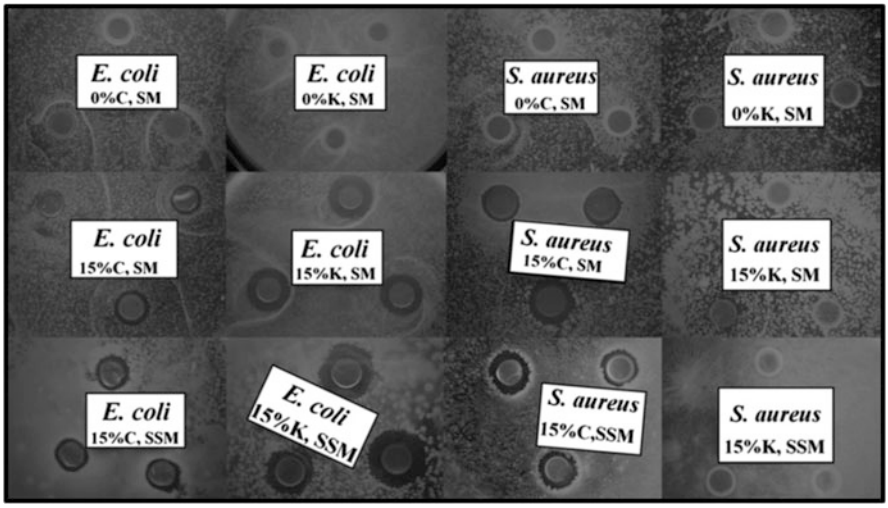

Fig. 3 Inhibition zone against *E. coli* and *S. aureus* bacteria with different concentration of potassium sorbate or chitosan incorporated starch-based films (Shen et al. 2010)

protection and most importantly antimicrobial efficacy of the nature-based nanocomposite were taken into account. The study reveals that when cinnamon essential oil was mixed in the matrix of sago starch, the increment of permeability to oxygen and water vapour was observed, whereas by the inclusion of nano-based titanium dioxide in starch matrix led to the decrement of the protection features the film. Furthermore, a decrease in moisture content was seen ranging from 12.96% to 8.04% along with a decrease in water solubility ranging from 25% to 13.7%. However, the mechanical properties of such a film was found to be more enhanced. The same starch-based film registered an outstanding antimicrobial property against different types of bacteria namely, *Escherichia coli*, *Salmonella typhimurium* and *Staphylococcus aureus*. Such nature-based nanocomposite does have its end uses in industries related to packaging of food and freshly extracted pistachio (Arezoo et al. 2019).

Spiridon et al. have explored the idea of blending various natural waste products in the matrix of starch along with poly(butylene adipate-co-terephthalate) to prepare a natural composite material. For example, by inclusion of lignin into the blended bio-composite it showed improvement in both the tensile and impact strength, whereas the rate of water absorption got reduced. Also, incorporation of lignin proved a better microbial resistant property against both the Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*). Such bio-composite comprising noticeable properties related to water prevention, mechanical and most importantly protection against different bacteria make the composite to have its end uses in manufacturing packages (Spiridon et al. 2019).

In a novel approach, Fang et al. prepared a bio-composite of starch film blended with salicylic acid and nanoparticles made up of maize starch along with

κ-carrageenan as shown in Fig. 4a, to improve antimicrobial as well as mechanical characteristics. Such fabrication was made possible by a process of enzymolysis and re-crystallisation, along with addition of κ-carrageenan in a stepwise manner. They have also mentioned about inclusion of a filler and stabiliser in the structure of a film containing 0–9% hydroxypropyl tapioca starch. SEM images as shown in Fig. 4b–i demonstrated that such bio-composite starch-based films can have regular and even structure. The study proved that such bio-composite starch-based film can significantly improve the tensile strength, barrier to water vapour, and stability from heat. However, transparency goes down along breaking elongation, as compared to virgin starch without incorporation of any such composite materials. These bio-composites have their enormous usage in the field of food industry due to its outstanding physical, mechanical and microbial resistance properties against bacteria like *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* as shown in Fig. 4 (Fang et al. 2019).

Starch included films show excellent optical, organoleptic and gas barrier characteristics, but they exhibit lower mechanical properties as studied by Thakur et al. To improve the mechanical and tensile properties of such starch-based films different natural polymers or additives can be included. It has been demonstrated by the researchers in their study that the characteristics of such film based materials can be effected by various parameters like, the type of starch, temperature, duration of film preparation, plasticisers, other natural polymers and conditions used for storage (Thakur et al. 2019).

Sen et al. in their work has proposed the idea of using a blend containing corn starch (7.50 g) as main component along with PVA (0.875 g) and glutaraldehyde (0.125 g). They have evaluated the influence of benzoic acid (BA), potassium sorbate (PS) and sodium propionate (SP) as microbial growth preventers on the different major properties such as strength, breaking elongation, permeability to water vapour and optical features. It has been justified that when 1.79 g of 100 g polymer was taken, the benzoic acid and potassium sorbate antimicrobial agents lowered the ultimate tensile strength of control film by 24.01% and 26.84%, whereas sodium propionate increased the strength by 12.35%. Furthermore, benzoic acid showed a decrease in the extent of breaking elongation by 82.82%, whereas potassium sorbate and sodium propionate showed an increase by 12.73% and 167.52%. The antimicrobial agents used in the study led to the rise in permeability to water. Considering all the results, it was concluded that sodium propionate is the best antimicrobial agent recommended due to its good water vapour permeability, which has wide applications in the field of storing fresh fruits and vegetables (Sen and Das 2019).

Pal et al. developed a new type of starch containing cations made up of N-(3-chloro-2-hydroxypropyl) trimethyl ammonium chloride along with the aid of sodium hydroxide as shown in Fig. 5a. Such prepared starch was investigated by different characterisation techniques like Fourier Transform Infrared Spectroscopy as demonstrated in Fig. 5b and also by measuring its viscosity. The flocculation property of the starch was tested by using silica suspension. It has been observed that

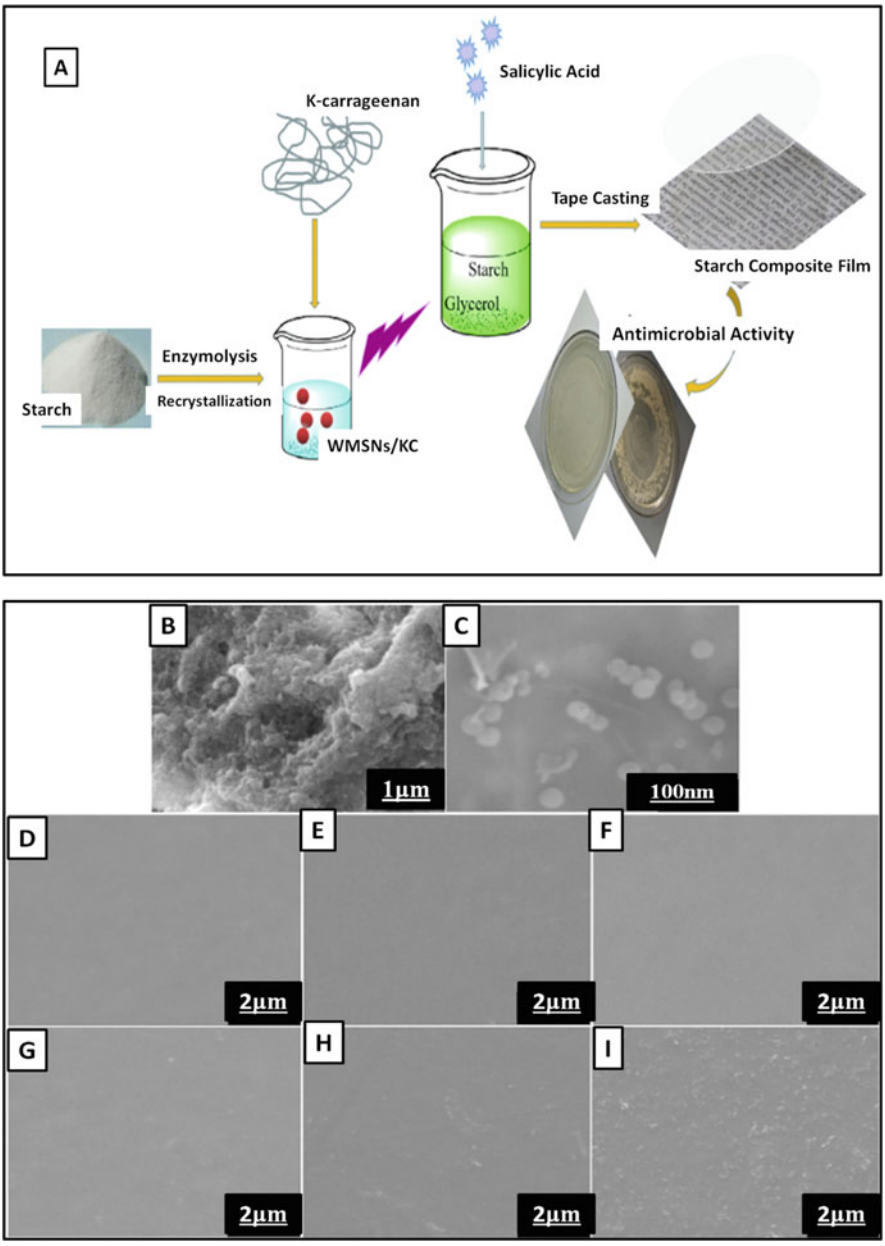

Fig. 4 (**a**) Preparation of starch based nanocomposite film, Scanning Electron Microscope pictures of composites at different magnification ranging from (**b**) 5000 to (**c**) 12,000 along with surface morphology of the film containing different concentration of composites ranging from (**d**) 0%, (**e**) 1, (**f**) 3%, (**g**) 5%, (**h**) 7% and (**i**) 9% at a magnification range of 4000 (Fang et al. 2019)

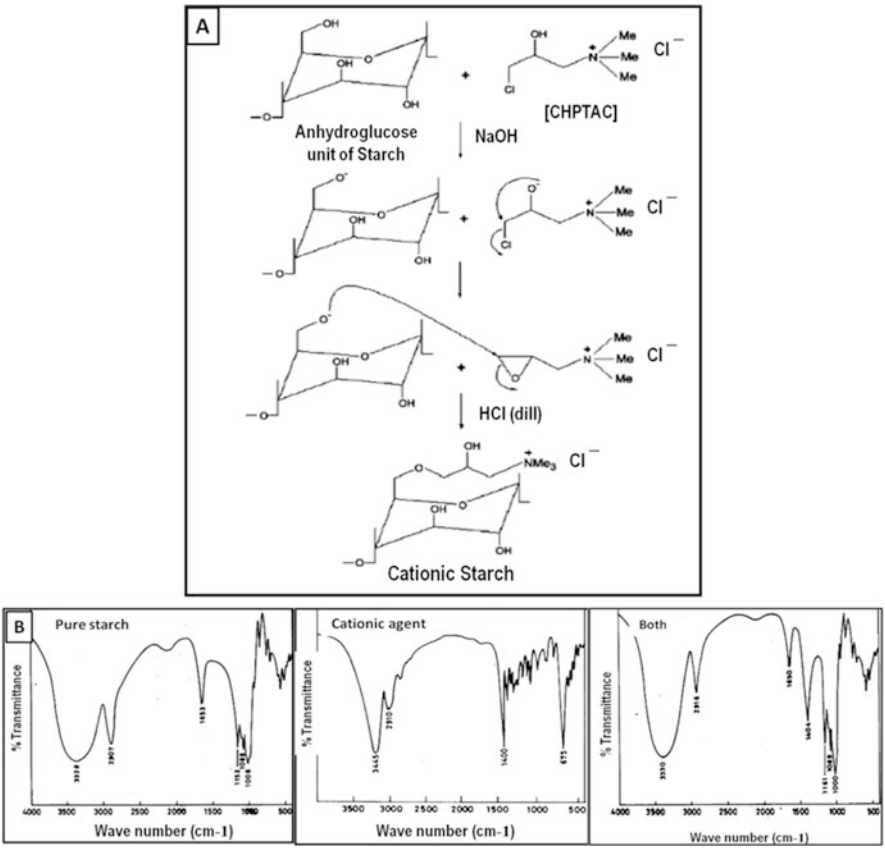

Fig. 5 (**a**) Preparation of starch made up of cationic agent, (**b**) Fourier Transform Infrared Spectroscopy of pure starch, cationic agent (N-(3-chloro2-hydroxypropyl) trimethyl ammonium chloride) and starch incorporated with above-stated cationic agent (Pal et al. 2005)

the starch with longer chain length shows the better flocculation property when compared with the starch having shorter chain length (Pal et al. 2005).

Guan et al. have reported the use of guanidine polymer in the structure of starch extracted from potato by the process of coupling to imbue the antimicrobial property. The guanidine modified starch showed good antibacterial activity against both the Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria tested in shaking flask and diffusion method (Guan et al. 2008).

Effective cationisation of starch with the aid of glycidyl trimethyl ammonium chloride and maintaining the reaction parameters like catalyst concentration (NaOH), temperature along with the components used in the reaction were studied by Kavaliauskaite et al. They have stated that cationisation of starch at a low temperature has enhanced efficiency as energy required for activation of the reaction with glycidyl trimethyl ammonium chloride is much less when compared with the

side reactions taking place. The concentration of sodium hydroxide affects both the main and side reaction. Cationisation of starch takes place when the total amount of sodium hydroxide available in the reaction gets adsorbed by starch in its non-solid state. The study entirely deals with the reaction factors which influence the cationisation of starch, which can be used as a promising antimicrobial agent. Such cationised starch has various other applications ranging from its usage in various industries and as a substitute which can replace the synthetic flocculants or sorbents, which has environmental pollution at an uncontrolled rate (Kavaliauskaite et al. 2008).

In a study, Salleh et al. have used lauric acid along with chitosan as an agent which prevents the growth of microbes in the structure of wheat starch. The main aim of this study was to prevent the growth of microbes in the food packages, which spoil the food stuffs. The tests were carried out against *Bacillus subtilis* and *Escherichia coli* bacteria. Both the solid media and liquid culture test methods were employed to investigate the growth of bacteria. Both the standard and antimicrobial films comprising lauric acid along with chitosan were prepared by casting process. The results from solid media test demonstrated a visible inhibition zone against *Bacillus subtilis* (Gram-positive) bacteria whereas, a much less visible inhibition zone was observed in case of *Escherichia coli* (Gram-negative bacteria). This study illustrates that starch incorporated films can contribute a major antimicrobial property to the food packaging industries (Salleh and Muhamad 2010). In another study, the use of the same material was used but in a different way, where starch and chitosan blend were used in series including lauric acid (8%). Functional groups of starch (OH groups) and chitosan (OH, NH_2 groups) can lead to a very good interaction of the two components in the blend and make the two polymers miscible. Their study revealed that the antimicrobial starch/chitosan/lauric acid incorporated film has an improved rate of transmission of water vapour and is transparent in nature with a yellowish tint with increasing content of chitosan. Such property related to water vapour of the blended film is mainly due to the hydrophobic characteristics of lauric acid. The blended film also showed an outstanding permeability to oxygen, which can enable such materials to be used in antimicrobial packaging and can be a substitute for synthetic polymers for packaging to prevent the food materials from oxidation reaction (Salleh et al. 2009).

Ali et al. reported the use of the peel extracted from pomegranate fruit as shown in Fig. 6a–c which acted as a promising antimicrobial agent along with a supporting material, to develop starch films. In this study they have incorporated water and glycerol as plasticiser into starch containing higher percentage of amylose. Both the surface characteristics and the nature of the film were evaluated by scanning electron microscope as demonstrated in Fig. 6d, e, optical microscope, X-ray diffraction, dynamic mechanical analyser, tensile testing, drop impact testing and disc diffusion test. Reports illustrated that pomegranate peel prevented the microbial growth against *S. aureus* and *Salmonella* bacteria. Pomegranate peel causes an increase in Young's modulus, tensile strength and rigidity of the starch incorporated film (Ali et al. 2019).

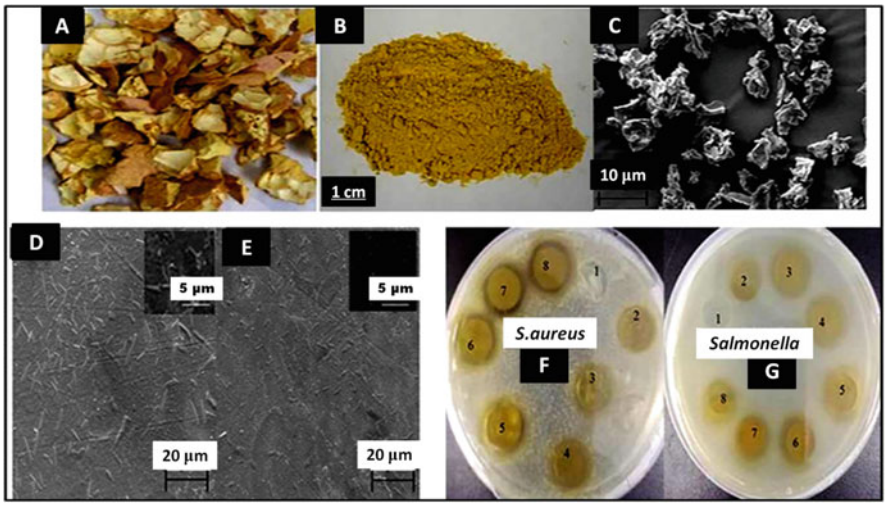

Fig. 6 Images of dried pomegranate peel in a fridge, (**a**) Granules of pomegranate peel, (**b**) Granules of pomegranate peel characterised by scanning electron microscope, (**c**) Pictures of starch based films containing pomegranate peel concentration of (**d**) 2% and (**e**) 10%, respectively. Inhibition zones of starch films with pomegranate peel against bacteria (**f**) *S. aureus* and (**g**) *Salmonella* (Ali et al. 2019)

Pelissari et al. revealed a novel approach of preparation of a film consisting of starch, chitosan incorporated with oregano essential oil. The zone of inhibition of such film was measured against a range of bacteria such as *Bacillus cereus*, *Escherichia coli*, *Salmonella enteritidis* and *Staphylococcus aureus*. Results illustrated that the film imbued with oregano essential oil effectively showed inhibition against the four above-stated bacteria along with a noticeable barrier characteristic. The existence of such oil in the film also added value to increase the elastic nature of the film. Furthermore, pure chitosan did not show much antimicrobial property against the bacteria as stated, instead the flexibility and water vapour permeability of the starch-based film get reduced. Thermal gravimetric analysis justified that no change in the stability to heat of such film was noticed by the inclusion of chitosan along with the oil. Such blended film can be a promising candidate to be used to provide resistance to bacterial growth (Pelissari et al. 2009).

Tang et al. used di-aldehyde starch, acted as a crosslinking agent, for the improvement of the mechanical property and water absorbency property of the films comprised of chitosan. FTIR and XRD showed that the crystallisation of chitosan is influenced by Schiff's base. A crosslinking content of 5% demonstrated the optimised tensile strength of 113.1 MPa and elongation at break of 27%. Such optimised chitosan-based film was observed to exhibit noteworthy antimicrobial properties against *Escherichia coli* and *Staphylococcus aureus* bacteria. These kinds of films can have their huge application in the field of biomedicines (Tang et al. 2003).

Yoksan et al. in their study has synthesised Ag nanoparticles with the incorporation of $AgNO_3$ in a solution of chitosan. Such fabricated sliver nanoparticles showed stability for a period more than 6 months. Transmission electron microscopy showed that these particles exhibited the form of a sphere having an approximate dimension ranging from 20 to 25 nm. Minimum inhibitory concentration of the fabricated material against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus cereus* bacteria was noted to be 5.64 μg/mL. Solution cast procedure was used to prepare this film. Results demonstrated that inclusion of Ag nanomaterials in the structure of chitosan led to the enhancement of the tensile property, oxygen barrier property, but lowered the permeability to water or moisture. Furthermore, this specially blended chitosan-based film showed outstanding prevention against bacterial growth. This blended film can possibly have its applications in the field of packaging food and medicines (Yoksan and Chirachanchai 2010).

Jung et al. invented a novel approach of using starch-based Ag nanoparticles prepared by solution cast method in one step by ultra-sonication of the blend as described in the Fig. 7a. Here, starch was used both as an antimicrobial and reducing agent. To prepare paper that can be utilised for packaging can be obtained from the solution coated mixture of sliver nanoparticles incorporated starch. Results demonstrated that such coated films have a property of good resistance to oil along with outstanding property to prevent the microbial growth against *Escherichia coli* and *Staphylococcus aureus* bacteria as shown in Fig. 7b–d, which can find applications in food packaging, etc. (Jung et al. 2018).

Usman et al. fabricated a nanocomposite film made up of PVA, graphene oxide and Ag included in the structure of chitosan. Evaluations of various properties like mechanical, thermal and antimicrobial efficacy of the starch-based film was taken into account. The nanocomposite witnessed an enhanced tensile strength, stability to heat property by the inclusion of graphene oxide in polyvinyl alcohol. Due to the durable bonds between graphene oxide and the blended film, a thermal barrier effect was noticed. Antimicrobial properties of the prepared films were investigated against *Escherichia coli* and *Staphylococcus aureus* bacteria. Figure 8 illustrated the antimicrobial characteristics of the polyvinyl alcohol based blend of graphene oxide, sliver, graphene oxide/sliver and graphene oxide/sliver/starch (Usman et al. 2016).

Ortega et al. (2017) elaborated the use of Ag nanoparticles for studying the antimicrobial properties of corn starch-based films, used in packaging of food. The study showed Ag nanoparticles have no toxic effect on the cells. Electron microscopy analysis exhibited that the spherical shaped particles have a diameter ranging from 5 to 20 nm. Results showed that Ag nanoparticles increased the thickness of the film and it was impervious in nature. Also, with increase in the concentration of the nanoparticles, a decrease in the permeability to water was observed. Sliver nanoparticles led to the strengthening of the film along with the development of a durable and rigid material, showing an even surface as depicted in the scanning electron microscope images. Such films also exhibited the property of showing prevention against the bacteria, *E. coli* and *Salmonella* spp., which cause different food related diseases. Considering, different concentration of the sliver nanoparticles, as shown in Fig. 9a, the one containing 143 ppm of the nanoparticles

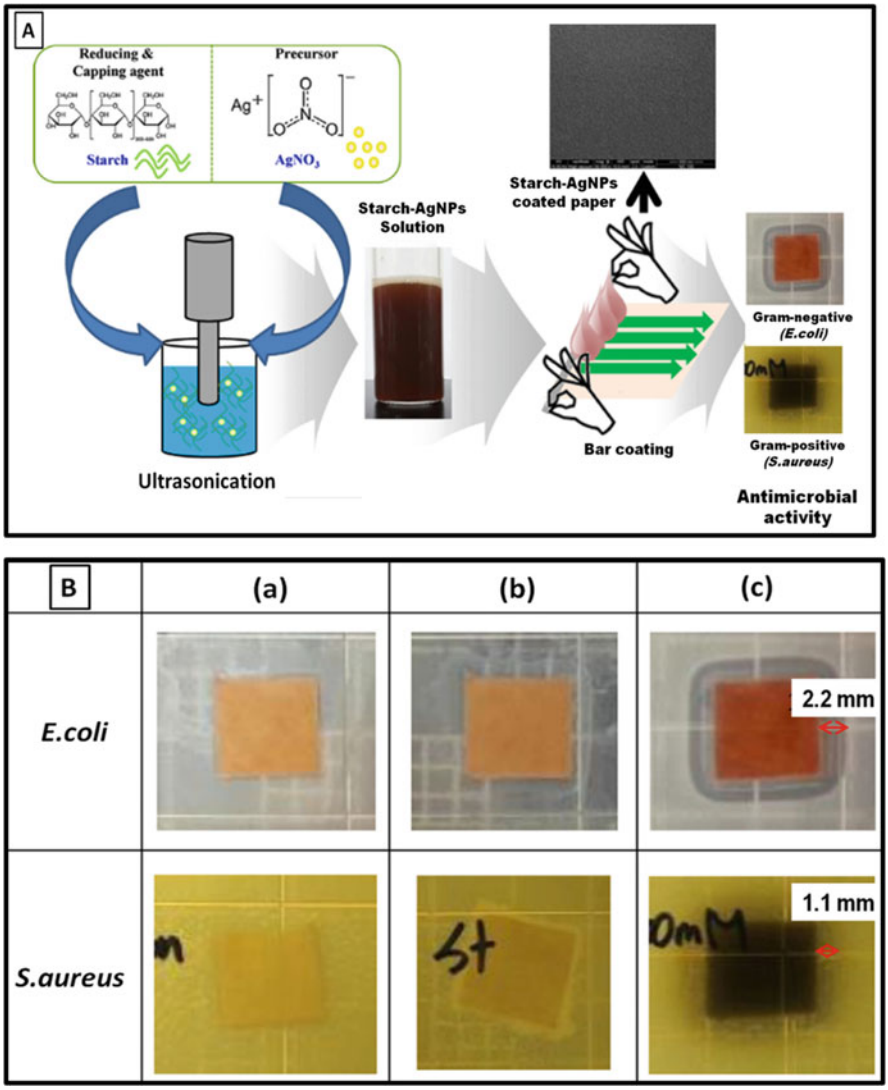

Fig. 7 (**a**) Schematic diagram showing the starch based sliver nanoparticles coated with paper along with its use in different antibacterial activities, (**b**) Pictures showing the antibacterial features of the uncoated paper (**a**), starch-coated paper (**b**), and starch based sliver coated paper (**c**) against bacteria *E. coli* and *S. aureus* (Jung et al. 2018)

was observed to show the optimised antimicrobial property. Such films were considered to keep cheese trials fresh for twenty-one days as shown in Fig. 9b (Ortega et al. 2017).

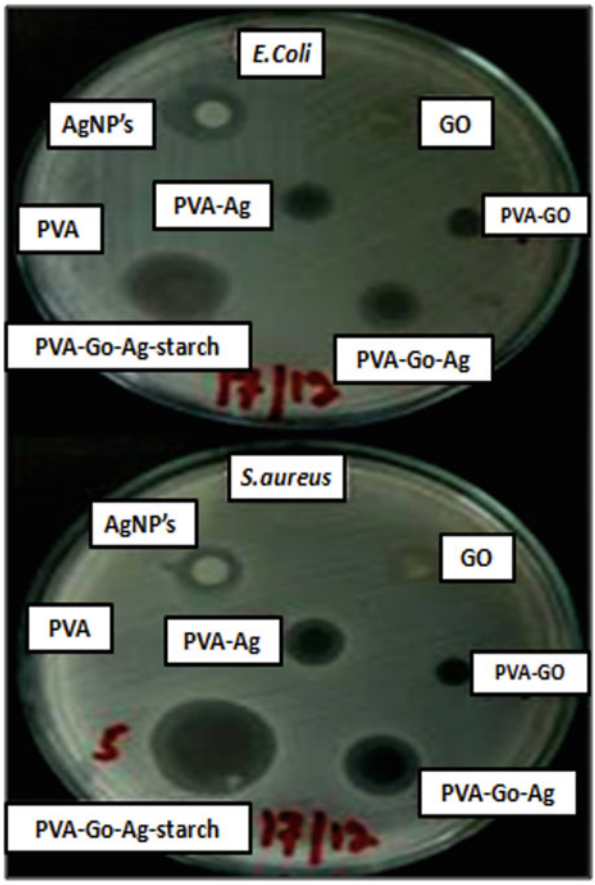

Fig. 8 Picture depicting the resistance of composite polymer film to bacterial growth against *E. coli* and *S. aureus* bacteria (Usman et al. 2016)

4 Summary

The recent statistics show that the consumption of food along with its production occupies 9 GJ of energy/year. Therefore, it is very important for us to lessen the wastage of food. After, keeping the food products for a longer period of time the growth of fungi and bacteria prevails. So, it is very essential to prevent such bacterial growth in the food products along with the packages in which they are stored. Starch, as stated by the researchers, has gained much attention for food packaging due to its biodegradability, biocompatibility, easy availability, and certainly it is cheaper. But it has limitations like it is hydrophilic in nature, prone to bacterial growth and brittle in nature. Different plasticisers are used to blend with starch to get rid of this brittleness. Still they are not suitable for its practical applications as it lags in mechanical features. Inclusion of various nano-based materials like clay, zinc oxide, titanium dioxide and magnesium oxide can improve the bacterial barrier, physical, chemical, mechanical and heat stability of starch. TiO_2 has been widely

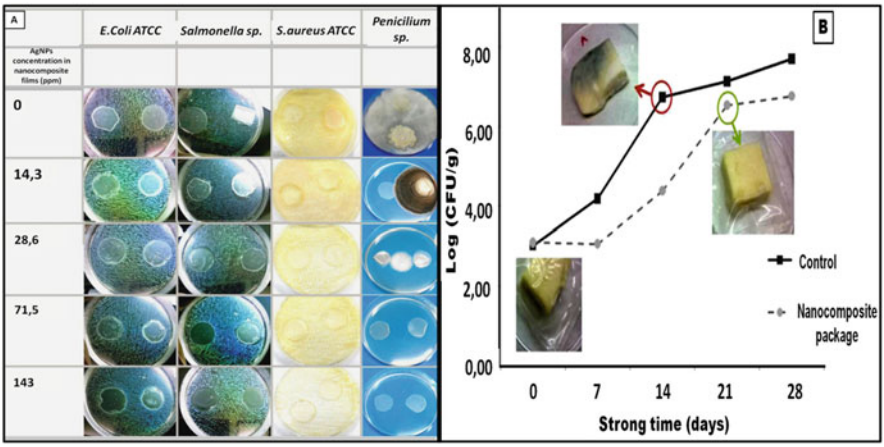

Fig. 9 (**a**) Minimum inhibitory concentration zone of sliver nanoparticles included in corn starch against bacteria *E. coli*, *Salmonella* spp., *S. aureus* and *Penicillium* spp., (**b**) Image demonstrating the influence on the shelf period of cheese trials kept in the composite film at a temperature of 4 °C (Ortega et al. 2017)

used in food and bio-medicine application due to its property to absorb ultra-violet rays and has ability to keep the food products fresh and hygienic. Nano-sized titanium dioxide prevents the growth of bacteria like *Escherichia coli* and *Staphylococcus aureus*. This material is basically synthetic in origin and offers various environmental pollution issues. So, to overcome the usage of such synthetic antimicrobial agents, use of different nature-based materials have huge scope to replace the ill effects of the synthetic category. For example, oils extracted from plants provide good and safe antimicrobial properties. Such natural materials have other properties too like it prevents oxygen gas permeability, that inhibits the growth of bacteria. For example, cinnamon essential oil is being used to pack bread and other food products. Also, such cinnamon essential oil improves antioxidant, antimicrobial, mechanical and physical features of starch-based chitosan nanocomposite materials. Therefore, it can be concluded from this chapter that different starch-based nanocomposite material, which are available in nature, can be a promising candidate in the field of food packaging and bio-medicine industries.

References

Abreu AS, Oliveira M, De Sá A et al (2015) Antimicrobial nanostructured starch based films for packaging. Carbohydr Polym 129:127–134. https://doi.org/10.1016/j.carbpol.2015.04.021

Ali A, Chen Y, Liu H et al (2019) Starch-based antimicrobial films functionalized by pomegranate peel. Int J Biol Macromol 129:1120–1126. https://doi.org/10.1016/j.ijbiomac.2018.09.068

Arezoo E, Mohammadreza E, Maryam M, Abdorreza MN (2019) The synergistic effects of cinnamon essential oil and nano TiO2 on antimicrobial and functional properties of sago starch films. Int J Biol Macromol. https://doi.org/10.1016/j.ijbiomac.2019.11.244

Ashjari HR, Dorraji MSS, Fakhrzadeh V et al (2018) Starch-based polyurethane/CuO nanocomposite foam: antibacterial effects for infection control. Int J Biol Macromol 111:1076–1082. https://doi.org/10.1016/j.ijbiomac.2018.01.137

Bangyekan C, Aht-Ong D, Srikulkit K (2006) Preparation and properties evaluation of chitosan-coated cassava starch films. Carbohydr Polym 63:61–71. https://doi.org/10.1016/j.carbpol.2005.07.032

Bum C (n.d.) Utilization of chitin prepared from the shellfish crust 2. Effect of chitosan film packing on quality of lightly-salted and dried horse mackerel

Chen CH, Kuo WS, Lai LS (2013) Development of tapioca starch/decolorized Hsian-Tsao leaf gum-based antimicrobial films: physical characterization and evaluation against listeria monocytogenes. Food Bioprocess Technol 6:1516–1525. https://doi.org/10.1007/s11947-012-0822-9

Clegg F, Breen C, Muranyi P, Schönweitz C (2019) Antimicrobial, starch based barrier coatings prepared using mixed silver/sodium exchanged bentonite. Appl Clay Sci 179:105144. https://doi.org/10.1016/j.clay.2019.105144

Fang Y, Fu J, Tao C, et al (2019) Mechanical properties and antibacterial activities of novel starch-based composite films incorporated with salicylic acid. Int J Biol Macromol. https://doi.org/10.1016/j.ijbiomac.2019.11.110

Guan Y, Qian L, Xiao H, Zheng A (2008) Preparation of novel antimicrobial-modified starch and its adsorption on cellulose fibers: part I. Optimization of synthetic conditions and antimicrobial activities. Cellulose 15:609–618. https://doi.org/10.1007/s10570-008-9208-6

Hu X, Jia X, Zhi C et al (2019) Improving the properties of starch-based antimicrobial composite films using ZnO-chitosan nanoparticles. Carbohydr Polym 210:204–209. https://doi.org/10.1016/j.carbpol.2019.01.043

Jung J, Raghavendra GM, Kim D, Seo J (2018) One-step synthesis of starch-silver nanoparticle solution and its application to antibacterial paper coating. Int J Biol Macromol 107:2285–2290. https://doi.org/10.1016/j.ijbiomac.2017.10.108

Kavaliauskaite R, Klimaviciute R, Zemaitaitis A (2008) Factors influencing production of cationic starches. Carbohydr Polym 73:665–675. https://doi.org/10.1016/j.carbpol.2008.01.019

Ortega F, Giannuzzi L, Arce VB, García MA (2017) Active composite starch films containing green synthetized silver nanoparticles. Food Hydrocoll 70:152–162. https://doi.org/10.1016/j.foodhyd.2017.03.036

Pal S, Mal D, Singh RP (2005) Cationic starch: an effective flocculating agent. Carbohydr Polym 59:417–423. https://doi.org/10.1016/j.carbpol.2004.06.047

Parra DF, Tadini CC, Ponce P, Lugao AB (2004) Mechanical properties and water vapor transmission in some blends of cassava starch edible films. Carbohydr Polym 58:475–481. https://doi.org/10.1016/j.carbpol.2004.08.021

Pelissari FM, Grossmann MVE, Yamashita F, Pined EAG (2009) Antimicrobial, mechanical, and barrier properties of cassava starch-chitosan films incorporated with oregano essential oil. J Agric Food Chem 57:7499–7504. https://doi.org/10.1021/jf9002363

Pyla R, Kim TJ, Silva JL, Jung YS (2010) Enhanced antimicrobial activity of starch-based film impregnated with thermally processed tannic acid, a strong antioxidant. Int J Food Microbiol 137:154–160. https://doi.org/10.1016/j.ijfoodmicro.2009.12.011

Salleh E, Muhamad II (2010) Starch-based antimicrobial films incorporated with lauric acid and chitosan. AIP Conf Proc 1217:432–436. https://doi.org/10.1063/1.3377861

Salleh E, Muhamad I, Khairuddin N (2009) Structural characterization and physical properties of antimicrobial (AM) starch-based films. World Acad Sci 3:428–436

Sen C, Das M (2019) Antimicrobial compound incorporated corn starch based self-supporting film and its properties. Int Food Res J 26:573–584

Shen XL, Wu JM, Chen Y, Zhao G (2010) Antimicrobial and physical properties of sweet potato starch films incorporated with potassium sorbate or chitosan. Food Hydrocoll 24:285–290. https://doi.org/10.1016/j.foodhyd.2009.10.003

Spiridon I, Anghel NC, Darie-Nita RN, et al (2019) New composites based on starch/Ecoflex®/biomass wastes: mechanical, thermal, morphological and antimicrobial properties. Int J Biol Macromol. https://doi.org/10.1016/j.ijbiomac.2019.11.185

Taheri S, Baier G, Majewski P et al (2014) Synthesis and antibacterial properties of a hybrid of silver-potato starch nanocapsules by miniemulsion/polyaddition polymerization. J Mater Chem B 2:1838–1845. https://doi.org/10.1039/c3tb21690j

Tang R, Du Y, Fan L (2003) Dialdehyde starch-crosslinked chitosan films and their antimicrobial effects. J Polym Sci Part B Polym Phys 41:993–997. https://doi.org/10.1002/polb.10405

Thakur R, Pristijono P, Scarlett CJ et al (2019) Starch-based films: major factors affecting their properties. Int J Biol Macromol 132:1079–1089. https://doi.org/10.1016/j.ijbiomac.2019.03.190

Torres FG, Commeaux S, Troncoso OP (2013) Starch-based biomaterials for wound-dressing applications. Starch 65:543–551. https://doi.org/10.1002/star.201200259

Usman A, Hussain Z, Riaz A, Khan AN (2016) Enhanced mechanical, thermal and antimicrobial properties of poly(vinyl alcohol)/graphene oxide/starch/silver nanocomposites films. Carbohydr Polym 153:592–599. https://doi.org/10.1016/j.carbpol.2016.08.026

Vásconez MB, Flores SK, Campos CA et al (2009) Antimicrobial activity and physical properties of chitosan-tapioca starch based edible films and coatings. Food Res Int 42:762–769. https://doi.org/10.1016/j.foodres.2009.02.026

Yadav L, Tripathi RM, Prasad R, Pudake RN, Mittal J (2017) Antibacterial activity of Cu nanoparticles against *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Nano Biomed Eng 9(1):9–14. https://doi.org/10.5101/nbe.v9i1.p9-14

Yoksan R, Chirachanchai S (2010) Silver nanoparticle-loaded chitosan-starch based films: fabrication and evaluation of tensile, barrier and antimicrobial properties. Mater Sci Eng C 30:891–897. https://doi.org/10.1016/j.msec.2010.04.004

Cellulose-Based Antimicrobial Materials

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Abstract Cellulose is a widely studied natural polymer due to its availability, biodegradability, non-toxicity, and ease of chemical modification. Currently, cellulose has many applications in science and technology, but it has vast relevance in biomedical applications, such as a protective coating for wound dressing in skin burns, and injuries to avoid bacterial infections. This chapter describes some properties of cellulose such as structure, and biocompatibility. Besides this chapter also describes some methods used to endow cellulose with antimicrobial activity by means of the addition of biocidal groups as *N*-halamines, quaternary ammonium salts, nanoparticles, enzymes, or through the incorporation of antibiotics for controlled drug delivery.

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1 Introduction

Cellulose has been widely studied as a biomaterial because it is one of the most abundant and biodegradable natural polymers. This possesses remarkable physical and biological properties and an adequate surface chemistry (Zhu et al. 2010; Zhu and Zhuang 2012). Besides, its hydrophilicity, transparency, and innocuousness make it an alternative for various applications, especially to develop materials related to wound dressings and nanomaterials for severe skin burns, injuries, and bacterial infections treatment. Other cellulose applications include tissue engineering, controllable delivery systems, sensors, agriculture, and water and blood purification (Chang and Zhang 2011). For medical treatments, plant-based cellulose has been mainly used as cotton for wound dressing, sutures, and dialysis membranes (Cross et al. 2006). Nevertheless, the plant-based cellulose is not produced in its purest form, lignin, hemicelluloses, and other compounds are part of its composition, and purifying it for medical applications is a highly complex process. The production of bacterial cellulose (BC) is a cleaner alternative; BC is biosynthesized by several bacteria and shares the same chemical structure with plant cellulose, except that it exhibits the highest purity making it suitable for medical device applications. Some bacteria of genera *Acetobacter*, *Rhizobium*, *Agrobacterium*, *Aerobacter*, *Achromobacter*, *Azotobacter*, *Salmonella*, *Escherichia*, and *Sarcina* produce BC (Shoda and Sugano 2005).

BC is well-known for being superior compared to plant cellulose regarding sustainability, biocompatibility, biodegradability, ability to be chemically modified, and surface area. BC is endowed with unique properties such as high water holding capacity, a high degree of polymerization, high mechanical strength, and high crystallinity (Esa et al. 2014). Furthermore, the bacterial production of nanocellulose is the most optimal and efficient industrial method yielding a pure product (Kang et al. 2012). All these features make BC an outstanding material for biomedical applications (Vasconcelos et al. 2017).

The continuous interaction between the human body and pathogens is a constant risk for health because of the possibility of acquiring infections, which are produced by viruses, fungi, and bacteria. However, bacterial infections are the most frequent acute and chronic infections and the major cause of morbidity in the world. Currently, the accelerated increase of untreatable bacterial infections is a disturbing issue and is caused by a rise in antibiotic-resistant bacteria strains (Khatoon et al. 2018). In this area, attention has been placed on nanocellulose to develop biocompatible, non-toxic, non-leachable, and antibacterial materials with prolonged biocidal activity (Tayeb et al. 2018; Tavakolian et al. 2020). Some studies have reported innovative and effective technologies that can enhance microbial inactivation by

incorporating biocidal agents in nontoxic and biocompatible materials to avoid bacterial resistance (Delezuk et al. 2017).

Methodologies used to synthesize cellulose antimicrobial materials include surface modification, loading or incorporation of drugs or inorganic nanomaterials, and blending with antibacterial polymers. Antimicrobial materials may include in their composition some agents such as quaternary ammonium compounds, zwitterions, inorganic nanocomposites, and nanoparticles (NPs), being silver and zinc the most widely used to produce NPs (Chen et al. 2012a, b, 2014; Llorens et al. 2012; Heli et al. 2016). Antimicrobial cellulose-based materials expand the cellulose applicability in medical therapies where it can be used to improve wound dressing, packaging materials, and medical prosthesis or to act as drug carriers.

Wound dressing has an important role in the healing process whether surgical, burns, or accidents. Initially, it was considered as passive protection of the wound, which main functions were to keep the wound dry (adsorbing the exudate) and prevent the bacterial proliferation and the incorporation of external agents. However, this concept has changed significantly, and the bandage is now considered an active component during the healing process and has a great importance for the treatment of chronic wounds. The new designs and materials seek to provide a healing microenvironment appropriate for the growth of new tissue (warm and humid environments) but controlling the development of infections by using antimicrobial materials. In this context, cellulose excellent properties make it an interesting material for this application since even though cellulose does not have antimicrobial activity, in its natural form, it can be easily modified to load medications or copolymerize with antimicrobial substances, which will allow preventing or eradicating a possible wound infection. Furthermore, as it is a material with a high affinity for bioactive substances, it accelerates recovery (Bergstrom et al. 2005).

2 Properties of Cellulose

Cellulose is a straight-chain polysaccharide whose monomeric unit is the D-glucose dimer, consisting of two glucose molecules linked through a β-1-4-glycosidic bond, in which the C1 carbon of a glucose molecule and the C4 of the other are covalently bound to an oxygen atom (Azizi Samir et al. 2005). The glucoside bond is stabilized by the hydrogen bonds between glucose hydroxyl groups and the oxygen in the bond, resulting in the linear configuration of the polymer. The aforementioned microscopic configuration of cellulose allows a more feasible interaction between chains, thus forming microfibrils bonded by Van der Waals forces and intermolecular hydrogen bonds, which promote the assembling of multiple cellulose chains stacking them in a stable and resistant three-dimensional structure. Microfibrils are made up of two structural regions: a crystalline structure, in which the cellulose chains are organized in a very orderly way, and an amorphous region, where the chains are disordered (Nishiyama 2009). The crystalline regions can be extracted from the cellulose microfibrils by acid treatment, resulting in cellulose

nanocrystals (CNC) or nanofibers (CNF) depending on the extraction material. The use of nanotechnology techniques allows the design and manufacture of natural cellulose NPs with different dimensions from 1 to 100 nm, from the fibers by homogenization, hydrolysis, or combined chemical and mechanical processes. Cellulose NPs give versatility and improve the properties of a given material (Vasconcelos et al. 2017).

Crystalline cellulose has four widely studied polymorphs (I, II, III, and IV). The first, cellulose type I, is the most abundant in nature since it is produced by plants, urochordates, algae, and bacteria. This structure can be modified to the other polymorphs (O'Sullvian 1997), through a solubilization-recrystallization processes or by mercerization (aqueous sodium hydroxide treatments). Cellulose II has a monoclinic structure that gives it the greatest stability and has been used to produce various materials including cellophane, rayon, and synthetic textile fibers as the Tencel (Klemm et al. 2005). On the other hand, cellulose III is obtained from cellulose I or II by treatments with liquid ammonia. And finally, cellulose IV is produced by heat treatments of cellulose III (Ishikawa et al. 1997).

Additionally, cellulose I is formed by two coexisting crystalline structures, whose proportion depends on the source of cellulose extraction; a triclinic structure (Iα) and a monoclinic structure (Iβ), which are named depending on their arrangement "parallel upwards" or "antiparallels" (Azizi Samir et al. 2005; Nishiyama 2009). Although the polymorph Iα can be converted into Iβ through hydrothermal treatments (~260 °C) in alkaline solution (Yamamoto and Horii 1993; Watanabe et al. 2006; Horikawa and Sugiyama 2009) or high-temperature treatments in organic solvents and inert atmosphere (Debzi et al. 1991) complete conversion is not achieved.

For example, bacterial cellulose fibrils, when treated, can produce micro or nanofibrils (Costa et al. 2017), without altering their crystallinity, in general, the geometry of the BC is determined by intramolecular and intermolecular forces such as bonds of hydrogen and hydrophobic and Van der Waals interactions, and forms parallel chains (cellulose I). When carrying out the mercerization process (treatment with 5–30 wt% of sodium hydroxide), this material forms a type II antiparallel structure, mostly stabilized by hydrogen bonds, which generates a more stable three-dimensional arrangement than cellulose I and nanofibers with random structure and high Young modulus, 118 GPa for a single BC filament almost comparable to Kevlar® and steel (Picheth et al. 2017). Cellulose micro and nanofibrils have a high surface area, which is related to high porosity and allows greater interaction between the fibrils and decreases the permeability of the material to oxygen. Furthermore, due to a large number of free hydroxyl groups, they show great adsorption of water and the formation of high-viscosity gels. Another advantage of hydroxyl groups is that they can be functionalized by esterification, oxidation, or sulfonation, altering the properties of the biopolymer and expanding the application (Berto and Arantes 2019).

2.1 Biocompatibility

Cellulose is an adequate material for skin engineering materials and medical devices. The toxicity of cellulose has been evaluated through techniques such as cytometric assays, for instance, in an in vivo mice surgeries and in vitro human umbilical vein endothelial cells assays. These assays indicated a nonvisible difference in morphology (Jeong et al. 2010). In another assay, cellulosic composites were implanted into mice and they were successfully integrated into the mice skin. Hence, cellulose cell attachment and proliferation supported that cellulose is non-toxic and biocompatible.

In another study, a synthesis of a composite scaffold by modification of cellulose with poly(3-hydroxubutyrate-co-4-hydroxubutyrate) (P(3HB-co-4HB)) exhibited cell adhesion on Chinese Hamster Lung (CHL) fibroblast cells (Wang et al. 2009). The results indicated better biocompatibility for the BC composite scaffold (P (3HB-co-4HB)/BC) composite scaffold than that for pure P(3HB-co-4HB) scaffold (Zhijiang et al. 2012). On another hand, Lin et al. studied the effectiveness and biocompatibility of cellulose hydrogels as supports for the storage and delivery of extracellular matrices such as collagen, elastin, and hyaluronan, as well as growth factors including the basic fibroblast growth factor (B-FGF), human epidermal growth factor (H-EGF), and keratinocyte growth factor (KGF) (Lin et al. 2011). In vitro cell viability evaluations showed that 95% of the mesenchymal stem cells added to the cellulose support were alive, and could form interactions with collagen, these results showed that cellulose-based materials can promote tissue regeneration and they could be used in skin substitutes (Zhijiang and Guang 2011).

3 Chemical Modification of Cellulose

Cellulose has a large number of hydroxyl groups, which are reactive and act as active sites, allowing a wide variety of chemical modifications that result in unique cellulose derivatives (Jedvert and Heinze 2017).

Chemical modifications provide cellulosic materials with antimicrobial activity by incorporating biocidal agents either by covalent bonds or cellulose binding interactions. The main chemical methods of cellulose modification include esterifications, etherifications, and hydroxyl group oxidation reactions. Other chemical modifications include ionic and radical grafting, acetylation, and deoxyhalogenation (Fig. 1). These chemical modifications may provoke drastic changes in the cellulose solubility allowing water and organic solvents to dissolve it.

Chemical modification of cellulose with different functional groups allows the design of antiadhesive and biocidal materials. Functional groups include siloxanes, silanes, amines, hydrazide, acyl hydrazide, aminooxy, alkenes, alkoxysilanes, acyl chlorides, epoxides, and isocyanates. Although cellulose may require a pretreatment to insert more complex functional groups, the chemical modification is a great alternative for the fabrication of diverse materials at different scales, which is

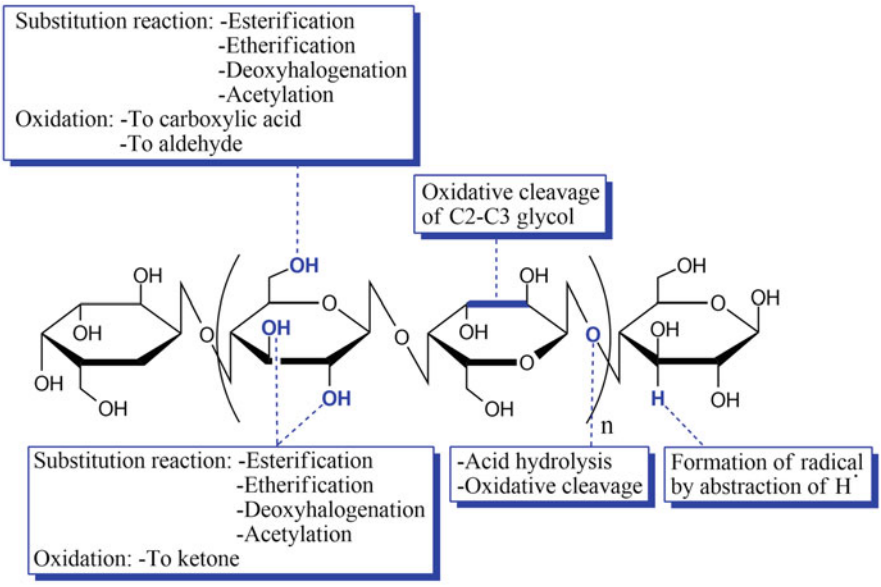

Fig. 1 Chemical reaction on backbone cellulose

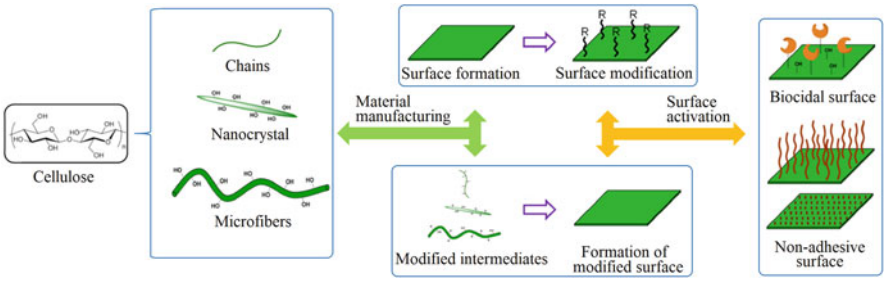

Fig. 2 Chemical modifications are useful to develop cellulose-based antimicrobial materials

achieved by two approaches: from intermediates or semi-finished materials, Fig. 2 shows an overview of the chemical modification process of cellulose.

3.1 Covalent Attachment of Biocide Compounds

Although there are several reports of biocidal agents, *N*-halamines stand out owing to their effective activity against microorganisms such as bacteria, fungi, and viruses. *N*-halamines have in their structure one or more nitrogen-halogen covalent bonds (N-X), which can be formed by halogenation of imides, amides, or amines (Chen et al. 2007). These molecules have generated keen interest due to their stability,

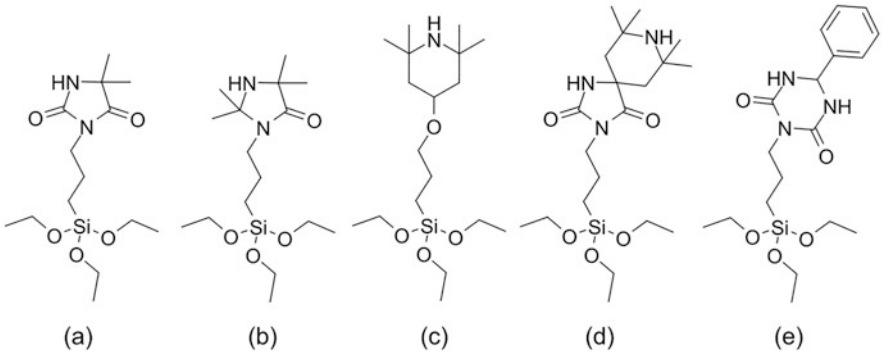

Fig. 3 Chemical structure of *N*-halamines functionalized with siloxanes linkage groups (**a**–**e**) for grafting on cellulose

rechargeability, and non-toxicity (Dart et al. 1991; Sun and Sun 2002; Yuyu and Gang 2002; Kitkulnumchai et al. 2008; Liu and Sun 2008, 2009; Skorb et al. 2008; Jeong et al. 2010; Jiang et al. 2011; Chen et al. 2012a, b). When *N*-halamine precursors are exposed to a sodium hypochlorite solution, chlorinated nitrogenous structures are produced and their antibacterial mechanism is given by oxidative chlorine release. So the interaction between microorganisms and *N*-halamines produces a halogen exchange reaction that causes cell death (Chen et al. 2007). A singular feature of this biocide is that its oxidative chlorine can be regenerated by new exposition to a sodium hypochlorite solution. These characteristics make *N*-halamine an excellent candidate to develop antimicrobial materials from cellulose (Sun and Sun 2003; Liu and Sun 2006, 2009).

In this context, several functional groups have been used to incorporate as *N*-halamine moieties into cellulose, *N*-halamine compounds with siloxane linkage groups (Fig. 3) are one of the most used methods for covalent bond or coating onto cotton fabrics. Siloxane *N*-halamine groups provide to materials antimicrobial activity against Gram-negative and Gram-positive bacteria (Liang et al. 2005, 2007; Barnes et al. 2006, 2007; Liu and Sun 2006, 2008). For example, polymers synthesized through a hydrosilylation reaction with polymetylhydrosiloxane were used to coat cellulose fibers (Chen et al. 2012a, b) and chemical bonding between the siloxane and the cellulose fiber was achieved by copolymerization with siloxane monomer (Kocer et al. 2011a, b), thus providing cellulose with antimicrobial activity against both Gram-negative and Gram-positive bacteria.

Siloxane groups are not the only functional group to graft or form covalent coats with *N*-halamine on cellulose. *N*-halamine with hydroxyl or epoxy group moieties can react with cellulosic materials through the formation of ether bonds, followed by activation using a NaClO solution. However, in these conditions grafting is difficult since the epoxy groups have relatively low activity toward cellulose. Nevertheless there are other alternatives such as the use of vinyl monomers containing amide bonds to induce the graft onto cellulose by free radical polymerization reactions (Liu

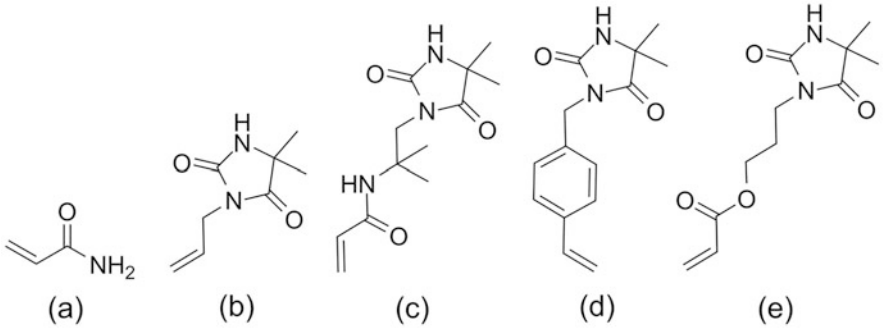

Fig. 4 Chemical structure of *N*-halamines functionalized with vinyl groups (**a**–**e**) for radical grafting on cellulose

and Sun 2006, 2009) or admicellar polymerization, which widen the application range of *N*-halamine compounds (Fig. 4 a–e). For example, the monomer 3--(4′vinylbenzyl)-5,5-dimethylhydantoin (Fig. 4d) was grafted on cellulosic fibers by admicellar polymerization using a cationic surfactant (Ren et al. 2008), the final material exhibited an excellent antibacterial activity (Ren et al. 2009; Cerkez et al. 2011, 2012; Ma et al. 2013).

Another technique used to provide cellulose with *N*-halamines antimicrobial activity is by the layer-by-layer deposition method which is achieved with no covalently bonding groups. In this method, precursors are typically water-soluble, avoiding the use of organic solvents. For instance, poly(2,2,6,6-tetramethyl-4-piperidylmethacrylate-co-trimethyl-2-methacryloxy-ethylammonium chloride) and poly(2,2,6,6- tetramethyl-4-piperidyl methacrylate-co-acrylic acid potassium salt) were used to coat on cellulose fibers by this method (Cerkez et al. 2011).

3.2 Quaternary Ammonium Salts

Nowadays, quaternary ammonium compounds are considered important antibacterial agents since they exhibit antibacterial activity against broad spectrum of bacteria and fungi (Gao and Cranston 2008; Murguía et al. 2008; Massi et al. 2009). The antibacterial activity of quaternary ammonium compounds is mainly attributed to two mechanisms of action: (1) an electrostatic interaction between the cationic charge of the quaternary ammonium with the anionic charge of the cell wall and (2) non-polar interactions and penetration of the quaternary ammonium hydrophobic moiety into the cell wall (CW). These interactions cause the formation of a complex surfactant with the CW, which interrupts the activity of proteins and influences key functions in the cell membrane and even in the bacterial DNA. Another important feature is that the increase in the alkyl chain length improves the antimicrobial activity of the quaternary ammonium compounds; however, if the

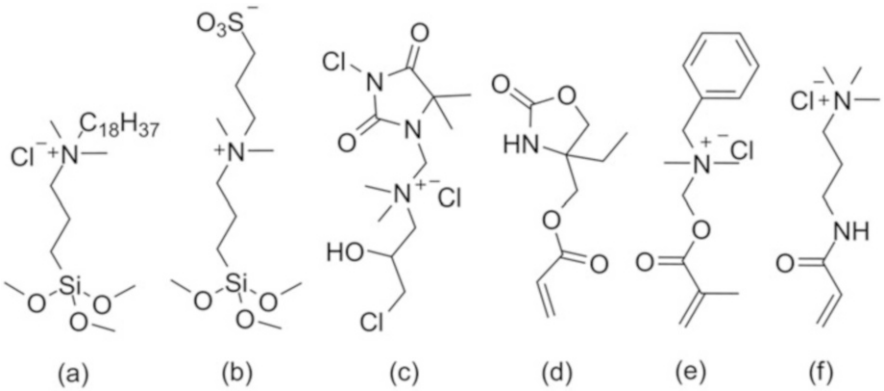

Fig. 5 Cellulose grafts with functionalized ammonium salts, alkoxysilanes (**a**–**b**), alkyl halides (**c**), and vinyls (**d**–**f**)

length is excessive, length may affect the antimicrobial activity due to the formation of micelle-like structures (Tiller et al. 2001; Gilbert and Moore 2005).

Quaternary ammonium compounds have been designed in a similar way to *N*-halamines compounds, groups such as siloxanes and alkoxysilanes are used to covalently bond quaternary ammonium salts to cellulose (Fig. 5). For example, DC-5700 (organosilicon quaternary salt) (Fig. 5a) and sulfopropylbetaine (Fig. 5b) containing reactive alkoxysilane groups were hydrolyzed to form silanol groups (Si-OH), which further reacted with the hydroxyl group (–OH) of cotton fibers and forming covalent bonds (Chen et al. 2011). The toxicological studies on the modified cotton indicated that these quaternary salts cannot be absorbed into the body by contact and the DC-5700 mean lethal dose (LD50) was 12.27 g $kg^{-1} \pm 0.116$ (Li et al. 2012).

3.3 Nanoparticles of Noble Metals and Metal Oxides

The performance of antibacterial NPs depends directly on the particle size and shape. A nanosized structuration renders the capability to translocate in cells and functional organelles, resulting in genotoxicity and cell death. In vitro studies conducted by exposure to NPs have shown that smaller particles and lower concentration can cause greater bactericidal effects (Sudha et al. 2018).

The use of compounds containing noble metals and metal oxide NPs is an adequate alternative for antibacterial materials due to the low corrosion rates and high biocompatibility (Christensen et al. 2010) as well as the correct mechanical properties (Shiraishi et al. 2009). Some metal oxide NPs have been discovered as natural antimicrobials and are incorporated in different nanomaterials, being the most interesting those that contain oxides as CoO, MnO, and Fe_2O_3, which have

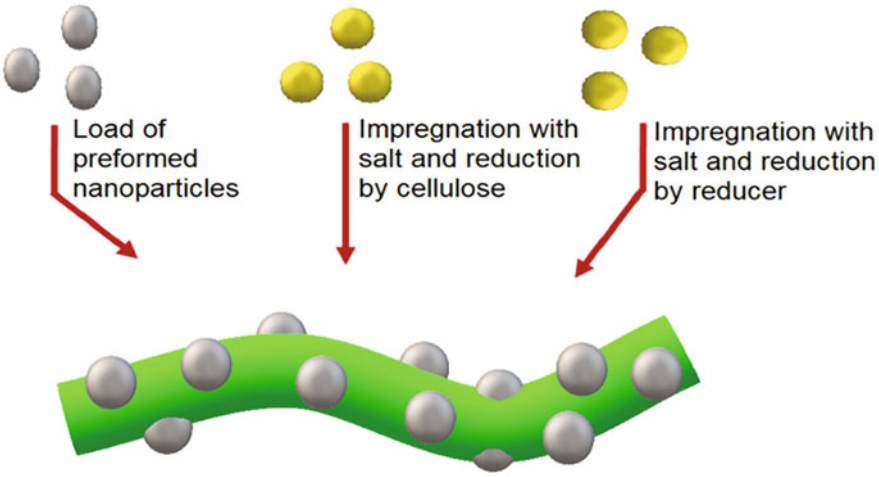

Fig. 6 Methodologies of load NPs on cellulose

shown an excellent antimicrobial activity (Dhineshbabu et al. 2014; Rajendran et al. 2014; Gouda et al. 2015). For example, ZrO_2 NPs is an antimicrobial material that has shown good washing durability and adherence after treatment with microwaves (Gouda and Keshk 2010; Gouda 2012). NPs obtained from metals such as Au, Ag, Pt, and Pd, also known as noble metal NPs, have been extensively investigated due to their unique belongings and applications in science, as they own remarkable biocidal properties when doping in different supports (Fig. 6).

In this context, BC is a common raw material in the production of composites as BC/Ag. Impregnation is a method to provide the BC with biocidal properties for its potential application in skin tissue repair. According to literature, for example, BC is immersed in a silver nitrate solution, followed by in situ metallation using a sodium borohydride solution to reduce the absorbed Ag^+ to Ag(0) NPs. As a result, the obtained BC exhibited strong antimicrobial activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* (Maneerung et al. 2008).

Even though cellulose is quite stable, new strategies are under development to improve the properties of derivated materials, one of which is the incorporation of NPs in the material. In some cases, the modification of functional groups in cellulose is necessary to get a functional composite with NPs. Covalent and electrostatic binding are strategies to modify the cellulose chains (e.g., siloxane, amines, acyl chloride, and carboxylic acid, among others), the binders must have functional groups available to bind with NPs through electrostatic interactions or covalent bonds. In this regard, Fig. 7 shows the NPs loading in a functionalized cellulose with different chemical groups.

Another strategy to produce antimicrobial cellulose-based materials consists in the coordination of metal centers at the surface. For example, sulfadiazine moieties were used as ligands to obtain a coordination complex with Ag^+; the resulting Ag-sulfadiazine complex was used for the immobilization of antimicrobial cotton

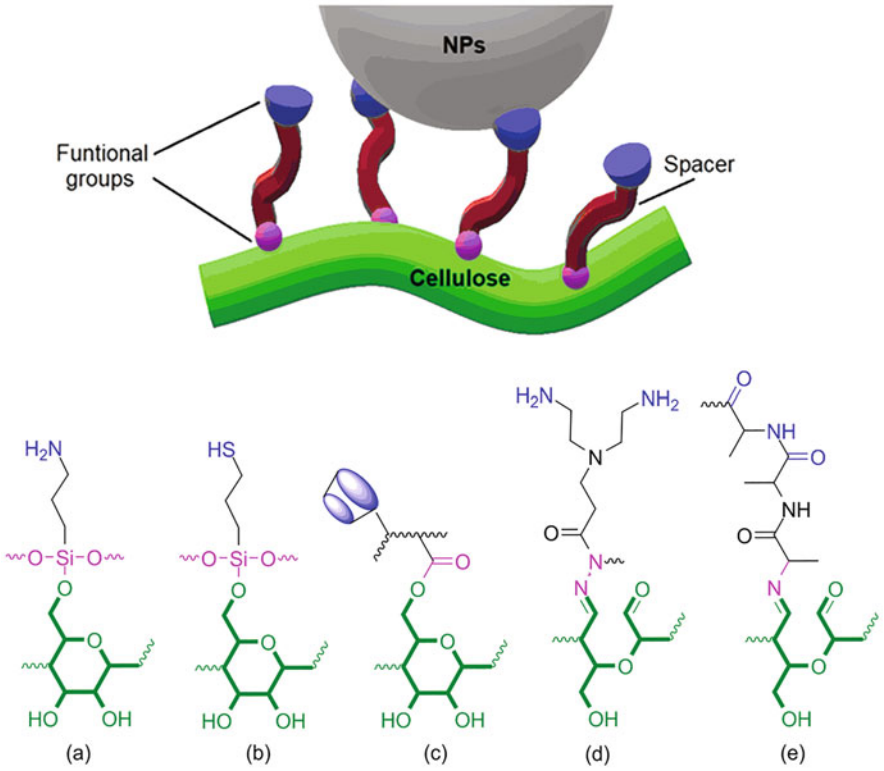

Fig. 7 Binding agents used to improve the load of NPs on cellulose

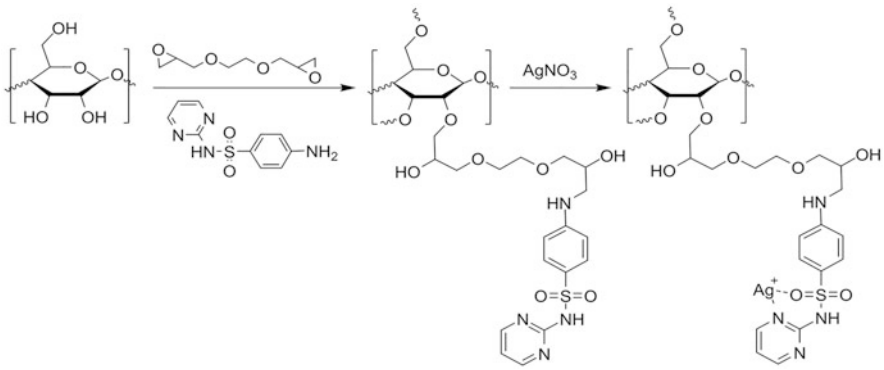

Fig. 8 Scheme synthesis of Ag-sulfadiazine coordination complex on cellulose

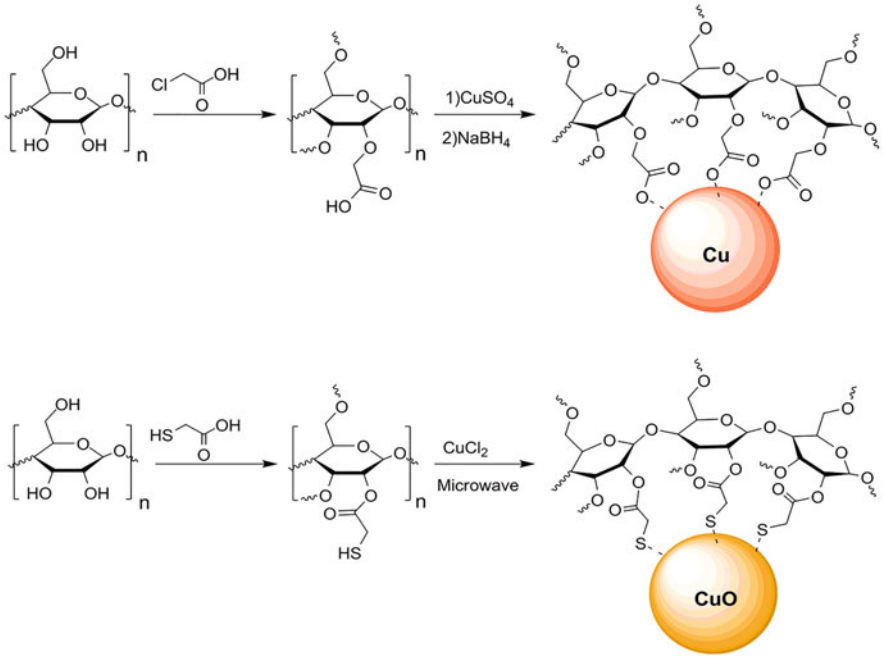

Fig. 9 Cu and CuO NPs complexed with carboxylate- and thiol-fragments on modified cotton via microwave irradiation (Gouda et al. 2015)

fabrics. The methodology is described in Fig. 8, ethylene glycol ether was used as a linking agent to bond the sulfadiazine moiety to the cellulose chain. After forming the Ag-sulfadiazine complex, the modified cotton fabrics showed a lasting antimicrobial activity after 50 wash cycles. Bioassays demonstrated that the modified cotton fabrics were biocompatible with mammalian cell lines. Also, this material may be easily reactivated with a $AgNO_3$ solution (Cao et al. 2013).

The binder not only improves the incorporation of NPs but also can stabilize them, as in the case of Cu NPs, which are loaded and stabilized by carboxylate groups to avoid metal oxidation. Also, the chemical groups integrated into cellulose allow the application of NPs nucleation methods such as microwaves irradiation as in the case of the incorporated thiol groups (Fig. 9).

ZnO is possibly the most studied inorganic compound and in the last years, ZnO NPs have got a resurgence because of its excellent antimicrobial properties and low toxicity to human cells (Shateri-Khalilabad and Yazdanshenas 2013; Bhuyan et al. 2015). ZnO NPs have additional advantages over other metal and metal oxide NPs, for example, comparing the properties of ZnO NPs with Ag NPs (i.e., UV protection, lack of staining, and costs) Zn is just standing out. However, the problems in the production of ZnO/cellulosic NPs are related to stability and antimicrobial performance. Therefore, to enhance the material stability and antimicrobial activity, cellulose must be pretreated or modified with binders.

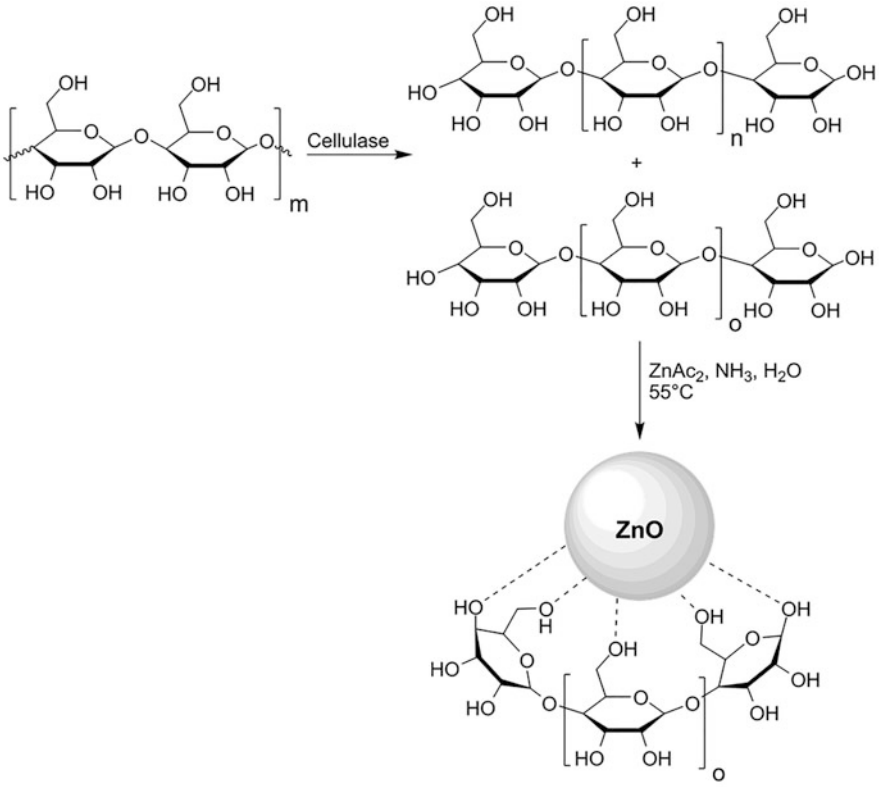

Fig. 10 ZnO NPs loading onto pretreated cellulose with cellulase enzyme (Perelshtein et al. 2012)

Polyvinyls are a type of ligands widely reported to stabilize ZnO NPs, some examples are poly-*N*-vinyl-2-pyrrolidone (PVP) (Selvam and Sundrarajan 2012), poly(allylamine hydrochloride) (Manna et al. 2013), polystyrene-block-poly(acrylic acid) copolymer (PS-b-PAA) (Çakir et al. 2012). On the other hand, natural polymers as chitosan (Perelshtein et al. 2013) and derivatives as carboxymethyl chitosan (El.shafei and Abou-Okeil 2011) are also common options in the stabilization of ZnO NPs, even natural plant extracts have been tried (Yuvakkumar et al. 2014). However, only some matrices improve antimicrobial durability (Manna et al. 2013).

The so-called cellulose pretreatment is an alternative way to improve the attachment of ZnO NPs in cellulose. When cellulose fibers are pretreated with ultrasonic irradiation and enzymes, hydroxyl groups are generated, these groups are involved during the nucleation process to yield ZnO NPs (Fig. 10). An increase in hydroxyl groups not only generates ultra-small ZnO NPs, but also promotes a uniform distribution along the cellulose fibers and an enhancement in the anchoring of the ZnO NPs. In this context, a study reported the obtention of cotton fibers loaded with ZnO NPs, which exhibited antimicrobial features (Petkova et al. 2014). In another work, a cellulosic/ZnO NPs based material was prepared by the solvent evaporation

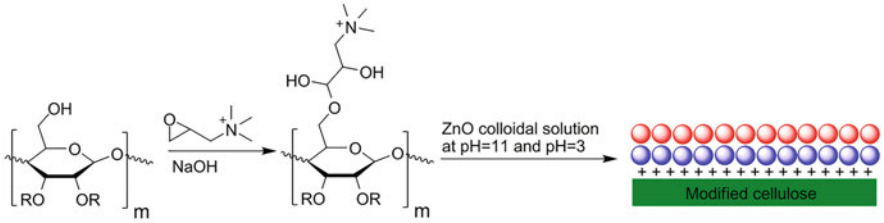

Fig. 11 ZnO loading via layer-by-layer deposition method onto cellulose functionalized with a quaternary ammonium salt

method. The obtained nanocomposites showed adequate properties as thermal stability and antimicrobial performance, regarding bacterial exposure, the maximum inhibition was achieved from the first 3 to 6 h after exposure. In general, cellulosic/ZnO NPs systems show well stability under aqueous environments, besides these materials may be designed with different shapes and sizes (Fu et al. 2015).

The layer-by-layer deposition is an option to modify cotton fabrics, for example, the endowing of cotton surface with an antimicrobial surface may be achieved by alternating layers of 2,3-epoxypropyl trimethylammonium chloride with layers of ZnO colloidal solutions, thus forming anionic/cationic ZnO NPs that after thermal treatment at 130 °C, the material showed antibacterial activity and reusability (Fig. 11) (Uğur et al. 2010).

Similarly, TiO_2 NPs are also widely used for manufacturing broad-spectrum antimicrobial cellulosic materials (Sato and Taya 2006). Also, TiO_2 NPs have photochemical properties under UV irradiation due to the formation of electron-hole pairs (Rincón and Pulgarin 2003). Also, TiO_2 NPs are reactive species that exhibit photochemical activity against microorganisms, viruses, and even cancer cells (Sunada et al. 1998; Nonami et al. 2004; Maneerat and Hayata 2006). In a study, TiO_2-coated antibacterial cotton fabrics, prepared by a sol–gel process in water, presented self-cleaning properties and were able to photocatalytic decomposition of dyes via a photodegradation mechanism (Wu et al. 2009). In this context of photoactivity, TiO_2 semi-spherical NPs (10 nm) were incorporated onto cotton to evaluate their antibacterial activity against different microorganisms under visible and black light as well as darkness to study the effect of light in the bacterial inhibition (Kangwansupamonkon et al. 2009).

3.4 Composites

Enhancing wound dressing of cellulose materials is also possible by incorporating macromolecules as collagen type I (Phisalaphong et al. 2008), alginate (Chiaoprakobkij et al. 2011), polyethylene glycol (PEG) (Cai and Kim 2010), or chitosan/lignosulfonate (Fig. 12) (Li and Peng 2015). The combination of cellulose with organic precursors preserves dermic compatibility, wettability, mechanical

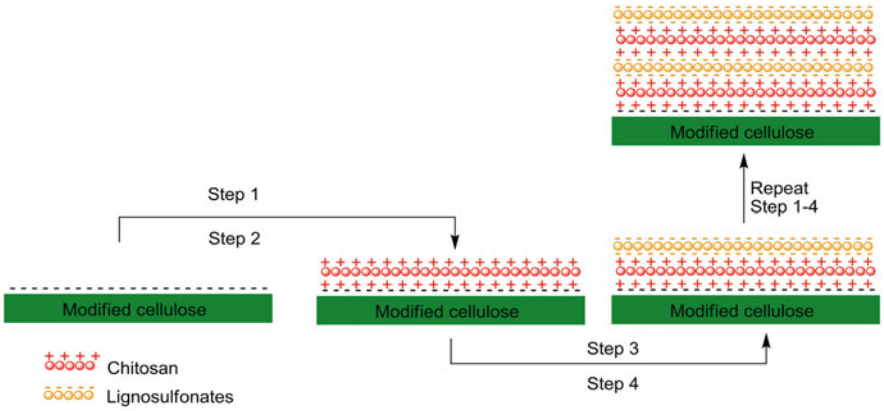

Fig. 12 Schematic representation of cellulose/lignosulfonates multilayer process on fiber surfaces (Li and Peng 2015)

strength, antifouling, and thermal stability (Chiaoprakobkij et al. 2011). In a study focused on skin tissue regeneration, cellulose–gelatin membranes were used as regeneration template (Chiaoprakobkij et al. 2011). The obtained material was combined with biocides such as benzalkonium chloride and vancomycin to develop functional antimicrobial properties. The addition of biocides was achieved by immersion of the composite in the drug solution followed by freeze-drying cycles (Wei et al. 2011).

Likewise, a composite of cellulose-chitosan-lignosulfonate was synthesized by layer-by-layer deposition via electrostatic interactions. Cellulose was oxidated by free radicals to form carboxylic groups then a layer of positively charged chitosan and negatively charged lignosulfonate was deposited as shown in Fig. 12. The result indicated an improvement in its antimicrobial activity against *Escherichia coli*, exhibiting the maximum activity when the chitosan was on the outer layer (Li and Peng 2015). In another example, a thermoresponsive microfilms composite of cellulose@nylon-6 was grafted with *N*-vinyl caprolactam by gamma-rays. The antimicrobial activity of this composite was provided by benzalkonium chloride and vancomycin loading. The biocide activity was assessed against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, exhibiting an excellent antimicrobial activity (Fig. 13). Further studies indicated that the loading of biocidal agents improved when the grafting degree increased, thus increasing the antimicrobial activity of the composite (Flores-Rojas et al. 2020).

3.5 Antimicrobial Enzymes and Peptides

Covalent immobilization of enzymes or peptides such as lysostaphin onto cellulose (Llorens et al. 2012) endows bioactivity against pathogenic bacteria like *Staphylococcus aureus* (Miao et al. 2011) or *Listeria monocytogenes* (Nguyen et al.

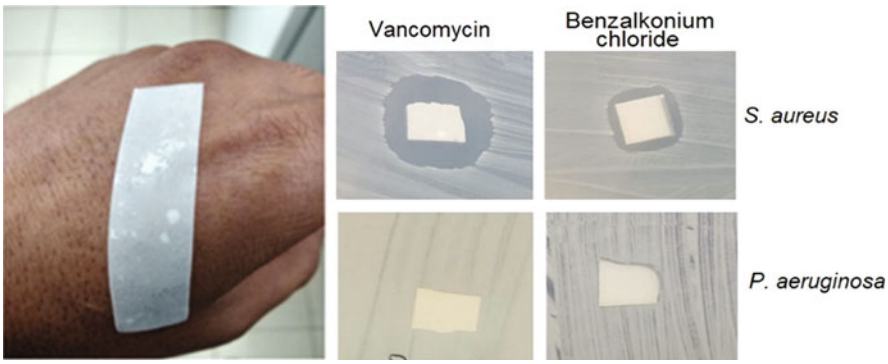

Fig. 13 Antimicrobial activity of cellulose@nylon-6 modified with *N*-vinyl caprolactam loaded with vancomycin and benzalkonium chloride

2008), the addition of natural molecules with bactericidal features allows the use of cellulose-based materials as potential candidates in the food industry as packing materials. Also, natural aminoglycoside antibiotics as gentamicin and RGDC peptides can be integrated into cellulosic materials for biomedical devices (Rouabhia et al. 2014).

Antimicrobial peptides are proteins isolated from natural sources, which despite their structure, show a cationic and amphiphilic behavior due to the hydroxyl, amine, and hydrophobic alkyl chains attached. Up to date, various models have been explored to describe the mechanism of action of peptides against bacteria (Matsuzaki 1999; Zasloff 2019). Cationic peptides are first attracted through electrostatic interactions to the bacterial surface, in a second step there is a lipid displacement that causes a disturbance in the membrane structure, and in some cases, the peptide enters into the target cell. In other cases, once the peptides reach the cytoplasmic membrane, they get attached to the cell, to finally form transmembrane pores. For instance, in a study, BC membranes functionalized with bacteriocin peptides by physical entrapment exhibited good antimicrobial activity against *Listeria monocytogenes*, a foodborne pathogen that causes more casualties than any other food pathogen (Malheiros et al. 2018).

4 Applications

4.1 Applications for Skin Tissue Repair

Cellulose outstanding biocompatibility and high water retention ability make it an excellent raw material for the manufacture of novel wound dressing materials for skin burns and chronic wounds. Moreover, cellulose works as a scaffold in the regeneration of tissues (Czaja et al. 2006; Siró and Plackett 2010). Traditionally,

most repairing materials have important characteristics such as the ability to absorb and retain exudate while in use, and non-adherence to wound due to exudate absorption followed by trauma when it is removed. A new generation of skin tissue repair materials exhibit good permeability and absorbance, also they can keep a humidity level that guarantees easy removal from the wound. However, they absorb exudate and high humidity around the wound and might contribute to the proliferation of pathogen microorganisms. In this context, cellulose-based antimicrobial materials have been endowed with antimicrobial properties, making them very promising materials in clinical applications, such as contact lenses, artificial vessels, wound dressing, cartilages, heart valves, artificial bones, among others.

Cellulose-based contact lenses have excellent oxygen permeability thus preventing hypoxia, where the most common complication is keratitis, a bacterium associated with ocular illness (Dart et al. 1991; Bourcier et al. 2003). Microorganisms involved in keratitis are *Staphylococcus aureus*, *Fusarium solani*, *Pseudomonas aeruginosa*, *coagulase-negative Staphylococci*, *Escherichia coli*, *Serratia marcescens*, *Candida albicans*, and *Acanthamoeba castellanii* (Green et al. 2008; Tu and Joslin 2010; Cerkez et al. 2011).

The load of drug in lens can provide both an eye bacterial infection and allergies treatment when drugs are maintained in an adequate concentration. For example, the loading of ciprofloxacin/γ-cyclodextrin into cellulose spawned a great prospect material for wound dressing in eye surgery, with non-adhesion properties, and antibacterial activity which inhibited growth or proliferation of bacteria on the lens surface and surrounding area, hence limiting the use of antibiotics eye drops or ameliorating in the case of eye burns symptoms (Cavicchioli et al. 2015).

4.2 Artificial Blood Vessels

Cellulose may help in reconstructive procedures associated with injuries, degenerative processes, or vascular diseases. Cellulose may be attached in the affected zone to stimulate cell growth. In this context, cellulosic composites obtained by grafting PEG onto cellulose exhibited an improved cellular adhesion. Additionally, these materials showed improved hydrophilicity since the water contact angle was reduced by PEG coat (da Silva et al. 2016). In another work, PEG-modified material was used in the adhesion of 3T3 fibroblast cells (Cai and Kim 2010). Overall, antibacterial cellulosic based biomaterials are plausible to be integrated into artificial blood vessels or heart valves.

4.3 Wound Dressing

As previously described, cellulose-based materials are excellent for wound dressing in preventing infections and helping to reduce local pain (Czaja et al. 2006). In this

context, silver/cellulose composites have been used for wound dressings due to the bactericide features of nano-Ag, likewise the use of materials containing Ag NPs has been widely reported in the inhibition of both Gram-positive and Gram-negative bacteria (Schluesener and Schluesener 2013; Li et al. 2019; Prasad 2014; Aziz et al. 2016, 2019). In this type of material, the cellulose acts as a stabilizer able to control the Ag nucleation process (Maneerung et al. 2008). Cellulose fabrics work as stabilizing agents because their porosity and hydrophilicity facilitate the growth of metal NPs (Eardley et al. 2012), these properties turn cellulose/Ag composites as prominent candidates for wound dressing and burn treatments.

5 Conclusion

In summary, cellulose is a natural polymer with the potential for the development of antimicrobial devices as well as wound healing systems. Engineering of pristine and modified cellulose structures have been extensively evaluated, the high biocompatibility and mechanical properties of derivative materials allow an easy adaptation and suggest its implementation in tissue repair and regeneration. The literature has backed cellulose as a highly versatile material, highlighting its potential for biomedical applications. Therefore, it can be assumed that cellulose will be a primordial biomaterial in the near future.

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References

Azizi Samir MAS, Alloin F, Dufresne A (2005) Review of recent research into cellulosic whiskers, their properties and their application in nanocomposite field. Biomacromolecules 6(2):612–626. https://doi.org/10.1021/bm0493685

Aziz N, Pandey R, Barman I, Prasad R (2016) Leveraging the attributes of *Mucor hiemalis*-derived silver nanoparticles for a synergistic broad-spectrum antimicrobial platform. Front Microbiol 7:1984. https://doi.org/10.3389/fmicb.2016.01984

Aziz N, Faraz M, Sherwani MA, Fatma T, Prasad R (2019) Illuminating the anticancerous efficacy of a new fungal chassis for silver nanoparticle synthesis. Front Chem 7:65. https://doi.org/10.3389/fchem.2019.00065

Barnes K, Liang J, Wu R, Worley SD, Lee J, Broughton RM, Huang TS (2006) Synthesis and antimicrobial applications of 5,5′-ethylenebis[5-methyl-3-(3-triethoxysilylpropyl)hydantoin]. Biomaterials 27(27):4825–4830. https://doi.org/10.1016/j.biomaterials.2006.05.023

Barnes K, Liang J, Worley S, Lee J, Broughton R, Huang T (2007) Modification of silica gel, cellulose, and polyurethane with a sterically hindered N-halamine moiety to produce antimicrobial activity. J Appl Polym Sci 105:2306–2313. https://doi.org/10.1002/app.26280

Bergstrom N, Horn SD, Smout RJ, Bender SA, Ferguson ML, Taler G, Sauer AC, Sharkey SS, Voss AC (2005) The national pressure ulcer long-term care study: outcomes of pressure ulcer treatments in long-term care. J Am Geriatr Soc 53(10):1721–1729. https://doi.org/10.1111/j.1532-5415.2005.53506.x

Berto GL, Arantes V (2019) Kinetic changes in cellulose properties during defibrillation into microfibrillated cellulose and cellulose nanofibrils by ultra-refining. Int J Biol Macromol 127:637–648. https://doi.org/10.1016/j.ijbiomac.2019.01.169

Bhuyan T, Mishra K, Khanuja M, Prasad R, Varma A (2015) Biosynthesis of zinc oxide nanoparticles from *Azadirachta indica* for antibacterial and photocatalytic applications. Mater Sci Semicond Process 32:55–61

Bourcier T, Thomas F, Borderie V, Chaumeil C, Laroche L (2003) Bacterial keratitis: predisposing factors, clinical and microbiological review of 300 cases. Br J Ophthalmol 87(7):834–838. https://doi.org/10.1136/bjo.87.7.834

Cai Z, Kim J (2010) Bacterial cellulose/poly(ethylene glycol) composite: characterization and first evaluation of biocompatibility. Cellulose 17(1):83–91. https://doi.org/10.1007/s10570-009-9362-5

Çakir BA, Budama L, Topel Ö, Hoda N (2012) Synthesis of ZnO nanoparticles using PS-b-PAA reverse micelle cores for UV protective, self-cleaning and antibacterial textile applications. Colloids Surf A Physicochem Eng Asp 414:132–139. https://doi.org/10.1016/j.colsurfa.2012.08.015

Cao Z, Sun X, Yao J, Sun Y (2013) Silver sulfadiazine-immobilized celluloses as biocompatible polymeric biocides. J Bioact Compat Polym 28(4):398–410. https://doi.org/10.1177/0883911513490340

Cavicchioli M, Corso CT, Coelho F, Mendes L, Soares CP, Souza FO, Franchi LP, Ticiana SO, Scarel-caminaga RM, Messaddeq Y, Lima SJ (2015) Characterization and cytotoxic, genotoxic and mutagenic evaluations of bacterial cellulose membranes incorporated with ciprofloxacin: a potential material for use as therapeutic contact lens. World J Pharm Pharm Sci 4(7):1626–1647

Cerkez I, Kocer H, Worley S, Broughton R, Huang T (2011) N-Halamine biocidal coatings via a layer-by-layer assembly technique. Langmuir 27:4091–4097. https://doi.org/10.1021/la104923x

Cerkez I, Kocer HB, Worley SD, Broughton RM, Huang TS (2012) Epoxide tethering of polymeric N-halamine moieties. Cellulose 19(3):959–966. https://doi.org/10.1007/s10570-012-9699-z

Chang C, Zhang L (2011) Cellulose-based hydrogels: present status and application prospects. Carbohydr Polym 84(1):40–53. https://doi.org/10.1016/j.carbpol.2010.12.023

Chen Z, Luo J, Sun Y (2007) Biocidal efficacy, biofilm-controlling function, and controlled release effect of chloromelamine-based bioresponsive fibrous materials. Biomaterials 28(9):1597–1609. https://doi.org/10.1016/j.biomaterials.2006.12.001

Chen S, Chen S, Jiang S, Xiong M, Luo J, Tang J, Ge Z (2011) Environmentally friendly antibacterial cotton textiles finished with siloxane sulfopropylbetaine. ACS Appl Mater Interfaces 3:1154–1162. https://doi.org/10.1021/am101275d

Chen S, Guo Y, Chen S, Ge Z, Yang H, Tang J (2012a) Fabrication of Cu/TiO 2 nanocomposite: toward an enhanced antibacterial performance in the absence of light. Mater Lett 83:154–157. https://doi.org/10.1016/j.matlet.2012.06.007

Chen Y, Zhong XS, Zhang Q (2012b) Synthesis of CO 2-philic polysiloxane with N-halamine side groups for biocidal coating on cotton. Ind Eng Chem Res 51(27):9260–9265. https://doi.org/10.1021/ie300378b

Chen S, Guo Y, Zhong H, Chen S, Li J, Ge Z, Tang J (2014) Synergistic antibacterial mechanism and coating application of copper/titanium dioxide nanoparticles. Chem Eng J 256:238–246. https://doi.org/10.1016/j.cej.2014.07.006

Chiaoprakobkij N, Sanchavanakit N, Subbalekha K, Pavasant P, Phisalaphong M (2011) Characterization and biocompatibility of bacterial cellulose/alginate composite sponges with human keratinocytes and gingival fibroblasts. Carbohydr Polym 85(3):548–553. https://doi.org/10.1016/j.carbpol.2011.03.011

Christensen FM, Johnston HJ, Stone V, Aitken RJ, Hankin S, Peters S, Aschberger K (2010) Nano-silver - feasibility and challenges for human health risk assessment based on open literature. Nanotoxicology 4(3):284–295. https://doi.org/10.3109/17435391003690549

Costa AFS, Almeida FCG, Vinhas GM, Sarubbo LA (2017) Production of bacterial cellulose by Gluconacetobacter hansenii using corn steep liquor as nutrient sources. Front Microbiol 8:1–12. https://doi.org/10.3389/fmicb.2017.02027

Cross CF, Cross CF, Bevan EJ (2006) Cellulose for medical applications: past, present, and future. Bioresources 1(2):270–280. https://doi.org/10.15376/biores.1.2.270-280

Czaja W, Krystynowicz A, Bielecki S, Brown RM (2006) Microbial cellulose - the natural power to heal wounds. Biomaterials 27(2):145–151. https://doi.org/10.1016/j.biomaterials.2005.07.035

da Silva R, Sierakowski MR, Bassani HP, Zawadzki SF, Pirich CL, Ono L, de Freitas RA (2016) Hydrophilicity improvement of mercerized bacterial cellulose films by polyethylene glycol graft. Int J Biol Macromol 86:599–605. https://doi.org/10.1016/j.ijbiomac.2016.01.115

Dart JKG, Stapleton F, Minassian D, Dart JKG (1991) Contact lenses and other risk factors in microbial keratitis. Lancet 338(8768):650–653. https://doi.org/10.1016/0140-6736(91)91231-I

Debzi EM, Chanzy H, Sugiyama J, Tekely P, Excoffier G (1991) The Iα →Iβ transformation of highly crystalline cellulose by annealing in various mediums. Macromolecules 24 (26):6816–6822. https://doi.org/10.1021/ma00026a002

Delezuk JAM, Ramírez-Herrera DE, Esteban-Fernández de Ávila B, Wang J (2017) Chitosan-based water-propelled micromotors with strong antibacterial activity. Nanoscale 9(6):2195–2200. https://doi.org/10.1039/c6nr09799e

Dhineshbabu NR, Manivasakan P, Karthik A, Rajendran V (2014) Hydrophobicity, flame retardancy and antibacterial properties of cotton fabrics functionalised with MgO/methyl silicate nanocomposites. RSC Adv 4(61):32161–32173. https://doi.org/10.1039/c4ra03348e

Eardley WGP, Watts SA, Clasper JC (2012) Extremity trauma, dressings, and wound infection: should every acute limb wound have a silver lining? Int J Low Extrem Wounds 11(3):201–212. https://doi.org/10.1177/1534734612457028

El.shafei A, Abou-Okeil A (2011) ZnO/carboxymethyl chitosan bionano-composite to impart antibacterial and UV protection for cotton fabric. Carbohydr Polym 83(2):920–925. https://doi.org/10.1016/j.carbpol.2010.08.083

Esa F, Tasirin SM, Rahman NA (2014) Overview of bacterial cellulose production and application. Agric Agric Sci Proc 2:113–119. https://doi.org/10.1016/j.aaspro.2014.11.017

Flores-Rojas GG, López-Saucedo F, Vázquez E, Hernández-Mecinas E, Huerta L, Cedillo G, Concheiro A, Alvarez-Lorenzo C, Bucio E (2020) Synthesis of polyamide-6@cellulose microfilms grafted with N-vinylcaprolactam using gamma-rays and loading of antimicrobial drugs. Cellulose 27(5):2785–2801. https://doi.org/10.1007/s10570-020-02986-1

Fu F, Li L, Liu L, Cai J, Zhang Y, Zhou J, Zhang L (2015) Construction of cellulose based ZnO nanocomposite films with antibacterial properties through one-step coagulation. ACS Appl Mater Interfaces 7(4):2597–2606. https://doi.org/10.1021/am507639b

Gao Y, Cranston R (2008) Recent advances in antimicrobial treatments of textiles. Text Res J 78 (1):60–72. https://doi.org/10.1177/0040517507082332

Gilbert P, Moore LE (2005) Cationic antiseptics: diversity of action under a common epithet. J Appl Microbiol 99(4):703–715. https://doi.org/10.1111/j.1365-2672.2005.02664.x

Gouda M (2012) Nano-zirconium oxide and nano-silver oxide/cotton gauze fabrics for antimicrobial and wound healing acceleration. J Ind Text 41(3):222–240. https://doi.org/10.1177/1528083711414960

Gouda M, Keshk SMAS (2010) Evaluation of multifunctional properties of cotton fabric based on metal/chitosan film. Carbohydr Polym 80(2):504–512. https://doi.org/10.1016/j.carbpol.2009.12.011

Gouda M, Aljaafari A, Al-Fayz Y, Boraie WE (2015) Preparation and characterization of some nanometal oxides using microwave technique and their application to cotton fabrics. J Nanomater 2015:586904. https://doi.org/10.1155/2015/586904

Green M, Apel A, Stapleton F (2008) Risk factors and causative organisms in microbial keratitis. Cornea 27(1):22–27. https://doi.org/10.1097/ICO.0b013e318156caf2

Heli B, Morales-Narváez E, Golmohammadi H, Ajji A, Merkoçi A (2016) Modulation of population density and size of silver nanoparticles embedded in bacterial cellulose: via ammonia exposure: visual detection of volatile compounds in a piece of plasmonic nanopaper. Nanoscale 8(15):7984–7991. https://doi.org/10.1039/c6nr00537c

Horikawa Y, Sugiyama J (2009) Localization of crystalline allomorphs in cellulose microfibril. Biomacromolecules 10(8):2235–2239. https://doi.org/10.1021/bm900413k

Ishikawa A, Okano T, Sugiyama J (1997) Fine structure and tensile properties of ramie fibres in the crystalline form of cellulose I, II, IIII and IVI. Polymer 38(2):463–468. https://doi.org/10.1016/S0032-3861(96)00516-2

Jedvert K, Heinze T (2017) Cellulose modification and shaping - a review. J Polym Eng 37 (9):845–860. https://doi.org/10.1515/polyeng-2016-0272

Jeong SI, Lee SE, Yang H, Jin YH, Park CS, Park YS (2010) Toxicologic evaluation of bacterial synthesized cellulose in endothelial cells and animals. Mol Cell Toxicol 6(4):373–380. https://doi.org/10.1007/s13273-010-0049-7

Jiang S, Chen S, Chen S (2011) Novel antibacterial cotton textiles finished with siloxane sulfopropylbetaine. In: Fiber Society Spring 2011 Conference, pp 263–264

Kang YJ, Chun SJ, Lee SS, Kim BY, Kim JH, Chung H, Lee SY, Kim W (2012) All-solid-state flexible supercapacitors fabricated with bacterial nanocellulose papers, carbon nanotubes, and triblock-copolymer ion gels. ACS Nano 6(7):6400–6406. https://doi.org/10.1021/nn301971r

Kangwansupamonkon W, Lauruengtana V, Surassmo S, Ruktanonchai U (2009) Antibacterial effect of apatite-coated titanium dioxide for textiles applications. Nanomedicine 5 (2):240–249. https://doi.org/10.1016/j.nano.2008.09.004

Khatoon Z, McTiernan CD, Suuronen EJ, Mah TF, Alarcon EI (2018) Bacterial biofilm formation on implantable devices and approaches to its treatment and prevention. Heliyon 4(12):e01067. https://doi.org/10.1016/j.heliyon.2018.e01067

Kitkulnumchai Y, Ajavakom A, Sukwattanasinitt M (2008) Treatment of oxidized cellulose fabric with chitosan and its surface activity towards anionic reactive dyes. Cellulose 15(4):599–608. https://doi.org/10.1007/s10570-008-9214-8

Klemm D, Heublein B, Fink HP, Bohn A (2005) Cellulose: fascinating biopolymer and sustainable raw material. Angew Chem Int Ed 44(22):3358–3393. https://doi.org/10.1002/anie.200460587

Kocer HB, Cerkez I, Worley SD, Broughton RM, Huang TS (2011a) Polymeric antimicrobial N-halamine epoxides. ACS Appl Mater Interfaces 3(8):2845–2850. https://doi.org/10.1021/am200351w

Kocer HB, Worley SD, Broughton RM, Huang TS (2011b) A novel N-halamine acrylamide monomer and its copolymers for antimicrobial coatings. React Funct Polym 71(5):561–568. https://doi.org/10.1016/j.reactfunctpolym.2011.02.002

Li H, Peng L (2015) Antimicrobial and antioxidant surface modification of cellulose fibers using layer-by-layer deposition of chitosan and lignosulfonates. Carbohydr Polym 124:35–42. https://doi.org/10.1016/j.carbpol.2015.01.071

Li J, Zhang Q, Wang Y, Zhang W, Li T (2012) Synthesis and properties of organosilicon quaternary salts surfactants. J Surfactant Deterg 15(3):339–344. https://doi.org/10.1007/s11743-011-1306-z

Li Y, Jiang H, Zheng W, Gong N, Chen L, Jiang X, Yang G (2019) Correction: Bacterial cellulose–hyaluronan nanocomposite biomaterials as wound dressings for severe skin injury repair. J Mater Chem B 7(11):1962. https://doi.org/10.1039/C9TB90027F

Liang J, Wu R, Huang TS, Worley SD (2005) Polymerization of a hydantoinylsiloxane on particles of silicon dioxide to produce a biocidal sand. J Appl Polym Sci 97(3):1161–1166. https://doi.org/10.1002/app.21814

Liang J, Barnes K, Akdag A, Worley SD, Lee J, Broughton RM, Huang TS (2007) Improved antimicrobial siloxane. Ind Eng Chem Res 46(7):1861–1866. https://doi.org/10.1021/ie061583+

Lin YK, Chen KH, Ou KL, Liu M (2011) Effects of different extracellular matrices and growth factor immobilization on biodegradability and biocompatibility of macroporous bacterial cellulose. J Bioact Compat Polym 26(5):508–518. https://doi.org/10.1177/0883911511415390
Liu S, Sun G (2006) Durable and regenerable biocidal polymers: acyclic N-halamine cotton cellulose. Ind Eng Chem Res 45(19):6477–6482. https://doi.org/10.1021/ie060253m
Liu S, Sun G (2008) Biocidal acyclic halamine polymers: conversion of acrylamide-grafted-cotton to acyclic halamine. J Appl Polym Sci 108(6):3480–3486. https://doi.org/10.1002/app.27958
Liu S, Sun G (2009) New refreshable N-halamine polymeric biocides: N-chlorination of acyclic amide grafted cellulose. Ind Eng Chem Res 48(2):613–618. https://doi.org/10.1021/ie8007902
Llorens A, Lloret E, Picouet PA, Trbojevich R, Fernandez A (2012) Metallic-based micro and nanocomposites in food contact materials and active food packaging. Trends Food Sci Technol 24(1):19–29. https://doi.org/10.1016/j.tifs.2011.10.001
Ma K, Liu Y, Xie Z, Li R, Jiang Z, Ren X, Huang TS (2013) Synthesis of novel N -halamine epoxide based on cyanuric acid and its application for antimicrobial finishing. Ind Eng Chem Res 52(22):7413–7418. https://doi.org/10.1021/ie400122h
Malheiros PS, Jozala AF, Pessoa A, Vila MMDC, Balcão VM, Franco BDGM (2018) Immobilization of antimicrobial peptides from Lactobacillus sakei subsp. sakei 2a in bacterial cellulose: structural and functional stabilization. Food Packag Shelf Life 17:25–29. https://doi.org/10.1016/j.fpsl.2018.05.001
Maneerat C, Hayata Y (2006) Antifungal activity of TiO2 photocatalysis against Penicillium expansum in vitro and in fruit tests. Int J Food Microbiol 107(2):99–103. https://doi.org/10.1016/j.ijfoodmicro.2005.08.018
Maneerung T, Tokura S, Rujiravanit R (2008) Impregnation of silver nanoparticles into bacterial cellulose for antimicrobial wound dressing. Carbohydr Polym 72(1):43–51. https://doi.org/10.1016/j.carbpol.2007.07.025
Manna J, Begum G, Kumar KP, Misra S, Rana RK (2013) Enabling antibacterial coating via bioinspired mineralization of nanostructured ZnO on fabrics under mild conditions. ACS Appl Mater Interfaces 5(10):4457–4463. https://doi.org/10.1021/am400933n
Massi L, Guittard F, Levy R, Géribaldi S (2009) Enhanced activity of fluorinated quaternary ammonium surfactants against Pseudomonas aeruginosa. Eur J Med Chem 44(4):1615–1622. https://doi.org/10.1016/j.ejmech.2008.07.032
Matsuzaki K (1999) Why and how are peptide-lipid interactions utilized for self-defense? Magainins and tachyplesins as archetypes. Biochim Biophys Acta 1462(1–2):1–10. https://doi.org/10.1016/S0005-2736(99)00197-2
Miao J, Pangule RC, Paskaleva EE, Hwang EE, Kane RS, Linhardt RJ, Dordick JS (2011) Lysostaphin-functionalized cellulose fibers with antistaphylococcal activity for wound healing applications. Biomaterials 32(36):9557–9567. https://doi.org/10.1016/j.biomaterials.2011.08.080
Murguía MC, Machuca LM, Lurá MC, Cabrera MI, Grau RJ (2008) Synthesis and properties of novel antifungal gemini compounds derived from n-acetyl diethanolamines. J Surfactant Deterg 11(3):223–230. https://doi.org/10.1007/s11743-008-1076-4
Nguyen VT, Gidley MJ, Dykes GA (2008) Potential of a nisin-containing bacterial cellulose film to inhibit Listeria monocytogenes on processed meats. Food Microbiol 25(3):471–478. https://doi.org/10.1016/j.fm.2008.01.004
Nishiyama Y (2009) Structure and properties of the cellulose microfibril. J Wood Sci 55 (4):241–249. https://doi.org/10.1007/s10086-009-1029-1
Nonami T, Hase H, Funakoshi K (2004) Apatite-coated titanium dioxide photocatalyst for air purification. Catal Today 96(3):113–118. https://doi.org/10.1016/j.cattod.2004.06.112
O'Sullvian ACC (1997) Cellulose: the structure slowly unravels. Cellulose 4(3):173–207
Perelshtein I, Ruderman Y, Perkas N, Traeger K, Tzanov T, Beddow J, Joyce E, Mason TJ, Blanes M, Mollá K, Gedanken A (2012) Enzymatic pre-treatment as a means of enhancing the antibacterial activity and stability of ZnO nanoparticles sonochemically coated on cotton fabrics. J Mater Chem 22(21):10736–10742. https://doi.org/10.1039/c2jm31054f

Perelshtein I, Ruderman E, Perkas N, Tzanov T, Beddow J, Joyce E, Mason TJ, Blanes M, Mollá K, Patlolla A, Frenkel AI, Gedanken A (2013) Chitosan and chitosan-ZnO-based complex nanoparticles: Formation, characterization, and antibacterial activity. J Mater Chem B 1 (14):1968–1976. https://doi.org/10.1039/c3tb00555k

Petkova P, Francesko A, Fernandes MM, Mendoza E, Perelshtein I, Gedanken A, Tzanov T (2014) Sonochemical coating of textiles with hybrid ZnO/chitosan antimicrobial nanoparticles. ACS Appl Mater Interfaces 6(2):1164–1172. https://doi.org/10.1021/am404852d

Phisalaphong M, Suwanmajo T, Tammarate P (2008) Synthesis and characterization of bacterial cellulose/alginate blend membranes. J Appl Polym Sci 107(5):3419–3424. https://doi.org/10.1002/app.27411

Picheth GF, Pirich CL, Sierakowski MR, Woehl MA, Sakakibara CN, de Souza CF, Martin AA, da Silva R, de Freitas RA (2017) Bacterial cellulose in biomedical applications: a review. Int J Biol Macromol 104:97–106. https://doi.org/10.1016/j.ijbiomac.2017.05.171

Prasad R (2014) Synthesis of silver nanoparticles in photosynthetic plants. J Nanopart, Article ID: 963961. https://doi.org/10.1155/2014/963961

Rajendran V, Dhineshbabu NR, Kanna RR, Kaler KVIS (2014) Enhancement of thermal stability, flame retardancy, and antimicrobial properties of cotton fabrics functionalized by inorganic nanocomposites. Ind Eng Chem Res 53(50):19512–19524. https://doi.org/10.1021/ie502584m

Ren X, Kou L, Kocer HB, Zhu C, Worley SD, Broughton RM, Huang TS (2008) Antimicrobial coating of an N-halamine biocidal monomer on cotton fibers via admicellar polymerization. Colloids Surf A Physicochem Eng Asp 317(1–3):711–716. https://doi.org/10.1016/j.colsurfa.2007.12.007

Ren X, Akdag A, Kocer HB, Worley SD, Broughton RM, Huang TS (2009) N-Halamine-coated cotton for antimicrobial and detoxification applications. Carbohydr Polym 78(2):220–226. https://doi.org/10.1016/j.carbpol.2009.03.029

Rincón AG, Pulgarin C (2003) Photocatalytical inactivation of E. coli: effect of (continuous-intermittent) light intensity and of (suspended-fixed) TiO 2 concentration. Appl Catal B Environ 44(3):263–284. https://doi.org/10.1016/S0926-3373(03)00076-6

Rouabhia M, Asselin J, Tazi N, Messaddeq Y, Levinson D, Zhang Z (2014) Production of biocompatible and antimicrobial bacterial cellulose polymers functionalized by RGDC grafting groups and gentamicin. ACS Appl Mater Interfaces 6(3):1439–1446. https://doi.org/10.1021/am4027983

Sato T, Taya M (2006) Copper-aided photosterilization of microbial cells on TiO2 film under irradiation from a white light fluorescent lamp. Biochem Eng J 30(2):199–204. https://doi.org/10.1016/j.bej.2006.04.002

Schluesener JK, Schluesener HJ (2013) Nanosilver: application and novel aspects of toxicology. Arch Toxicol 87(4):569–576. https://doi.org/10.1007/s00204-012-1007-z

Selvam S, Sundrarajan M (2012) Functionalization of cotton fabric with PVP/ZnO nanoparticles for improved reactive dyeability and antibacterial activity. Carbohydr Polym 87(2):1419–1424. https://doi.org/10.1016/j.carbpol.2011.09.025

Shateri-Khalilabad M, Yazdanshenas ME (2013) Bifunctionalization of cotton textiles by ZnO nanostructures: antimicrobial activity and ultraviolet protection. Text Res J 83(10):993–1004. https://doi.org/10.1177/0040517512468812

Shiraishi K, Koseki H, Tsurumoto T, Baba K, Naito M, Nakayama K, Shindo H (2009) Antibacterial metal implant with a TiO2-conferred photocatalytic bactericidal effect against Staphylococcus aureus. Surf Interface Anal 41(1):17–22. https://doi.org/10.1002/sia.2965

Shoda M, Sugano Y (2005) Recent advances in bacterial cellulose production. Biotechnol Bioprocess Eng 10:1–8. https://doi.org/10.1007/BF02931175

Siró I, Plackett D (2010) Microfibrillated cellulose and new nanocomposite materials: a review. Cellulose 17(3):459–494. https://doi.org/10.1007/s10570-010-9405-y

Skorb EV, Antonouskaya LI, Belyasova NA, Shchukin DG, Möhwald H, Sviridov DV (2008) Antibacterial activity of thin-film photocatalysts based on metal-modified TiO2 and TiO2: In2O3 nanocomposite. Appl Catal B Environ 84(1–2):94–99. https://doi.org/10.1016/j.apcatb.2008.03.007

Sudha PN, Sangeetha K, Vijayalakshmi K, Barhoum A (2018) Nanomaterials history, classification, unique properties, production and market. Emerg Appl Nanopart Arch Nanostruct Curr Prospects Future Trends 2018:341–384. https://doi.org/10.1016/B978-0-323-51254-1.00012-9

Sun Y, Sun G (2002) Synthesis, characterization, and antibacterial activities of novel N-halamine polymer beads prepared by suspension copolymerization. Macromolecules 35(23):8909–8912. https://doi.org/10.1021/ma020691e

Sun Y, Sun G (2003) Novel refreshable N-halamine polymeric biocides: Grafting hydantoin-containing monomers onto high performance fibers by a continuous process. J Appl Polym Sci 88(4):1032–1039. https://doi.org/10.1002/app.11772

Sunada K, Kikuchi Y, Hashimoto K, Fujishima A (1998) Bactericidal and detoxification effects of TiO2 thin film photocatalysts. Environ Sci Technol 32(5):726–728. https://doi.org/10.1021/es970860o

Tavakolian M, Jafari SM, Van De Ven TGM (2020) A review on surface - functionalized cellulosic nanostructures as biocompatible antibacterial materials. Nano Micro Lett. https://doi.org/10.1007/s40820-020-0408-4.

Tayeb AH, Amini E, Ghasemi S, Tajvidi M (2018) Cellulose nanomaterials-binding properties and applications: a review. Molecules 23(10):1–24. https://doi.org/10.3390/molecules23102684

Tiller JC, Liao CJ, Lewis K, Klibanov AM (2001) Designing surfaces that kill bacteria on contact. Proc Natl Acad Sci U S A 98(11):5981–5985. https://doi.org/10.1073/pnas.111143098

Tu EY, Joslin CE (2010) Recent outbreaks of atypical contact lens-related keratitis: what have we learned? Am J Ophthalmol 150(5):602–608. https://doi.org/10.1016/j.ajo.2010.06.045

Uğur ŞS, Sarıışık M, Aktaş AH, Uçar MÇ, Erden E (2010) Modifying of cotton fabric surface with nano-ZnO multilayer films by layer-by-layer deposition method. Nanoscale Res Lett 5 (7):1204–1210. https://doi.org/10.1007/s11671-010-9627-9

Vasconcelos NF, Feitosa JPA, da Gama FMP, Morais JPS, Andrade FK, de Souza Filho M, de Rosa MF (2017) Bacterial cellulose nanocrystals produced under different hydrolysis conditions: properties and morphological features. Carbohydr Polym 155:425–431. https://doi.org/10.1016/j.carbpol.2016.08.090

Wang Z-L, Jia Y-Y, Shi Y, Cong D-L, Chen Y-Y, Jia S-R, Zhou Y-L (2009) Research on characterization and biocompatibility of nano-bacterial cellulose membrane. Gaodeng Xuexiao Huaxue Xuebao 30:1553–1558

Watanabe A, Morita S, Ozaki Y (2006) Study on temperature-dependent changes in hydrogen bonds in cellulose Iβ by infrared spectroscopy with perturbation-correlation moving-window two-dimensional correlation spectroscopy. Biomacromolecules 7(11):3164–3170. https://doi.org/10.1021/bm0603591

Wei B, Yang G, Hong F (2011) Preparation and evaluation of a kind of bacterial cellulose dry films with antibacterial properties. Carbohydr Polym 84(1):533–538. https://doi.org/10.1016/j.carbpol.2010.12.017

Wu D, Long M, Zhou J, Cai W, Zhu X, Chen C, Wu Y (2009) Synthesis and characterization of self-cleaning cotton fabrics modified by TiO2 through a facile approach. Surf Coat Technol 203 (24):3728–3733. https://doi.org/10.1016/j.surfcoat.2009.06.008

Yamamoto H, Horii F (1993) CPMAS carbon-13 NMR analysis of the crystal transformation induced for Valonia cellulose by annealing at high temperatures. Macromolecules 26 (6):1313–1317. https://doi.org/10.1021/ma00058a020

Yuvakkumar R, Suresh J, Nathanael AJ, Sundrarajan M, Hong SI (2014) Novel green synthetic strategy to prepare ZnO nanocrystals using rambutan (Nephelium lappaceum L.) peel extract and its antibacterial applications. Mater Sci Eng C 41:17–27. https://doi.org/10.1016/j.msec.2014.04.025

Yuyu S, Gang S (2002) Synthesis and antibacterial activities of novel N-halamine polymer beads prepared by suspension copolymerization. Macromolecules 35(23):8909–8912

Zasloff M (2019) Antimicrobial peptides of multicellular organisms: my perspective. Adv Exp Med Biol 1117(January):3–6. https://doi.org/10.1007/978-981-13-3588-4_1

Zhijiang C, Guang Y (2011) Bacterial cellulose/collagen composite: characterization and first evaluation of cytocompatibility. J Appl Polym Sci 120(5):2938–2944. https://doi.org/10.1002/app.33318

Zhijiang C, Chengwei H, Guang Y (2012) Poly(3-hydroxubutyrate-co-4-hydroxubutyrate)/bacterial cellulose composite porous scaffold: preparation, characterization and biocompatibility evaluation. Carbohydr Polym 87(2):1073–1080. https://doi.org/10.1016/j.carbpol.2011.08.037

Zhu JY, Zhuang XS (2012) Conceptual net energy output for biofuel production from lignocellulosic biomass through biorefining. Prog Energy Combust Sci 38(4):583–598. https://doi.org/10.1016/j.pecs.2012.03.007

Zhu JY, Pan X, Zalesny RS (2010) Pretreatment of woody biomass for biofuel production: energy efficiency, technologies, and recalcitrance. Appl Microbiol Biotechnol 87(3):847–857. https://doi.org/10.1007/s00253-010-2654-8

Polymerized Ionic Liquids as Antimicrobial Materials

Hamidreza Bagheri, Ali Mohebbi, Zahra Jayhani, and Mina Naderi

Abstract Ionic liquids (ILs) are salts composed of a large organic or inorganic cation in which an alkyl chain is replaced or inorganic or organic anions. Because of unique ILs properties, they have attracted significant attention from ecologists, medical scientists, and biochemists. Controlling the toxicity of ionic liquids by combining them with various substances is another important factor that has been investigated to make them better and easier to use in pharmaceutical applications. Therefore, the novel design and control of the molecular structure of these compounds can assist their antibacterial applications.

We reviewed antibacterial properties of ionic liquids derivatives including polymeric ionic liquids in pharmaceutical and medicine fields. ILs as drug formulation components in drug synthesis, their biological activities, and their possible applications in drug delivery systems were discussed. It was also discussed polymeric ionic liquids have higher antibacterial properties than conventional ionic liquids. The role of different factors including alkyl chain length and charge density, which affects the antibacterial properties of ionic liquids derivatives was scrutinized.

Keywords Antibacterial · Biological · Drug · Green solvent · Ionic liquid · Synthesis

1 Introduction

A solvent is a substance (usually a liquid) that dissolves something else and we use solvents for all kinds of things like cleaning products, chemical reactions, and so on. However, many solvents are hazardous and toxic. Green chemistry is employed to the design or creation of chemical processes and products with less dangerous

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substances (Ghalandari et al. 2020; Capello et al. 2007). This new chemistry branch looks for an alternative a new solvent with less harmful to the environment and human health to protect the ecosystem from hazardous conventional solvents (Bagheri et al. 2019a; Bagheri and Ghader 2017). Green chemistry basic principle is the design of processes to decrease waste production, decreasing harmful chemicals raw materials, and increasing the usage of more environmentally safe solvents. Supercritical fluids (SCF), ionic liquids (ILs), and water are known as green solvent (Bagheri et al. 2019b; Ivanković et al. 2017; McDowell and Bazan 2017). Many benefits are repeated about ionic liquids and supercritical fluids as green solvents to develop new processes. A supercritical fluid is a fluid state that its pressure and temperature is higher than its critical values and its properties is like liquid-like and gas-like (Bagheri et al. 2019c; Zhao et al. 2005). Two beneficial fluids, which are applied as supercritical fluid, are water and carbon dioxide (CO_2). CO_2 has moderate critical temperature and pressure, low cost, availability, and non-toxicity. However, supercritical water is highly corrosive. Due to the unique properties of supercritical fluids, they can be used instead of organic solvents in material processing and chemical reactions (Bagheri et al. 2018).

Wilkes and Zaworotko (1992) reported a kind of room-temperature liquid salts that is stable on air and moisture in 1992, for the first time. This type of liquid was named as "Ionic Liquid (IL)." Ionic liquids (ILs) are described as revolution in material science. Ionic liquids as a new class of solvent are unique topic from three decades ago and the number of published documents has grown rapidly (Aslanov 2011). These liquids have special properties like high thermal and chemical stability, low vapor pressure, good ionic and electrical conductivity, non-flammability, wide electrochemical range, and low melting point. The bonding between the two constituents of this substance is weak due to a difference in size between their anion and cation; therefore, they are liquid at $T < 100$ °C and have adjustable properties like solubility that can be changed by selecting appropriate constituent ions (Florio et al. 2019). ILs are low melting point organic salts, which causes to be liquids phase at ambient temperature. The thermal decomposition temperature of IL is in order of 474 K and their boiling points are not detectable. Furthermore, ILs specific gravities are in the range of 1.1–1.6; subsequently, they are heavier than water and useful in two-phase extraction (Somers et al. 2013). ILs can be composed of a large number of anions and cations. In most cases, there is a great inconformity in the size of ionic and at least one ion has a high asymmetry degree and weakly coordinating anions that this property causes low melting point. The ILs properties depend on the size and nature of both their anion and cation parts. Subsequently, by selecting of favorite anions and cations, many ILs are designed for various applications (Zec et al. 2018; Rogers and Seddon 2003). ILs have other scientific properties like outstanding thermal stability, organic and inorganic compounds, satisfactory dissolution properties with water, wide electrochemical windows, tunable viscosity, high ionic conductivity, and highly polar and no-coordinating (Marsousi et al. 2019; Bagheri and Mohebbi 2017; Sheikhi-Kouhsar et al. 2015; Welton 1999). The general properties of ILs and examples of anions and cations usually used in ionic liquids are given in Tables 1 and 2, respectively.

Table 1 Properties of ionic liquids

Property	Anion and or cation quite large
Liquid range	>200 °C
Freezing point	<100 °C
Viscosity	<100 cp
Thermal stability	High
Dielectric constant	<30
Molar conductivity	<10 Scm^2 mol^{-1}
Vapor pressure	Negligible
Specific conductivity	<10 m Scm^{-1}
Polarity	Mild

Modified after Somers et al. (2013)

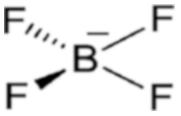
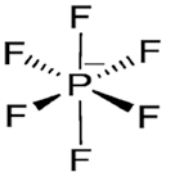
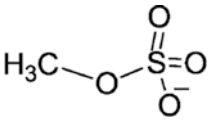
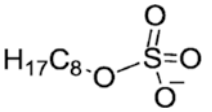
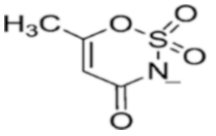
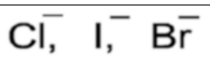
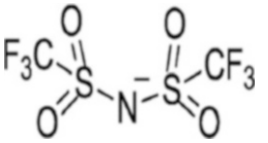
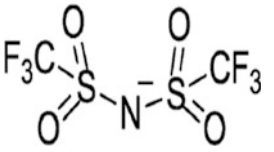
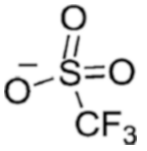
Further investigations have indicated that ILs are very effective in electrochemistry (MacFarlane et al. 2007), biomass conversion (Passos et al. 2014), catalysis and chemical synthesis, fuel processing and production, development of liquid crystal (Coleman et al. 2012), biotransformation (Dominguez de Maria 2008), biotechnology (Lee et al. 2007), and many other areas (Smiglak et al. 2014; Welton 1999). ILs have unique and tunable properties, therefore, these solvents can be used in novel valuable topics like medicine, biomedical, and life sciences applications and effective drugs referring to ILs considered for approval by food and drug administration (FDA) (Deetlefs et al. 2016; Ferraz et al. 2011; Zhang et al. 2009). Research acting in the ionic liquids topic has reached a surprising level with a huge studies number (see Fig. 1). The publications number and its increasing trend indicate the main role of ILs in the field of life-science like proteomics and genomics, which have critical influence in medicine and pharmaceutical development.

The main purpose of this chapter is to describe the attention of many researchers in biological, medical, and chemical fields for progress in pharmaceutical using ILs. Consequently, we investigate the application of ILs applying in modern pharmaceutical industry. Moreover, our purpose is to discuss polymerized ILs as antimicrobial materials. Repeated and indiscriminate employment of substances like antibiotics has caused to pathogenic bacteria resistance, especially in hospitals. Engineers thus, by manipulation of the alkyl chain and placement of the appropriate matrix (Polymers, Nanoscaffolds, and so on) (Mecerreyes 2011) or manipulating the anionic part of these substances (such as ampicillin) (Ferraz et al. 2014), have developed substances that, by testing on microorganisms, are trying to detect their toxicity and eventually use them in medicine (Docherty and Kulpa Jr 2005).

2 Application of Ionic Liquids in Pharmaceutical Field

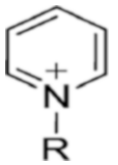
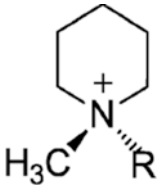
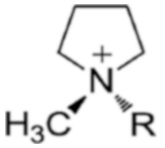
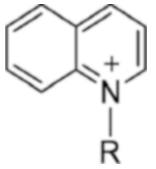
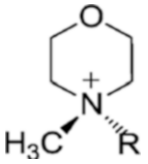
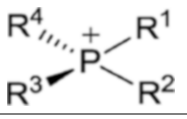
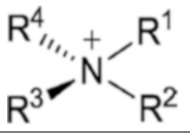
In general, there are four early phases in bacterial infection: the first phase is bacterial binding to host cells, the second phase is proliferation and formation of the colony, the third phase is invasion of host tissue, and the final phase is the destruction of host

Table 2 Some of anions and cations usually employed in ILs

Anion	Typical abbreviation	Structure
Tetrafluoroborate	BF_4	
Hexafluorophosphate	PF_6	
Methylsulfate	$MeSO_4$	
Octylsulfate	C_8SO_4	
Acesulfamate	Ace	
Halides	–	
Bis((trifluoromethane)sulfonyl)amide	NTF_2	
Dicyanamide	DCA	
Trifluoromethanesulfonate	TfO	

(continued)

Table 2 (continued)

Cation	Typical abbreviation	Structure
Imidazolium	MIM	
Pyridinium	PY	
Piperidinium	PP13	
Pyrrolidinium	P11	
Quinuclidine	Qu	
Morpholinium	MO	
Quaternary phosphonium	–	
Quaternary ammonium	–	

Modified after Egorova et al. (2017)

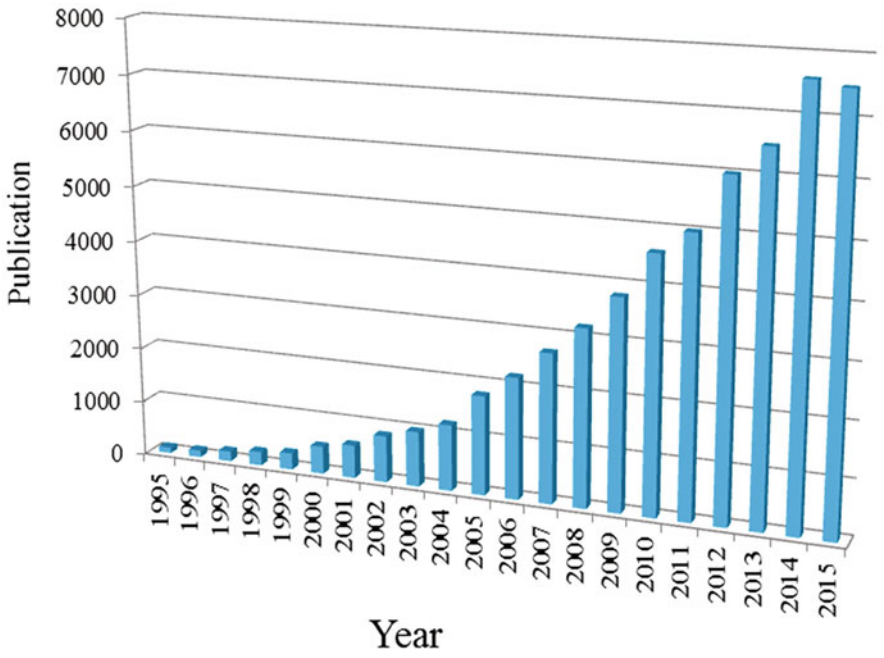


Fig. 1 Number of publications on the subject of ionic liquids. Modified after Egorova et al. (2017)

cells by toxins. Researchers by manipulating cations or anions of ionic substances are trying to design them in a way so that they can disrupt one or more of the mentioned phases; although, due to the rate of proliferation and colonization of microorganisms, it is better for the mentioned substance to have the ability to destroy colonies or at least disrupt their ability to reproduce. It is still unclear what is the reason for antibacterial and inhibitory effects of ionic liquids or to predict whether the reason for these effects is due to the type of bacteria (Gram negative or Gram positive) because the results for all species of a single class of bacteria were not the same (Docherty and Kulpa Jr 2005). Studies have shown that cationic groups play a key role because of their ability for electrostatic/lipophilic interactions with microorganism cell walls (Florio et al. 2019). In fact, polar groups' chemical composition and structure in the hydrophilic half of ILs could have a significant impact on their antimicrobial activity (Ferraz et al. 2014; Docherty and Kulpa Jr 2005). Although not yet proven, the antibacterial and toxic effects of ionic liquids are mainly driven by the alkyl branch by affecting the integrity of biological membrane (Florio et al. 2019) and the hydrophobicity of the cations, since there is an increase in the inhibition of growth with longer length alkyl chain (C_nH_{2n+1}) for all

microorganisms, the effect of toxic may be because of a common cellular structure (Docherty and Kulpa Jr 2005) and anions have an auxiliary role in modulating ionic liquids' activity such as their hydrophobicity (Docherty and Kulpa Jr 2005; Zhang et al. 2019). Consequently, we continue to explore some of the most conventional cations in creating ionic liquids and their combination with different anions and then we examine several anions.

2.1 Ionic Liquid Biological Activity

Ionic liquids as drug delivery, complementary components, and drug systems in the synthesis of drug can be used in pharmaceutical applications. H_2O is important for all conditions of living. Consequently, the solubility of IL in water and interaction between IL and water are main factors to determine the biological and environmental activities of IL. Most ILs, but not highly hydrophobic ILs, include some water. Furthermore, ILs can adsorb water from humid ambient. Moreover, ILs biological activity is depending on ILs hydration state. One of the drug tendencies in a salt is a usual method to enhance drug solubility; consequently, due to ILs are liquid salts, using of them leads to increasing ILs bioavailability (Egorova et al. 2017; Kurnia et al. 2014). Among ILs with several cations, the ionic liquids water solubility is impressed by the IL aromaticity and IL cation size and it decreases as follows: imidazolium > pyrrolidinium > pyridinium > piperidinium (Egorova et al. 2017). Some cations like pyridinium, imidazolium, ammonium, piperidinium, and pyrrolidinium can inhibit the activity of pathogenic and nonpathogenic fungi and bacteria (Elshaarawy et al. 2016; Papaiconomou et al. 2010; Dominguez de Maria 2008). In biological activity field, ILs can be used as anticancer agents. The ILs cytotoxicity depends on ILs structure and widely of varies, in the range of micromolar to millimolar. For example, pyridinium and imidazolium are more cytotoxicity than cholinium ILs. Once the ionic liquids toxic activity has become obvious, investigations on possible ILs using as anticancer agents have started. The main driving force of study on ILs anticancer agents is ILs high tunability (Egorova et al. 2017).

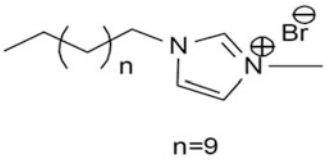
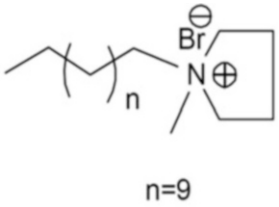
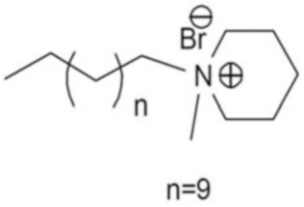
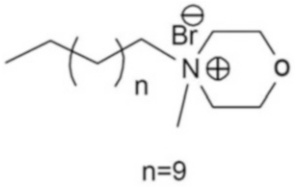
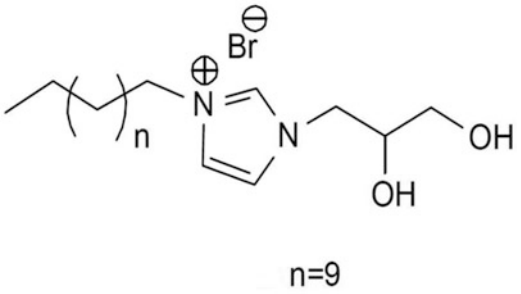
Studies have showed that the antibacterial effects of ionic liquids containing pyridinium are driven by alkyl branches and cation hydrophobicity (Docherty and Kulpa Jr 2005). This trend increases with increase in c-1alkyl chain (McCrary et al. 2013; Pernak et al. 2004). This process is applied to numerous bacteria like *Vibrio ficheri*, which inhibits the breathing of the organism; *Coccus* representing the Gram-positive bacterium and *yeast* representing Gram-negative bacterium; *B. subtilis*, which is a Gram-positive aerobic bacterium and *Staphylococcus aureus*, which is an anaerobic bacterium; *E. coli,* which is an anaerobic Gram-negative bacteria and *P. fluorescens*, which is an anaerobic Gram-negative bacteria were tested and the results confirmed the increase in toxicity; however, each of these bacteria received a different effect amount. For example, all ionic liquids were inhibitor of *B. subtilis. E. coli,* and *P. fluorescens* were dramatically affected or

S. aureus, *Coccus,* and *S. cerevisiae*, which is yeast, received the least impact. One way that researchers have been working to add toxicity and antibacterial to ionic liquids is to change the alkyl chain length or replace it with different groups. The results of methyl group substitution experiments around the pyridinium ring in anionic series Bromi and Dicyanamide ($(CN_2)_2$)-indicate the increased toxicity of these substances for *V. ficheri* bacteria. The toxicity of cation pyridinium also increases with the addition of methyl branches, for example,1-butyl-3,5-dimethyl pyridinium is more toxic than 1-butyl-3-methyl pyridinium and this substance is more toxic than 1-butyl pyridinium (Docherty and Kulpa Jr 2005; Pernak et al. 2004). ILs replacing butyl shows intense antimicrobial effects especially on more complex organisms such as *Daphnia magna*. Among the alternative groups around the pyridinium ring, the most effective colony formation inhibition was related to [Ompyr][Br] and the ionic liquids of the group Hexyl showed the least inhibitory effects. The antimicrobial effects of octyl substituents also depend on the microorganism studied. [Bpyr][Cl] substance attacks lipid glands in cytoplasmic membrane and destroys them by creating superoxide radicals (Docherty and Kulpa Jr 2005).

One of the mostly used cations in creating ionic liquids is imidazolium cation. Antibacterial effects of ionic liquids containing imidazolium alike pyridinium cation are directed by alkyl branches and cation hydrophobicity and with increase in c-1 Alkyl chain length this process also increases. For instance, the more alkyl chain length of the groups replacing *c-1* in 1-alkyl-3-methyl imidazolium increases, the more hydrophobic it gets, and shows more toxicity than *V. ficheri* bacteria. Almost, all ILs including imidazolium-based cations are inhibitors of the three bacteria, namely *P. fluorescens*, *E. coli*, and *B. subtilis*. Among the ionic liquids containing imidazolium, [Omim][Br] substance has the most effective inhibition of colony formation against bacteria *Coccus*, *yeast*, *Daphnia magna* (Docherty and Kulpa Jr 2005). In order to investigate the ionic liquids from different aspects, the ILs given in Table 3, are studied. IL1-4 have similar Alkyl chain lengths but their cations are different. Commonly for an easier and more straightforward description of antibacterial effects, an indicative substance named "Minimum inhibitory concentration" (MIC) is defined. The lower this value, the lower the amount of ionic liquid needed to kill the bacteria, thus the probability of IL being harmful to human body or cause toxication would decrease. Among these, IL1 had minimum MIC value against bacteria *S. epidermidis*, *E. faecalis,* and *S. aureus*. Antimicrobial property of IL1-IL4 against bacteria *E. coli*, *Enterococcus faecalis*, *S. epidermidis*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* is as follows: IL1 > IL3 > IL2 > IL4.

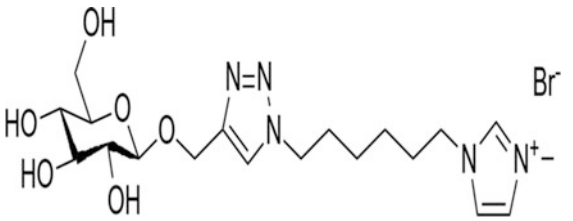
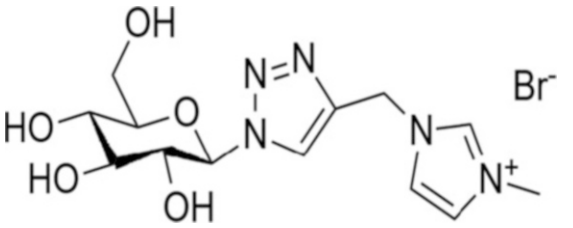
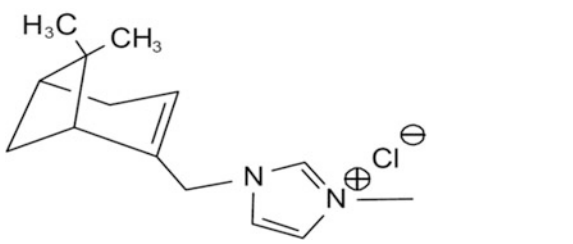
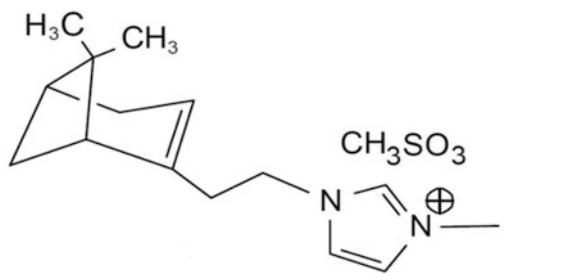
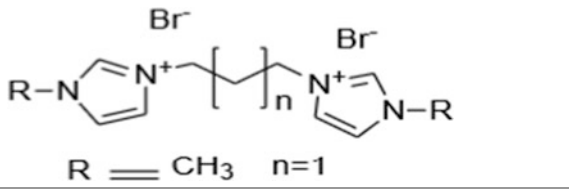
IL1-IL3 are able to inhibit the bacteria colony formation. Even for *S. aureus*, colony formation inhibition is also remarkable in half MIC. IL5 is similar to IL1 with the only difference that one diol was placed on its nitrogen. Comparison of their antimicrobial activity indicates that antimicrobial activity of IL5 decreased with respect to IL1 except for *P. aeruginosa* and this result indicates that hydroxy groups are impairing antimicrobial activity. The results have shown that the presence of some specific groups like amids, esters, carboxyls, and hydroxyls in the cation chain leads to reduction in the toxicity of ILs and increases their degradability (Florio et al.

Table 3 Chemical structure of ILs 1–15

Ionic liquid	Structure
IL1	
IL2	
IL3	
IL4	
IL5	

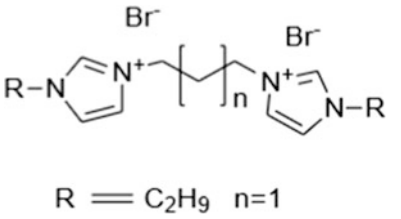
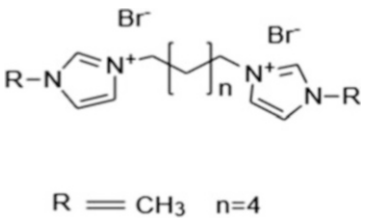
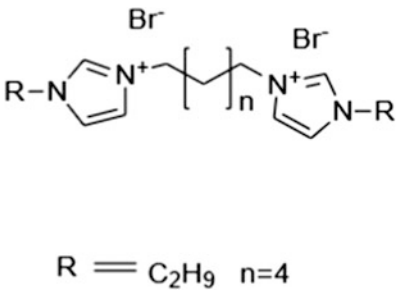
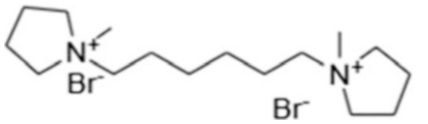
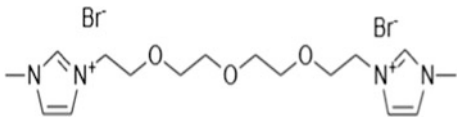
(continued)

Table 3 (continued)

Ionic liquid	Structure
IL6	
IL7	
IL8	
IL9	
IL10	

(continued)

Table 3 (continued)

Ionic liquid	Structure
IL11	
IL12	
IL13	
IL14	
IL15	

Modified after Florio et al. (2019)

2019). IL6-7 that includes Triazole links showed a sharp reduction in antimicrobial strength. IL9 compared with IL8 has about twice as much higher antibacterial potential except against *S. aureus* and that is while, IL9 has an extra methyl group than IL8. To check for the presence of excess cation IL10-15 was made. Among these six cationic ionic liquids, IL13 has the longest alkyl chain. The results of the researchers' experiments (Florio et al. 2019) have shown that IL13 has the highest antimicrobial activity among the anti-cationic liquid groups, especially against

Table 4 Minimum inhibitory concentration of ionic liquids 1–15

Ionic liquid	MIC value for				
	Escherichia coli	*Staphylococcus epidermidis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Enterococcus faecalis*
1	20 μg/mL	2.5 μg/mL	2.5 μg/mL	160 μg/mL	5 μg/mL
2	80 μg/mL	10 μg/mL	10 μg/mL	312.5 μg/mL	20 μg/mL
3	40 μg/mL	5 μg/mL	5 μg/mL	312.5 μg/mL	10 μg/mL
4	156.2 μg/mL	20 μg/mL	20 μg/mL	312.5 μg/mL	40 μg/mL
5	80 μg/mL	10 μg/mL	10 μg/mL	160 μg/mL	20 μg/mL
6	>5 mg/mL	>5 g/L	>5 g/L	>5 mg/mL	5 g/L
7	>5 mg/mL	5 g/L	>5 g/L	>5 mg/mL	>5 g/L
8	1.25 mg/mL	312.5 μg/mL	625 μg/mL	2.5 mg/mL	1.25 g/L
9	625 μg/mL	160 μg/mL	160 μg/mL	1.25 mg/mL	625 μg/mL
10	10 mg/mL	>10 g/L	>10 mg/mL	>10 mg/mL	>10 mg/mL
11	>10 mg/mL	5 g/L	>10 g/L	>10 mg/mL	10 mg/mL
12	>10 mg/mL	10 g/L	10 g/L	>10 mg/mL	>10 mg/mL
13	2.5 mg/mL	2.5 g/L	5 g/L	>10 mg/mL	10 mg/mL
14	>10 mg/mL	10 g/L	>10 g/L	>10 mg/mL	>10 mg/mL
15	>10 mg/mL	>10 g/L	>10 g/L	>10 mg/mL	>10 mg/mL

Modified after Florio et al. (2019)

S. epidemidis, *E. coli,* and *S. aureus* bacteria. IL1 and IL5 were compared to each other in order to study the effect of antimicrobial activity on alkyl chain length, which are the same in terms of cation and anion but IL5 is taller in terms of chain length. The results showed that antimicrobial activity of IL5 is far less than IL1. This suggests that the alkyl chain (C_nH_{2n+1}) length is partly effective on antimicrobial activity. In general, ionic liquids with the alkyl chain length of twelve to fourteen carbon atoms indicated the highest antimicrobial activity. However, the antibacterial activity in chains above 16 carbon atoms and lower than 10 carbon atoms was significantly reduced (Florio et al. 2019). MIC is defined for some ionic liquids in Table 4, which is described in the following. In general, the activity of ionic liquids against Gram-negative bacteria in particular *P. aeruginosa* is less than other bacteria. As one can see in Table 4, this process also holds about MIC values. The outer membrane of Gram-negative bacterium could be one reason for it.

2.1.1 Polymeric Ionic Liquids

Polymeric ionic liquids (PILs) which deal with polyelectrolytes are a class of polymers that are formed by ionic liquid monomers and they are synthesized from solid salt monomers. These liquids are better than their IL sample in some properties such as hydrophobicity (Mecerreyes 2011). These polymers can be used to create antibacterial surfaces. PILs of antimicrobial typically relying on cationic groups like: (a) 1,2-thiazolium, (b) quaternary ammonium, (c) phosphonium,

(d) pyrrolidinium, (e) imidazolium, (f) guanidinium, (g) pyridinium, (h) 1,2,4-thiazolium, and so on. They are synthesized fundamentally with three ways: (1) polymerization of ionic liquid monomers directly, (2) synthetic precursor polymers are actually modified chemically through a quaternization reaction, (3) by grafting after ILs polymerization through effective ligation reactions (Muñoz-Bonilla and Fernández-García 2018). An ion exchange step is often required in these strategies. Although the main method of reducing Poly (ionic liquid) s is the radical polymerization of conventional ionic liquid monomers, in recent years polymerization control techniques have become important because they allow the accurate design and precise control of the structures of macromolecule. In some cases, PILs could be chemically modified by polymers that were formerly polymerized, making it difficult to create some structures or chemicals with directly IL monomers' polymerization (Muñoz-Bonilla and Fernández-García 2018). Plenty of PILs is produced and tested like antimicrobial compounds, including the cationic section of the moving anions and the polymer backbone (Muñoz-Bonilla and Fernández-García 2018). However, few studies have assessed active and cationic counter ions with anionic PILs (Muñoz-Bonilla and Fernández-García 2018). Figure 2 clearly illustrates the comparison of different PILs performance against *E. coli* and *S. aureus*, *C. albicans*, *MRSA* bacteria (Xu et al. 2017).

One of the most important characteristics of an antibacterial substance is the ability killing the bacteria colony. PILs containing Zinc was able to completely eliminate the bacteria colonies of *E. coli*, *S. aureus*, *C. albicans,* and *MRSA* after 4 h. There are two factors contributing to this result (Xu et al. 2017): (1) Electrostatic interaction of Zinc with teichoic acids available in the membranes of microorganism. (2) Resulted Zn^{2+} can produce active oxygen in the cell, thereby prolonging the growth delay phase and inhibiting the synthesis of cell wall and ultimately growth and death of germs. In addition, an ideal antibacterial substance should have good biocompatibility, high efficiency, long-term activities, easy combination, and low cost (Guo et al. 2012). The ionic substance made of imidazolium cation, styrene, and acrylonitrile is expected to have good antibacterial properties since poly (styrene-acrylonitrile) is a copolymer substance, which has high chemical resistance and is predicted to have the ability to form strong membrane. Because the hydrophobic region of membrane PIL units facilitate antimicrobial activity, while hydrophobic region provides high mechanical resistance (Guo et al. 2012; Viau et al. 2010). PIL-Br membrane showed effective antibacterial properties compared to two bacteria *E. coli* and *S. aureus*. Antimicrobial activity of this membrane was more than *S. aureus* compared to *E. coli*. These different antibacterial efficiencies could be related to the different structures of the cell membranes. *E. coli* is a Gram-negative bacterium. The cell wall of this bacterium is more sensitive to Gram-positive, anionic, and hydrophilic bacteria. Thus, it is assumed that higher antimicrobial activity is resulted from a stronger electrostatic interaction between imidazolium cation and anionic cell wall and the same interaction is why the membrane works better than *E. coli* (Guo et al. 2012). Among the polymeric membranes poly ionic liquid-Br (PIL-Br), poly ionic liquid-Pro (PIL-Pro), PIL-Trp, and poly ionic liquid-Trp (PIL- Trp) showed the highest antibacterial activity such that in duration of

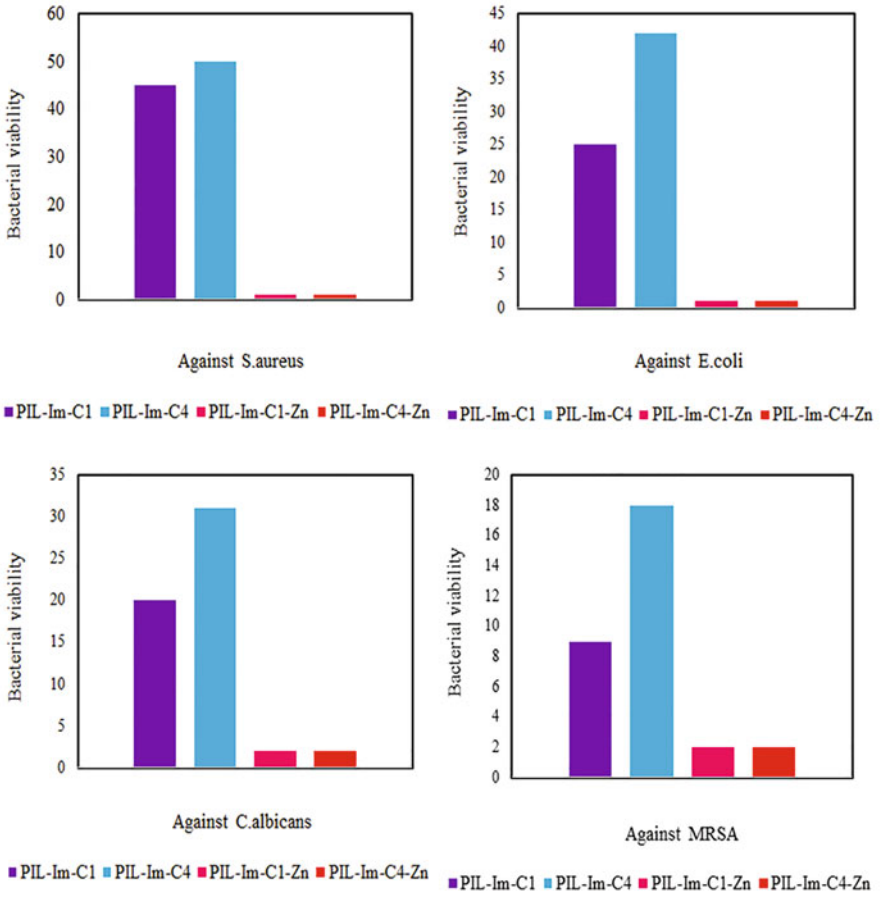


Fig. 2 Comparison of viability bacteria in the presence of IL-Im and PIL-Im. Modified after Xu et al. (2017)

1 hour, approximately 80–90 % of *E. coli* and *S. aureus* were killed. Furthermore, approximately 98% *S. aureus* and *E. coli* were killed and disappeared in four hours. The results of the hemolysis procedure for these polymeric ionic liquids showed that all membranes based on synthesized PIL are biocompatible with human cells. In addition, these polymeric membranes are easily recyclable without significant reduction in antimicrobial activity (Guo et al. 2012). Traditional dressing like cotton wool, bandages, and gauzes cause the wound to dry out while the wet wound bed promotes angiogenesis and when the wound heals, the epithelial cells in this environment are more active than in the dry environment. Hydrogels have a three dimensional network structure that adsorb a lot of water or biological fluids (Yu et al. 2020). PVA (Poly vinyl alcohol), a non-toxic polymer, is biodegradable and water-soluble and has hydrophobic nature. Hydrogels based on PVA have many useful properties, for example, high biocompatibility, biodegradability, good viability, and

adhesion performance (Yu et al. 2020). $B(OH)_4$ has interaction with two separate groups of cis-diol on PVA to create a hydrogel system. Hence, antibacterial hydrogels by combining antibiotics in PVA-$B(OH)_4$ hydrogels provide versatility and responsiveness. Introducing borate ester bonds leads to change in PVA/$B(OH)^-_4$ hydrogels rheological properties in the presence of $C_6H_{12}O_6$ since borate esters formed in the another competing presence saccharide molecule like $C_6H_{12}O_6$ are separated (Yu et al. 2020). In order to measure glucose ($C_6H_{12}O_6$) or their insulin secretion, these hydrogels can be adjusted depending on their glucose ($C_6H_{12}O_6$) response, system of PVA/C_4 MPBr/B $(OH)_4$ has furthermore responded to $C_6H_{12}O_6$. In addition, responsive behavior to pH from hydrogels were tested and considering the binding among the cis-diols and boric acid group, which is highly pH dependent and reversible, hydrogels PVA/C_4 MPBr/$B(OH)_4$ exhibits responsive properties to pH (Yu et al. 2020).

To evaluate antibacterial ILs activity, the results indicate that without addition of C_n MPBr, pure hydrogels PVA did not show any antibacterial property. But the prepared hydrogel demonstrated effective antimicrobial reaction against *S. aureus* and *E. coli*. It should be noted that the hydrogels containing IL with longer alkyl chains ($C_nH_{2n\ +\ 1}$) have more prominent antibacterial characteristics. Retention of moisture, self-healing, and behavior of being multiresponse together with antibacterial characteristics of hydrogels have made them ideal applicants as multifunctional dressings in order to heal the skin wounds (Yu et al. 2020). Since joints often move, a joint wound dressing which is ideal should make proper touch with the skin lacking preventing movement. Hydrogels that are generated from natural polymers have proper expandable properties and can applied to simulate the human skin tissue expansion capability. PVA/C_n MPBr/$B(OH)_4$ hydrogels tensile characteristics have been proven through tensile testing. In addition, hydrogels have good adhesion characteristics on human skin. Hence, these antimicrobial hydrogels have applications of potential for dressing substances to heal skin wounds (Yu et al. 2020; Soni et al. 2015). To investigate the antimicrobial effect on a set of chiral imidazolium ($C_3H_5N_2^+$) ILs containing amino acid, ester (R′COOR) and features of dipeptidyl, medicinal properties of chiral ionic liquids (CILs) as shown in Fig. 3 were against Methicillin-resistant *Staphylococcus aureus* (Coleman et al. 2012).

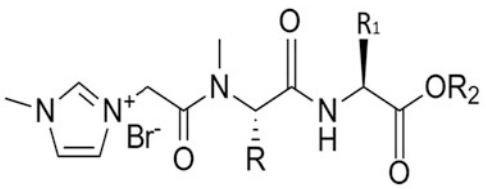


Fig. 3 Chemical structure of CIL1-4 (R=$CH_2(C_6H_5)$ and for CIL1: R_1=$CH(CH_3)_2$, R_2=C_2H_5, for CIL2: R_1=$CH_2CH(CH_3)_2$, R_2=CH_3, for CIL3: R_1=CH_3, R_2=CH_3, for CIL4: R_1=$CH_2(C_6H_5)$, R_2=C_2H_5). Modified after Coleman et al. (2012)

CIL1 showed inhibitory effect in small quantities of MIC. This CIL also has antifungal toxicity, low antibacterial toxicity with selectivity established for MRSA inhibition. CIL2, CIL3, and CIL4 also showed anti-bacterial behavior against bacteria. The relationship between these CIL structures and the results of their biological activities are remarkable. The presence of lipophilic and aromatic phenylalanine ($C_9H_{11}N_1O_2$) units in the dipeptidyl side chain of ILs led to properties of antibacterial being highlighted. CIL4 with a Phe-Phe sequence was more active. It was assumed that an antibacterial selective MRSA ionic liquid would have less toxicity in a toxicity experiment, than a proven antimicrobial biocidal (Coleman et al. 2012).

Among other choices for ionic liquid cations or maybe in some ways the best choice is quaternary ammonium or in short Qa. Researchers' results so far have been satisfying and promising for all the synthesized samples containing Qa. For example, PIL-Qa-C1 was tested on *MRSA* Gram-negative bacteria, which is a resistant bacterium and the effectiveness of the substance was proven as an antibacterial (Xu et al. 2017). IL-Qa-C4 showed good antibacterial properties on *E. coli*, *MRSA*, *S. aureus* bacteria and also *C. albicans* fungus, so that the properties of these materials have been much better compared to those of imidazolium cation. Antibacterial activity of IL-Qa-Br has also improved significantly compared to other cations (Jin et al. 2019). PILs, which have been synthesized from Qa cation and Zn anion like Poly Ionic Liquid-Quaternary ammonium-C4-Zinc (PIL-Qa-C4-Zn) and Poly Ionic Liquid-Quaternary ammonium-C1-Zinc (PIL-Qa-C1-Zn), have been reported to be biologically safe so that researchers are evaluating their application for operational medical use and are expected to be used in manufacturing wound dressing or antibacterial surfaces soon (Zhang et al. 2019; Zheng et al. 2017). Figure 4 compares of viability bacteria in the presence of ILs containing the Qa cation and polymeric ionic liquids containing Qa.

So far, in this chapter we have studied ionic liquids (ILs) from the perspective of their cations. But we know that an IL is formed of a cation and an anion. In order to get a better conclusion on their properties, we give a brief description of anions and researches conducted around them. The most common anions used in the ionic liquids synthesis are Hexafluorophosphate (PF^-_6) and Tetrafluoroborate (BF_4), which are hydrophobic, while Chloride (Cl^-), Bromide (Br^-), and Iodide (I^-) are hydrophilic. The mechanism of phosphate anions is that there is an electrostatic interaction among the phosphate (PO_4^{3-}) groups on the bacteria cell membrane and the ionic liquids positive charge, thus the cell membrane permeability increases and causes the cytoplasmic contents of the bacterium to leak and eventually death of the cell (Zhang et al. 2019; Fang et al. 2019; Florio et al. 2019). On the other hand, the hydrophobic part of the anion enters the lipid membrane of the bacterium and penetrates it (Zhang et al. 2019; Fang et al. 2019). Trp^- is another anion that a high antibacterial efficiency was reported for it compared with other anions of this substance (Xu et al. 2017).

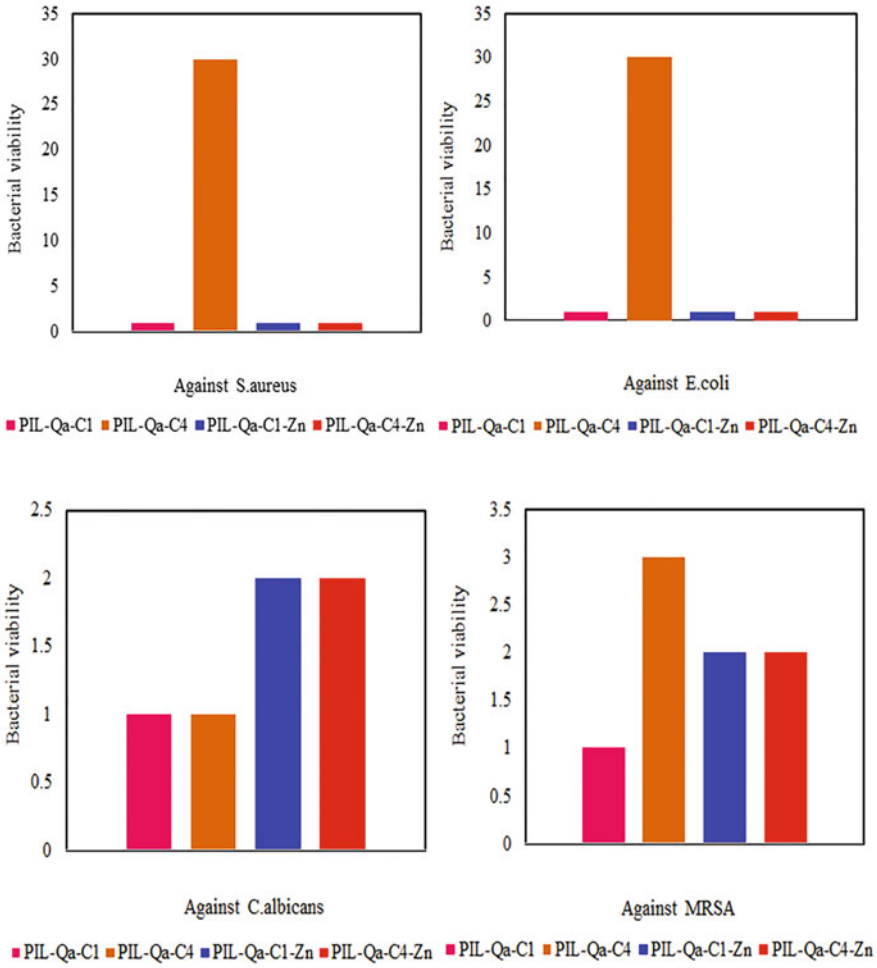


Fig. 4 Comparison of viability bacteria in the presence of IL-Qa and PIL-Qa. Modified after Xu et al. (2017)

In total, about those polymers based on cation, the PILs chemical structure containing hydrophobicity, molecular weight, and charge density should be completely intentional until achieving low toxicity and high antimicrobial efficiency (Muñoz-Bonilla and Fernández-García 2018). It has also to be recommended that ILs have been got attention like hopeful candidates for prohibiting biofilm development and counteracting pathogens. However, there have been few studies on their toxicity. Poly ionic liquids (PILs) are a combination of the antimicrobial ability of ILs and the ability of polymers processing, which have got much attention in antibacterial applications (Fang et al. 2019). Furthermore, one of the most important

factors affecting antibacterial activities to take into consideration is the counter ions (Muñoz-Bonilla and Fernández-García 2018).

Charge density and alkyl chain length affect the antibacterial properties of *N*-alkyl imidazolium-based PILs. A longer alkyl chain leads to an increase in the antibacterial activity of the PIL suspension, but for the PIL-based copolymer membranes, a longer alkyl chain leads to a decrease in the antibacterial activity of the PIL. However, higher charge density in both the PIL membrane and PIL suspension comforted the progress in antibacterial activity (Fang et al. 2019). When PIL nanoparticles are adsorbed by electrostatic interaction on the surface of the bacteria, the hydrophobic PIL alkyl chains enter into the hydrophobic bacteria membrane section, resulting in bacteria death and membrane separation. For instance, the activity of antibacterial poly [CnVIm] [Br^-] nanoparticles is powerfully associated to the alkyl chain length, i.e. C12 > C16 > C10 > C8 (Fang et al. 2019). This revealed that to improve the antibacterial effect the long alkyl side chains were required, while excess hydrophobic side chains played instead of an opposing role. Further, the anion interactions depend on the length of the alkyl chain. For instance, anion exchange from $Trp^-$to Br^- in the poly [CnVIm] [Br] nanoparticles, caused an increase in antibacterial properties for C8 and C12, but a decrease for C16. The relationship between structure and antibacterial effect plays an important role in the optimized modeling and the structure of the antibacterial property of medicine (Fang et al. 2019). The longer alkyl chains, the lower minimum inhibitory concentration values in ionic liquid monomers. Moreover, the imidazolium cations charge density is related to the ionic liquid monomers antibacterial activities (Zheng et al. 2017). The bis-imidazolium IL shows more activities of antibacterial than monoimidazolium analogs, which is characterized that if the charge density becomes greater, the minimum inhibitory concentrations of the ionic liquid monomers decrease. For example, the minimum inhibitory concentration values for compounds [OVIM][Br] (1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide (IL-C6-Im-C8)) and [C_{12}VIm][Br] (1-dodecyl-3-vinylimidazolium bromide (IL-C12)), respectively, are much lower than those for compounds [EVim][Br] (1-ethyl-3-vinylimidazolium bromide (IL-C2)) and [PBVIm][Br] (1-butyl-3-vinylimidazolium bromide (IL-C4)), which justify the preceding explanation. It is assumed that the cationic compounds (or polymers) antibacterial mechanism makes the electrostatic interaction of cell wall phosphates with cationic portions. Cell death occurs when the hydrophobic portions of the polymers (or compounds) enter the lipid membrane of the bacteria, which destroys the membrane of the cell. In addition, it is obvious that stronger electrostatic interactions among groups of phosphate of the cell wall and cations increase the antibacterial efficiency (Zheng et al. 2017).

The investigation of polymeric membranes with their hard and flexible properties is essential among the antibacterial materials. Moreover, those membranes, which have major antibacterial properties, are essential for medical applications. Colony counting is one way of describing the poly ionic liquids membranes antibacterial properties. In fact, number of bacterial colonies on the culture plate indicates their antibacterial activity (Zheng et al. 2017). Accordingly, it is acquired that the activities of antibacterial of PIL membranes based on bis-imidazolium are higher

than that of monoimidazolium. However, length of carbon chain in antibacterial effects of PIL membranes is distinct from the factors of ionic liquid monomers and poly ionic liquids. As a mismatch might be because of various orientations of the carbon chains in the PIL membrane surfaces and IL monomers (or PIL) suspensions. Tending hydrophobic groups of carbon (C–) chains into hydrophobic wall of cell enhance the activities of antimicrobial. Nevertheless, the manufactured poly ionic liquid membranes antimicrobial properties depend on both the molecular surface structure and the chemical composition (Zheng et al. 2017). However, the poly ionic liquid membranes antimicrobial properties can be related to their molecular surface structure and chemical composition, so which, the groups end strongly influence the poly ionic liquid membrane surface that forms a fully different composition from the bulk. About the PIL membranes, the imidazolium-based cations as hydrophilic groups remain in the bulk part and the long carbon chains of hydrophobic groups tend to separate to the interface between polymer and membrane. However, after suspending the bacteria on the surface of the membrane, the cations based on imidazolium are likely to spread in H_2O and the interface of polymer, therefore significantly decrease the efficiency of antimicrobial. Hence, the longer carbon chains of PIL membranes treated with weaker antibacterial properties (Zheng et al. 2017).

In the biomedical analysis of ILs, the importance of APIs (active pharmaceutical ingredient) of RTIL (room-temperature ionic liquids) compounds, which were chosen, has been totalized with two significant issues regarding the RTILs potential as an adjuvant to drug formulation and plenty potential of RTILs applications in biomedicine (Benedetto and Ballone 2016). The available bioavailability or their slow release upon formation of RTIL micelles or vesicles in physiological solutions improves with the chemical-physical properties of RTILs. These investigations link the room-temperature ionic liquid pharmacology biochemical aspects to the biology of system, and also analyze how a metabolite, in this case the RTIL ions, becomes available to an organism. Most significantly, the RTILs based on the liquid phase might prohibit drug polymorphism problems, which illustrate the challenge to drug development (Benedetto and Ballone 2016).

The cell boundary is known to perform many proceedings, from sticking with layer and cell attachment in tissues to intercellular relations through conveyancing. For example, adhesion is because of variegation of proteins protruding from membranes of the cell, attaining into a layer, in other cells, or an environment like a gel (extracellular matrix) between cells. Every one of these components properties was affected with RTILs, possibly increasing cell adhesion or prohibiting them from adhering to the surface or each other (Benedetto and Ballone 2016). Therefore, its adhesion or absence affects the crawling of cells on their surfaces and rheology in tissues (Benedetto and Ballone 2016). All viewpoints are of medical and diagnostic significance and can supply wide RTILs applications. The new RTIL classes, magnetic ion liquids (MILs), contain organic compounds. $[FeCl_4]^-$, $[MnBr_3]^-$ and $[CoCl_3]^-$ are instances of MIL anions (Benedetto and Ballone 2016). A few studies of these systems have been published so far; none of them attached biological implications. One day, the exact nature of the magnetic conditions was unknown,

and due to the small anisotropy forces, it was unclear how the magnetic moment orientation affected the ions structures and dynamics in the phase of liquid at ambient temperature, though it was estimated that itinerant exchange interactions and low molecular symmetry might be effective (Benedetto and Ballone 2016). For example, in the long-domain magnetic sorting compounds (ferric-, ferro-, and antiferro-) none of them are above the temperature of a few Kelvin. Nevertheless, the properties and their dynamics responses are paramagnetic to higher ranges. This affects their interaction with biosystems. We need to improve the dependence of magnetic MIL anions to amplify this effect using biomaterials or the transition of magnetic function to cations in which properties of biomembranes are already apparent (Benedetto and Ballone 2016). Given the versatility of RTILs, both options should be available. Using magnetic resonance as a reaction, upon reaching this tuning, like MILs, can modify the cells interact with the surroundings via forces coming out of their boundaries. The possibility of this method is supported by the results of many studies achieving the same outcome by magnetic forces by driving nanoparticles to cells (Benedetto and Ballone 2016). The magnetic material is distributed throughout the system in the MIL method, or more absolutely, it penetrates the cell's biomembranes. As such, due to the magnetic forces pervasiveness, they may be topically less severe. The last important point in expanding the domain of the applications of RTIL to their theoretical extent is the derivation of a large number and different kinds of chemical features of these compounds. In addition, new applications are restricted to popular compounds and limit the opportunities introduced via RTILs (Benedetto and Ballone 2016).

2.2 Ionic Liquid as Drug Formulation Components

Drug delivery is one of the hot topics in pharmaceutical field and recently ILs have been able to play an effective role in drug delivery field. Drug efficiency depends on its bioavailability, solubility, and permeability, so that lower solubility can lead to lower drug absorption and dissolution rates and subsequently, higher doses must be consumed for attainment and effect of therapeutic (Savjani et al. 2012). To overcome the mentioned problem, many researchers have suggested that drug formulations should be improved. The critical approaches to better solubility of drug are comminution, dispersion or micellization, usage of alternative solvents or co-solvents, preparation of solvates and hydrates, reducing the drug particle size, applying solubilizing attachments, charged, and polar group and prodrugs. However, reducing the drug particle size is very popular approach to increase drug dissolution and solubility rate because of increasing surface area (Feeney et al. 2016). For instance, in applying solubilizing method, solubilized attachments are added to the molecule of drug and drug active part stays intact. Amides, hydroxyl and amines groups are popular solubilizing. Furthermore, prodrug is promising method to improve the bioavailability and solubility of drug. A prodrug can modify chemically a drug and by increasing lipophilicity, stability, solubility, and action period of

pharmaceutical molecule leads to improve drug delivery (Clas et al. 2014). Ionic liquids are potential substance for drug formulation. As mentioned, ILs are green solvent and environmentally friendly chemical components, which are an adequate candidate for toxic conventional solvents. Many drugs are water-soluble and many ILs have good solubility in water; therefore, leads to increase absorption, rate of dissolution, and hydrophobic drugs targeting ability. Hydrophilic drugs indicate well hydrophilic ILs solubility and drugs with hydrophobic properties choose solvents with hydrophobic features. However, the effect of the anion part of IL on drug solubility is complicated (Balk et al. 2015). In total, ILs may be employed as emulsifiers, copolymers, solvents, anti-solvents, and co-solvents for drug formulation. Table 5 gives examples of ILs application to increase drug emulsifying agents and solubility. From this table, the ionic liquids activity can be as anesthetics, antioxidants, antimicrobial and antiviral agents, anticancer drugs, nonsteroidal anti-inflammatory, and anticoagulants.

Researches have shown that in addition to solubility, anions are somewhat effective in toxicity, especially in applications where toxicity is even harmful in small quantities. Therefore, certain anions should be selected for special purposes such as medical and pharmaceutical (API-IL). Here are some examples to make the problem clearer. A team of researchers used the metathesis response to produce ionic liquids containing quaternary ammonium (NR_4^+) with long alkyl chain (C_nH_{2n+1}) length and Ampicillin (AMP) anion, which is an antibiotic for bacterial infections. Prepared IL was tested with significant pathogenic germs like *Staphylococcus aurous* resistant to Methicillin and the results showed satisfactory antibacterial properties. In short, all ionic liquids that contain Ampicillin are non-toxic to human except $P_{6,6,6,14}$. Figure 5 indicates $P_{6,6,6,14}$ (Ferraz et al. 2014). Table 6 gives the value of MIC for both Gram-negative and Gram-positive bacteria groups for ionic liquids containing AMP (Ferraz et al. 2014).

To compare the effect of Ampicillin anion, some ILs are collected in Table 3, the cations of which are the same as those of the substances in Table 7 and their anion is Cl^-. The reason for the choosing Cl^- is that some chlorine-containing ionic materials are now being used in some products such as mouthwashes and toothpastes. By comparing them we can find that except in a few cases, chloride ILs toxicity in dilute solution has the same effect as that of Ampicillin (Ferraz et al. 2014).

Ferrocene (FC) an organometallic compound is a blend of aromatic, organic, and orange powder and has a sandwich structure, which is highly regarded because of its characteristics such as low toxicity, relative lipophilicity, and high thermal stability in solution. In addition, it can be incorporated as a positive property of ionic liquids. Ionic liquids having FC groups showed more antibacterial activity than the same IL without FC group against different Gram-positive and Gram-negative bacteria species. The relationship between antimicrobial toxicity and environmental toxicity is complicated. Antimicrobial toxicity determines the toxicity of a strain, while to check the environmental toxicity, it has to be determined for the entire society of living. Biodegradation studies of CIL5 (see Fig. 6) and CIL2 show that these two ionic liquid have passed "CO_2 Headspace Test" and are biodegradable (Coleman et al. 2012). The carbon dioxide headspace test describes a technique to determine the test items biodegradability using measuring the carbon dioxide-evolution in

Table 5 Ionic liquid as solubility emulsifiers and enhancers in delivery of drug

Drug	Role	Ionic liquid	Reference
Acetaminophen	Analgesic	[C_4MIM][BF_4] [C_8MIM][BF_4] [C_4MIM][PF_6] [C_4MIM][Br] [C_6MIM][Br]	Mehrdad and Miri (2016), Egorova et al. (2017)
Albendazole	Antiparasitic agent	[C_4MIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)
Acyclovir	Antiviral drug	[C1MIM][DMP]	Egorova et al. (2017)
Coumarin	Anticoagulant	[C_{10}MIM][NTf_2] [$(C6)_3C_{14}P$][Cl] [$(C_6)_3C_{14}P$][NTf_2]	Egorova et al. (2017)
Curcumin	Antioxidant Anti-inflammatory Antitumor agent	[C_4MIM][BF_4]	Egorova et al. (2017)
4-hydroxycoumarin	Anticoagulant	[EMIM][OTf]	Egorova et al. (2017)
Dehydroepiandrosterone	Steroid hormone	[C_4MIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)
Danazol	Steroid drug	[C_6C_6OCOPy][NTf_2] [C_8MIM][PF_6] [BMIM][PF_6] [C_6C_6OCOPy][$N(CN)_2$] [BMIM][BF_4]	Williams et al. (2014) Egorova et al. (2017)
Diclofenac	NSAID[a]	[C_6MIM][Br] [C_{12}MIM][Br] [C_{14}MIM][Br]	Egorova et al. (2017) Singh et al. (2009)
Dexamethasone	Steroid drug	[BMIM][PF_6] [C_6MIM][PF_6] [C_8MIM][PF_6]	Egorova et al. (2017)

(continued)

Table 5 (continued)

Drug	Role	Ionic liquid	Reference
5-fluorouracil	Antitumor agent	[BMIM][Br] [C_4MIM] [PF_6]	Goindi et al. (2015)
Etodolac	NSAID	[C_4MIM] [PF_6]	Goindi et al. (2015)
Glibenclamide	Antidiabetic drug	[Cho][Trp]	Alawi et al. (2015)
Isoniazid	Antituberculosis agent	[C_{10}MIM] [TFO]	Egorova et al. (2017)
Ibuprofen	NSAID	[$(C_6)_3C_{14}$P] [Cl] [$(C_6)_3C_{14}$P] [NTf_2] [C_2MIM] [NTf_2]	Egorova et al. (2017) Weber et al. (2015)
Ibuprofen	NSAID	[C_{12}MIM][Cl] [C_{12}MIM] [Ibu]	Egorova et al. (2017)
4′-isobutylacetophenone	Precursor in ibuprofen synthesis	[$(C_6)_3C_{14}$P] [Cl] [$(C_6)_3C_{14}$P] [NTf_2]	Egorova et al. (2017)
Methotrexate	Anticancer Anti-autoimmune Disease agent	[C_1MIM] [DMP]	Egorova et al. (2017)
Lidocaine hydrochloride	Local anesthetic	[C_{12}MIM][Cl] [C_{14}MIM][Cl]	Egorova et al. (2017)
Penicillin V	Antibiotic	[C_6MIM] [PF_6] [C_8MIM] [PF_6] [BMIM][PF_6]	Egorova et al. (2017)
Nimesulide	NSAID	[EMIM][BF_4] [EMIM][OTf] [EMIM][Ms]	Egorova et al. (2017)
Rutaecarpine	Plant alkaloid	[C_{12}MIM][Br]	Egorova et al. (2017)
Progesterone	Steroid hormone	[C_6MIM] [PF_6] [C_8MIM] [PF_6] [BMIM][PF_6]	
Pyrazine-2-carboxamide	Antituberculosis agent	[$(C_{10})_2(C_1)_2$N] [NO_3] [C_{10}MIM] [OTf]	Egorova et al. (2017)

[a]Nonsteroidal anti-inflammatory drug

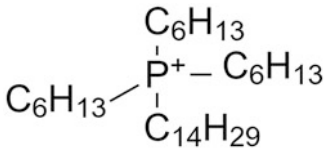


Fig. 5 Chemical structure of $[P_{6,6,6,14}]^+$. Modified after Ferraz et al. (2014)

sealed serum flasks by a headspace volume of about a third of the total flask volume. Since low toxicity in an ecotoxicity experiment does not make sure the biodegradation. Recalcitrant parent compounds durability or breakdown products should also be considered.

Cationic PILs in a wide range have been extended to applications of antimicrobial; however, those PILs based on imidazolium are the most extensively inspected (Muñoz-Bonilla and Fernández-García 2018). Thermal stability is one of the excellent properties of PIL that prepares a situation for non-crystalline polymers with low T_g (glass-transition temperature) amounts in comparability with the others like pyridinium and ammonium kinds of PILs, because of their easy syntheses (Muñoz-Bonilla and Fernández-García 2018). Further, derivatives of polymer and imidazolium salts have showed a wide range of activities of antimicrobial. A basic study of the correlation of the antibacterial structure-activity on IL monomers based on imidazolium, PILs, and membranes of PILs was published by Zheng et al. (2017). The characterization and imidazolium synthesis cation referring to antibacterial substances in Fig. 7 can be seen. A set of bis-imidazolium and mono ionic liquid monomers by different substitutions were synthesized and characterized by their antibacterial activities.

Following these different kinds of structure, the replacement carbon (C–) chain length at N3 positions was different, and also the activities and charge density were measured against both bacteria Gram-positive named *S. aureus* and Gram-negative named *E. coli*. Antibacterial properties of IL monomers and polymers change with concentration, they increase with minimal inhibitory concentration (MIC), because of increasing the alkyl chain length and higher charge density (Muñoz-Bonilla and Fernández-García 2018). As ILs based on pyrrolidinium have usually lower toxicity than imidazolium variants, studies are limited to antimicrobial drugs. A set of IL monomers based on pyrrolidinium was also developed by Zheng et al. (2017) that connected PILs through RAFT (reversible addition-fragmentation chain transfer) polymerization controlling (Muñoz-Bonilla and Fernández-García 2018). The results obtained for IL and PILs based on imidazolium revealed, the capability of antimicrobial against *S. aureus* and *E. coli* was enhanced with increasing the alkyl chain length. On the other hand, PILs indicate better antimicrobial activities because of lower MIC quantity than their corresponding IL monomers (Muñoz-Bonilla and Fernández-García 2018). In total, the values of MIC are lower in these IL structures based on pyrrolidinium than those in imidazolium-like structures. The low activity of PILs based on quaternary ammonium was reported in other studies (Muñoz-Bonilla and Fernández-García 2018). For example, the antimicrobial activity of some ionic liquid monomers and polymers stand on 2-(methacryloyloxy) ethyl]

Table 6 Minimum inhibitory concentration of ionic liquids containing AMP

Ionic liquid	MIC value for (mM)				
	Enterococcus faecalis	*Staphylococcus epidermidis*	*Staphylococcus aureus* ATCC 25923	*K. pneumoniae*	*Escherichia coli* ATCC 25922
[Na][Amp]	0.05	0.05	0.005	2.5	0.05
[TEA][Amp]	>5	>5	>5	>5	>5
[$P_{6,6,6,14}$][Amp]	0.05	0.05	0.05	5	2.5
[C_{16}Pyr][Amp]	0.005	0.005	0.005	0.05	0.5
[choline][Amp]	>5	>5	>5	>5	>5
[EMIM][Amp]	>5	>5	>5	>5	>5
[C_2OHMIM][Amp]	5	2.5	>5	>5	5

Modified after Ferraz et al. (2014)

Table 7 Minimum inhibitory concentration of ionic liquids containing Cl

Ionic liquid	MIC value for (mM)				
	Enterococcus faecalis	*Staphylococcus epidermidis*	*Staphylococcus aureus* ATCC 25923	*K. pneumoniae*	*Escherichia coli* ATCC 25922
[$P_{6,6,6,14}$][Cl]	>5	2.5	2.5	2.5	2.5
[C_{16}Pyr][Cl]	0.5	2.5	0.5	2.5	0.5
[choline][Cl]	>5	>5	2.5	>5	>5
[C_2OHMIM][Cl]	5	5	>5	>5	5

Modified after Ferraz et al. (2014)

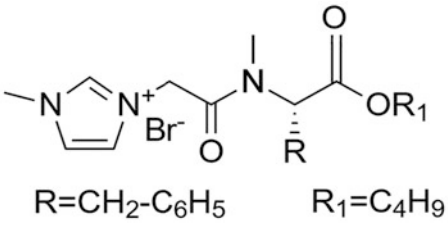


Fig. 6 Chemical structure of CIL5. Modified after Coleman et al. (2012)

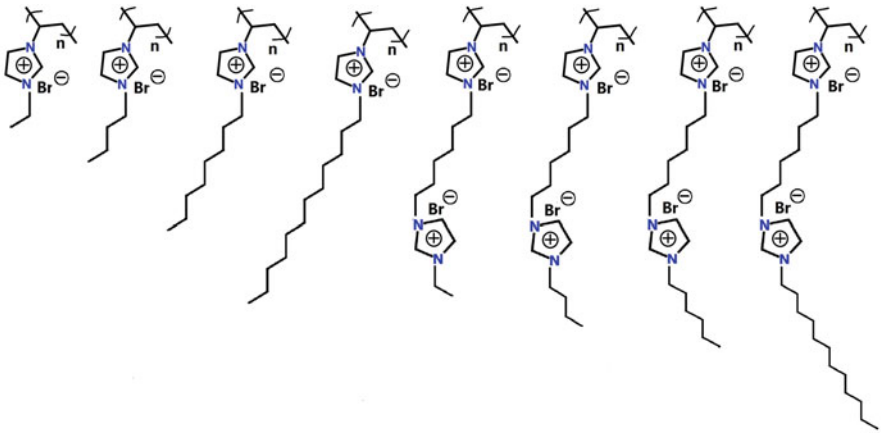


Fig. 7 Chemical structures of imidazolium type PILs. Reprinted with permission of Muñoz-Bonilla and Fernández-García (2018)

dimethyl heptyl ammonium cation and different ions was reported: bis (trifluoromethylsulfonyl)-imide, 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro undecanoate, decanesulfonate, heptadecafluoro octane sulfonate, nonafluoro-1-butane sulfonate, and dodecyl benzenesulfonate. This activity was examined against Gram-positive bacteria named *Micrococcus luteus (M. luteus)*, Gram-negative bacteria named *Stenotrophomonas maltophilia (S. maltophilia)*, *dematiaceous hyphomycetes Cladosporium* sp., and black yeast *Aureobasidium pullulans (A. pullulans)* (Muñoz-Bonilla and Fernández-García 2018). In this case, the IL monomers represented antimicrobial activity, while PILs did not indicate any significant activity. The cause of this low activity for PILs is the powerful electrostatic interaction among poly-cations and anion counterparts. This emphasized that the counter-ion decreases the activity of antimicrobial in these systems (Muñoz-Bonilla and Fernández-García 2018).

In total, anionic PILs, which contain sulfonate and carboxylate polymers with large organic counter ions, are much limiter than cationic PILs (Muñoz-Bonilla and Fernández-García 2018). In particular, most polymer systems for antimicrobial

applications are named cationic polyelectrolytes, since this process mechanism entails interactions of electrostatic with the membranes of bacterial cell based on negatively charged. Numerous systems are stand on poly ionic liquids including AMPS (2-acrylamido-2-methyl propane sulfonic acid) that is simply polymerized using radical polymerization. For instance, anionic poly ionic liquids with antimicrobial properties were produced from AMPS as quaternary salts. Besides, AMP-based polyanionic membranes were developed, for example, acrylonitrile, divinylbenzene, and anionic monomer by several cations, containing imidazolium, metal cations and ammonium. Finally, there are a few studies about anionic PILs so far, though these hopeful components for antimicrobial activity in which the moveable cationic counter ions can display a role of decisive (Muñoz-Bonilla and Fernández-García 2018). According to earlier reports, the counter ions have an important effect on the antimicrobial performance for the anionic and cationic poly ionic liquids. Counter ions are typically responsible for the antimicrobial activity in anionic PILs. For example, the cation effects on polyanionic membranes including anionic sulfate units (AMPS) by the activity of exchanging cation with imidazole and trimethylamine in the role of several metal cations and organic groups were measured using salt (K^+, Na^+, Zn^{2+}, Fe^{3+}, Cu^{2+}, and Ag^+). The polyionic membranes antimicrobials activities were evaluated versus *C. albicans*, *E. coli,* and *S. aureus* strains. Using Zn^{2+}, Fe^{3+}, Cu^{2+}, Ag^+ and the membranes activity was much more prominent than in the case of K^+ and Na^+ with imidazolium, the organic counter ions or quaternary ammonium. In the cationic poly ionic liquids stand on imidazolium groups, the metal ions effect on activities of antimicrobial was investigated (Muñoz-Bonilla and Fernández-García 2018). The counter ions were bromotrichloro ferrates, bromodichloro zincate, and anionic bromodichloro cuprate (Fig. 8). In comparison, the original bromide systems tolerated like a counter-ion and showed higher activity with metal ions, while PILs reacted poorly with iron ions (Muñoz-Bonilla and Fernández-García 2018).

2.3 Drug Synthesis Using Ionic Liquid

ILs are applied in many processes like fascinating usage in the drugs and pharmaceutical components synthesis. Ionic liquids are also used in heterocyclic molecules synthesis, like quinolones, thiazoles, oxazoles, furans, and imidazoles, which are employed in medicine and biology. Ionic liquids can influence the enzymes selectivity used in biotechnological processes. For instance, Monteiro et al. (1997) used a method to produce the nonsteroidal anti-inflammatory drug (NSAID) (S)-naproxen. They applied [BMIM][BF_4] as media. Some instances of advanced drugs molecules synthesis by IL media are given in Table 8.

Some of the most exciting and hopeful findings are the ILs usage for controlling the selectivity and stability of enzymes. Actually, usage of IL leads to increase enzymes activity and stabilization (Dang et al. 2007), permits (controls), proteins reversible folding or unfolding and decreases protein aggregation. Furthermore, ILs

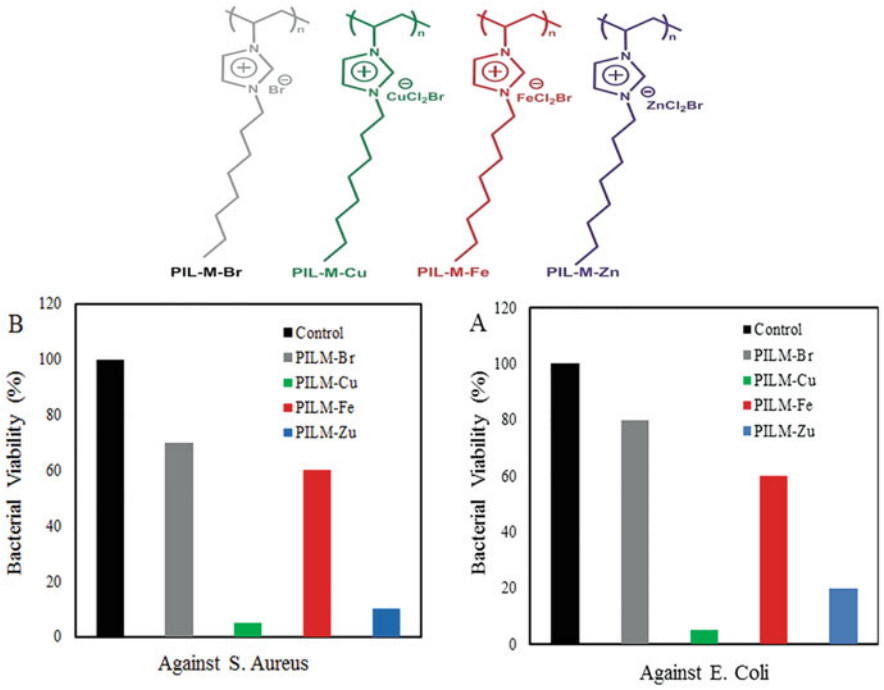


Fig. 8 Chemical structure of PILs containing different metal counter-anions; and bacterial viability of the corresponding membranes against (**a**) *S. aureus* and (**b**) *E. coli*. Modified after Muñoz-Bonilla and Fernández-García (2018)

are able to stabilize protein molecules by divided into structuring ions (Benedetto and Ballone 2016).

ILs are used in drug delivery systems preparation. In these systems IL roles are as solvent, functionalization agent, microporosity enhancers, catalyst and reaction media, additive for microsphere preparation, media for self-assembly of enzyme nanospheres, dispersing agent, and so on. A summary of ILs application in drug delivery systems is given in Table 9. A one can see from Table 9, imidazolium ILs are frequently employed as dispersion agents and media (Fileti and Chaban 2014; Wood et al. 2011; Weuster-Botz 2007; Pfruender et al. 2004).

2.3.1 Production of an Antibacterial Substance from ILs

The function and structure of the hydrophobic material are not affected by the unique assembly IL. However, ionic liquid shows the toxicity to ordinary cells. Afterward, the ionic liquid toxicity is a problem, which needs to resolve. One of the necessary constituents in the cell wall of both Gram-positive and Gram-negative bacteria is peptidoglycans, which was identified as an initial antibacterial target of antibiotics

Table 8 Application of ionic liquids in the drugs synthesis

Compound	Activity	Ionic liquid	Role of ionic liquid	Reference
(R,S)-ibuprofen	NSAID	[BMIM][PF_6] [C_8C1Py] [BF_4]	Enzymatic media	Egorova et al. (2017) Hongwei et al. (2005)
Iodoquinol and clioquinol	Antiprotozoal and antifungal drug	[C_4C_1Py] [ICl_2]	Iodinating reagent	Deshmukh et al. (2015)
Pravadoline	NSAID	[C_4MIM][PF_6]	Media	Egorova et al. (2017)
(R)-modafinil	Wakefulness-promoting agent	[EMIM][Br]	Enzymatic media	Egorova et al. (2017)
Stavudine	Anti-HIV[a] drug	[C_1OC_2MIM] [Ms] [C_4MIM] [TFa]	Media	Egorova et al. (2017)
Brivudine	Anti HSV[b] drug	[C_1OC_2MIM] [Ms] [BMIM] [TFa]	Media	Egorova et al. (2017)
Trifluridine	Anti HSV drug	[C_1OC_2MIM] [Ms] [BMIM] [TFa]	Media	Egorova et al. (2017)
(S)-naproxen	NSAID	[BMIM][BF_4]	Media	Egorova et al. (2017)
Tioconazole	Antifungal drug	[AlkMIM][Br]	Catalyst	Egorova et al. (2017)
Hydrocortisone	Steroid hormone	[EMIM][BF_4] [C_1MIM] [BF_4] [BMIM] [PF_6]	Catalyst	Egorova et al. (2017)
Hydrazinyl phthalazines	Antimalarial agents	[C_1C_1MIM] [C_1SO_4]	Dehydrating agent	Egorova et al. (2017)
Ciclesonide	Anti-asthmatic Anti-allergenic drug	Acidic ILs	Media, catalyst	Egorova et al. (2017)
α-Tocopherol succinate	Vitamin E ester	[C_5MIM] [NO_3]	Media, catalyst	Egorova et al. (2017)
Modafinil and its derivatives	Stimulant for sleep disorders treatment	[BMIM][PF_6]	Media	Egorova et al. (2017)
Isoxazolines	Antimicrobial agents precursor	[BMIM][BF_4]	Media	Chakraborty and Sharma (2013)
(S)-3-chloro-1-phenyl-1-propanol	Antimicrobial agents precursor	[BMIM] [NTf_2]	Ionic liquid phase Whole cell catalysis	Choi et al. (2011)
(R)-phenylacetylcarbinol	Precursor of (1R,2S) ephedrine	[BMIM][PF_6]	Ionic liquid phase	Kandar et al. (2015)

(continued)

Table 8 (continued)

Compound	Activity	Ionic liquid	Role of ionic liquid	Reference
	and (1S,2S) pseudoephedrine		Whole cell catalysis	
3-Phenylglycidol	Precursor of various drugs	[BMIM] [NTf_2]	Media	Egorova et al. (2017)
11α-hydroxy-16α 17-epoxyprogesterone	Intermediate in the steroidal drugs synthesis	[BMIM][PF_6]	Media for enzymatic enantioselective esterification	Egorova et al. (2017)
(R)-1-trimethylsilylethanol	Key synthon for various silicon-containing drugs	[BMIM][PF_6]	IL phase Whole-cell catalysis	Zhang et al. (2009)

[a]Human immunodeficiency virus
[b]Herpes simplex virus

(Wang et al. 2016). Therefore, targeting peptidoglycans can reduce ionic liquid side effects such as toxicity. Wang et al. (2016) in their study used chlorine e6 (Ce6) as an anion containing three COO^- and [C_{12}vim] cation that could bind to the cell wall. This new antibacterial had various properties, including reducing IL toxicity and removing the active cell wall barrier. Morphology and antimicrobial mechanism showed that increasing the concentration of Ce6 in the bacteria and Ce6-IL could remove the cell wall barrier. Ce6-IL eliminated pathogenic bacteria by direct and indirect contact methods according to the binary function of anion and cation. The in vivo experiments have shown that bacterial infection and wound healing could be controlled by Ce6-IL. The safety assessment results have revealed that Ce6-IL works with good biocompatibility. Consequently, there is a new antibacterial agent instead of antibiotics that is made of ionic liquids and photosensitizer to treat wound infection. The new antibacterial agent due to the presence of Ce6-IL has excellent biocompatibility and high antimicrobial activity (Wang et al. 2016). Patachia and Damian (2014) determined the appropriate situation for poly vinyl alcohol cryogels ions loading, to obtain both conductive and antimicrobial gels. ILs antibacterial behavior was in agreement with their positive charge from large organic cations, which makes breaking down the cell wall. The behavior of cryogels of poly vinyl alcohol through plunging in solutions of IL indicates that due to the desalination or desalination capacity, the nature of the IL anions affects the decay and swelling poly vinyl alcohol hydrogels process more than cations (Patachia and Damian 2014). How do cations show their effect on the swelling of hydrogels? The efficiency of cations depends on the time of contact between the ionic liquid and gel. However, due to the low cations diffusion coefficient of them, cations are less effective than anions. Research has shown that in the contact between chloride ionic liquids and poly vinyl alcohol gel throughout the first 70 min, a slightly gel collapse was observed, and had observed that a longer chain of hydrocarbon adhered to the imidazolium ring causes a more initial collapse in the gel. Osmotic pressure is an effective factor in the first moments of ionic liquid solutions contact with the gel.

Table 9 ILs application in the drug delivery systems preparation

Drug delivery system	Ionic liquid	Role of ionic liquid	Reference
Microporous poly(lactic acid) scaffolds	[BMIM][OTf] [BMIM][Cl] [BMIM][BF_4] [BMIM][SbF_6]	Microporosity enhancers	Dorj et al. (2014)
Polylactic acid, Polycaprolactone Membranes, microspheres	[$(C_8)_3$C1N][Cl] [BMIM][NTf_2] [BMIM][PF_6] [BMIM][BF_4] [BMIM][OTf] [BMIM][Cl] [BMIM][SbF_6]	Additive for microsphere preparation	Egorova et al. (2017) Shin and Kim (2012)
Cellulose-biopolymer composite hydrogel	[EMIM][OAc]	Solvent	Egorova et al. (2017)
Cellulose-graf t-poly (L-lactide)	[BMIM][Cl] [AlkMIM][Cl]	Solvent	Egorova et al. (2017) Guo et al. (2012)
Cellulose/SWCNT complex	[BMIM][Br]	Solvent	Egorova et al. (2017)
Cellulose-nanohydroxyapatite composite scaffolds	[BMIM][Cl]	Solvent	Tsioptsias and Panayiotou (2008)
Cellulose, keratin Chitosan composite materials	[BMIM][Cl]	Solvent	Tran and Mututuvari (2015)
Chitosan-based nanocarriers	[BMIM][Cl]	Solvent	Egorova et al. (2017)
Linoleic acid-grafted chitosan micelles	[BMIM][OAc]	Solvent	Egorova et al. (2017)
Benzylpyrazolyl coumarin scaffolds	[C_5MIM][Br]	Catalyst Reaction media	Egorova et al. (2017)
Fullerenes	[C_4MIM][BF_4]	Fullerene dispersion enhancer	Fileti and Chaban (2014)
Silica particles	[C_4MIM][BF_4]	Solvent	Egorova et al. (2017)
Starch nanoparticles	[C_8MIM][OAc] +[C_{16}MIM] [Br] [BMIM][PF_6] [C_{16}MIM][Br] [C_{16}MIM][Br] +[C_8MIM][NTf_2]	Microemulsion cross-linking reaction	Wang et al. (2016) Egorova et al. (2017)

This is why poly vinyl alcohol cryogels membranes were selected for immersion in molar isomeric ILs, which considers the osmotic pressure effect (Patachia and Damian 2014). Another factor affecting the adsorption of IL inside the gel is the IL contact volume. The low contact volume of the IL increases its uptake. The gel loading capacity depends on the amount of the PVA cryogel swelling is affected

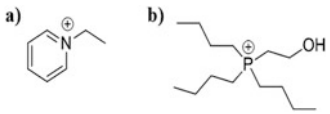


Fig. 9 Chemical structures of the IL as precursors: (**a**) 1-ethylpyridinium, (**b**) tributyl(2-hydroxyethyl) phosphonium. Modified after Choi et al. (2011)

using the concentration and nature of the contacted IL (Patachia and Damian 2014). Choi et al. (2011) studied the antimicrobial activity of two ionic liquids (Fig. 9), namely, 1-ethylpyridinium dactate (IL1) and tributyl (2-hydroxyethyl) phosphonium (IL2). They are effective plasticizers for PVC, and had antibiotic-forming and antimicrobial properties.

The cationic precursor of the bromide salt of the Epy^{+} did not show an important antimicrobial effect, despite having a structure usually used in a wide antimicrobials range and disinfectants (Choi et al. 2011). As previously mentioned, it is not from the cation; however, originates from the anion and is not limited to the length of alkyl chain in the ions (Choi et al. 2011). To study the incorporation of ionic liquids into polymers (encapsulating) as antibacterial agents, different interactions must be considered, for instance, those among anion and cation and their solubility that may repress the antimicrobial activity of a specific ionic liquid. The ionic liquid, in aqueous solution, may show antibacterial and anti-adherence activities; however, its encapsulation into a polymer results in a decrease in antibacterial activities (Choi et al. 2011).

2.3.2 ILs Applications in Pharmacy

Obviously, pharmacology will develop significantly in room-temperature ionic liquid-based research. This discussion is shortened to the pharmacology of room-temperature ionic liquid, which is straightly associated with their interactions with biomembranes (Benedetto and Ballone 2016). The pharmacology basis is based on the difference of properties and different cells membrane structure similar eukaryotic cells and bacteria or diseased and healthy cells like cells of cancer. These differences, together with the inherent versatility of RTILs, represent a choice in the biomembrane of RTIL interactions and finding the way to influencing the destiny of cells and final behavior. Eventually, it could be assumed that biomembranes based on phospholipid (see Fig. 10) encircle a variety of organs of cellular (ribosomes, chloroplast, mitochondria, vacuoles, nucleus, and so on).

The unique and structural composition of each membrane provides the basis for the room-temperature ionic liquids selective interaction with intracellular organelles. Thus, it can be concluded that RTIL's biological activity includes general cytotoxicity and widespread antibacterial activity against not only both Gram-positive and Gram-negative bacteria but also mycobacteria and fungi (Benedetto and Ballone 2016). These properties are common to all RTIL groups, among those based on

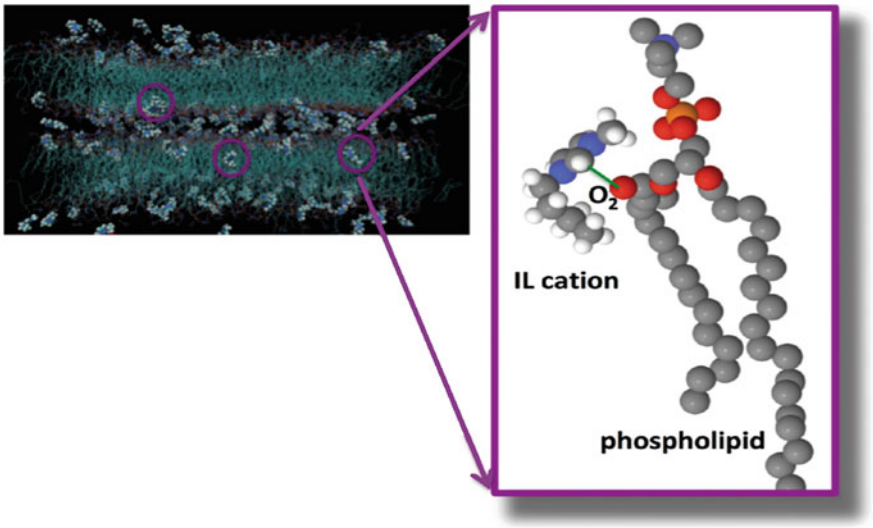


Fig. 10 Pictures from recent MD simulations. Simulation snapshot showing [C_4C1Im][PF_6] ions on POPC in water. Comparison of the density distribution of cations and anions in [C_4C1Im][Cl] and in [C_4C1Im][PF_6]. Reprinted with permission of Benedetto and Ballone (2016)

pyridinium, imidazolium, phosphonium, and ammonium. The experimental evidence indicates that the active mechanism of RTIL is not significant because the toxicity and activity of bactericides appear via collapsing of them (Benedetto and Ballone 2016). It should recommend that bacterial activities are not similar to common toxicity. For instance, pyridinium salts, especially, destroy bacteria without injuring mammalian cells. This is a fundamental property for any pharmaceutical application (Benedetto and Ballone 2016). Now using the quantitative structure-activity relationship (QSAR) model, the cytotoxicity and ability of bactericidal agents can be almost exclusively obtained. No general database of any property is retained. The antibacterial activity of RTILs and the cytotoxicity are not unexpected. Most of the known antibiotics are based on cation and prepared like a salt, due to medium-high and unidentified melting point they are not classified as RTI. The activities of antimicrobial based on peptides (a short chain of amino acids) forcefully depend on their electrostatic effect, which is the first interaction with the external bacteria's membrane. Beside, quaternary ammonium cations have known with their antimicrobial properties. In addition, the quaternary activity of phosphonium cations depends on the alkane chain length. Imagine this compound against Gram-negative bacteria with external wall completed of a peptidoglycan gel layer (Benedetto and Ballone 2016). In RTILs the bactericidal ability is attributed to one or both ions, in fact the pure RTILs antibacterial activity is usually maintained in aqueous solution because they are nominally dissociated. Therefore, the common role of cations is identified according to previous sections. The common structure of RTILs consists of a cationic core (quaternary, ammonium, imidazolium, and pyridinium) and one or

more polar branches, and this structure is common to active RTILs (Benedetto and Ballone 2016). Cations become determinants when pass through the membrane, like making stable complexes by core acids electrostatic signatures are often anionic. Other evidences are that known RTIL anions are involved in known antibacterial activity; however, new compounds shown to have the activity of both cations and anions (Benedetto and Ballone 2016). Actually, their capability of antielectrostatic is moderated using antielectrostatic interaction by the phospholipid bilayer surface. Astonishingly, this property displays positive connection with activity of antibacterial, at least for cholinium-based RTILs. However, there is not a similar correlation for other RTILs families, like those stand on phosphonium. Because of the chemical physics prejudice, the discussion focused on the interaction of room-temperature ionic liquid with the biomembranes lipid fraction. However, protein segment interaction maybe even more important in pharmaceutical applications and may show the bacteria resistance to compounds of RTIL, same as what is known for common resistance of antibiotic (Benedetto and Ballone 2016). A series of IL monomers based on imidazolium, poly ionic liquids and poly ionic liquid membranes were synthesized such as agents of antibacterial (Zheng et al. 2017). Among the factors investigated were the effect of the imidazolium cations charge density on the antibacterial activities against *E. coli* and *S. aureus* and the effects of chemical structures containing length of carbon chain on the N3 substituents. The higher charge density and the longer chain of alkyl length result in a decrease in minimum inhibitory concentrations and higher properties of antibacterial of both poly ionic liquids and ionic liquid monomers in suspension of bacteria. Use of the properties of antibacterial of small molecules and homopolymers is required to evaluate polymeric membranes, as is the contrast between PILs, IL monomers, and related PIL membranes. Zheng et al. (2017) compared six panels (Fig. 11) for the comparison of antibacterial activity of PIL membranes against *E. coli* and *S. aureus*. Significant

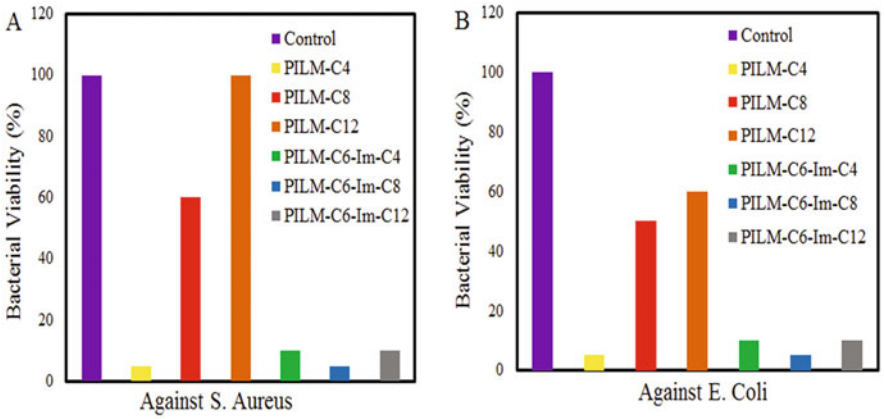


Fig. 11 Bacterial viabilities of (**a**) *S. aureus* and (**b**) *E. coli* after contacting with PIL membranes for 4 h, with PET membranes as controls (right two columns, an average of five samples). Modified after Zheng et al. (2017)

Table 10 IL antimicrobial activities monomers and poly ionic liquids measured as MIC

Samples	MIC (μmol mL^{-1})	
	S. aureus	*E. coli*
IL-C2	472.906	945.812
IL-C4	54.545	54.545
IL-C8	2.983	1.192
IL-C12	0.038	0.061
IL-C6-Im-C2	110.599	55.300
IL-C6-Im-C4	27.273	22.945
IL-C6-Im-C8	0.081	0.081
IL-C6-Im-C12	0.018	0.018
PIL-C2	110.345	110.345
PIL-C4	2.961	5.922
PIL-C8	1.491	1.192
PIL-C12	0.061	0.122
PIL-C6-Im-C2	33.180	33.180
PIL-C6-Im-C4	0.918	1.853
PIL-C6-Im-C8	0.081	0.041
PIL-C6-Im-C12	0.009	0.018

Modified after Zheng et al. (2017)

differences could be seen in the first 1 hour (see Table 10). The order of activity of antibacterial for synthesized poly ionic liquid membranes shows that poly ionic liquids membrane-C4 (1-butyl-3-vinylimidazolium bromide membrane) is more than poly ionic liquids membrane-C6-Im-C4 (1-butyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane) and poly ionic liquids membrane-C6-Im-C8 (1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane) and eventually poly ionic liquids membrane-C12 (poly (1-dodecyl-3-vinylimidazolium bromide) membrane) is the least one against *S. aureus* and poly ionic liquids membrane-C4 is more than 1-octyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane and 1-butyl-3-(1-vinylimidazolium-3-hexyl) imidazolium bromide membrane and also poly (1-dodecyl-3-vinylimidazolium) bromide is the lowest one against *E. coli*.

3 Conclusions

Bacterial infection and viruses illnesses are main causes of deaths in last decades because of the antibiotics overuse and multi-drug-resistant pathogens increase. Effective antibacterial materials are crucial. Consequently, drug delivery field must be developed. Pharmaceutics preparations were reformed from powders to diffusion in polymers to nanoparticles and micelles. Ionic liquids are new type of green solvents with unique properties, which leads to encourage generating and developing of new drugs. Some of advantages of ILs employment are as follow:

- Using ILs is a cost-efficient way to create biological active compounds.
- ILs present formation of ion control in solution and biological fluids adjustment and water solvation properties to prepare an approach for solubility bioavailability alleviation and conventional drugs polymorphism limitations.
- ILs permit easy readily developed ionic cores incorporation in current molecules of drug, also novel drugs design and active molecules of biologically.
- ILs indicate adjustable organization of structural reflected at the micro- and nanoscale levels with approach to several kinds of biological activity.
- Application of ILs permits to optimize the price of pharmaceutical compounds analytics or production and development of biosynthetic processes.

As emphasized in the chapter, ionic liquids are predicted to discovery various applications in pharmaceutical field like biological activity, drug formulation, and drug synthesis.

It is still unclear what the reasons for antibacterial and inhibitory effects of ionic liquids are and it is not possible to accurately predict which ionic liquids affect which bacteria since there is no same laboratory result for all varieties of a single class of bacteria. Extensive researches have been done on the antibacterial effects of ionic liquids, including factors known so far: altering the alkyl chain length and adding methyl branches to their structure. In general, ILs with the alkyl chain length of twelve to fourteen carbon atoms indicated the highest activity of antimicrobial. Ionic liquids with FC groups showed more antibacterial activity than similar sample without FC group against different species of bacteria. But some groups such as hydroxyl groups, disrupt antimicrobial activity. Triazole bonds also greatly reduce the antimicrobial power of ionic liquids. Polymeric ionic liquids have higher antibacterial properties than ionic liquids. These polymers can be used to create antibacterial surfaces. Polymeric ionic liquids containing zinc are very effective in the removal of bacterial colonies. Most ionic liquids that have been tested except for a few cases such as PIL-Br have more effect on Gram-positive bacteria than Gram-negative bacteria. The Gram-negative bacteria outer membrane could be one of the reasons for this. ILs based on polyvinyl alcohol, which are often in the form of a hydrogel have antibacterial properties. Antibacterial hydrogel combined with antibiotics have versatility and responsiveness capability. Hydrogels made of natural polymers also have good tensile properties. The results of the hemolysis procedure for polymeric ionic liquids have shown that all membranes based on PIL synthesized with human cells are biocompatible. Quaternary ammonium cation perhaps could be known as the best choice for the synthesis of ionic liquids because researchers' results so far have been satisfying for all synthesized samples containing quaternary ammonium. Poly ionic liquids which are synthesized from Qa cations and Zn anion are biologically safe so that researchers consider them functional for medical purposes and so on they are expected to be used in order to create wound dressings or used in antibacterial surfaces. Researches have shown that anions, in addition to solubility, are partially effective in the toxicity of ionic liquids, especially in cases where toxicity is harmful even in small amounts. Therefore, since the anions are involved in the toxicity of ionic liquids, same as cations, they must be carefully

selected for specific purposes such as drug preparation. For example, most ionic liquids containing ampicillin are not toxic to human; ampicillin anion on the other hands is active against any bacteria because of an additional amino group. In general, polymer derivatives and imidazolium salts have a wide range of antimicrobial activities. As mentioned, the antibacterial ability of pure RTILs in aqueous solutions, it can be claimed that this ability is dependent on both ions. One of the factors affecting the antibacterial ability is the alkyl chain effect, increasing the alkyl chain length increases the antibacterial activity of the PIL suspension and decreases the activity of the PIL-based copolymer membrane. In addition, it was shown that small molecules antibacterial properties and homopolymers are applied to evaluate polymeric membranes. Another factor affecting the antibacterial activity of ionic liquid monomers and polymers is the concentration, subsequently the lower the minimal inhibitory concentration (MIC), the greater their antibacterial activity.

References

Alawi MA, Hamdan II, Sallam AA, Heshmeh NA (2015) Solubility enhancement of glibenclamide in choline–tryptophan ionic liquid: preparation, characterization and mechanism of solubilization. J Mol Liq 212:629–634

Aslanov LA (2011) Ionic liquids: liquid structure. J Mol Liq 162(3):101–104

Bagheri H, Ghader S (2017) Correlating ionic liquids density over wide range of temperature and pressure by volume shift concept. J Mol Liq 236:172–183

Bagheri H, Mohebbi A (2017) Prediction of critical temperature, critical pressure and acentric factor of some ionic liquids using Patel-Teja equation of state based on genetic algorithm. Korean J Chem Eng 34(10):2686–2702

Bagheri H, Mansoori GA, Hashemipour H (2018) A novel approach to predict drugs solubility in supercritical solvents for RESS process using various cubic EoS-mixing rule. J Mol Liq 261:174–188

Bagheri H, Hashemipour H, Ghader S (2019a) Population balance modeling: application in nanoparticle formation through rapid expansion of supercritical solution. Comput Part Mech 6 (4):721–737

Bagheri H, Hashemipour H, Mirzaie M (2019b) Investigation on hydrodynamic and formation of nano particle by RESS process: the numerical study. J Mol Liq 281:490–505

Bagheri H, Ghader S, Hatami N (2019c) Solubility of ibuprofen in conventional solvents and supercritical CO_2: evaluation of ideal and non-ideal models. Chemistry 13(1):1–10

Balk A, Holzgrabe U, Meinel L (2015) 'Proetcontra' ionic liquid drugs-challenges and opportunities for pharmaceutical translation. Eur J Pharm Biopharm 94:291–304

Benedetto A, Ballone P (2016) Room temperature ionic liquids interacting with bio-molecules: an overview of experimental and computational studies. Philos Mag 96(7-9):870–894

Capello C, Fischer U, Hungerbühler K (2007) What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chem 9(9):927–934

Chakraborty B, Sharma CD (2013) A new route to the synthesis of isoxazoline derivatives from dihydropyran via cycloaddition reaction in ionic liquid. Tetrahedron Lett 54(40):5532–5536

Choi HJ, Uhm KN, Kim HK (2011) Production of chiral compound using recombinant Escherichia coli cells co-expressing reductase and glucose dehydrogenase in an ionic liquid/water two phase system. J Mol Catal B 70(3-4):114–118

Clas SD, Sanchez RI, Nofsinger R (2014) Chemistry-enabled drug delivery (prodrugs): recent progress and challenges. Drug Discov Today 19(1):79–87

Coleman D, Špulák M, Garcia MT, Gathergood N (2012) Antimicrobial toxicity studies of ionic liquids leading to a 'hit' MRSA selective antibacterial imidazolium salt. Green Chem 14 (5):1350–1356

Dang DT, Ha SH, Lee SM, Chang WJ, Koo YM (2007) Enhanced activity and stability of ionic liquid-pretreated lipase. J Mol Catal B 45(3-4):118–121

Deetlefs M, Fanselow M, Seddon KR (2016) Ionic liquids: the view from mount improbable. RSC Adv 6(6):4280–4288

Deshmukh A, Gore B, Thulasiram HV, Swamy VP (2015) Recyclable ionic liquid iodinating reagent for solvent free, regioselective iodination of activated aromatic and heteroaromatic amines. RSC Adv 5(107):88311–88315

Docherty KM, Kulpa CF Jr (2005) Toxicity and antimicrobial activity of imidazolium and pyridinium ionic liquids. Green Chem 7(4):185–189

Dominguez de Maria P (2008) "Nonsolvent" applications of ionic liquids in biotransformations and organocatalysis. Angew Chem Int Ed 47(37):6960–6968

Dorj B, Won JE, Purevdorj O, Patel KD, Kim JH, Lee EJ, Kim HW (2014) A novel therapeutic design of microporous-structured biopolymer scaffolds for drug loading and delivery. Acta Biomater 10(3):1238–1250

Egorova KS, Gordeev EG, Ananikov VP (2017) Biological activity of ionic liquids and their application in pharmaceutics and medicine. Chem Rev 117(10):7132–7189

Elshaarawy RF, Refaee AA, El-Sawi EA (2016) Pharmacological performance of novel poly-(ionic liquid)-grafted chitosan-N-salicylidene Schiff bases and their complexes. Carbohydr Polym 146:376–387

Fang H, Wang J, Li L, Xu L, Wu Y, Wang Y, Fei X, Tian J, Li Y (2019) A novel high-strength poly (ionic liquid)/PVA hydrogel dressing for antibacterial applications. Chem Eng J 365:153–164

Feeney OM, Crum MF, McEvoy CL, Trevaskis NL, Williams HD, Pouton CW, Charman WN, Bergström CA, Porter CJ (2016) 50 years of oral lipid-based formulations: provenance, progress and future perspectives. Adv Drug Deliv Rev 101:167–194

Ferraz R, Branco LC, Prudencio C, Noronha JP, Petrovski Ž (2011) Ionic liquids as active pharmaceutical ingredients. ChemMedChem 6(6):975–985

Ferraz R, Teixeira V, Rodrigues D, Fernandes R, Prudêncio C, Noronha JP, Petrovski Ž, Branco LC (2014) Antibacterial activity of ionic liquids based on ampicillin against resistant bacteria. RSC Adv 4(9):4301–4307

Fileti EE, Chaban VV (2014) Imidazolium ionic liquid helps to disperse fullerenes in water. J Phys Chem Lett 5(11):1795–1800

Florio W, Becherini S, D'Andrea F, Lupetti A, Chiappe C, Guazzelli L (2019) Comparative evaluation of antimicrobial activity of different types of ionic liquids. Mater Sci Eng 104:109907

Ghalandari V, Hashemipour H, Bagheri H (2020) Experimental and modeling investigation of adsorption equilibrium of CH_4, CO_2, and N_2 on activated carbon and prediction of multi-component adsorption equilibrium. Fluid Phase Equilib 508:112433

Goindi S, Kaur R, Kaur R (2015) An ionic liquid-in-water microemulsion as a potential carrier for topical delivery of poorly water soluble drug: development, ex-vivo and in-vivo evaluation. Int J Pharm 495(2):913–923

Guo Y, Wang X, Shu X, Shen Z, Sun RC (2012) Self-assembly and paclitaxel loading capacity of cellulose-graft-poly (lactide) nanomicelles. J Agric Food Chem 60(15):3900–3908

Hongwei Y, Jinchuan W, Chi BC (2005) Kinetic resolution of ibuprofen catalyzed by Candida rugosa lipase in ionic liquids. Chirality 17(1):16–21

Ivanković A, Dronjić A, Bevanda AM, Talić S (2017) Review of 12 principles of green chemistry in practice. Int J Sust Green Energy 6(3):39

Jin L, Shi Z, Zhang X, Liu X, Li H, Wang J, Liang F, Zhao W, Zhao C (2019) Intelligent antibacterial surface based on ionic liquid molecular brushes for bacterial killing and release. J Mater Chem B 7(36):5520–5527

Kandar S, Suresh AK, Noronha SB (2015) (R)-PAC biosynthesis in [BMIM][PF_6]/aqueous biphasic system using Saccharomyces cerevisiae BY4741 cells. Appl Biochem Biotechnol 175(4):1771–1788

Kurnia KA, Sintra TE, Neves CM, Shimizu K, Lopes JN, Gonçalves F, Ventura SP, Freire MG, Santos LM, Coutinho JA (2014) The effect of the cation alkyl chain branching on mutual solubilities with water and toxicities. Phys Chem Chem Phys 16(37):19952–19963

Lee SH, Doan TT, Ha SH, Chang WJ, Koo YM (2007) Influence of ionic liquids as additives on sol-gel immobilized lipase. J Mol Catal B 47(3-4):129–134

MacFarlane DR, Forsyth M, Howlett PC, Pringle JM, Sun J, Annat G, Neil W, Izgorodina EI (2007) Ionic liquids in electrochemical devices and processes: managing interfacial electrochemistry. Acc Chem Res 40(11):1165–1173

Marsousi S, Karimi-Sabet J, Moosavian MA, Amini Y (2019) Liquid-liquid extraction of calcium using ionic liquids in spiral microfluidics. Chem Eng J 356:492–505

McCrary PD, Beasley PA, Gurau G, Narita A, Barber PS, Cojocaru OA, Rogers RD (2013) Drug specific, tuning of an ionic liquid's hydrophilic-lipophilic balance to improve water solubility of poorly soluble active pharmaceutical ingredients. New J Chem 37(7):2196–2202

McDowell C, Bazan GC (2017) Organic solar cells processed from green solvents. Curr Opin Green Sust Chem 5:49–54

Mecerreyes D (2011) Polymeric ionic liquids: broadening the properties and applications of polyelectrolytes. Prog Polym Sci 36(12):1629–1648

Mehrdad A, Miri AH (2016) Influence of 1-butyl-3-methyl imidazolium bromide, ionic liquid as co-solvent on aqueous solubility of acetaminophen. J Mol Liq 221:1162–1167

Monteiro AL, Zinn FK, de Souza RF, Dupont J (1997) Asymmetric hydrogenation of 2-arylacrylic acids catalyzed by immobilized Ru-BINAP complex in 1-n-butyl-3-methylimidazolium tetrafluoroborate molten salt. Tetrahedron 8(2):177–179

Muñoz-Bonilla A, Fernández-García M (2018) Poly (ionic liquid) s as antimicrobial materials. Eur Polym J 105:135–149

Papaiconomou N, Estager J, Traore Y, Bauduin P, Bas C, Legeai S, Viboud S, Draye M (2010) Synthesis, physicochemical properties, and toxicity data of new hydrophobic ionic liquids containing dimethylpyridinium and trimethylpyridinium cations. J Chem Eng Data 55 (5):1971–1979

Passos H, Freire MG, Coutinho JA (2014) Ionic liquid solutions as extractive solvents for value-added compounds from biomass. Green Chem 16(12):4786–4815

Patachia S, Damian N (2014) Cryogels based on poly (vinyl alcohol)/ionic liquids: from obtaining to antimicrobial activity. Soft Mater 12(4):371–379

Pernak J, Goc I, Mirska I (2004) Anti-microbial activities of protic ionic liquids with lactate anion. Green Chem 6(7):323–329

Pfruender H, Amidjojo M, Kragl U, Weuster-Botz D (2004) Efficient whole-cell biotransformation in a biphasic ionic liquid/water system. Angew Chem Int Ed 43(34):4529–4531

Rogers RD, Seddon KR (2003) Ionic liquids-solvents of the future? Science 302(5646):792–793

Savjani KT, Gajjar AK, Savjani JK (2012) Drug solubility: importance and enhancement techniques. ISRN Pharm 2012:195727

Sheikhi-Kouhsar M, Bagheri H, Raeissi S (2015) Modeling of ionic liquid+ polar solvent mixture molar volumes using a generalized volume translation on the Peng–Robinson equation of state. Fluid Phase Equilib 395:51–57

Shin US, Kim JG (2012) 3D micromorphology producing within poly (lactic acid) skeleton using room-temperature ionic liquids: from particulate, fibrous or porous Scaffolds to beads. Bull Kor Chem Soc 33(7):2295–2298

Singh M, Singh RS, Banerjee UC (2009) Stereoselective synthesis of (R)-1-chloro-3 (3, 4-difluorophenoxy)-2-propanol using lipases from Pseudomonas aeruginosa in ionic liquid-containing system. J Mol Catal B 56(4):294–299

Smiglak M, Pringle JM, Lu X, Han L, Zhang S, Gao H, Macfarlane DR, Rogers RD (2014) Ionic liquids for energy, materials, and medicine. Chem Commun 50(66):9228–9250

Somers AE, Howlett PC, MacFarlane DR, Forsyth M (2013) A review of ionic liquid lubricants. Lubricants 1(1):3–21

Soni SK, Sarkar S, Selvakannan PR, Sarkar D, Bhargava SK (2015) Intrinsic therapeutic and biocatalytic roles of ionic liquid mediated self-assembled platinum–phytase nanospheres. RSC Adv 5(77):62871–62881

Tran CD, Mututuvari TM (2015) Cellulose, chitosan, and keratin composite materials. Controlled drug release. Langmuir 31(4):1516–1526

Tsioptsias C, Panayiotou C (2008) Preparation of cellulose-nanohydroxyapatite composite scaffolds from ionic liquid solutions. Carbohydr Polym 74(1):99–105

Viau L, Tourné-Péteilh C, Devoisselle JM, Vioux A (2010) Ionogels as drug delivery system: one-step sol-gel synthesis using imidazolium ibuprofenate ionic liquid. Chem Commun 46 (2):228–230

Wang X, Chen H, Luo Z, Fu X (2016) Preparation of starch nanoparticles in water in oil microemulsion system and their drug delivery properties. Carbohydr Polym 138:192–200

Weber CC, Kulkarni SA, Kunov-Kruse AJ, Rogers RD, Myerson AS (2015) The use of cooling crystallization in an ionic liquid system for the purification of pharmaceuticals. Cryst Growth Des 15(10):4946–4951

Welton T (1999) Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev 99(8):2071–2084

Weuster-Botz D (2007) Process intensification of whole-cell biocatalysis with ionic liquids. Chem Rec 7(6):334–340

Wilkes JS, Zaworotko MJ (1992) Air and water stable 1-ethyl-3-methylimidazolium based ionic liquids. J Chem Soc 13:965–967

Williams HD, Sahbaz Y, Ford L, Nguyen TH, Scammells PJ, Porter CJ (2014) Ionic liquids provide unique opportunities for oral drug delivery: structure optimization and in vivo evidence of utility. Chem Commun 50(14):1688–1690

Wood N, Ferguson JL, Gunaratne HN, Seddon KR, Goodacre R, Stephens GM (2011) Screening ionic liquids for use in biotransformations with whole microbial cells. Green Chem 13 (7):1843–1851

Xu Q, Zheng Z, Wang B, Mao H, Yan F (2017) Zinc ion coordinated poly (ionic liquid) antimicrobial membranes for wound healing. ACS Appl Mater Interfaces 9(17):14656–14664

Yu Y, Yang Z, Ren S, Gao Y, Zheng L (2020) Multifunctional hydrogel based on ionic liquid with antibacterial performance. J Mol Liq 299:112185

Zec N, Idrissi A, Bešter-Rogač M, Vraneš M, Gadžurić S (2018) Insights into interactions between 1-butyl-3-methylimidazolium dicyanamide and molecular solvents: γ-valerolactone, γ-butyrolactone and propylene carbonate. Volumetric properties and MD simulations. J Mol Liq 268:481–489

Zhang X, Li X, Li D, Qu G, Wang J, Loiseau PM, Fan X (2009) Ionic liquid mediated and promoted eco-friendly preparation of thiazolidinone and pyrimidine nucleoside-thiazolidinone hybrids and their antiparasitic activities. Bioorg Med Chem Lett 19(22):6280–6283

Zhang T, Guo J, Ding Y, Mao H, Yan F (2019) Redox-responsive ferrocene-containing poly (ionic liquid) s for antibacterial applications. SCIENCE CHINA Chem 62(1):95–104

Zhao H, Xia S, Ma P (2005) Use of ionic liquids as 'green'solvents for extractions. J Chem Technol Biotechnol 80(10):1089–1096

Zheng Z, Guo J, Mao H, Xu Q, Qin J, Yan F (2017) Metal-containing poly (ionic liquid) membranes for antibacterial applications. ACS Biomater Sci Eng 3(6):922–928

Silver Composites as Antimicrobial Materials

David Romero-Fierro, Moisés Bustamante-Torres, Sandra Hidalgo-Bonilla, and Emilio Bucio

Abstract There are a great number of diseases associated with bacteria accumulation on medical devices, which have been studied in the last years. The constant negatives effects that can be produced in human health are a big deal for science. The biomedical investigation is not only concerned to avoid or eliminate the bacteria proliferation but to find materials that present better properties as a benefit for the humans. The ONU proposed focused on raw materials that must be renewables and natural materials. This is following the green chemistry instructions as well as maintaining the world sustainability. Silver is a rare but important element that has been employed for a long period of time as an antimicrobial agent. Based on these principles, its inhibitory activity will depend on the silver form, synthesis, and some other environmental factors such as pH, temperature, among others. This chapter details the synthesis of silver composites based on the combination with a natural or synthetic compound like chitosan, silicon, cotton, polyurethane epoxy, and polyester. The importance of choosing the correct and natural compound, enhancing its properties as well as reducing risks to human health. Thus, silver element can be used in other applications fields like the food industry that also is important for general health.

Keywords Silver · Composite · Antimicrobial activity · Natural compounds · Properties · Biomedical applications

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1 Introduction

1.1 Infectious Diseases and the Need for Antimicrobial Agents

Silver is one of the first metals discovered and used due to its potential antimicrobial activity. For this reason, it has been used for a long period of time. It can be founded in nature (minerals and rivers) but it is a rare element. Silver exists primarily as metal ions or nanoparticles and, therefore, applications are based on the properties and raw materials from where they are obtained. Thus, based on the reducing bacteria activity, it can be used primarily for antimicrobial effects that reduce the accumulation or spread of different pathogenic microorganisms associated with serious issues.

Infectious diseases are caused by hazardous microorganisms that mainly are pathogenic. These diseases are transmitted either directly or indirectly from bacteria, viruses, parasites, or fungi and even from one person to another one. However, the mortality rate from infectious diseases has been reduced worldwide since the eighteenth century due to the adoption of new hygiene patterns within human society (José and Borgaro 1989). In recent years, it has not only doubled but even tripled life expectancy worldwide. Thus, as living standards have increased, the causes of death have changed, although they vary by country and income level. Despite this decrease, infections continue to be a serious threat to public health and have a great impact on social, economic, and even political aspects, especially in developing countries (Matharu et al. 2018).

However, the high frequency of infections caused by employing medical devices such as joint prostheses or intravascular catheters represents a key factor to take into account during medical practices. Infections associated with biomedical devices involve very complex interrelationships between the microorganism, the implant surface, and the host. Once the microorganisms colonize the device, they are able to develop on the surface device a biolayer that is determinant in the pathogenesis of these infections. Therefore, it emerges as a big deal in world medicine.

At first glance, the need has arisen to create biomedical devices by antibacterial materials that present a high efficiency. Therefore, it could provide the prevention of biofilm infections in biomedical devices and address an urgent demand within the public health system. Antimicrobial materials have been listed as the main strategy to solve infectious diseases.

The discovery of antimicrobial agents represents an important advance in the medical field. Antimicrobial materials are defined as the base materials for the construction of biomedical devices with bactericidal properties and with high resistance to infection. Subsequent improvements in the interaction between medical devices and these new antimicrobial materials have been studied deeply, which can obtain the ability to administer medical substances, which fulfill the function of preventing, treating, or reducing latent or existing infections. Today, these powerful materials save lives. However, it is also important to take into account the evolution in the resistance of bacterial strains against common antimicrobial compounds.

2 Silver

Historically, silver has shown great antimicrobial activity that was approved by the FDA since 1920. This property has been widely studied and has found a wide variety of applications, due to its low toxicity in human cells (Clement and Jarrett 1994; Melaiye and Youngs 2005; Sim et al. 2018). Silver ions are widely known to have inhibitory, bactericidal, and broad-spectrum antimicrobial properties. Likewise, some silver salts have proven effective against skin burns, critical chronic osteomyelitis, urinary tract infections, and central venous catheter infections. Thus, it has also been shown that silver is effective against several types of pathogenic microorganisms that are found in infected biomedical devices including *Escherichia coli*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* (Panáček et al. 2018; Sun et al. 2015). Nowadays, biomedical applications of silver are focused on the interaction with the polymeric matrix. The matrix could be made from different raw materials that are known as polymers that present a great biocompatibility.

2.1 Action of Silver on Microorganisms

The precise mechanism of action of silver is not fully identified and it remains a topic of debate and study in the scientific community. Silver is an element that has been widely studied as an antimicrobial since it is effective in reducing different bacteria strains, fungi, and certain viruses. However, pure metallic silver does not present reactivity in contact with human tissue or kill microorganisms until it reaches its ionic state. Thus, positively charged silver ions (Ag^+) are those that have an antimicrobial effect (Lansdown 2010; Percival et al. 2012). These ions are obtained in a simple way when the metallic silver is in an aqueous medium. Silver ions act on microorganisms in different ways. One of the most studied ways describes that silver ions are adapted into the cell membranes of bacteria and link to proteins present in membrane which have the job to transport a variety of substances in and out of bacterial cells. Also, silver ions move inside the cell and avoid cell division when they bind to DNA. Besides, silver ions block all respiratory systems of the bacteria and, therefore, finish the production of energy in the cell. Finally, there will be a collision of the cell membrane and the bacteria will die (Melaiye and Youngs 2005) (Fig. 1).

Many mechanisms have been reported as responsible for the biocidal action of materials composed of silver. One of the possibilities states that the production of large amounts of free radicals by silver nanoparticles and oxygen reactive species induces oxidative stress in the cell (Prasad 2014; Aziz et al. 2014, 2015, 2016, 2019). This mechanism has been studied by electron spin resonance spectroscopy, finding that these free radicals penetrate the cell membrane, making it more porous and lead to cell death.

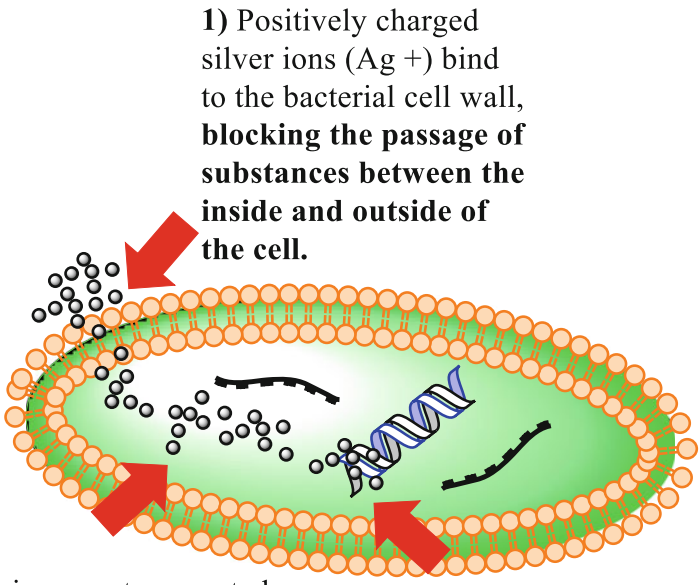

Fig. 1 Schematic representation of a possible mechanism of action of silver

Mei and his collaborators explored the antimicrobial action of silver nanocomposites. The study shows that synthesized nanocomposites can effectively kill both Gram-positive and Gram-negative bacteria without showing resistance from these bacteria. The observations were made using TEM and that its effect begins with the breaking of the bacterial membrane, followed by diffusion of the silver nanoparticles inside the cell and subsequent inhibition of intracellular enzyme activity (Mei et al. 2014).

In the same way, it has been found that nanoparticles control signal transduction in bacteria. In this sense, phosphorylation of protein substrates in bacteria influences signal transduction. On the other hand, the dephosphorylation process is notorious only in the tyrosine residues of Gram-negative bacteria. Thus, the phosphotyrosine genetic profile of bacterial peptides is disturbed by silver nanoparticles. Therefore, the silver nanoparticles allow dephosphorylation of the peptide substrates into tyrosine residues, which drives to an inhibition of signal transduction and thus, finally, at the end of growth (Shrivastava et al. 2007). However, as mentioned above, it is necessary to recognize that more research on the subject is required to elucidate the claims.

2.2 Silver Toxicity

Silver is a rare but naturally occurring element (Drake and Hazelwood 2005). The diverse application presents different routes of administration to biological systems. Ingestion is the primary route of entry for silver compounds and colloidal silver proteins (Silver 2003). Inhalation of silver-containing clouds of dust or fumes occurs in occupational settings (ATSDR 1990). Thus, it can produce side effects in the human body. An example was demonstrated at 7 g dosage of intrauterine silver nitrate as an abortion procedure caused mortality (Hadrup et al. 2018). Besides, it can get other hazards effects during the contact with the skin through to jewelry, or creams to burns application, deodorant, textile clothes, and mucosal surfaces. Even, some medical devices contain silver. Thus, the constant exposure for the population presents a potential risk to health.

The new strategies to determine the toxicity effects of the materials will be indispensable in the next years. A toxic effect is defined as an unwanted effect on health (Phillip et al. 2000). In this case, silver toxicity will depend on the concentrations, morphology, size distribution, complexity of biological systems, among other features. Silver can exist in two different physical forms, either ions or metallic.

Silver ion is one of the most toxic forms of heavy metal, this has been assigned to the highest toxicity class, together with cadmium, chromium (VI), copper, and mercury (Albright et al. 1972; Doudoroff and Katz 1953).

It is well known the metallic silver nanoparticles (AgNPs) can inhibit the replication of several bacteria strains. It has been proposed that AgNPs interact with the glycoprotein 120 (gp120), which blocking the viral activity in a wide range of bacteria.

AgNPs also inhibit influenza virus inhibiting viral penetration into the host cell (Mehrbod et al. 2016). However, it also can present a great efficacy against either prokaryotic or eukaryotic cells. At a cellular level, the complexity of biological systems does not matter regarding AgNPs toxicity (Vazquez-Muñoz et al. 2017). An estimated 20 tons of silver nanomaterials were produced in the United States during 2010 (Hendren et al. 2011). There is a great difference in the inhibition between unicellular and pluricellular effects. The pluricellular organisms present a major mechanism of defense than another one, like different barrier beginning from the skin, and immune system. These characteristics allow them to withstand some toxic compounds, like metallic nanoparticles.

Silver can be released into the air, water, and soil. The total U.S. release into the atmosphere was approximately 77,700, 125,000 into the water, and 1.01 million of kg into the land in 1978 (Scow et al. 1981). Silver particles are emitted from the burning of fossil fuels, it can undergo deposition into the atmosphere when are coated with silver oxide, silver sulfide, among others (ATSDR 1990). In freshwater, silver may form complex ions with chlorides, ammonium, and sulfates (ATSDR 1990). Meanwhile, it is known that the soils inhibiting the bacteria multiplication.

2.2.1 Common Problems Associated with Silver

Silver into its different forms can produce different issues in the body. It still has not been demonstrated death causes assigned to silver compounds. Besides, the mortality of these compounds has been studied in animals and humans showing different negative effects.

Genotoxicity

Genotoxicity refers to processes that alter the structure, information content, or segregation of DNA and that are not necessarily associated with mutagenicity (Pellevoisin et al. 2018). According to Hadrup, Sharma, and Loeschner, silver can bind to nitrogen bases and produce a significant change into the genes. Although the studies keep at the top of the science actually, it has been demonstrated the silver ions and AgNPs have effects on the DNA of mammalian cells. Thus, the only silver ion is genotoxic but no mutagenic. Meanwhile metallic silver can affect genetics into mononuclear cells.

Respiratory Effects

Respiratory effects have not been reported in many cases related by inhalation to silver compounds. One reported patient was reported to be affected in the work environment, unfortunately, the concentration, doses, and chemical composition were unknown but it could recover fully in animals, scientists demonstrated that silver compounds remain mainly in a little portion into the lungs, in contrast, the liver presents a major amount of concentration after 225 days (77%).

Dermal/Ocular Effects

The skin and eyes can suffer a disease known as argyria. It has been described as blue-gray discoloration of the skin due to the deposition of silver (Hadrup et al. 2018). It determines that the main causes are the frequent exposure to silver, like workers who stay directly in contact for a long time with this compound, even at minimum doses. However, not only can it affect the skin but eyes, internal organs, or nails, beginning from the mouth. Unfortunately, the previous studies have shown that is a rare but permanent issue.

Neurological Effects

Several reports of a woman who present a nasal treatment containing silver nitrate have been demonstrating that it can affect the central nervous system (time and doses unknown). Therefore, no enough evidence confirms how the silver works over the nervous system.

3 Silver Composites

The medical applications of silver have been detailed throughout history. For example, the Romans, in 69 BC, used $AgNO_3$ to avoid wound and burn infections. Moyer proposed and reintroduced the biomedical use of silver ions, conducting an experiment in which he demonstrated that silver shows antibacterial properties against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa (*Moyer et al. 2013*)*. Even though the mechanism of action of silver has not yet been clarified, these discoveries motivated the progress of a variety of silver-based composites. However, there are still many controversies about its biomedical use, because silver ions at high doses could lead to intoxication.

3.1 Classification of Silver Composites

Silver composites present a great number of different applications. Based on the raw materials it can get different properties that can be adapted into several biomedical field. Therefore, they can be different based on interaction between the silver and the raw compound.

3.1.1 Silver–Chitosan Composites

Chitosan is a polysaccharide that contains in its structure linear chains of glucosamine [β-(1-4)-D-glucosamine] and N-acetyl-D-glucosamine [β-(1-4)-N-acetyl-D-glucosamine], in lower proportion. Chitosan shares a similar chemical structure to cellulose; therefore, it confers to this polymer a rigid structure without branching. The main difference between both molecules is the abundance of reactive functional groups like hydroxyl and amino groups (Fig. 2). This fact allows the molecule to build intermolecular and intramolecular hydrogen bonds, providing the capacity to create water-insoluble crystalline aggregates, which are soluble in acid solutions (Moyer et al. 2013). Another important detail of these functional groups, especially amino groups, is the fact that they are capable of being ionized (becoming cationic) and, therefore, to form hydrophobic interactions. (Lizardi-Mendoza et al. 2016). These differences in chemical structure confer to chitosan different functions in

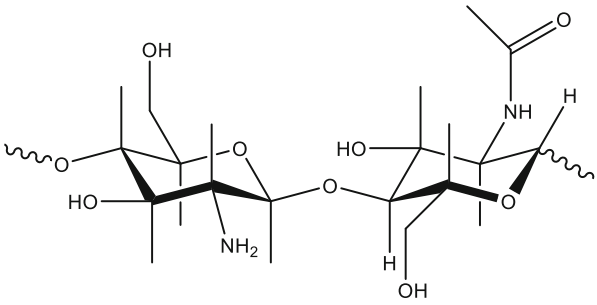

Fig. 2 Chemical structure of chitosan

comparison with cellulose. One of the more remarkable characteristics is its thermal stability because it decomposes at 170 °C and degrades before melting (Aragón et al. 2018). The polycationic character of chitosan is responsible for the interactions with diverse types of molecules. This character along with its structural capacities, biocompatibility, and related properties, making chitosan an attractive biopolymer for the development and production of functional materials to be applied in some fields.

In recent years, countless projects and experiments have been carried out which demonstrate that chitosan acts as an antimicrobial agent, that is alone or in conjunction with other natural polymers (Kong et al. 2010; Goy et al. 2016). Its mode of action has been described using the ionizable groups that its structure presents. These groups allow the union of the polysaccharide to the cell wall of pathogenic microorganisms. This interaction allows the hydrolysis of peptidoglycans in the cell wall of the microorganism, which causes the release of intracellular electrolytes, causing the death of the microorganism (Goy et al. 2016). Among the spectrum that includes microorganisms that are susceptible to the antimicrobial activity exhibited by chitosan are Gram-positive, Gram-negative bacteria, and fungi (Goy et al. 2009).

However, this inhibitory activity depends on several environmental factors. For example, it has been shown that this antimicrobial capacity shows better results in an acidic environment, which are reduced as the pH increases. This fact is attributed to the fact that at pH >7 there is a presence of positively charged amino groups, as well as a very poor solubility of the polysaccharide. Many studies have been conducted using an acid reaction medium, but not using alkaline conditions.

Another important factor to take into account is the ionic strength. It has been shown that if changes in ionic strength occur, chitosan inhibitory activity will be affected, which could be attributed to two mechanisms. First, an increase in metal ions, especially those with a valence value of 2, can affect the intrinsic chelating capacity of chitosan. In one study it was found that by adding 0.05M of magnesium ions in the reaction medium, the chitosan inhibition radius decreased greatly and even became inverted. In another study, this parameter was evaluated, but using smaller concentrations of barium, calcium, and magnesium metal ions (10 and 25 mM), checking that the chitosan bactericidal capacity against *E. coli* is affected by this ionic strength disturbance (Tsai and Su 1999). The second mechanism can be

associated with the chitosan polycationic character. This is since cations can emerge in the environment that can interact competitively with negatively charged components that occur in the cell wall, which leads to a decrease in antimicrobial activity (Kong et al. 2010).

As mentioned before, chitosan acts as an antimicrobial agent individually, even without the adhesion of any component; however, numerous studies demonstrated that the adhesion of silver in its structure improves its antimicrobial properties (Matharu et al. 2018). In one study, the antimicrobial features of some chitosan silver nano composites (CAgNCs) were demonstrated employing the pathogen *Vibrio tapetis* as model bacteria. Through turbidimetric and agar disk diffusion tests, it was concluded that these composites can avoid the growth of the model pathogen in a concentration-dependent way. Thus, the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of CAgNCs against *V. tapetis* were 50 μg/mL and 100 μg/mL, respectively. Also, through the use of Field Emission Scanning Electron Microscopy (FE-SEM), the severe cellular damage that the pathogen suffered after its treatment with CAgNCs with a concentration of 75 μg/mL was compared with an untreated bacterium. The study confirms this damage by stating that the composite induces the release of nucleic materials (DNA and RNA), causing a decrease in cell viability, oxidative stress, and inhibition of protein expression. Besides, it is concluded that the excessive generation of ROS, the loss in the integrity of the cell membrane, and the inhibition of protein synthesis are the mode of action of the composite that produces cell death (Godahewa 2014).

Another study shows the preparation and characterization studies of chitosan–ascorbic acid–silver nanocomposites as films that exhibit excellent antimicrobial activity and non-cytotoxicity for cells from human origin. The stabilizing and reductive activity of chitosan and ascorbic acid is determinant in the preparation of silver nanoparticles (AgNPs). The films obtained show a continuous distribution of small silver nanoparticles (<10 nm) and at the same time have a high antimicrobial activity against biofilm that forms fungal and bacterial strains of *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. The final solid shows cytotoxicity totally or partially excluded from somatic cells and tumor cells. Therefore, it is concluded that this material is very promising in the treatment of infections related with microorganisms without harmful effects (Regiel-Futyra et al. 2017).

In another investigation, gelatin, chitosan (CS), and silver (Ag), (Gelatin/CS/Ag) composites are prepared, using gelatin as a stabilizing and reducing agent to re-establish silver nanoparticles in situ. AgNPs are mixed with CS, cross-linked with tannic acid, and then lyophilized to get the synthesized composite, which will present a dense pore structure with a pore magnitude of about 100–250 μm. The characterization of the synthesized nanoparticles was carried out employing visible UV spectrophotometry, X-ray diffraction, and scanning electronic microscopy. In addition to showing excellent mechanical properties, water absorption, and humidity retention, the composite shows a good inhibitory effect against *E. coli* and *Staphylococcus aureus*, without showing cytotoxicity (good biocompatibility). This leads

the authors to conclude that the composite created has a promising future as an antimicrobial material (Ye et al. 2019).

Silver nanoparticles/chitosan composites exhibit an antiviral activity against the AH1N1 influenza virus (Mori et al. 2013). The compound was obtained as brown or yellow powders of the flocculated type following the reaction at room temperature in an aqueous media. Silver nanoparticles of different sizes (3.5, 6.5, and 12.0 nm) adhered to the chitosan matrix without aggregation or alternation of size. The results obtained show that, in the three nanoparticle sizes tested, the antiviral activity increases as the nanoparticle concentration increases. Another important conclusion is that this inhibitory activity is stronger when the smaller nanoparticles were deposited in the composite, which makes the inhibition dependent on size (Mori et al. 2013).

3.1.2 Silver–Silicon Composites

Silica is a non-combustible, colorless, or white crystal. When it forms networks, it is a ceramic that has drawn the attention of the scientific community for bone prostheses, sewage treatment, sanitary ware and glazing. By itself, silica does not show an antimicrobial activity but it uses silver as an antibacterial component.

The inhibitory capacity of silver–silica nanocomposites against some pathogens was reported in recent literature (Egger et al. 2009). Egger and his collaborators used a ceramic composite which in its structure contains silver nanoparticles submersed in an amorphous silicon dioxide matrix. AgNPs were situated on the surface and impregnated in the matrix. The results of this study showed that this composite has antibacterial activity against Gram-positive and Gram-negative bacteria, with high concentrations, in comparison with common silver-based composites like silver zeolite and silver nitrate (Egger et al. 2009).

This antibacterial activity also was studied with a composite of nanosilver–silica (Ag-SiO_2) composite, which was synthesized (Mosselhy et al. 2017). This composite shows prolonged in vitro antibacterial properties, against *S. aureus* and *E. coli*. As an application of the composite, it was impregnated in a common cotton gauze, showing better results of bacterial inhibition compared to a commercial dressing containing silver, which represents a potential application in the biomedical field for cutaneous wound healing. TEM and SEM analyzed were developed and their results revealed that the mechanism of action of silver ions is through an interaction with cytoplasmic constituents. This adhesion allows the silver to act and cause cell death, previously described (Mosselhy et al. 2017).

Another study shows the synthesis of nanosilver–silicone hydrogel (NAgSiH) contact lens composites (Helaly et al. 2017). The synthesized silicone hydrogel (SiH) is impregnated in silver nitrate solutions with a variety of concentrations (10, 20, 40, 60, and 80 ppm), and using sodium borohydride as a reducing agent for silver ions. The characterization of AgNPs was employed using UV-visible spectroscopy and EDX spectrum. The bactericidal activity of the composite was evaluated using *Pseudomonas aeruginosa*, *Bacillus subtilis*, *S. aureus*, and *E. coli* as

model bacteria. It was shown that hydrogels impregnated with the larger concentrations of silver nitrate (60 and 80 ppm) experience the best reduction process in bacterial viability both in solution and on the surface of the hydrogel. Therefore, the authors conclude that the inclusion of AgNPs in SiH films reduces bacterial growth and prevents colonization (Helaly et al. 2017).

3.1.3 Silver–Cotton Composites

Cotton is a textile fiber of plant origin that grows near the seeds of the cotton plant, a shrub of the genus *Gossypium*, belonging to the family of the *Malvaceae*. The chemical composition of cotton consists of 94% cellulose, 1.23% protein, 1.2% pectic substances, 1.2% mineral materials, 0.6% wax, 0.3 sugar and the rest for other minority elements.

Its major component, cellulose, is a natural polymer (Fig. 3). Cellulose is formed by the union of several β-D-glucose molecules through β-1-4-O-glucosidic bonds. Therefore, using hydrolysis process, glucose can be obtained. Cellulose is a long polymer chain of variable molecular weight, with an empirical formula $(C_6H_{10}O_5)_n$, with a minimum value of $n = 2000$ (Elliott 1957) (Fig. 4).

Cellulose has a linear or fibrous structure, in which multiple hydrogen bonds are set between the hydroxyl groups of different superimposed glucose chains, making

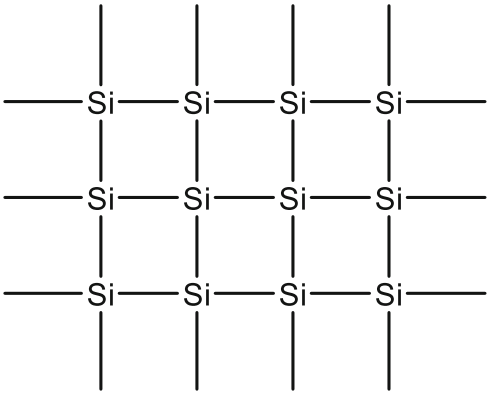

Fig. 3 Common silicon lattice structure

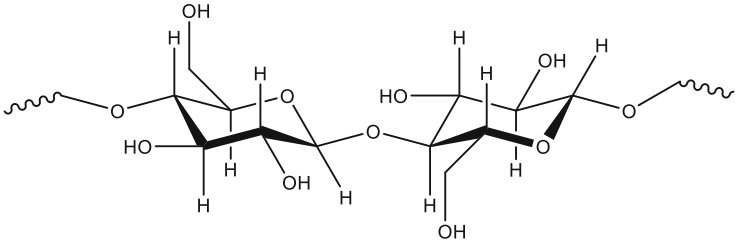

Fig. 4 Chemical structure of α-cellulose

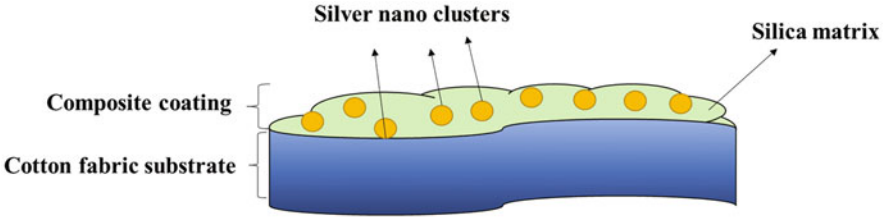

Fig. 5 Schematic diagram of the silver nanoclusters/silica composite embedded into cotton fabric

them impenetrable to water, which makes it insoluble in water, and causing compact fibers that constitute the cell wall of the plant (Elliott 1957).

The use of cotton in the textile industry has been recorded since prehistoric times. Cotton is a very popular material due to its high absorption capacity, which allows it to retain liquids and moisture. This quality is because its structure allows it to establish hydrogen bonds with several molecules. However, this valuable quality also allows the retention of microorganisms and pathogens, which means the proliferation of infections. For this reason, many previous treatments are done to prevent microbial spread. Thus, among those treatments, silver–cotton nanocomposites stand out, which have showed antimicrobial activity (Matharu et al. 2018).

In a study conducted by Irfan, a cotton functionalization is carried out with a silver nanoclusters silica composite through the RF co-sputtering technique (Irfan et al. 2017) (Fig. 5). For this, the composite is deposited by radiofrequency co-sputtering in cotton fabric. Characterization studies of morphology, composition, metallic silver content, antimicrobial properties, in vitro tests of silver penetration through human skin, contact angle, and air permeability were performed. The correct deposition of the coating was confirmed by FE-SEM, EDX, and XPS. The new composite has inhibitory activity against certain model pathogens such as *Candida albicans*, *E. coli*, and *S. aureus*. This inhibitory effect is shown even up to three days after immersion of the sample during the silver leaching test (Irfan et al. 2017).

Another clear example of this type of composite is one that is made of cotton fabric with a hydrogel that supports silver nanoparticles (Staneva et al. 2016). The synthesis was produced in two steps and by a simultaneous in situ synthesis of AgNPs under the effect of visible light irradiation. The characterization was performed to assess the influence of the concentration of silver on the hydrogel, as well as the properties of the silver nanoparticles were developed by colorimetric analysis, SEM, and TEM. The antimicrobial study was developed using *Acinetobacter johnsonii* and *E. coli*, as model bacteria, in an agar medium. As expected, excellent results were obtained for both crops, but expressed better against the first bacteria (Staneva et al. 2016).

Dodecanethiol-capped silver nanoparticles were added in silica sol via the sol-gel procedure (Tarimala et al. 2006). For this study, the modified composite was used to change the cotton surface. The study presents sufficient arguments to conclude that cotton doped with silver exhibits bactericidal behavior when it is hatched in a

suspension of *E. coli* during 5 h. In addition, it is found that the composite with a higher concentration of dodecanethiol-capped silver nanoparticles shows better performance since it completely cancels bacterial growth (Tarimala et al. 2006).

3.1.4 Silver–Polyurethane Composites

Polyurethanes are a family of polymeric materials that differ from the rest of plastic materials in that it has no urethane monomer and the polymer is almost invariably created in the manufacturing process of a particular object (Burke and Hasirci 2004).

Polyurethanes are synthesized by means of exothermic reactions between alcohols (with two or more reactive hydroxyl groups –OH per molecule) and isocyanates (with one or more reactive isocyanate –NCO groups per molecule). As an example of this synthesis, the following reaction that results in the formation of polyurethane is shown (Fig. 6):

The group formed by the reaction between both molecules is known as "urethane linkage," which constitutes a fundamental part of the polyurethane molecule.

Polyurethanes have certain properties that make it a very versatile polymer, for various biomedical applications. Among these properties are its biocompatibility, biodegradability, good mechanical properties, and its physical and chemical forms (Prabhakar et al. 2011). Polyurethanes have been applied in multiple areas including

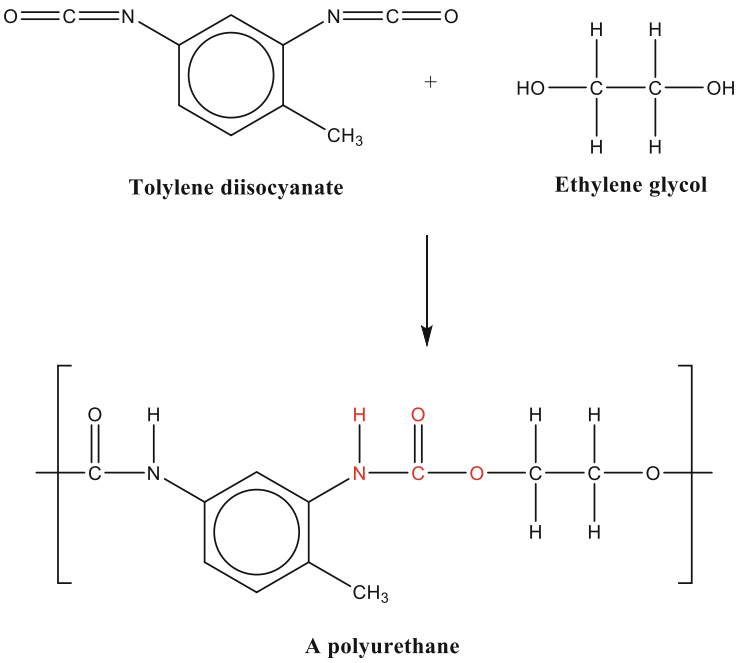

Fig. 6 Reaction to formation of a polyurethane

catheters, antibacterial surfaces, stents, in drug delivery systems, tissue engineering, nerve regeneration, cardiac patches, and coatings for implants (Burke and Hasirci 2004). However, despite their great advantages, polyurethanes have a tendency to assimilate in their structure pathogens, allowing the formation of microbial biofilms, which are commonly difficult to eradicate (Mtimet et al. 2012).

To avoid this disadvantage of the material, various modifications have been made with an antimicrobial element such as silver. For example, a study conducted to determine the impact of silver nanoparticles that are in photocured materials, in order to verify antimicrobial activity, showed interesting results (Zeytuncu and Morcali 2015). For this, AgNPs were synthesized and added to the polymer matrix of the polyurethane. This polymer modification was characterized by means of FTIR and SEM. The results of the SEM exhibited the dispersion of the nanoparticles on the surface, as well as their sizes. In addition, mechanical tests show that those silver-coated materials have a better Young's modulus and improved thermal behavior. To evaluate the antimicrobial activity, they used *Staphylococcus aureus* and *E. coli*, which are annihilated in the presence of photocured materials containing AgNPs (Jain and Pradeep 2005).

Certain common polyurethane (PU) foams can be coated with nanoparticles, by nightly exposure of the foams to colloidal nanoparticle suspensions (Jain and Pradeep 2005). Thus, to have a uniform coating on the material, washing and air-drying cycles are performed. It proved that silver nanoparticles are stable when loaded into PU foams, without affecting the morphology of the same. This stability is related with the interaction of the nanoparticles and the nitrogen atom of the polyurethane. Antimicrobial studies were carried out in drinking water flows. Therefore, at a flow rate of approximately 0.5 L/min, when the contact time was of the order of one second, the *E. coli* count was completely zero when the inlet water had a bacterial load of 105 units colony-forming (CFU) per milliliter. This concludes that this new composite could be used as a water filter, to prevent bacterial pollution that is harmful to health (Jain and Pradeep 2005).

A recent study shows the synthesis of silver nanoparticles by irradiation with microwave to a silver nitrate aqueous solution ($AgNO_3$) in poly (ethylene glycol), without using other chemical reagents (Mtimet et al. 2012). By means of microscopic tests, stable, monodispersed, and spherical nanoparticles with an approximate diameter of 35 nm are obtained. The conditions that were used for the synthesis were 20 min of irradiation, 120 °C temperature, and in the presence of PEG 2000. Subsequently, the water-based PU was deposited in colloidal suspensions of nanoparticles with PEG at different times. In the same way, it was found that the nanoparticles were well dispersed in the PU. Through thermo-mechanical tests, it was determined that the inclusion of nanoparticles did not affect the behavior of PU. Finally, it was determined that both the nanoparticles synthesized in PEG and the composite of PU/PEG/AgNPs show biocidal behavior against *Pseudomonas aeruginosa* and *Enterococcus faecalis* (Mtimet et al. 2012). This study is novel because it is a green synthesis because it does not use reagents that contribute to environmental problems.

3.1.5 Silver–Epoxy/Clay Composites

Composites based on epoxy–clay systems have been studied in detail and have shown interesting mechanical, structural, and barrier properties that make them versatile materials for application in different fields, both industrial and biomedical. These properties and the structure of the composites will depend on several factors such as curing agents, clay modifier, and the processing method (Zabihi et al. 2018; Azeez et al. 2013).

Epoxy–clay nanocomposites are commonly synthesized by an in situ polymerization reaction. The first step of this preparation is a dispersion of the clay in the epoxy resin, prior to the curing process. This dispersion establishes the morphology of the clay that it will have in the nanocomposite structure. Therefore, a homogeneous distribution allows to improve the percentage of exfoliation and, in contrast, a poorly dispersed clay will not allow good penetration of the epoxy monomer in the clay galleries. This clay dispersion can be achieved by some methods such as ultrasonication, high shear mixing, mechanical stirring, slurry process, and mixing with high pressure. These methods can be more efficient through the use of solvents, creating more homogeneous dispersed surfaces. For example, in one study it was determined that the application of acetone as a low boiling solvent in the mixing process does not vary the properties and morphology of the synthesized composite, it only facilitates its processability due to the reduction in the viscosity in the system (Zabihi et al. 2018; Brown et al. 2000).

Various investigations have been carried out that show that incorporating silver nanoparticles in the epoxy–clay composite reduces or completely eliminates microbial contamination. A study shows the coating made of hyperbranched epoxy/clay nanocomposites with silver nanoparticles (Roy et al. 2013). The characterization confirming the synthesis of AgNPs was confirmed by UV-Visible, XRD, and SEM study of mechanical properties. When comparing the new composite with the silver-free composite, the gloss varies from 70 to 90°, scratch hardness changes from 4 to 5.8 kg, the impact force from 60 to 90 cm, bond strength from 5 to 7.1×10^9 N/m, flexibility of >6 to <4 mm and a thermostability of 230 to 260 °C for the synthesized composite. The new nanocomposite shows some bactericidal activity against the *S. aureus*, *B. subtilis*, *E. coli*, *P. aureus*, and *K. pneumoniae* model bacteria when in an agar solution, which determines that these composites can be used as antimicrobial materials (Roy et al. 2013).

3.1.6 Silver–Polyester Composites

Polyesters are polymers whose structure is based on hydrocarbon chains containing ester bonds. The structure of Fig. 7 is called poly (ethylene terephthalate) or PET because it has ethylene and terephthalate groups. The ester groups in the polyester chain are polar, where the oxygen atom of the carbonyl group has a negative charge and the carbon atom of the carbonyl has a positive charge. The negative and positive

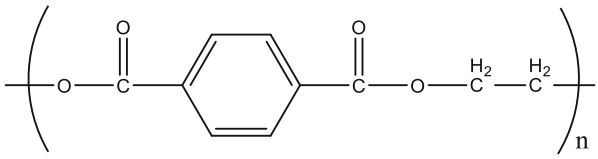

Fig. 7 Chemical structure of polyester

charges of the various ester groups attract each other. This allows the ester groups of neighboring chains to align with each other in a crystalline form and, as a result, give rise to resistant fibers.

Synthetic materials such as polyester have been widely used in industry and in health care facilities in recent years. However, these materials have no resistance to colonization of pathogenic microorganisms. Due to this problem, antimicrobial polyesters that have been modified with silver have proved to be very attractive in the scientific world and industry. As mentioned during this chapter, materials with antimicrobial activity are synthesized by means of surface modification, adding the bactericidal agent into a polymeric matrix. This surface modification can be achieved by means of various techniques such as in situ synthesis of AgNPs, dip-coating method, deposition technique, a magnetron sputtering method, and by means of ionizing radiation (gamma rays and plasma). Each of these techniques has advantages and disadvantages that are related to its application as a biomaterial. For example, the dip-coating technique is a quick method but offers durability problems. On the other hand, from the deposition techniques, the magnetron sputtering method offer stability and durability of the material, but the nanofiller dispersion does not turn out to be satisfactory.

Knowing the antimicrobial capacity of silver nanoparticles, several researchers have tried to incorporate them into polyester matrices or other types of textiles, to avoid microbial colonization and contamination of the material. Thus, the bactericidal effect of polyester and silver-based composites has been quantitatively and qualitatively proven against *S. aureus*, *Streptococcus pneumoniae*, and *E. coli* (Lee et al. 2003; Perelshtein et al. 2008). All studies show that bacterial cultures have been significantly reduced (>84%) or have been completely annihilated after one hour of treatment with the silver–polyester composite (Lee et al. 2003; Perelshtein et al. 2008).

An example of the in situ synthesis of silver nanoparticles is that carried out using tamarind leaf extract as a reducing agent and several silver nitrate solutions as a source in polyester fabrics (Pusphalatha et al. 2019). Modified fabrics were characterized by some techniques such as SEM, FTIR, X-ray diffraction, and antimicrobial tests. Through this procedure, nanoparticles with a size in a range from 50 to 120 nm were obtained, which were verified by SEM. The X-ray analysis allowed to determine that both AgNPs and AgO nanoparticles were generated within the composite. Finally, antimicrobial tests proved that composite polyester fabrics have good bactericidal activity against Gram-positive bacteria such as Gram-negative, so this composite could be used for the development of antimicrobial textiles (Pusphalatha et al. 2019).

In another study, silver nanoparticles with a hydrophobic surface (HS-nano-Ag) with a size smaller than 10 nm and also coated with 18 wt% aliphatic acids are prepared (Sun et al. 2014). These nanoparticles were designed precisely to enhance dispersibility and phase compatibility with a polyester matrix. In this sense, several polyester-based composites with different HS-nano-Ag contents (0.1, 0.5, 1, and 20 wt.%) were synthesized by means of melt processing. The properties and of the polyester matrix and the effect of the additive on the structure were studied. Therefore, employing a TEM analysis, it was determined that the HS-nano-Ag additive shows a fine and continuous dispersion in the polyester matrix. As for antimicrobial tests, polyester fibers modified with the additive show a bactericidal effect (>96%) against *Staphylococcus aureus* and *E. coli* when the content of the HS-nano-Ag additive in the matrix is low (100 ppm) (Sun et al. 2014).

4 Perspectives and Conclusions

Due to the great interest that has connoted the use of composite materials based on biologically active components, such as silver, for an antimicrobial application it is not surprising that this type of materials will expand in other areas and applications.

The most important requirement that such materials should have will be the total absence of a risk to human health. For this challenge it will be very important to continue investigating the mechanisms of action of these composites when interacting with the biological environment. So far what has been shown in the different studies is the ability to annihilate silver composites on bacteria, however, it will be necessary to determine if an application in direct contact with the human body is possible. In this regard, importance should be given to the synthesis of silver nanoparticles, in the production of composites and reagents used in these processes. Indeed, the green chemistry and sustainability postulates must be taken into account for a more environmentally friendly synthesis of silver nanoparticles in order to replace conventional synthetic models.

For the purposes described above, the utilization of natural polymers such as alginate, chitosan, and cellulose offers a myriad of benefits for the preparation of composite materials starting with the vast appearance of these polymers in nature make large-scale industrial production to be possible. In this sense, the results obtained with the chitosan and cellulose-based silver composites seem to be quite encouraging in terms of their effective response against Gram-positive and Gram-negative bacteria, without showing toxicity against eukaryotic cells.

Among the various techniques mentioned in this chapter for obtaining silver composites, electrophoretic deposition is shown to have great potential, particularly for biomedical applications. Indeed, electrophoretic deposition appears as a versatile technique to obtain homogeneous coatings of greater thickness on a surface of some material, since there is absolute control over the process. In addition, materials with a high degree of purity are obtained. Likewise, this technique offers the opportunity to modify the surface of biomaterials without affecting the bulk properties they possess.

Based on the successful results obtained for composites in biomedical applications, one might think that these materials would be very successful in other areas such as the food industry, whose main purpose is to prolong the effective half-life of food. As far as these materials, coatings based on some polysaccharide and modified with silver nanoparticles appear as a novel opportunity for the future packaging of fresh food.

There are countless composites based on metal particles; however, silver-based composites have shown great effectiveness for biomedical and industrial applications. It is expected that scientific advances and greater knowledge on the subject will allow these materials to be used daily in real life.

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References

Albright LJ, Wentwort JW, Wilson E (1972) Technique for measuring metallic. Water Res 6:1589. https://doi.org/10.1016/0043-1354(72)90083-8

Aragón B, Alberto L, Mejía J, Meza L, Edmundo J, Lara L, Damián P (2018) Composites of silver-chitosan nanoparticles: a potential source for new antimicrobial therapies. Rev Mexic Cienc Farm 47(4):7–25

ATSDR (1990) Toxicological profile for silver

Azeez AA, Rhee KY, Park SJ, Hui D (2013) Epoxy clay nanocomposites - processing, properties and applications: a review. Compos Part B Eng 45(1):308–320. https://doi.org/10.1016/j.compositesb.2012.04.012

Aziz N, Fatma T, Varma A, Prasad R (2014) Biogenic synthesis of silver nanoparticles using *Scenedesmus abundans* and evaluation of their antibacterial activity. J Nanopart, Article ID: 689419. https://doi.org/10.1155/2014/689419

Aziz N, Faraz M, Pandey R, Sakir M, Fatma T, Varma A, Barman I, Prasad R (2015) Facile algae-derived route to biogenic silver nanoparticles: synthesis, antibacterial and photocatalytic properties. Langmuir 31:11605–11612. https://doi.org/10.1021/acs.langmuir.5b03081

Aziz N, Pandey R, Barman I, Prasad R (2016) Leveraging the attributes of *Mucor hiemalis*-derived silver nanoparticles for a synergistic broad-spectrum antimicrobial platform. Front Microbiol 7:1984. https://doi.org/10.3389/fmicb.2016.01984

Aziz N, Faraz M, Sherwani MA, Fatma T, Prasad R (2019) Illuminating the anticancerous efficacy of a new fungal chassis for silver nanoparticle synthesis. Front Chem 7:65. https://doi.org/10.3389/fchem.2019.00065

Brown JM, Curliss D, Vaia RA (2000) Thermoset-layered silicate nanocomposites. Quaternary ammonium montmorillonite with primary diamine cured epoxies. Chem Mater 12 (11):3376–3384

Burke A, Hasirci N (2004) Polyurethanes in biomedical applications. Adv Exp Med Biol 553:83–101. https://doi.org/10.1201/9780203742785-9

Clement JL, Jarrett PS (1994) Antibacterial silver. Methods Based Drugs 1(5–6):467–482. https://doi.org/10.1155/mbd.1994.467

Doudoroff P, Katz M (1953) Critical review of literature on the toxicity of industrial wastes and their components to fish. Sewage Ind Waste 25(7):802–839

Drake PL, Hazelwood KJ (2005) Exposure-related health effects of silver and silver compounds: a review, vol 49. Oxford University Press, Oxford, pp 575–585. https://doi.org/10.1093/annhyg/mei019

Egger S, Lehmann RP, Height MJ, Loessner MJ, Schuppler M (2009) Antimicrobial properties of a novel silver-silica nanocomposite material. Appl Environ Microbiol 75(9):2973–2976. https://doi.org/10.1128/AEM.01658-08

Elliott JR (1957) The development of cotton wool as a wound dressing. Med Hist 1(4):362–366. https://doi.org/10.1017/S002572730002161X

Godahewa GI (2014) Chitosan silver nano composites (CAgNCs) as potential antibacterial agent to control vibrio tapetis. J Vet Sci Technol 5:5. https://doi.org/10.4172/2157-7579.1000209

Goy RC, De Britto D, Assis OBG (2009) A review of the antimicrobial activity of chitosan. Polimeros 19(3):241–247. https://doi.org/10.1590/S0104-14282009000300013

Goy RC, Morais STB, Assis OBG (2016) Evaluation of the antimicrobial activity of chitosan and its quaternized derivative on E. coli and S. aureus growth. Braz J Pharmacogn 26(1):122–127. https://doi.org/10.1016/j.bjp.2015.09.010

Hadrup N, Sharma AK, Loeschner K (2018) Toxicity of silver ions, metallic silver, and silver nanoparticle materials after in vivo dermal and mucosal surface exposure: a review. Regul Toxicol Pharmacol. https://doi.org/10.1016/j.yrtph.2018.08.007

Helaly FM, El-Sawy SM, Hashem AI, Khattab AA, Mourad RM (2017) Synthesis and characterization of nanosilver-silicone hydrogel composites for inhibition of bacteria growth. Cont Lens Anterior Eye 40(1):59–66. https://doi.org/10.1016/j.clae.2016.09.004

Hendren C, Mesnard X, Dröge J, Wiesner M (2011) Estimating production data for five engineered nanomaterials as a basis for exposure assessment. Environ Sci Technol 7(45):2562–2569. https://doi.org/10.1021/es103300g

Irfan M, Perero S, Miola M, Maina G, Ferri A, Ferraris M, Balagna C (2017) Antimicrobial functionalization of cotton fabric with silver nanoclusters/silica composite coating via RF co-sputtering technique. Cellulose 24(5):2331–2345. https://doi.org/10.1007/s10570-017-1232-y

Jain P, Pradeep T (2005) Potential of silver nanoparticle-coated polyurethane foam as an antibacterial water filter. Biotechnol Bioeng 90(1):59–63. https://doi.org/10.1002/bit.20368

José MV, Borgaro R (1989) Historia universal de la mortalidad. Salud Publica Mex 31(1):3–17

Kong M, Chen XG, Xing K, Park HJ (2010) Antimicrobial properties of chitosan and mode of action: a state of the art review. Int J Food Microbiol 144(1):51–63. https://doi.org/10.1016/j.ijfoodmicro.2010.09.012

Lansdown A (2010) Silver in healthcare: its antimicrobial effects and safety in use. Curr Probl Dermatol 33:274

Lee HJ, Yeo SY, Jeong SH (2003) Antibacterial effect of nanosized silver colloidal solution on textile fabrics. J Mater Sci 38(10):2199–2204. https://doi.org/10.1023/A:1023736416361

Lizardi-Mendoza J, Argüelles Monal WM, Goycoolea Valencia FM (2016) Chemical characteristics and functional properties of chitosan. Elsevier, London. https://doi.org/10.1016/B978-0-12-802735-6.00001-X

Matharu RK, Ciric L, Edirisinghe M (2018) Nanocomposites: suitable alternatives as antimicrobial agents. Nanotechnology 29:28. https://doi.org/10.1088/1361-6528/aabbff

Mehrbod P, Amini E, Tavassoti-Kheiri M (2016) Antiviral activity of garlic extract on influenza virus. Iran J Virol 3(1):19–23. https://doi.org/10.21859/isv.3.1.19

Mei L, Lu Z, Zhang X, Li C, Jia Y (2014) Polymer-Ag nanocomposites with enhanced antimicrobial activity against bacterial infection. Appl Mater Interfaces 6:15813–15821

Melaiye A, Youngs WJ (2005) Silver and its application as an antimicrobial agent. Expert Opin Ther Pat 15(2):125–130. https://doi.org/10.1517/13543776.15.2.125

Mori Y, Ono T, Miyahira Y, Nguyen VQ, Matsui T, Ishihara M (2013) Antiviral activity of silver nanoparticle/chitosan composites against H1N1 Influenza A virus. Nanoscale Res Lett 8(1):93. https://doi.org/10.1186/1556-276x-8-93

Mosselhy DA, Granbohm H, Hynönen U, Ge Y, Palva A, Nordström K, Hannula SP (2017) Nanosilver–silica composite: prolonged antibacterial effects and bacterial interaction mechanisms for wound dressings. Nanomaterials 7(9):1–19. https://doi.org/10.3390/nano7090261

Moyer C, Brentano L, Gravens D, Margraf H, Monafo W (2013) Treatment of large human burns with 0.5% silver nitrate solution. Arch Surg 90:812–867

Mtimet I, Lecamp L, Kebir N, Burel F, Jouenne T (2012) Green synthesis process of a polyurethane-silver nanocomposite having biocide surfaces. Polym J 44(12):1230–1237. https://doi.org/10.1038/pj.2012.90

Panáček A, Kvítek L, Smékalová M, Večeřová R, Kolář M, Röderová M, Dyčka F, Šebela M, Prucek R, Tomanec O et al (2018) Bacterial resistance to silver nanoparticles and how to overcome it. Nat Nanotechnol 13(1):65–71. https://doi.org/10.1038/s41565-017-0013-y

Pellevoisin C, Bouez C, Cotovio J (2018) Cosmetic industry requirements regarding skin models for cosmetic testing. In: Skin tissue models for regenerative medicine. Elsevier, London, pp 3–37. https://doi.org/10.1016/B978-0-12-810545-0.00001-2

Percival SL, Thomas J, Linton S, Okel T, Corum L, Slone W (2012) The antimicrobial efficacy of silver on antibiotic-resistant bacteria isolated from burn wounds. Int Wound J 9(5):488–493. https://doi.org/10.1111/j.1742-481X.2011.00903.x

Perelshtein I, Applerot G, Perkas N, Guibert G, Mikhailov S, Gedanken A (2008) Sonochemical coating of silver nanoparticles on textile fabrics (nylon, polyester and cotton) and their antibacterial activity. Nanotechnology 19(24):245705. https://doi.org/10.1088/0957-4484/19/24/245705

Phillip L, James RC, Roberts SM (2000) Principles of toxicology environmental and industrial. Wiley, Etobicoke

Prabhakar PK, Raj S, Anuradha PR, Sawant SN, Doble M (2011) Biocompatibility studies on polyaniline and polyaniline-silver nanoparticle coated polyurethane composite. Colloids Surf B Biointerfaces 86(1):146–153. https://doi.org/10.1016/j.colsurfb.2011.03.033

Prasad R (2014) Synthesis of silver nanoparticles in photosynthetic plants. J Nanopart, Article ID: 963961. https://doi.org/10.1155/2014/963961

Pusphalatha R, Ashok B, Hariram N, Rajulu AV (2019) Nanocomposite polyester fabrics with in situ generated silver nanoparticles using tamarind leaf extract reducing agent. Int J Polym Anal Charact 24(6):524–532. https://doi.org/10.1080/1023666X.2019.1614265

Regiel-Futyra A, Kus-Liśkiewicz M, Sebastian V, Irusta S, Arruebo M, Kyzioł A, Stochel G (2017) Development of noncytotoxic silver-chitosan nanocomposites for efficient control of biofilm forming microbes. RSC Adv 7(83):52398–52413. https://doi.org/10.1039/c7ra08359a

Roy B, Bharali P, Konwar BK, Karak N (2013) Silver-embedded modified hyperbranched epoxy/clay nanocomposites as antibacterial materials. Bioresour Technol 127:175–180. https://doi.org/10.1016/j.biortech.2012.09.129

Scow K, Goyer M, Nelken L, Payne E, Saterson K, Walker P, Wood M, Cruse P, Moss K (1981) An exposure and risk assessment for silver. Cambridge

Shrivastava S, Bera T, Roy A, Singh G, Ramachandrarao P, Dash D (2007) Characterization of enhanced antibacterial effects of novel silver nanoparticles. Nanotechnology 18(22):225103. https://doi.org/10.1088/0957-4484/18/22/225103

Silver S (2003) Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. Microbiol Rev 27:341–353. https://doi.org/10.1016/S0168-6445(03)00047-0

Sim W, Barnard RT, Blaskovich MAT, Ziora ZM (2018) Antimicrobial silver in medicinal and consumer applications: a patent review of the past decade (2007–2017). Antibiotics 7(4):1–15. https://doi.org/10.3390/antibiotics7040093

Staneva D, Vasileva-Tonkova E, Grabchev I (2016) Preparation, characterization and antibacterial activity of composite material cotton fabric/hydrogel/silver nanoparticles. J Biol Chem 2 (2):1–18. https://doi.org/10.1016/j.cya.2015.11.011

Sun B, Hua B, Ji X, Shi Y, Zhou Z, Wang Q, Zhu M (2014) Preparation of silver nanoparticles with hydrophobic surface and their polyester based nanocomposite fibres with excellent antibacterial

properties. Mater Res Innov 18:4869–4874. https://doi.org/10.1179/1432891714Z.000000000794

Sun D, Babar Shahzad M, Li M, Wang G, Xu D (2015) Antimicrobial materials with medical applications. Mater Technol 30(B2):B90–B95. https://doi.org/10.1179/1753555714Y.0000000239

Tarimala S, Kothari N, Abidi N, Hequet E, Fralick J, Dai LL (2006) New approach to antibacterial treatment of cotton fabric with silver nanoparticle-doped silica using sol-gel process. J Appl Polym Sci 101(5):2938–2943. https://doi.org/10.1002/app.23443

Tsai GJ, Su WH (1999) Antibacterial activity of shrimp chitosan against Escherichia Coli. J Food Prot 62(3):239–243. https://doi.org/10.4315/0362-028X-62.3.239

Vazquez-Muñoz R, Borrego B, Juárez-Moreno K, García-García M, Morales JDM, Bogdanchikova N, Huerta-Saquero A (2017) Toxicity of silver nanoparticles in biological systems: does the complexity of biological systems matter? Toxicol Lett 5:7. https://doi.org/10.1016/j.toxlet.2017.05.007

Ye H, Cheng J, Yu K (2019) In situ reduction of silver nanoparticles by gelatin to obtain porous silver nanoparticle/chitosan composites with enhanced antimicrobial and wound-healing activity, vol 121. Elsevier, London. https://doi.org/10.1016/j.ijbiomac.2018.10.056

Zabihi O, Ahmadi M, Nikafshar S, Chandrakumar Preyeswary K, Naebe M (2018) A technical review on epoxy-clay nanocomposites: structure, properties, and their applications in fiber reinforced composites. Compos Part B Eng 135:1–24. https://doi.org/10.1016/j.compositesb.2017.09.066

Zeytuncu B, Morcali MH (2015) Fabrication and characterization of antibacterial polyurethane acrylate-based materials. Mater Res 18(4):867–872. https://doi.org/10.1590/1516-1439.026515

Natural Antimicrobial Materials

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Abstract Microorganisms correspond to a wide variety of viruses, bacteria, among others, that can produce positive or negative effects on the environment. The accumulation of these microorganisms on surfaces is usually very associated with diseases. The Environmental Protection Agency (EPA) is an organization that controls possible risks to human health and the environment, in which it also participates in the study of some microorganisms. The research of this organization focuses on ecological processes associated with how to reduce or eliminate the negative consequences produced by a microbe. Therefore, the importance of following green synthesis and the use of renewable natural materials that show beneficial properties and improve global sustainability arises. Furthermore, antimicrobial agents emerge as a possible alternative to eliminate or reduce possible microorganisms. Materials like polymers, organic acids, peptides, polysaccharides are some examples of these bioactive compounds. Each of these materials has a specific mode of action (still unknown in some cases) and properties that have been demonstrated in different strains of bacteria. This chapter details the natural antimicrobial materials commonly used today and how they act on microbiological strains, with powerful biomedical applications.

Keywords Microorganisms · Bacteria strains · Natural antimicrobial materials · Environmental protection agency · Properties · Biomedical applications

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1 Introduction

1.1 Overview of Antimicrobial Materials

Microorganisms is a broad term used to encompass bacteria, yeast, fungi, and in some definition viruses (Batt 2016). Microorganisms have existed for millions of years ago, affecting directly or indirectly the living beings producing either positive or negative effects. Therefore, a wide range of microorganisms that are present into the microbiota showing a benefit symbiotic relation with the host. In contrast, some normal or critic diseases have been related to microorganisms.

Nowadays, medical devices are fundamentals for the medical field. They present a lot of problems related to microorganisms. Infections are the most common problem related to this issue. The biofilm formation arises as a result of bacteria deposition on the medical surface, which will be covered by a matrix polysaccharide. Based on this principle, the biofilm can be avoided by the immune system. Therefore, complexity will be progressive, making the elimination of bacteria more difficult as time goes by. Post-surgical effects generally pose huge risks to human health and as costs increase.

The biomedical field has been enhanced in the last years with antimicrobial materials based on different raw sources. The usage of various stents, heart valves, and different kinds of implant devices has been significantly increased (Sun et al. 2014). Therefore, nowadays the creation of medical devices with a potential antimicrobial activity is one of the objectives of the medical and scientific industry.

Besides, through food, different bacteria can enter the human body and produce diverse effects. Food-borne illnesses are mild but sometimes they can even be deadly (Bingöl and Bostan 2007). Food-borne pathogens (*Clostridium botulinum*, *Staphylococcus aureus*, *Campylobacter jejuni*, *Bacillus cereus*, *Listeria monocytogenes*, *Cryptosporidium*, *Escherichia coli O157:H7*, etc.) are the main concern regarding the safety of food (Demain 1992). The antimicrobial agents associated with the food industry must not only preserve and enhance the quality of the food but reduce the bacteria proliferation.

Nowadays, novel materials with a high biocompatibility and antimicrobial activity are fundamental to reduce or eliminate diseases associated to microorganisms. So, a lot of natural and synthetic elements present advantages and disadvantages during the interaction with biomaterials. Here, we review the most common natural antimicrobial materials that have been employed to different applications based on their properties and action mechanisms.

1.2 Natural Antimicrobial Materials (NAM)

1.2.1 Natural Antimicrobials

Although all materials are derived from nature, at some point in their manufacture, natural materials are subjected to less treatment and processing than man-made materials (Clairenstein 2020). Natural materials can be defined as any product that can be extracted from nature sources. NAM can be obtained from organic or inorganic sources and present thousands of applications such as textiles, food, medical devices, among others. Depending on their properties, natural compounds can be applied as antimicrobial agent. An antimicrobial is an agent that kills microorganisms or stops their growth (Antimicrobial 2020). Natural antimicrobial materials have been used for a long time because their excellent properties and easy extract from raw materials like plants or derivates of animals.

1.2.2 Sustainability

Sustainability is a spread problem related to economic factors. It is linked directly with the environments and advances in technology. The correct selection of materials and methodology can reduce the possible risks associated with the human health and environment. Consistent use of natural compounds as raw materials during research can support novel synthesis and applications, as well as reduce economic considerations.

Obtaining main natural antimicrobial compounds must follow the green chemistry. Green chemistry employs the correct design of chemical products and processes to avoid the generation of toxic or hazardous substance (Agency USEP n.d.). The chemical design must be properly effective or try to present minimum toxicity.

The employment of potential antimicrobial natural compounds based on renewables sources has been an important investigation field. Sources like fruits, herbs, spices among others have presented beneficial properties. Nowadays, there are more than 1350 plants with antimicrobial activities and more than 30,000 antimicrobial components have been extracted from plants (Tajkarimi et al. 2010).

1.2.3 Selectivity

Antimicrobial material usually show hazardous effects on some microorganisms. However, antimicrobial activity affects the normal cells as well. Selectivity is associated with the capacity to combat a specific class of organisms. The researcher tries to enhance the applications as well as reducing side effects on other parts of the body.

Many cases of influence are mainly transmitted by contact with the infected. However, the viruses can also be transmitted when a person touches respiratory droplets settled on an object or surface (Wright and Webster 2001). Therefore, some research fields are trying to fabricate an antimicrobial coating to avoid the spreading of different viruses. Another form to combat the bacterial growth is trying the initial adhesion to any surface. Some coatings are based on copper, silver, and organic acids (carboxylic acids).

1.2.4 Safety Assessment

Environmental protection agency (EPA) is an independent agency of the US federal government for environmental protection (Our Mission and What We Do 2017). The EPA regulates the manufacturing, processing, distribution, and use of chemicals and other pollutants (Kenton n.d.). This worldwide organization is focused on the protection of the human and environments and reduce possible risks that are involved daily. EPA organizations consist mainly of a specialized team like scientists, legal and financial technologies.

A wide range of bacterial strains have been studied and supervised by EPA. The antimicrobial tests employ *Staphylococcus aureus*, *Enterobacter aerogenes*, *Methicillin-resistant Staphylococcus aureus* (MRSA), *Escherichia coli 0157:H7*, and *Pseudomonas aeruginosa.*

1.3 Classification of Natural Antimicrobial Materials

1.3.1 Polymers

Natural antimicrobial polymers are highly effective and selective properties as well as reduces the environmental impact caused by microbial agents (Kenawy et al. 2007). They are also characterized by being chemically stable and non-volatile, which is feasible to develop high resistance polymer systems (Muñoz-Bonilla et al. 2014). Some characteristics of a promising microbial polymer include easy and economical synthesis, long-lived under different conditions, non-toxic, non-irritating, regenerating, not soluble in water, and biocide (Kenawy et al. 2007). To comply with these characteristics, certain parameters related to the microbial polymer must be taken into account. The principal factors are molecular weight, load distribution, hydrophobic or hydrophilic behavior, type of alkylation, and the form of action of the microbial material (Muñoz-Bonilla et al. 2014; Munoz-Bonilla and Fernández-García 2011).

There are different natural mechanisms to activate polymeric components that increase microbial activity. Moreover, the addition of active functional groups in the structure implies the improvement of the properties of the material (Sharifi et al.

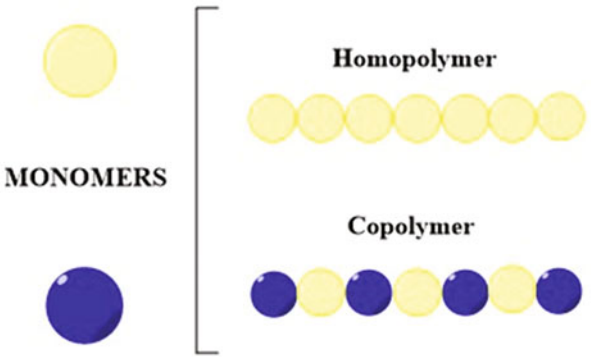

Fig. 1 Formation of homopolymers and copolymer from different monomers

2012). The functionalization can be carried out through microbial agents containing reactive groups such as hydroxyl, carboxyl, or amines, which can modify the hydrophilic and hydrophobic properties of the materials (Kenawy et al. 2007). This mechanism is favored with copolymer structures, which was synthesized from two different monomers as Fig. 1 represents (Al-Muaikel et al. 2000).

The mode of action could be explained in different ways: (1) Denaturalizing or altering the protein structure through the disruption of hydrogen and disulfide bonds; (2) Affecting the cell membrane proteins by denaturalization or the lipid membrane by dissolution; (3) Avoiding the formation of cellular wall; (4) Preventing cellular processes like replication, transcription, or transduction; (5) Altering the metabolic process (Muñoz-Bonilla et al. 2014).

The selectivity of the polymer and its antimicrobial activity is directly connected to the polymer chemical structure, bacterial structure, and biocompatibility (Brochu et al. 1995; Acharya et al. 2004; Rodríguez-Hernández 2017). Moreover, there are some factors as temperature, concentration, pH, and time, which are involved in the effectiveness of a antimicrobial agent (Muñoz-Bonilla et al. 2014). The area of application will depend fundamentally on the mentioned factors.

Natural polymers have excellent properties that promote their use for different applications. Its main application area focuses on the plastic, packaging, coatings, adhesives, textiles, agriculture, medical, and pharmaceutical industry (Sharifi et al. 2012). Some natural polymers like chitosan, alginate, starch, gelatin have been studied by its potential properties and promising uses (Palem et al. 2017; Arvanitoyannis et al. 1998; Kong et al. 2010; Haque et al. 2005; Gómez-Estaca et al. 2009; Prasad et al. 2017a).

As is known, the microbial activity varies according to the bacterial structure. On the one hand, Gram-positive, such like *S. aureus*, can have a loose cell membrane, unlike Gram-negative, as *E. Coli*, which are characterized by the presence of a membrane external to the cell wall, which serves as a barrier to foreign molecules. In previous studies, chitosan shows a relevant microbial activity against *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*, especially in copolymer structures and modified with quaternary functional groups (Kenawy et al. 2007). There was found a promising antimicrobial activity when the chitosan is

incorporated with gelatin or alginate, showing an effect against *Lactobacillus acidophilus*, *Pseudomonas fluorescens*, *Listeria innocua*, and *E. coli* (Gómez-Estaca et al. 2009; Haque et al. 2005). The material state is a relevant factor that has been studied, testing in solid state (Kong et al. 2010) or associated with nanoparticles of some metal like silver (Palem et al. 2017). The use of metal particles shows potential results as in the case of the alginate with Zn/Cu particles (Malagurski et al. 2018). However, most of the microbial activity varies according to some factors like polymer size, concentration, matrix, pH, temperature, among others.

1.4 Organic Acids

Organic acids are organic compounds that are produced naturally in vegetables and animal substrates. The most common are the carboxylic acids, distinguished by the presence of a functional group (COOH) in their structure. These could be classified according to their carbon-chain length into short (C1–C6), medium (C7–C10), and long (C11 or more) chain fatty acids (Cherringtona et al. 1991) as Fig. 2 represent. The antimicrobial activity is certainly related to short-chain acids which are partly dissociated by its weak acid nature. Each acid has a characteristic spectrum where the antimicrobial activity intensifies, for most of them, the specific pH is between 3 and 5, where the acid is half dissociated (Dibner and Buttin 2002). The length of the chain influences the microbial species on which it has an effective action. For example, in a study, it was obtained that formic acid was more effective in fighting *E. coli* and *Salmonella* spp., and long-chain acids were more effective against *C. perfringens (*Gómez-García et al. 2019*)* (Fig. 2).

Organic acids have a potential antimicrobial activity which is related to the ability to be integrated into the cellular membrane (Greenway and Dyke 1979). This mode of action is related to environments with low pH. The organic acids present a lipophilic behavior that permits diffusion across the lipid membrane (Davidson and Taylor 2007). As Fig. 3 shows, the mechanism of action is directly associated with pH and non-dissociated organic acid, which can penetrate the lipid bilayer of the cell membrane and once there, it dissociates when it comes into contact with a high pH (Davidson and Taylor 2007; Ricke 2003). Another mechanism is associated

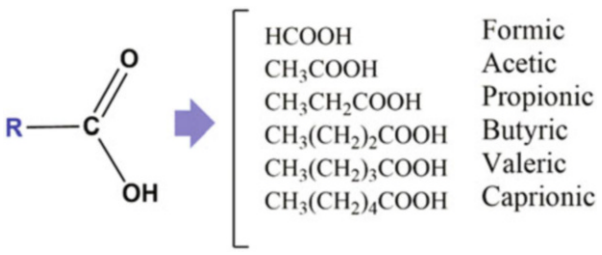

Fig. 2 Organic acids of short-chain length (C1-C6)

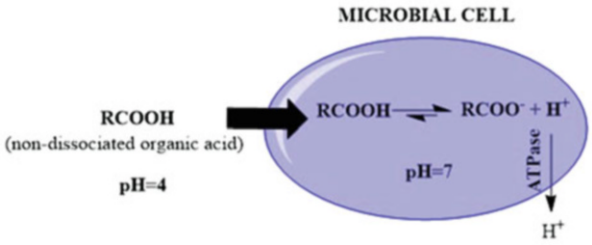

Fig. 3 Antimicrobial activity mechanism from organic acids

with the metabolic process that is affected by the high concentration of anions in the cellular cytoplasm, which increases the osmolarity of the cell (Paul and Hirshfield 2003).

However, microorganisms can develop a certain tolerance depending on the physiological conditions, pH, growth medium, methodology, and temperature (Brudzinski and Harrison 1998). It has been seen in previous research as species such as *Salmonella typhimurium* and *E. coli* have developed some tolerance response to organic acid in a certain pH range (Lin et al. 1995; Buchanan and Edelson 1999; Cheng et al. 2003).

The principal area in which it has been applied is as additives and preservatives to avoid food deterioration (Theron and Lues 2011). Their high efficiency and resistance are ideal to counter the effects of pathogen agents in food production environments (Ricke 2003). There are several studies on the microbial activity of organic acids; one of them describes the antimicrobial effect of organic acids from glucose fermentation, which were used against pathogenic bacteria such as *S. typhimurium*, *E. coli*, *E. faecalis*, *S. aureus*, and *C. difficile*, where it is observed that at a lower pH the area of inhibition is greater (Tejero-Sariñena et al. 2012). Other researchers confirm the influence of a certain pH in a better antimicrobial activity (Annuk et al. 2003; Røssland et al. 2003; Skřivanová and Marounek 2007).

1.5 Peptides

Antimicrobial peptides (AMPs) are ribosomally synthesized molecules, which are components of the immune system of multicellular organisms, which protect them from microbial agents (Alves and Pereira 2014). Potential properties have been found in animals, plants, bacteria, fungi, and viruses species (Alves and Pereira 2014; Costa et al. 2011; Hancock and Sahl 2006). Antimicrobial peptides are highly selective by their capacity to differentiate between the host and microbial cells. Besides, their microbial activity occurs over a wide range of microorganisms, and they are not slightly prone to develop microbial resistance (Alves and Pereira 2014; Altman et al. 2006).

AMPs manifest structural diversity, characterized by having chains between 10 and 25 amino acids, molecular weights between 1 and 5 kDa, cationic and

amphipathic character. These characteristics favor the interactions with membranes, cellular structures, and microbial surfaces (Costa et al. 2011; Andreu and Rivas 1998).

There is a wide mechanism that explains the AMPs activity as shown Fig. 4. However, most of AMPs are related to the cationic nature of antimicrobial peptides, which has an electrostatic attraction to negatively charged surface (Hancock and Lehrer 1998; Andreu and Rivas 1998). AMPs can disrupt the organization of the lipid membrane; produce porosity by which there is a loss of cellular content or even produce cell death (Melo et al. 2009). There are alternative mechanisms, among which is the so-called carpet effect, in which the peptides form a permeabilizing surface on the cytoplasmic membrane (Shai 1995) (Fig. 4).

Folded peptides are recognized in different structural groups: *β-sheet peptides*, which are characterized by intramolecular cysteine disulfide bridges (Montesinos 2007). These permit the peptides to fold into a compact structure with high chemical, thermal, and proteolytic structural stability (Campos et al. 2018); *α-helical peptides*, which is commonly induced in solvent presence and is positively linked to the antibacterial activity against Gram-positive and Gram-negative bacteria (Giuliani et al. 2008); *extended structures* rich in glycine, proline, tryptophan, arginine, and/or histidine; and *loop peptides* with one disulfide bridge (Hancock and Sahl 2006; Hancock and Lehrer 1998).

AMPs have antimicrobial activity over a wide spectrum of pathogen species. A previous test shows how cationic AMPs can disturb the lipid membrane of pathogens such as *S. aureus* (Omardien et al. 2016). Another study was focused on the antimicrobial effect of hydrolyzed proteins, which has activity against *Listeria innocua (*Aguilera-Aguirre et al. 2018*)*. Taking into account the importance of peptide amino acids, their effect on different species such as *Pseudomonas*, *Klebsiella*, *Staphylococcus*, *Proteus* was studied, in which positive results were found in some amino acid sequences (Lawyer et al. 1996). The inhibitory power against microbial agents can be classified as weak, medium, and strong. Microbial action of

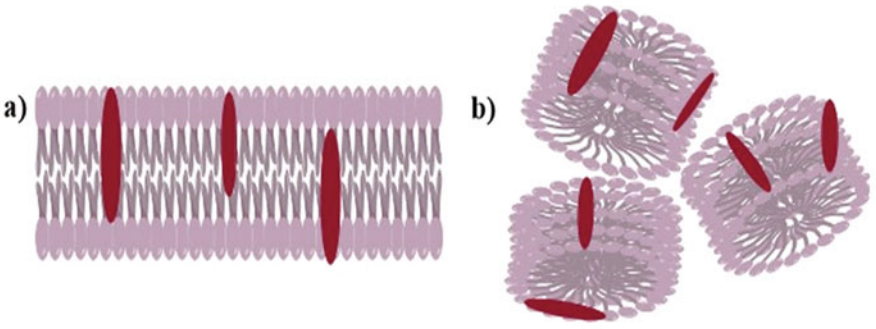

Fig. 4 Mechanism to explain the antimicrobial activity. (**a**) Perpendicular interference through the lipidic membrane. (**b**) "Carpet effect" permeabilization of the membrane surface

yerba mate has been reported against Gram-positive and Gram-negative species (Kungel et al. 2018a).

1.6 Polysaccharides

Polysaccharides are natural polymers characterized by their storage, structural, and protective functions. These substances could be obtained from animal and vegetable species, bacteria, and fungi (Coma 2013). The main known sources of polysaccharides are cellulose, starch, alginate, carrageenan, chitin, and glycogen. Figure 5 illustrates the structure of cellulose, which has been an important focus of research due to the major source of polysaccharides in cell walls in vegetable species.

Important characteristic related to polysaccharides is their structural variability, their role in molecular recognition and carrying of biological information (Krichen et al. 2015).

The mechanism of action has been in discussion. A possible way is related to iron inhibition. The antimicrobial agents form an impermeable layer around the cell, which prevents the entry of substances like iron; this is given by a polythetic phenomenon on the cell surface. It has been known that iron has an important role in bacterial growth and proliferation (Kungel et al. 2018b; Sun et al. 2011). This inhibition mechanism was tested against different bacterial species like *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella* spp. (Shao et al. 2017). The permeabilization effect has also been related to the cell nucleus, avoiding RNA or protein synthesis (Aranaz et al. 2009). It has been shown that different properties, including antimicrobial, can be improved through nanoparticles prepared from bioactive polysaccharides. This leads to better dispersibility, stability, and penetration of antimicrobial agents across the cell barrier based on reduced size and high surface/volume ratio (Qin et al. 2018; Prasad 2020).

There is a wide spectrum of polysaccharides sources with potential activity. Antimicrobial activity of polysaccharides was reported from vegetable species like oak or leaves of *Lapillius*, which was tested against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Aerobacter aerogenes*, and *Proteus vulgaris* (Tahmouzi 2014; Xie et al. 2012). However, pathogenic agents can develop resistance mechanisms. One of them is based on the capture of microbial peptides through polysaccharide capsules, which prevent peptides from coming into contact with the lipid membrane (Llobet et al. 2008; Mazareia et al. 2017). Another way to enhance the antimicrobial properties has been based on hybrid composites. The better microbial activity has been obtained by combining it between different polysaccharides such as cellulose and chitin, or by combining it with other compounds such as peptides (Castelletto et al. 2017; Duri et al. 2017).

These are important in the food industry, specifically by its hydrophilic, antimicrobial, and antiproliferative properties, which applies to the area of food preservation (Kuorwel and Kuorwel 2011; Heydarian et al. 2017). It is also useful in the pharmaceutical and biomedical industry (McCarthy et al. 2019; Arora et al. 2016;

Kumar et al. 2004; Tan et al. 2013). Their diverse potential applications could be enhanced by the capacity of the structure to be chemically modified.

1.7 Nanomaterials

The materials are considered nanometric when their dimensions are between 1 and 100 nm. The interest in developing nanomaterials (NM) is based on the detection of improved physical and chemical properties about bulk materials (Aruguete et al. 2013). Nanotechnology has been a useful tool to improve material properties through the modifications of nanoparticle features like size, shape, composition, and surface properties (Petros and DeSimone 2010). Moreover, there is attention in the functionalized treatment of NMs which allows providing potential properties to the materials (Daoud and Tung 2011).

The antimicrobial activity from nanomaterials can be explained by three mechanisms.

1. *Cell damage*: Electrostatic interactions between the nanomaterial and the cell membranes of pathogen agents, which leads to the loss of cell viability (Seil and Webster 2012). This mechanism is most effective when the size of the nanoparticles is less than 30 nm.
2. *Generation of reactive oxygen species (ROS)*: This mechanism is related to the generation of reactive oxygen species, which is associated with cellular damage, specifically to the degrading of organic compounds like DNA, RNA, and proteins (Aruguete et al. 2013).
3. *Release of toxic metals*: It is known that metal ions have a bactericidal toxic effect, whereby colloidal silver nanoparticles or other metal oxides may have antimicrobial properties (Aruguete et al. 2013; Lemire et al. 2013). The mechanism is associated with biocidal activity.

The nanomaterials based on natural products have become important mainly because of their non-toxicity, durability, and ecological acceptability (Simoncic and Tomsic 2010). There is a diversity of prominent sources such as polysaccharides, peptides, enzymes, organic acids, essential oils, among others. NMs can be associated with antimicrobial polymers that have the function of lysing selectively microbial membranes (Aruguete et al. 2013). Currently, nanomaterials are being used in countless applications. They have taken relevance in the consumer products industry due to the potentially developing properties. Also, they have been used for the study of targeted drug delivery. Natural antimicrobial agents have shown relevant properties associated with different shapes like in nanofibers, which could modify bacterial adherence to surface cellular reducing bacterial infections (Wang and Vermerris 2019). Another way to improve the effectiveness of the antimicrobial agents is the hybridization of two or more compounds for example cellulose-chitosan. These kinds of nanofibers commonly are obtained through the reaction of amination or acylation. In previous research, it was reported a principal change in

solvent compatibility (Du and Hsieh 2007, 2009). However, the area of greatest interest in medicine is related to the drug microorganism resistance and bacterial infections caused by material with non-appropriate biocompatibility. There are significant applications related to biomedical devices, prosthesis, tissue engineering, and nanostructures to drug delivery (Prasad et al. 2016, 2018). The main properties of NMs can be applied in innumerable proposes: biomedical devices, coatings, textiles, agriculture, among other novel materials with functional properties (Prasad 2017; Prasad et al. 2017b, c, d).

One of the main obstacles of NMs is the evaluation of possible reactions with cells, tissues, and organs. Despite its important benefits, it can generate multiorgan cytotoxicity, due to the accumulation of nanoparticles in different vital organs (Huh and Kwon 2011). Based on these precedents, the importance of obtaining naturally occurring nanomaterials with better biocompatibility arises. Certainly, there is a lack of knowledge about all the interactions between nanoparticles and the human body, so it is necessary to study factors such as doses and appropriate administration routes to reproduce the desired effects (Sandhiya et al. 2009).

2 Factors that Affect Antimicrobial Activity

The process of destruction of microorganisms and the subsequent inhibition of microbial colonization is not simple because it depends on several factors that affect the efficiency of the material with bactericidal capacity. The factors that affect this efficiency depend largely on the type of material being used.

2.1 Antimicrobial Properties

Essential Oils

Essential oils like plant extracts present antimicrobial agents and antioxidative and flavoring properties as well (Arshad and Batool 2017). The outstanding variability in the chemical composition of essential oils is linked to great multifunctionality as a consequence of their ability to interact with specific receptors for multiple biological targets. In this sense, many EOs have stood out for being efficient insecticides against a wide range of insects, in addition to possessing antimicrobial and phytotoxic activity. For this reason, essential oils have been used in traditional medicine, due to their antimicrobial capacity, in the treatment of infectious diseases since long before the existence of microorganisms was known. However, in recent years, antimicrobial resistance has been extensively studied. This effect is a factor that directly affects the efficiency of an antimicrobial (Can Başer and Buchbauer 2015; Kalagatura et al. 2020).

Some intrinsic and extrinsic factors are associated with the antimicrobial activity of essential oils. These include temperature, composition of the atmosphere, pH, redox

potential, and water activity, among others. In cases where the sample is exposed to an atmosphere containing the essential oil, the conditions must be carefully controlled to obtain significant results (Bakkali et al. 2008). The initial number of microorganisms must be consistent for the results to be reproducible. The effect of temperature is very important during incubation; it must be the optimal growth of the microorganism to evaluate, since in most cases, the increase in exposure temperature increases the antimicrobial effect of the oil. The atmosphere plays a very important role; it is necessary to define if the microorganism is anaerobic or not (Hyldgaard et al. 2012).

The antimicrobial activity of the phenolic compounds present in essential oils is favored by low pH values. This fact is attributed to the increased solubility and stability of these compounds. It is estimated that at low pH values, the molecules of phenolic compounds, such as thymol, are largely undissociated, with hydrophobic regions occurring in proteins and dissolving the lipid phase of the membrane better (Can Başer and Buchbauer 2015; Burt 2004; Tongnuanchan and Benjakul 2014).

Chitosan

It has been widely reported that the antimicrobial activity of chitosan is influenced by various factors, including the species and stage of development of the species, intrinsic factors and physical state of chitosan, and environmental factors (Kong et al. 2010).

The antimicrobial effect of chitosan can vary according to the microorganism under study, having a different behavior for fungi, Gram-positive and Gram-negative bacteria. This could be attributed to the external structures, characteristic of each microorganism. A study showed that the surface charge of cells varies with the growth phase, indicating that the susceptibility of the cells to antibiotics and chemical compounds also changes with that growth phase (Tsai and Su 1999). In this same sense, in another investigation the antimicrobial effect of various solutions of lactose-chitosan in water on *S. aureus* was analyzed and found that this microorganism is more susceptible at the end of the exponential growth phase (Chen and Chou 2005).

Among the intrinsic factors of chitosan, it is important to highlight the molecular mass and solubility of the material. Chitosan with a molecular mass between 4.6 and 100 kDa has been reported in the literature to have a good antimicrobial effect (Wright and Webster 2001). However, with molecular masses less than 4.6, such antimicrobial activity is negligible. Likewise, with masses greater than 100 kDa, chitosan does not present an antimicrobial effect due to the loss of its solubility, preventing its interaction with microorganisms (Aider 2010; Chen et al. 1998; Tokura et al. 1997; Dutta et al. 2009).

Deacetylation of chitin is the chemical process by which sodium hydroxide is used in order to hydrolyze the acetamido groups ($–NHCOCH_3$) to obtain as a result amino groups ($–NH_2$) that is innate of chitosan (Dutta et al. 2009). The degree of deacetylation is given between 0 and 100% where a higher degree of deacetylation is associated with a higher solubility and positive charge density. These two factors are very important for the adhesion of chitosan to the cell wall of microorganisms. In this

sense, a study evaluated the antimicrobial effect of chitosan with two different degrees of deacetylation (83.5 and 97.5%) on *S. aureus* in an acidic medium (pH = 5.5) and found that this effect was more evident using chitosan with a higher degree of deacetylation (Kong et al. 2010; Dutta et al. 2009; Ayala 2015).

The positive charge density in chitosan is defined as the capacity of this biopolymer to protonate its amino group and go from $–NH_2$ to $–NH_3^+$. This protonation process depends on the degree of deacetylation and the pH of your environment. $–NH_3^+$ groups are responsible for interacting with and destabilizing the external structures of the microorganisms (El Ghaouth et al. 1991).

Figure 5 shows the chemical structrue of chitosan, which is adequate to interact and form complexes with heavy metal ions such as Ni^{2+}, Zn^{2+}, Co^{2+}, Fe^{2+}, Mg^{2+}, and Cu^{2+}. This chelating capacity has been frequently used for the removal of heavy metals in different applications (Duarte 2009). On the other hand, the cell membrane of the microorganisms has Mg^{2+} and Ca^{2+} ions, which can be destabilized by interactions with chitosan, thus generating lysis of the cell membrane (Sadanand et al. 2016; Erdem et al. 2016) (Fig. 6).

In the literature it is reported that the antimicrobial activity of chitosan is greater when it is dispersed in a liquid medium compared to a solid medium. This fact is attributed to the greater diffusion capacity of the compound as it is dispersed in a liquid medium. In comparison, a chitosan membrane will only have antimicrobial activity on its surface (Chung et al. 2005; Xie et al. 2007).

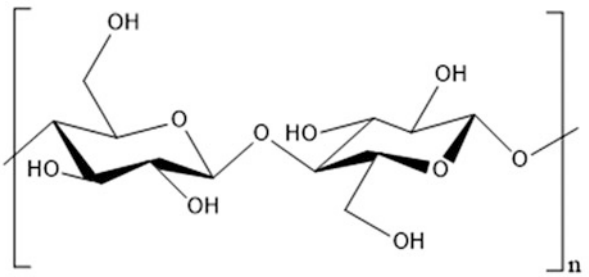

Fig. 5 Cellulose structure

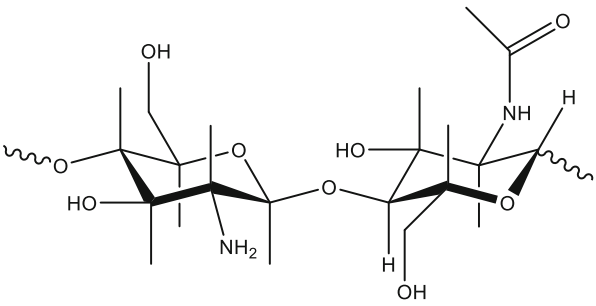

Fig. 6 Chemical structure of chitosan

The solubility of chitosan is a related to pH as well. Solubility occurs at an acidic pH and the antimicrobial effects is only achieved when this biopolymer is in an acidic medium, the pH is lower than the chitosan pH (pH < 6.3) what that allows the protonation of the amino groups (Tsai and Su 1999; Chung et al. 2005; Xie et al. 2007; No et al. 2002).

2.2 *Mode of Antimicrobial Activity*

In many of the antimicrobial materials, it has not been possible to determine precisely the mechanisms by which antimicrobial activity occurs. However, certain possibilities have been reported depending on the material in question.

Essential Oils

For example, in the case of essential oils (EOs) the synergistic action of secondary metabolites such as thymol, carvacrol, eugenol, p-cyneme, and cinnamaldehydes has been determined, which are commonly present in essential oils of plants such as oregano, rosemary, thyme, sage, and vanillin (Hyldgaard et al. 2012). P-cyneme is one of the terpenes that is found in greater proportion in essential oils, mainly in oregano and thyme. Although this metabolite has no innate antimicrobial capacity, it shows a great affinity for membrane cells, altering the properties of the bacteria and allowing the access of stronger antimicrobial compounds (Burt 2004).

On the other hand, several terpenoids such as thymol and carvacrol allow passive transport of ions through the membrane. This is due to the affinity that these compounds have for the cell membranes of bacteria. Thus, they can affect the membranes of both Gram-positive and Gram-negative bacteria, disintegrating them in the first case and altering their permeability affected the passage of cations such as H^+ and K^+, in the second case (Hyldgaard et al. 2012).

Finally, several phenylpropanoids have another type of interaction with the bacteria. These compounds permeabilize the cell membrane in a non-specific way and covalently intersect with DNA, altering its genetic configuration and subsequently producing cell death (Hyldgaard et al. 2012; Tongnuanchan and Benjakul 2014).

Chitosan

Chitosan is one of the most important natural polysaccharides. As in the case of essential oils, the mechanism of action of chitosan is still unknown; however, that antimicrobial capacity is attributed to the ability to inhibit microbial growth, which depends on several factors (Kong et al. 2010).

The polycationic nature of chitosan turns out to be ideal for antimicrobial activity. The pKa of chitosan and its derivatives are below the environmental pH, allowing electrostatic interactions between the chitosan and the anionic components of the microorganism surfaces. Thus, while the loading density of chitosan increases, in the same way the antimicrobial property will grow as has been proven in quaternized

chitosan (Dananjaya et al. 2014) and in chitosan metal complexes (Lizardi-Mendoza et al. 2016). On the other hand, if the pH of the medium is above pKa, hydrophilic and chelating effects will prevail over electrostatic interactions. These effects will be responsible for antimicrobial activity, as they will allow the chitosan to adhere to the cell membranes of the bacteria in order to alter its structure and allow cell death (Kong et al. 2010).

Nisin

Nisin is a bacteriocin (antimicrobial peptides with a potential bactericidal effects). The mechanism that reflects the antimicrobial capacity of nisin has been studied and documented. Nisin inhibits spore germination and the development of Gram-positive bacteria. As in the case of chitosan, nisin binds to the cell membrane through ionic interactions with the C-terminus, allowing the formation of pores in the membrane by penetrating the hydrophobic N-terminus (Bhatia and Bharti 2015). In addition, it was determined that nisin may have an inhibitory capacity for the formation of cell walls in bacteria by means of biosynthesis interference with a peptidoglycan layer. This process is independent of the mechanism of action through pore formation (Saini et al. 2016). On the other hand, it has been proven that this effectiveness increases when the nisin is exposed to a chelating agent.

2.3 Promising Antimicrobial Properties

Throughout the chapter the immense variety and application of natural materials has been demonstrated, which offers new opportunities for the synthesis of new antimicrobial fibers. However, to achieve this, certain challenges that must be taken into account and overcome them must be met. First, we have demonstrated that microbial populations have consubstantial genetic flexibility (Laxminarayan et al. 2013). This feature provides certain mechanisms of resistance to antibiotic agents by obtaining new biochemical functions. To combat this point, a thorough investigation is required to evaluate the potential of microorganisms to develop some resistance against natural materials, such as polysaccharides, which were described in this chapter. When the efficacy of these materials is known, a greater approach may be taken to prevent the spread of infections in patients who depend on these materials.

It is important to take into account that certain natural materials can develop microbial biofilms on their surface (Heunis et al. 2011), so in vivo tests must be developed to assess the stability and durability of the material. This is because the material can accumulate dead bacteria on its surface causing a decrease in its antimicrobial capacity as time progresses. One way to solve this problem is by studying and developing surfaces that have both antimicrobial and antifouling properties (Alves and Pereira 2014).

Significant advances have been made in the development of natural antimicrobial materials, which appear as a great promise for the new generation of antimicrobial biomaterials that present biodegradability and non-toxicity. With future research

covering the topics discussed above such as stability, durability, antibiotic resistance, these materials will undoubtedly offer a great contribution to high-level medical care for several generations.

3 Conclusion

Considerable advances have been obtained in the synthesis and development of NAMs with multiple applications. Renewable sources are fundamental to reduce or eliminate unnecessary risks for human health and the environment. Therefore, this chapter has summarized the main arguments from a scientific point of view.

There is great importance for betting on scientific research focused on NAMs, based on green chemistry processes (eco-friendly synthesis). However, it still is difficult to determine better compounds since there is no uniform research method in different laboratories. Therefore, nowadays, standards based on the quantitative comparison are not possible, and the mechanisms of action in some of them are not defined as well.

Based on the properties of the different NAMs, polymers have been most studied in the last decades. Due to their reactive functional groups, they can interact with other compounds, resulting in a potential improvement into its properties, even adopting another one as benefits for themselves. Silver compounds present a potential antimicrobial activity and a great affinity to form bonds with some polymers. The potential applications can be exploited in different industries, such as medical (reducing risks on human health), food (prolong the effective half-life), research, among others.

A wide range of natural material are available in the nature, which would be modified and promoting for a scientific approach. For these purposes, materials like polymers, polysaccharides, and peptides offer benefits during the interaction with other antimicrobial compounds, even at large-scale production.

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References

Acharya V, Prabha CR, Narayanamurthy C (2004) Synthesis of metal incorporated low molecular weight polyurethanes from novel aromatic diols, their characterization and bactericidal properties. Biomaterials 25(19):4555–4562

Agency USEP (n.d.) Basics of green chemistry

Aguilera-Aguirre S, Meza-Espinoza L, Hernández-Mendoza A, Vallejo-Córdoba B, González-Córdova AM-GE (2018) Evaluation of oxidative hemolytic inhibition capacity and antimicrobial activity of peptide fractions from egg, milk and soy protein hydrolysis using Bromelia pinguin and Bromelia karatas derived proteases. Rev Espec Cienc Quím Biol 21(S1):13–21

Aider M (2010) Chitosan application for active bio-based films production and potential in the food industry: review. LWT- Food Sci Technol 43(6):837–842
Al-Muaikel NS, Al-Diab SS, Al-Salamah AA, Zaid AM (2000) Synthesis and characterization of novel organotin monomers and copolymers and their antibacterial activity. J Appl Polym Sci 77:740–745
Altman H, Steinberg D, Porat Y, Mor A, Fridman D, Friedman M, Bachrach G (2006) In vitro assessment of antimicrobial peptides as potential agents against several oral bacteria. Antimicrob Chemoth 58(1):198–201
Alves D, Pereira MO (2014) Mini-review: antimicrobial peptides and enzymes as promising candidates to functionalize biomaterial surfaces. Biofouling 30(4):483–499
Andreu D, Rivas L (1998) Animal antimicrobial peptides: an overview. Pept Sci 47(6):415–433
Annuk H, Shchepetova J, Kullisaar T, Songisepp E, Zilmer M, Mikelsaar M (2003) Characterization of intestinal lactobacilli as putative probiotic candidates. J Appl Microbiol 94(3):403–412
Antimicrobial (2020) Merriam-Webster online dictionary. Accessed May 15, 2020
Aranaz I, Mengíbar M, Harris R, Paños I, Miralles B, Acosta N (2009) Functional characterization of chitin and chitosan. Curr Chem Biol 3(2):203–230
Arora D, Sharma N, Sharma V, Abrol V, Shankar R, Jaglan S (2016) An update on polysaccharide-based nanomaterials for antimicrobial applications. Appl Microbiol Biotechnol 100:2603–2615
Arshad MS, Batool SA (2017) Natural antimicrobials, their sources and food safety. Food Addit 2017:88–89
Aruguete D, Kim B, Hochella MF, Ma Y (2013) Antimicrobial nanotechnology: its potential for the effective management of microbial drug resistance and implications for research needs in microbial nanotoxicology. Environ Sci 15(1):93–102
Arvanitoyannis IS, Nakayama A, Aiba S (1998) Chitosan and gelatin based edible films: state diagrams, mechanical and permeation properties. Carbohydr Polym 37:12
Ayala G (2015) Efecto antimicrobiano del quitosano: una revisión de la literatura. Sci Agroaliment 2:32–38
Bakkali F, Averbeck S, Averbeck D, Idaomar M (2008) Biological effects of essential oils - a review. Food Chem Toxicol 46(2):446–475
Batt CA (2016) Microorganisms. Elsevier, London, pp 8–9
Bhatia S, Bharti A (2015) Evaluating the antimicrobial activity of nisin, lysozyme and ethylenediaminetetraacetate incorporated in starch based active food packaging film. J Food Sci Technol 52(6):3504–3512
Bingöl EB, Bostan K (2007) Effect of sodium lactate on the microbiological quality and shelf life of sausages. Turk J Vet Anim Sci 31:33–39
Brochu S, Prud'homme RE, Barakat I, Jérome R (1995) Stereocomplexation and morphology of polylactides. Macromolecules 28:5230–5239
Brudzinski L, Harrison MA (1998) Influence of incubation conditions on survival and acid tolerance response of Escherichia coli O157:H7 and non-O157:H7 isolates exposed to acetic acid. J Food Prot 61(5):542–546
Buchanan R, Edelson S (1999) pH-dependent stationary-phase acid resistance response of enterohemorrhagic Escherichia coli in the presence of various acidulants. J Food Prot 62 (3):211–218
Burt S (2004) Essential oils: their antibacterial properties and potential applications in foods—a review. Int J Food Microbiol 94(3):223–253. https://doi.org/10.1016/j.ijfoodmicro.2004.03.022
Campos M, Lião L, Alves E, Migliolo L, Dias S, Franco O (2018) A structural perspective of plant antimicrobial peptides. Biochem J 475(21):3349–3375
Can Başer KH, Buchbauer G (2015) Handbook of essential oils: science, technology, and applications, 2nd edn. Taylor & Francis, Milton Park
Castelletto V, Kaura A, HamleY I, Barnesa RH, Karatzasa K, Hermida-Merinob D, Swiokloc S, Connonc C, Stasiakd J, Rezae M, Ruokolainen J (2017) Hybrid membrane biomaterials from self-assembly in polysaccharide and peptide amphiphile mixtures: controllable structural and mechanical properties and antimicrobial activity. R Soci Chem 7:8366–8375

Chen YL, Chou CC (2005) Factors affecting the susceptibility of Staphylococcus Aureus CCRC 12657 to water soluble lactose chitosan derivative. Food Microbiol 22(1):29–35
Chen CS, Liau WY, Tsai GJ (1998) Antibacterial effects of N-sulfonated and N-sulfobenzoyl chitosan and application to oyster preservation. J Food Prot 61(9):1124–1128
Cheng H, Yu R, Chou C (2003) Increased acid tolerance of Escherichia coli O157:H7 as affected by acid adaptation time and conditions of acid challenge. Food Res Int 36(1):49–56
Cherringtona CA, Hintona M, Meada GC, Choprab I (1991) Organic acids: chemistry, antibacterial activity and practical applications. Adv Microb Physiol 32:87–108
Chung YC, Kuo CL, Chen CC (2005) Preparation and important functional properties of water-soluble chitosan produced through maillard reaction. Bioresour Technol 96(13):1473–1482
Clairenstein G (2020) Differences between natural & man-made materials. Accessed May 14, 2020
Coma V (2013) Polysaccharide-based biomaterials with antimicrobial and antioxidant properties. Polimeros 23(3):287–297
Costa F, Carvalho I, Montelaro R, Gomes P, Martins M (2011) Covalent immobilization of antimicrobial peptides (AMPs) onto biomaterial surfaces. Acta Biomater 7(4):1431–1440
Dananjaya SHS, Godahewa GI, Jayasooriya RGPT, Chulhong O, Jehee L, Mahanama DZ (2014) Chitosan silver nano composites (CAgNCs) as potential antibacterial agent to control Vibrio tapetis. J Vet Sci Technol 5(5):2–7
Daoud WA, Tung W (2011) Self-cleaning fibers via nanotechnology - a virtual reality. J Mater Chem 21:7858–7869
Davidson PM, Taylor TM (2007) Chemical preservatives and natural antimicrobial compounds. In: Food microbiology: fundamentals and frontiers, 3rd edn. ASM Press, Washington, pp 713–745
Demain AL (1992) Microbial secondary metabolism: a new theoretical frontier for academia, a new opportunity for industry. Second Metab Funct Evol 3:21–23
Dibner JJ, Buttin P (2002) Use of organic acids as a model to study the impact of gut microflora on nutrition and metabolism. J Appl Poult Res 11(4):453–463
Du J, Hsieh Y (2007) PEGylation of chitosan for improved solubility and fiber formation via electrospinning. Cellulose 14:543–552
Du J, Hsieh Y (2009) Cellulose/chitosan hybrid nanofibers from electrospinning. Cellulose 16:247–260
Duarte E (2009) Studies of chromium removal from tannery wastewaters by quitosan biosorbents obtained shrimp. Sci Technol 2(42):290–295
Duri S, Harkins AL, Frazier AJ, Tran CD (2017) Composites containing fullerenes and polysaccharides: green and facile synthesis, biocompatibility, and antimicrobial activity. ACS Sustain Chem Eng 5(6):5408–5417
Dutta PK, Tripathi S, Mehrotra GK, Dutta J (2009) Perspectives for chitosan based antimicrobial films in food applications. Food Chem 114(4):1173–1182
El Ghaouth A, Arul J, Ponnampalam R, Boulet M (1991) Chitosan coating effect on storability and quality of fresh strawberries. J Food Sci 56(6):1618–1620
Erdem B, Kariptas E, Kaya T, Tulumoglu S, Görgülü Ö (2016) Factors influencing antibacterial activity of chitosan against Aeromonas hydrophila and Staphylococcus aureus. Int Curr Pharm J 5(5):45–48
Giuliani A, Pirri G, Bozzi A, Di Giulio A, Aschi M, Rinaldi A (2008) Antimicrobial peptides: natural templates for synthetic membrane-active compounds. Cell Mol Life Sci 65 (16):2450–2460
Gómez-Estaca J, López de Lacey A, Gómez-Guillén MC, López-Caballero ME, Montero P (2009) Antimicrobial activity of composite edible films based on fish gelatin and chitosan incorporated with clove essential oil. J Aquat Food Prod Technol 18(1-2):46–52
Gómez-García M, Sol C, de Nova P, Puyalto M, Mesas L, Puente H, Mencía-Ares Ó, Miranda R, Argüello H, Rubio P, Carvajal A (2019) Antimicrobial activity of a selection of organic acids, their salts and essential oils against swine enteropathogenic bacteria. Porcine Health Manage 5:32
Greenway DL, Dyke KG (1979) Mechanism of the inhibitory action of linoleic acid on the growth of Staphylococcus aureus. J Gen Microbiol 115(1):233–245

Hancock R, Lehrer R (1998) Cationic peptides: a new source of antibiotics. Trends Biotechnol 16 (2):82–88
Hancock RE, Sahl H (2006) Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol 24(12):1551–1557
Haque T, Chen H, Ouyang W, Martoni C, Lawuyi B, Urbanska AM, Prakash S (2005) Superior cell delivery features of poly(ethylene glycol) incorporated alginate, chitosan, and poly-l-lysine microcapsules. Mol Pharm 2(1):29–36
Heunis T, Bshena O, Klumperman B, Dicks L (2011) Release of bacteriocins from nanofibers prepared with combinations of poly(D,L-Lactide) (PDLLA) and poly(ethylene Oxide) (PEO). Int J Mol Sci 12(4):2158–2173
Heydarian M, Jooyandeh H, Nasehi B, Noshad M (2017) Characterization of Hypericum perforatum polysaccharides with antioxidant and antimicrobial activities: Optimization based statistical modeling. Int J Biol Macromol 104(Pt A):287–293
Huh AJ, Kwon YJ (2011) Nanoantibiotics: a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release 156(2):128–145
Hyldgaard M, Mygind T, Meyer RL (2012) Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. Front Microbiol 3:1–24
Kalagatura NK, Gurunathan S, Kamasani JR, Gunti L, Kadirvelu K, Mohan CD, Rangappa S, Prasad R, Almeida F, Mudilii V, Siddaiah C (2020) Inhibitory effect of *C. zeylanicum, C. longa, O. basilicum, Z. officinale*, and *C. martini* essential oils on growth and ochratoxin A content of *A. ochraceous* and *P. verrucosum* in maize grains. Biotechnol Rep 27:e00490. https://doi.org/10.1016/j.btre.2020.e00490
Kenawy E, Worley SD, Broughton R (2007) The chemistry and applications of antimicrobial polymers: a state-of-the-art review. Biomacromolecules 8(5):1359–1384
Kenton W (n.d.) Environmental Protection Agency – EPA
Kong M, Chen XG, Xing K, Park H (2010) Antimicrobial properties of chitosan and mode of action: a state of the art review. Int J Food Microbiol 144(1):51–63
Krichen F, Karoud W, Sila A, Abdelmalek B, Ghorbel R, Ellouz-Chaabouni S, Bougatef A (2015) Extraction, characterization and antimicrobial activity of sulfated polysaccharides from fish skins. Int J Biol Macromol 75:283–289
Kumar MN, Muzzarelli C, Sashiwa H, Domb A (2004) Chitosan chemistry and pharmaceutical perspectives. Chem Rev 104(12):6017–6084
Kungel P, Correa VG, Correa R, Peralta R, Soković M, Calhelha R, Bracht A, Ferreira I, Peralta R (2018a) Antioxidant and antimicrobial activities of a purified polysaccharide from yerba mate (Ilex paraguariensis). Int J Biol Macromol 114:1161–1167
Kungel PT, Correa V, Corrêa R, Peralta R, Soković M, Calhelha R, Bracht A, Ferreira I, Peralta R (2018b) Antioxidant and antimicrobial activities of a purified polysaccharide from yerba mate (Ilex paraguariensis). Biol Micromol 114:1161–1167
Kuorwel M, Kuorwel K (2011) Antimicrobial activity of biodegradable polysaccharide and protein-based films containing active agents. J Food Sci 76(3):90–102
Lawyer C, Pai S, Watabe M, Borgia P, Mashimo T, Eagleton L, Watabe K (1996) Antimicrobial activity of a 13 amino acid tryptophan-rich peptide derived. FEBS Lett 390:95–98
Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H et al (2013) Antibiotic resistance-the need for global solutions. Lancet Infect Dis 13(12):1057–1098
Lemire J, Harrison J, Turner R (2013) Antimicrobial activity of metals: mechanisms, molecular targets and applications. Nat Rev Microbiol 11(6):371–384
Lin J, Lee IS, Frey J, Slonczewski J, Foster J (1995) Comparative analysis of extreme acid survival in Salmonella typhimurium, Shigella flexneri, and Escherichia coli. J Bacteriol 177 (14):4097–4104
Lizardi-Mendoza J, Argüelles Monal WM, Goycoolea Valencia FM (2016) Chemical characteristics and functional properties of chitosan. Elsevier, London
Llobet E, Toma JM, Bengoechea JA (2008) Capsule polysaccharide is a bacterial decoy for antimicrobial peptides. Microbiology 154:3877–3886

Malagurski I, Levic S, Mitric M, Pavlovic V, Dimitrijevic-Brankovic S (2018) Bimetallic alginate nanocomposites: new antimicrobial biomaterials for biomedical application. Mater Lett 212:32–36

Mazareia F, Jooyandehb H, Noshadc M, Hojjatib M (2017) Polysaccharide of caper (Capparis spinosa L.) leaf: extraction optimization, antioxidant potential and antimicrobial activity. Int J Biol Macromol 95:224–231

McCarthy RR, Ullah MW, Pei E, Yang G (2019) Antimicrobial inks: the anti-infective applications of bioprinted bacterial polysaccharides. Trends Biotechnol 37(11):1155–1159

Melo M, Ferre R, Miguel CMA (2009) Antimicrobial peptides: linking partition, activity and high membrane-bound concentrations. Nat Rev Microbiol 7(3):245–250

Montesinos E (2007) Antimicrobial peptides and plant disease control. FEMS Microbiol Lett 270 (1):1–11

Munoz-Bonilla A, Fernández-García M (2011) Polymeric materials with antimicrobial activity. Prog Polym Sci 37:281–339

Muñoz-Bonilla A, Cerrada M, Fernández-García M (2014) Polymeric materials with antimicrobial activity from synthesis to application. The Royal Society of Chemistry, Cambridge

No HK, Young Park N, Ho Lee S, Meyers SP (2002) Antibacterial activity of chitosans and chitosan oligomers with different molecular weights. Int J Food Microbiol 74(1–2):65–72

Omardien S, Brul S, Sebastian A, Zaat J (2016) Antimicrobial activity of cationic antimicrobial peptides against gram-positives: current progress made in understanding the mode of action and the response of bacteria. Front Cell Dev Biol 4:111

Our Mission and What We Do. 2017

Palem RR, Saha N, Shimoga GD, Kronekova Z, Sláviková M, Saha P (2017) Chitosan-silver nanocomposites: new functional biomaterial for healthcare application. Int J Polym Mater Polym Biomater 66:1–10

Paul B, Hirshfield I (2003) The effect of acid treatment. Res Microbiol 154(2):115–121

Petros RA, DeSimone JM (2010) Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov 9(8):615–627

Prasad R, Pandey R, Barman I (2016) Engineering tailored nanoparticles with microbes: quo vadis. WIREs Nanomed Nanobiotechnol 8:316–330. https://doi.org/10.1002/wnan.1363

Prasad R (2017) Fungal nanotechnology: applications in agriculture, industry, and medicine. Springer Nature Singapore Pte Ltd., Singapore. ISBN 978-3-319-68423-9

Prasad R, Pandey R, Varma A, Barman I (2017a) Polymer based nanoparticles for drug delivery systems and cancer therapeutics. In: Kharkwal H, Janaswamy S (eds) Natural polymers for drug delivery. CAB International, Wallingford, pp 53–70

Prasad R, Bhattacharyya A, Nguyen QD (2017b) Nanotechnology in sustainable agriculture: recent developments, challenges, and perspectives. Front Microbiol 8:1014. https://doi.org/10.3389/fmicb.2017.01014

Prasad R, Kumar M, Kumar V (2017c) Nanotechnology: an agriculture paradigm. Springer Nature Singapore Pte Ltd., Singapore. ISBN: 978-981-10-4573-8

Prasad R, Kumar V, Kumar M (2017d) Nanotechnology: food and environmental paradigm. Springer Nature Singapore Pte Ltd., Singapore. ISBN 978-981-10-4678-0

Prasad R, Jha A, Prasad K (2018) Exploring the realms of nature for nanosynthesis. Springer International Publishing, Cham. ISBN 978-3-319-99570-0. https://www.springer.com/978-3-319-99570-0

Prasad R, Siddhardha B, Dyavaiah M (2020) Nanostructures for antimicrobial and antibiofilm applications. Springer International Publishing, Cham. ISBN 978-3-030-40336-2. https://www.springer.com/gp/book/9783030403362

Qin Y, Xiong L, Li M, Liu J, Wu H, Qiu H, Mu H, Xu X, Sun Q (2018) Preparation of bioactive polysaccharide nanoparticles with. J Agric Food Chem 66(17):4373–4343

Ricke S (2003) Perspectives on the use of organic acids and short chain fatty acids antimicrobials. Poult Sci 82:632–639

Rodríguez-Hernández J (2017) Polymers against microorganisms on the race to efficient antimicrobial materials. Springer, Madrid

Røssland EAGI, Langsrud T, Sørhaug T (2003) Inhibition of Bacillus cereus by strains of Lactobacillus and Lactococcus in milk. Int J Food Microbiol 89(2-3):205–212
Sadanand V, Rajini N, Satyanarayana B, Rajulu AV (2016) Preparation and properties of cellulose/silver nanoparticle composites with in situ-generated silver nanoparticles using Ocimum sanctum leaf extract. Int J Polym Anal Charact 21(5):408–416
Saini S, Sillard C, Naceur Belgacem M, Bras J (2016) Nisin anchored cellulose nanofibers for long term antimicrobial active food packaging. RSC Adv 6(15):12422–12430
Sandhiya S, Dkhar SA, Surendiran A (2009) Emerging trends of nanomedicine-an overview. Fundam Clin Pharmacol 23(3):263–269
Seil J, Webster TJ (2012) Antimicrobial applications of nanotechnology: methods and literature. Int J Nanomedicine 12(7):2767–2781
Shai Y (1995) Molecular recognition between membrane-spanning polypeptides. Trends Biochem Sci 20(11):460–464
Shao L, Xu J, Shi M, Wang X, Li Y, Kong L, Hider RC, Zhou T (2017) Preparation, antioxidant and antimicrobial evaluation of hydroxamated degraded polysaccharides from Enteromorpha prolifera. Food Chem 237:481–487
Sharifi M, Ebrahimi D, Hibbert D, Hook J, Hazell S (2012) Bio-activity of natural polymers from the genus Pistacia: a validated model for their antimicrobial action. Global J Health Sci 4 (1):149–161
Simoncic B, Tomsic B (2010) Structures of novel antimicrobial agents for textiles - a review. Text Res J 80:1721–1737
Skřivanová E, Marounek M (2007) Influence of pH on antimicrobial activity of organic acids against rabbit enteropathogenic strain of Escherichia coli. Folia Microbiol 52:70–72
Sun H, Lu X, Gao P (2011) The exploration of the antibacterial mechanism of Fe^{3+} against bacteria. Braz J Microbiol 42:410–414
Sun D, Shahzad MB, Li M, Wang G, Xu D (2014) Antimicrobial materials with medical applications. Mater Technol Adv Performed Mater 1:1–7
Tahmouzi S (2014) Optimization of polysaccharides from Zagros oak leaf using RSM: antioxidant and antimicrobial activities. Carbohydr Polym 107:238–246
Tajkarimi M, Ibrahim S, Cliver D (2010) Antimicrobial herb and spice compounds in food. Food Control 21:1199
Tan H, Ma R, Lin C, Liu Z, Tang T (2013) Quaternized chitosan as an antimicrobial agent: antimicrobial activity, mechanism of action and biomedical applications in orthopedics. Int J Mol Sci 14(1):1854–1869
Tejero-Sariñena S, Barlow J, Costabile A, Gibson GR, Rowland I (2012) In vitro evaluation of the antimicrobial activity of a range of probiotics against pathogens: evidence for the effects of organic acids. Anaerobe 8(5):530–538
Theron M, Lues R (2011) Organic acids and food preservation. Taylor & Francis, Boca Raton
Tokura S, Ueno K, Miyazaki S, Nishi N (1997) Molecular weight dependent antimicrobial activity by chitosan. Macromol Symp 120:1–9
Tongnuanchan P, Benjakul S (2014) Essential oils: extraction, bioactivities, and their uses for food preservation. J Food Sci 79(7):1231–1249
Tsai GJ, Su WH (1999) Antibacterial activity of shrimp chitosan against Escherichia Coli. J Food Prot 62(3):239–243
Wang J, Vermerris W (2019) Antimicrobial nanomaterials derived from natural products—a review. A review. Materials 9(4):255
Wright P, Webster RG (2001) Orthomyxoviruses. In: Knipe DM, Howley PM, Griffin DE, Martin MA, Lamb RA, Roizman B (eds) Fields virology. Lippincott-Raven Publishers, Philadelphia, pp 1533–1579
Xie Y, Liu X, Chen Q (2007) Synthesis and characterization of water-soluble chitosan derivate and its antibacterial activity. Carbohydr Polym 69(1):142–147
Xie J-H, Shen M-Y, Xie M-Y, Nie S-P, Chen Y, Li C, Wang Y-X (2012) Ultrasonic-assisted extraction, antimicrobial and antioxidant activities of Cyclocarya paliurus (Batal.) Iljinskaja polysaccharides. Carbohydr Polym 89(1):177–184

Advanced Antimicrobial Materials and Applications: Maleic Anhydride Antimicrobial Polymers

Katarzyna Wal, Wojciech Stawiński, Anna Dmochowska, and Piotr Rutkowski

Abstract Care for human life should be a priority for all the people on Earth. The number of elements jeopardizing human life, including pathogenic microbes, has been increasing. Many microbial infections are often challenging to treat and result in the patient's death. Moreover, the currently applied decontamination methods are often not effective. Therefore, research around the world has been focused on developing new solutions to fight against harmful microbes. An interesting and promising concept in this field are polymers exhibiting antimicrobial activity. Among such polymers, much attention has been paid to maleic anhydride-derived materials. Maleic anhydride is a well-known raw material used in a wide spectrum of industries. Due to its specific structure it finds its applications in many polymerization and copolymerization processes. Some of the products possess antimicrobial properties and can be used as protective coatings or drug carriers. This chapter presents the examples of the scientists achievements in the field of antimicrobial maleic anhydride polymers.

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1 Introduction

The term microbes depicts a large group of microorganisms, the oldest forms of life on Earth, whose existence traces date back more than 3.5 billion years (Kumar and Chordia 2017). It is estimated that the number of microbe types can reach up to 10^{30} with bacteria, fungi, viruses, protozoa, microalgae, and archaea being the most important representatives (Bisen et al. 2012a; Lustgarten 2016; Dodds and Whiles 2020). Vast majority of them inhabit the human body constituting its natural microbiome. The digestive gut, mouth, skin, and nose are the places where most of the microorganisms can be found. Their occurrence is essential for proper functioning of the human organism (Grice and Segre 2012; National Academies of Sciences Engineering and Medicine 2017; Smith 2020). Some, like the probiotics, help to keep the intestinal microbial balance (Hatti-Kaul et al. 2016; Rani et al. 2019), others, inhabiting the human reproduction system, are essential for the reproduction (Sun and Chang 2014; Atanasova and Yilmaz 2015; Kumar and Chordia 2017).

Despite all the positive aspects, some microbes, the pathogens, cause infections (Singh et al. 2014; Chatterjee and Raval 2019). Microbes and the diseases they cause are a serious threat to human life (Institute of Medicine 2003). Death as a result of microorganisms infections is such a frequent phenomenon, that the amount of the fatal cases is much higher than the number caused by any other factors (Huang et al. 2016). Harmful microorganisms can be transferred to organisms through food, air, or water (Chatterjee and Raval 2019; Pigłowski 2019). In recent years the outbreaks of severe acute respiratory syndrome (SARS) (2002–2003), Ebola virus (2014–2016), or Zika virus (2016) posed a serious threat for the global population (Groneberg et al. 2005; Schlagenhauf et al. 2017; Den Boon et al. 2019; Noorbakhsh et al. 2019). Moreover, the world has been facing a severe problem of the increasing antimicrobial resistance (AMR) restricting the human ability to fight against bacterial infections (Nicolle 2011; Brinkac et al. 2017; Mcewen and Collignon 2017; Septimus 2018). Once bacterium is defeated by a certain class of drugs, it can acquire resistance and further usage of the drug will be ineffective (Mcewen and Collignon 2017; Smith 2020). First reports of AMR date back to 1942 when *Staphylococcus aureus* strains showed resistance to penicillin (Ben Maamar et al. 2020). Nowadays, microbial infections require the development of new drug types that have the ability to combat multi-drug resistant pathogens (Hacker and Dobrindt 2006; Brown 2015; Andersson et al. 2016; Miró-Canturri et al. 2019).

Among other areas, health care and food packaging and storage are the most exposed ones to harmful microorganisms (Kenawy et al. 2007). Nowadays, most common microbial pathogens causing dangerous infections belong to the bacteria group (Nicolle 2011; Chatterjee and Raval 2019). *Escherichia coli* is one of their most common representatives. The first reports on its occurrence are dated to 1885

when Theodor Escherich isolated this bacterium strain (Croxen et al. 2013). It is responsible for diarrhea and extraintestinal diseases such as blood stream and urinary tract infections (Nicolle 2011; Croxen et al. 2013; Gomes et al. 2016). Another quite common bacteria is *Salmonella* which is transmitted to human mainly through infected foods such as eggs (Chlebicz and Śliżewska 2018). In most cases, *Salmonella* causes diarrhea; however, almost 5% of the patients can develop bacteremia, a state in which bacteria is present in the bloodstream (Pegues et al. 2006). Bacteria from the *Shigella* species are known for causing shigellosis, a disease which manifests mostly through diarrhea and can be dangerous for both children and adults. In 2010 almost 40,000 people in the age above five died from it, while in 2013 it caused deaths of 34,400 children below that age (Mani et al. 2016; Chatterjee and Raval 2019). Another microbe, *S. aureus*, affects mostly the human skin. It causes wounds creation and skin diseases; however, it is also responsible for the majority of post-surgery infections and problems with blood stream (Nicolle 2011; Chatterjee and Raval 2019). *Listeria monocytogenes* is a common bacteria causing listeriosis. The disease manifests mostly through fever, headache, diarrhea, vomiting, and nausea; in pregnant women it can result in miscarriage (Hernandez-Milian and Payeras-Cifre 2014; Chlebicz and Śliżewska 2018).

2 Prevention, Control, and Treatment Methods Against Microbes

The growing awareness of the threat has led to stronger emphasis on hygiene, education on antimicrobial resistance, and effective sanitation (World Health Organization 2015). Hygiene is strongly related to antiseptics, which are widely used in the health care. Sterilization is probably the oldest approach to microorganisms control. This method, based on application of steam, hydrogen peroxide gas plasma, UV irradiation, gamma irradiation, ethylene oxide, vaporized hydrogen peroxide, kills all the microbes (Hogg 2005; Rutala and Weber 2019). Antiseptic agents such as chlorhexidine, alcohol, or iodophor reduce the number of microorganisms on the skin surface (Williamson et al. 2017; Rutala and Weber 2019). Surgery has a high risk of infection, therefore the strongest antiseptics agents such as ethylene oxide and hydrogen peroxide are used in this case. All the medical equipment used during surgery is subjected to a high-level disinfection before the contact with patient. The procedure kills almost all the microbes; however, some bacterial spores are resistant to this method. Other hospital equipment such as wheelchairs, blood pressure cuffs, bed rails, bedpans, bedside tables are treated with low-level disinfection method. This approach is milder and successful in elimination of some viruses, fungi, and vegetative bacteria species. However, it is not strong enough for spores and mycobacteria (Rutala and Weber 2019).

Disinfection methods are also used against airborne microbes, especially in ventilation systems (Wang et al. 2019a). Special particulate filters in heating systems, air conditioning (HVAC) systems, and ventilation are used to a limited number of pathogens (Möritz et al. 2001; González et al. 2016; Stockwell et al. 2019).

Another tool for air disinfection is UV germicidal irradiation successfully applied in many systems (Tseng and Li 2005; Memarzadeh et al. 2010; Reed 2010; National Academies of Sciences Engineering and Medicine 2017).

The preventive approach to microbes is very important in the area of the food industry for food preservation. Reducing the microbes growth extends the product shelf-life. The most common techniques applied for that purpose are drying, boiling, oxidation, freezing, smoking, UV irradiation, ultrahigh water pressure, and usage of chemical preservatives (Bisen et al. 2012b; Chatterjee and Abraham 2018).

The methods described above, unfortunately, cannot be applied universally in everyday life due to technical and/or economic barriers and the possible insufficiency. Alarming is the fact that there are not many ways to efficiently eliminate pathogens from our surroundings. Despite the constant development in medicine and technology, there are still limitations in controlling and preventing infections. However, there are other ways to fight the microorganisms. One of them is the employment of antimicrobial polymers that can act as surface coatings and drug carriers hindering the microorganisms growth (Siedenbiedel and Tiller 2012; Musumeci and Puglisi 2013; Zhang and Wagner 2017; Tiwari and Chaturvedi 2018; Kamaruzzaman et al. 2019; Nagaraja et al. 2019).

3 Antimicrobial Polymers

Antimicrobial agents are substances developed for two purposes: reducing the growth or killing microorganisms. They are divided into groups based on their action mechanism or their chemical structure (Musumeci and Puglisi 2013).

Antimicrobial polymers are the agents that became the subject of intensive academic research during the last few years (Kenawy et al. 2007; Rodríguez-Hernández 2017; Yang et al. 2018). Polymers classified as antimicrobial either exhibit their own antimicrobial activity or are conjugated to other antimicrobial compounds such as antibiotics (Kamaruzzaman et al. 2019). The antimicrobial activity is strictly related to several factors such as the molecular weight, counterions type, length of spacer located between polymer and the active site, or hydrophilic–hydrophobic balance. There are three types of antimicrobial polymers (Siedenbiedel and Tiller 2012; Huang et al. 2016; Benčina et al. 2018):

- polymeric biocides—polymers linked with covalent bonds to bioactive antimicrobial repeating units such as the carboxyl, hydroxyl, or amino groups,
- biocidal polymers that possess antibacterial activity in their whole chain. They contain biocides such as quaternary ammonium, tertiary sulfonium, guanidinium, or phosphonium,
- biocide-releasing polymers with two subgroups:
  - the biocide-releasing compounds are attached to the polymeric backbone,
  - composites consisting of polymer and biocide-releasing molecules.

The usage of antimicrobial polymers has multiple advantages compared to the conventional solutions. First of all, they are long-term-activity materials; second, they are non-toxic, chemically stable, nonvolatile; third, they can act selectively; fourth, the skin is an impassable barrier for them. Moreover, in some cases, they exhibit greater operational efficiency than the conventional antimicrobial agents (Kenawy et al. 2007). The great application potential of antimicrobial polymers is exploited in the food, medical, and textile industries. Primarily they are used as antimicrobial surfaces and coatings on medical devices, implants, as antimicrobial packing films and textile fibers (Bastarrachea and Goddard 2015; Huang et al. 2016; Zhang and Wagner 2017; Ergene et al. 2018; Zhong et al. 2020; Prasad et al. 2020). Maleic anhydride-based polymers are one of the examples of such materials.

4 Maleic Anhydride

Maleic anhydride, also known as 2-5-furandione or maleic acid anhydride, was synthesized for the first time around 1830 (Gooch 2007; Hernández-Moreno et al. 2014). This material is a solid in room temperature; it is colorless or slightly white and has irritating odor. Its chemical structure bases on heterocyclic ring containing oxygen and four carbon atoms; two carbonyl groups are present at the C_2 and C_5 positions and a double bond between the third and fourth carbon atom (Fig. 1) (Musa 2016).

Maleic anhydride is produced at industrial scale from butane gas or benzene, in fixed or fluidized-bed processes, or in oxidation in the presence of vanadium oxide catalysts (Higgins and Hutchings 1980; Edwards 1985; Dente et al. 2003; Gascón et al. 2005). Maleic anhydride is also obtained as a by-product in production of phthalic anhydride (Hernández-Moreno et al. 2014).

The occurrence of the double bond renders the compound highly reactive. Additionally, the electron withdrawing forces from the two electron-deficient C=O substituent groups are responsible for strong electron-accepting properties. These features make maleic anhydride widely used as an intermediate product in reactions based on electrophilicity, in the Michael reactions, alkylation, acylation, halogenations, sulfonation, formation of Diels–Alder adducts, photodimerization, or free radical polymerization (Parker et al. 2001; Musa 2016). It is used for production of unsaturated polyester resin, copolymers, food additives, agricultural chemicals, alkyl succinic anhydrides, cosmetics, oil additives, detergents, malic and fumaric acid (Hernández-Moreno et al. 2014; Ashland 2017).

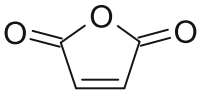

Fig. 1 The structure of maleic anhydride

4.1 Maleic Anhydride Polymers

As a monomer, maleic anhydride exhibits very low tendency to homopolymerize. However, copolymerization reactions with donor monomers are its main field application (Nasirtabrizi et al. 2013).

Free radical polymerization of maleic anhydride and alkyl vinyl ether leads to development of high molecular weight alternating copolymers. Their modification by exchange of α-olefins in the place of alkyl vinyl ether monomer results in synthesis of terpolymers (Musa 2016).

Unsaturated polyester resins can be synthesized in condensation reaction of dibasic organic acids such as maleic and phthalic anhydride with dihydric alcohols, for example propylene glycol (Bodnar et al. 1990; Ahamad et al. 2001). They can also be obtained in a more sustainable way from polyethylene terephthalate (PET) waste and maleic anhydride (Vaydya and Nadkarni 1987). Maleic anhydride can also be used for modification of alkyd resins as its presence in the structure impacts the color and water resistance of the resin (Boruah et al. 2012).

Polyolefins modified with maleic anhydride are an interesting class of copolymers from the industrial point of view. They can be obtained in free radical processes. However, this type of production leads to degradation and troublesome changes in the products' rheological properties. To overcome these obstacles, a process based on pericyclic mechanism such as the Alder-Ene reactions may be employed. The product is characterized by high adhesion, paintability, and compatibility (Vicente et al. 2008).

The maleic anhydride polymers group includes also acrylic and N-vinyl amide/maleic anhydride copolymers. Synthesis of the first is based on conventional free radical mechanism, whereas, complex radical copolymerization is responsible for the synthesis of the second. Both groups are effective corrosion inhibitors and antifouling agents (Veron et al. 2001; Temiz et al. 2006; Musa 2016).

One of the most known alternating maleic anhydride copolymers is styrene-maleic anhydride copolymer. It has unique thermal and mechanical properties; it is transparent and can be modified for example with hydroxyl or amino groups. It finds the application in many fields including the packaging, and the automotive and construction industries. It can be produced in several ways such as conventional free radical copolymerization and controlled polymerization processes: the nitroxide mediated polymerization (NMP) and the reversible addition-fragmentation chain transfer (RAFT) (Huang and Turner 2017).

Ring-opening metathesis polymerization (ROMP) is a method for olefin metathesis reactions. It has been known since the 1950s as a living polymerization technique for polymers chain growth. The mechanism of this method consists of the conversion of cyclic olefins to a polymeric material. The ROMP reactions are catalyzed by transition metal compounds such as tungsten, tantalum, molybdenum, ruthenium, and titanium (Bielawski and Grubbs 2007). Some of the monomers applied in the ROMP are maleic anhydride derivatives. The obtained products are used for development of functionalized unsaturated polymers (Musa 2016).

4.2 Antimicrobial Maleic Anhydride Polymers

4.2.1 Poly(Styrene-Maleic Anhydride)

Poly(styrene-maleic anhydride) is the most common material from antimicrobial maleic anhydride polymers group (Fig. 2).

One of first reports on evaluation of its antimicrobial activity was made by Jeong et al. (2001). The antimicrobial properties were acquired upon introduction of antimicrobial groups to the polymer structure. The unmodified copolymer was synthesized in reaction of styrene and maleic anhydride in anhydrous N, N-dimethylformamide solution with azobisisobutyronitrile as the free radical polymerization initiator. The modification was based on the interaction of the copolymer with 4-aminobenzoic or 4-hydroxybenzoic acid in the presence of triethylamine. Both occurred as a result of the ring opening between the succinic anhydride unit and the active agent. The reactions caused the formation of the amide and ester bond between 4-aminobenzoic and 4-hydroxybenzoic acid, respectively.

The materials were subjected to antifungal tests with *Aspergillus niger* and antibacterial studies with *Escherichia coli* and *Staphylococcus aureus*. The results showed that the pure 4-aminobenzoic acid and 4-hydroxybenzoic acid had higher antifungal activity than the modified copolymers. At the same time, the copolymer sample modified with 4-aminobenzoic acid exhibited 10% fungal growth, while modification with 4-hydroxybenzoic acid resulted in 30% fungal growth. The collected data indicated that the antimicrobial agents release rate driven by hydrolysis was too slow, as the pristine active agents gave better results. The problem could be solved by changing one of the factors such as temperature, pH, or the solution ionic strength.

Outcomes from the antibacterial measurements were more promising. The modified copolymers exhibited excellent antibacterial properties. The *S. aureus* growth reduction was almost 100% for both modifications. The antibacterial action of the 4-hydroxybenzoic acid modified copolymer against *E. coli* was also good; however, the 4-aminobenzoic acid sample caused only 45% reduction. The antimicrobial agents alone eliminated the bacteria with efficiency of 93%.

Jeong et al. (2002) conducted a modification of poly(styrene-*alt*-maleic anhydride) copolymer with 4-aminophenol. The conjugation of the copolymer and the active agents occurred due to the ring-opening reaction.

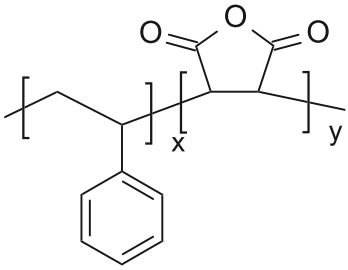

Fig. 2 Poly(styrene-*alt*-maleic anhydride)

Antibacterial experiments were performed with *Staphylococcus aureus* and *Escherichia coli.* In both cases, the pristine 4-aminophenol exhibited a 100% effective antibacterial action. The modified copolymer had a higher activity against *S. aureus* strains (99.9%) than against *E. coli* (95.3%). This was attributed to the longer time needed for the conjugate to diffuse through the pathogen's cellular membrane—in comparison to the time required by the pristine active agent. Furthermore, the copolymer contained only 35% of 4-aminophenol in its structure. Additional tests indicated that 4-aminophenol was not released from the polymer matrix. This suggests that the modified copolymer exhibited its own bactericidal activity related to the presence of phenylic hydroxyl group.

Fang et al. (2009) examined poly(styrene-*alt*-maleic anhydride) derivatives obtained by amidation or hydrolysis in different conditions as anti-HIV agents. All the tests were carried out in in vitro conditions, in accordance with the cellular model. The products showed positive outcomes against the virus. The most promising material was poly[styrene-*alt*-(maleic acid, sodium salt)] which was developed on the way of hydrolysis of poly(styrene-*alt*-maleic anhydride) in the presence of sodium hydroxide.

Cloete et al. (2013) modified poly(styrene-*co*-maleic anhydride) by partial imidization in the presence of 3-dimethylamino-1-propylamine and used it as a waterborne coating component. The product was additionally ammonolyzed to make it soluble in water. The copolymer was then used as a surfactant in emulsion polymerization of styrene and n-butyl acrylate. The final product, latex modified with the copolymer, acquired antibacterial and antifungal properties that were tested in composite bacterial and yeast suspension.

Copolymer of styrene and maleic anhydride is also a potential choice as a carrier for antimicrobial substances. It does not exhibit any teratogenic or toxic effects; it can additionally improve the pharmaceuticals' circulatory half-life as well as their solubility in lipids (Huang and Turner 2017).

Patel et al. (1998) examined the copolymer synthesized in the solution copolymerization as a carrier for covalently bonded acriflavine. The coupling of the active substance was carried out in N,N-dimethylformamide in the presence of triethylamine catalyst. The antimicrobial tests conducted against *Bacillus subtilis* indicated inhibition of the microbes growth due to slow release of the drug from the polymer matrix.

Patel et al. (1999) applied this copolymer as the ampicillin carrier. Poly(styrene-*co*-maleic anhydride) was synthetized in the solution copolymerization in the presence of benzoyl peroxide catalyst. The antimicrobial compound was bounded to the polymer's anhydride groups by amide bond formation in the presence of triethyl amine catalyst. The ampicillin release rate was evaluated in 37 °C during 8 days. The impact of maleic anhydride content in the copolymer on the growth of *E. coli*, *B. subtilis,* and *S. aureus* was determined. The content of maleic anhydride in the polymer had a major influence on the drug release rate and it could be used to control the release; the bacteria growth was inhibited within 8–16 h.

Moghadam et al. (2010) examined the release of ceftriaxone antibiotic from poly (styrene-*alt*-maleic anhydride) and the impact of the bonding type on the release.

Two types of copolymers were prepared: the first one on the way of chemical grafting of ceftriaxone by the amidation reaction between the copolymer's anhydride groups and the antibiotic; the second one by the modification of the copolymer with isopropyl amine what led to formation of poly(styrene-*alt*-maleic anhydride)-isopropyl amide to which the antibiotic was physically loaded. The chemical grafting allowed to achieve higher ceftriaxone release than the physical forces-driven modification.

Khazaei et al. (2013) investigated the release of antiviral amantadine from poly (styrene-*alt*-maleic anhydride). The active component was linked to the copolymer's surface by reaction between its amino groups and the polymer's anhydride groups. The grafting resulted in the formation of the amide bond. The product was suitable for the drug delivery system.

4.2.2 Poly(Methyl Methacrylate-*Co*-Maleic Anhydride)

Patel et al. (1997) used poly(methyl methacrylate-*co*-maleic anhydride) (Fig. 3) as a carrier for antimicrobial acriflavine. The material's synthesis was based on the solution copolymerization of maleic anhydride with methyl methacrylate. The coupling reaction was carried out in dry dimethylformamide in the presence of triethylamine. The performed tests confirmed the active agent release from the polymer matrix and the growth inhibition of *E. coli*, *B. subtilis,* and *S. aureus* after 8–16 h.

Antimicrobial properties of several methyl methacrylate and maleic anhydride copolymers were examined by Abd El-Rehim et al. (2004). The syntheses were carried out under gamma rays irradiation. The copolymers were modified with sulfa drugs, hydroxylamine hydrochloride, and 4-amino salicylic acid, what resulted in the introduction of amino groups into the copolymer's anhydride rings. Antimicrobial tests revealed that the raw copolymer exhibited its own antimicrobial activity against *S. aureus*. The material modified with sulfa drugs, such as sulfanilamide, sulfaguanidine, and sulfaquinoxaline, showed the most significant growth inhibition of *E. coli* and *Candida albicans*.

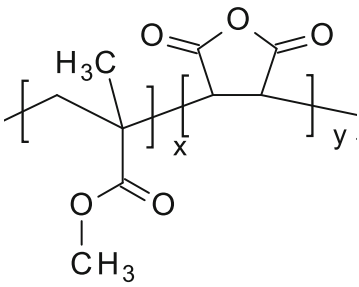

Fig. 3 Poly(methyl methacrylate-*co*-maleic anhydride)

4.2.3 Poly(Maleic Anhydride-*Alt*-Acrylic Acid)

Can et al. (2014) examined the possibility of using poly(maleic anhydride-*alt*-acrylic acid) (Fig. 4) as acriflavine carrier. The water soluble copolymer was obtained through the free radical polymerization process. The reaction was performed in the solution of 1,4-dioxane, and benzoyl peroxide as the radical initiator. Modification of the obtained product with acriflavine was conducted in dimethylformamide in the presence of triethylamine catalyst. The conjugate showed antibacterial properties against enterohemorrhagic *Escherichia coli* (EHEC) and *S. aureus*. However, the results from the antimicrobial tests against *Enterococcus faecium* and *Listeria monocytogenes* indicated unrestricted growth of these bacteria.

4.2.4 Poly(Maleic Anhydride-*Co*-Vinyl Acetate)

Another polymer evaluated for the role of a polymeric carrier for antiexternal fungal acriflavine was poly(maleic anhydride-*co*-vinyl acetate) (Fig. 5). The free radical copolymerization process was applied as the copolymer development method. The reaction between the maleic anhydride and the vinyl acetate took place in methyl ethyl ketone solvent and benzoyl peroxide initiator. Acriflavine was covalently bonded to the copolymer as a result of the amidization reaction. The substrates of the copolymer/acriflavine conjugate were mixed in the ratio of 1:1 and 1:2 for the polymer and the active agent, respectively. The better outcomes were achieved for sample prepared in the 1:1 ratio (Karakuş 2016).

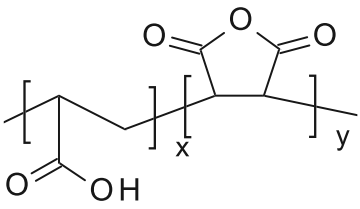

Fig. 4 Poly(maleic anhydride-*alt*-acrylic acid)

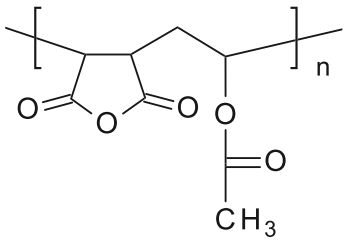

Fig. 5 Poly(maleic anhydride-*co*-vinyl acetate)

4.2.5 N-vinyl Amide/Maleic Anhydride Copolymers

The most widely used antimicrobial polymer from this group is the poly(N-vinyl pyrrolidone-maleic anhydride) (Fig. 6) and its derivatives.

Temiz et al. (2006) investigated N-vinyl pyrrolidone-maleic anhydride copolymers modified with poly(ethylene imine). The raw copolymer was synthesized in the free radical solution copolymerization in 1,4-dioxane with azobisisobutyronitrile as the free radical initiator. The material was hydrolyzed and subjected to the complexation reaction with poly(ethylene imine). Two samples containing different ratios of the copolymer and poly(ethylene imine) were prepared for the tests: the first one consisted of the copolymer and poly(ethylene imine) in 1:1 ratio (COOH/N molar ratio 1:1.5), the ratio in the second one was 1:0.67 (COOH/N molar ratio 1:1). Gram-positive bacteria (*Listeria monocytogenes* and *S. aureus*) and Gram-negative bacteria (*E. coli* and *Salmonella enteritidis*) were chosen for the tests. The materials were unable to inhibit the Gram-negative bacteria growth. However, both modified copolymers possessed antimicrobial activity against the Gram-negative *L. monocytogenes*; in the case of *Staphylococcus aureus*, only the first material, with increased concentration of carboxylic groups, exhibited the desired effect. Hence, the greater the amount of –COOH groups in the polymer structure, the better the antibacterial activity against *S. aureus* strains.

Talu et al. (2010) synthesized a terpolymer consisting of N-vinyl-2-pyrrolidone, maleic anhydride, and N-isopropyl acrylamide. The monomers were mixed during the free radical polymerization in 1:2:1 ratio, respectively. Several terpolymerization reactions were carried out in various reaction time of 6, 12, 24, and 36 h. Evaluation of their antimicrobial activity against six bacterial species: Gram-positive—*S. aureus*, *Streptococcus faecalis* and Gram-negative—*Salmonella enteritidis*, *E. coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* showed that all the terpolymers exhibited antimicrobial properties. However, the antibacterial action against the Gram-negative bacteria was weaker compared to the Gram-positive ones. The highest growth reduction was for *S. aureus* strains; the reaction time had an impact on the antimicrobial properties and the materials obtained after 36 h exhibited the highest activity. This phenomenon was attributed to the larger number of carboxylic group in the structure as a result of a longer development process time.

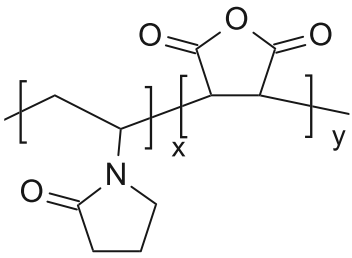

Fig. 6 Poly(N-vinyl pyrrolidone-maleic anhydride)

Hemalatha et al. (2014) modified N-vinylpyrrolidone and maleic anhydride copolymer with N,N-diethylaminoethanol and subjected it to antibacterial tests against four Gram-negative strains: *Klebsiella aerogenes*, *E. coli*, *Pseudomonas aeruginosa*, *Pseudomonas desmolyticum* and one Gram-positive bacteria: *S. aureus*. All the materials exhibited antimicrobial properties for the Gram-negative bacteria, however not for the Gram-positive ones, which was due to a different bacterias' surface response mechanisms.

4.2.6 N-halamine Polymeric Compounds

N-halamine compounds constitute a group of substances with at least one covalent bond between the nitrogen and a halogen such as chlorine or bromine. Their interaction with microbes causes the bond break. As a consequence, the halogen is released causing disruption of the cell and oxidation of the thiol groups in the microbe's cell membrane. Moreover, the N-halamines may be "recharged" which results in their unending antimicrobial activity. Their significance in the antimicrobial field has been growing over the years (Cerkez 2018).

An antimicrobial coating made of branched poly(ethylene imine) and styrene-maleic anhydride copolymer was used to cover the surface of polypropylene pellets (Bastarrachea and Goddard 2015). The antimicrobial tests on *Listeria monocytogenes* were conducted using chlorinated and unchlorinated pallets. The chlorination was necessary as N-halamines-derived coatings possess weak microbe growth inhibition efficiency in their unchlorinated state. Both pellet forms inactivated *L. monocytogenes*. The antibacterial driving force was the unique chemical system consisting of the cationic amine groups and N-halamine forming groups arising from chlorination (Bastarrachea and Goddard 2015). The outcome is in agreement with the conclusions drawn from studies of antimicrobial properties of cationic polymers (Yang et al. 2018). In addition, it was possible to "recharge" the material by means of rechlorination (Bastarrachea and Goddard 2015). Similar results were presented for the coating made of poly(ethylene imine) and styrene-maleic anhydride copolymer against *Escherichia coli* O157:H7 (Bastarrachea and Goddard 2016).

A copolymer of acrylamide and maleic anhydride was chlorinated to convert its amide groups to acyclic N-halamine and was applied as a coating for cotton fabrics (Wang et al. 2019c). The modified copolymer, unlike its unchlorinated version, displayed antimicrobial properties against *S. aureus* and *E. coli.*

4.2.7 Maleic Anhydride Polymers with Quaternary Ammonium Salts

Quaternary ammonium compounds are well-known cationic surfactants which exhibit strong antibacterial and antifungal activity. They consist of a positively charged, quaternary nitrogen atom connected to a hydrophobic tail. In addition,

most of them have four carbon-nitrogen bonds that allow them to carry an indefinite positive charge (Morrison et al. 2019). The quaternary ammonium compounds usually belong to the chloride or bromide salts group, less often iodide salts group (Jiao et al. 2017).

Their antimicrobial properties are connected to the ionic and hydrophobic interactions between the quaternary ammonium compounds, which are positively charged, and the components of the bacteria cell membrane, mostly the heads of the phospholipid bilayers, which are negatively charged. The interactions lead to damage of the membranes and cells' death (Majumdar et al. 2009; Gliścińska et al. 2013; Jiao et al. 2017; Noh et al. 2017; Morrison et al. 2019; Zeng et al. 2020). Due to the efficiency against various pathogens, quaternary ammonium compounds have been widely used as disinfectants and detergents in commercial products (Kenawy et al. 2002; Sauvet et al. 2003; Xue et al. 2015). Nevertheless, the salts are volatile and highly toxic to the environment (Wang et al. 2019b).

It is believed that quaternary ammonium functional polymers are less harmful to mammalian cells and have an increased action selectivity and efficiency. This originates from their higher positive charge density that yields greater affinity for the negatively charged microorganisms' cell membranes (Majumdar et al. 2009). Moreover, the polymeric compounds may be modified with cationic and hydrophobic side chains and therefore display amphiphilicity. It has been reported that amphiphilicity affects the activity of polymers containing quaternary ammonium salts against pathogens (Timofeeva and Kleshcheva 2011). Because of all these properties, quaternary ammonium polymeric compounds have become the research scope for many scientists (Dizman et al. 2004; Majumdar et al. 2009; Wang et al. 2019b).

Conventionally, polymeric materials containing quaternary ammonium compounds can be synthesized by two approaches. In the first one, the post-polymerization, the quaternization of the reactive polymer precursors is conducted. The products may vary in the cationization degree. In the second approach, the monomers containing quaternary ammonium functional groups are copolymerized within the polymer network. The final product has the most functionality; however, its molecular characterization may be a challenging task (Jiao et al. 2017).

Many different antimicrobial polymers with quaternary ammonium salts have been reported and described in the literature, including pyridine quaternary ammonium salt polymer nanocapsules (Zeng et al. 2020), poly(ethylene-*co*-acrylic acid) copolymers grafted with aliphatic quaternary ammonium salts (Noh et al. 2017), polysiloxane copolymers (Sauvet et al. 2003), polyurethane coatings with quaternary ammonium salts (Nurdin et al. 1993), various acrylamide homopolymers and copolymers (Zhang et al. 2015), acrylate homopolymers (Zhong et al. 2017), polystyrenes grafted with different quaternary ammonium groups (Jiang et al. 2006), modified polyvinylpyridines (Tiller et al. 2001), and cationic polycarboxybetaine esters (Zhang et al. 2008).

However, the number of studies and literature reports on maleic anhydride polymers with incorporating quaternary ammonium salts is limited. Wang et al. (2012) developed antimicrobial compounds containing quaternary ammonium salts and

their polymers using natural resin acids which acted as active hydrophobic components. The resin acids were mainly composed of diterpene resin acids. The analysis of the products' bactericidal activity was performed using the disk-diffusion method and tested against various Gram-negative bacteria: *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Enterobacter agglomerans*, *Salmonella typhimurium*, *Alcaligenes faecalis* and Gram-positive bacteria: *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus pyogenes*, *Micrococcus luteus*, *Mycobacterium smegmatis*, *Corynebacterium xerosis*. The viability of the bacteria strains has decreased significantly due to the hydrophobicity and the distinctive structure of the materials.

Dominic et al. (2016) presented a novel route for the synthesis of quaternary ammonium dialkyl maleates and their copolymerization with methyl methacrylate. The activity against modified *E. coli*, which showed a resistant behavior against ampicillin, was tested. The atomic force microscopy technique revealed the mechanism behind the activity against the bacteria. The activity was connected to the electrostatic interactions between the bacteria and cationic quaternary ammonium group, and also to the long alkyl chain poking the cell and breaching its membrane. The process resulted in breaking the bacterial cells into pieces. Moreover, the obtained copolymer was degradable.

Ganewatta et al. (2014, 2015) reported the antibacterial properties of surfaces grafted with resin acid derived cationic compounds containing immobilized quaternary ammonium. The surfaces were prepared by the copper-catalyzed azide−alkyne 1,3-dipolar cycloaddition and surface-initiated atom transfer radical polymerization. The antibacterial assay was conducted against Gram-negative *E. coli* and Gram-positive *S. aureus* bacteria strains. A significant change in the cells viability was observed. There was a variation between the biocidal activity against *E. coli* and *S. aureus* which was due to the structural differences—an additional outer cell wall in Gram-negative bacteria. Additionally, the prevention of the biofilm formation was observed, and the minimal cytotoxicity was noted.

Uppu and Haldar (2016) reported the syntheses of antibacterial amphiphilic polymers derived from poly(isobutylene-*alt*-maleic anhydride). First, the polymeric derivative, the poly(isobutylene-*alt*-N-(N′,N′- dimethylaminopropyl)-maleimide) was prepared, then it was modified to obtain alkyl chain quaternized polymers and amide- or ester-quaternized polymers. The final products differed in the structure, molecular weight, as well as the quaternization degree. The goal of the modifications was to form a polymer with a specific function. Its purpose was to imitate the behavior of peptides displaying the antibacterial activity against bacterial endotoxins. Lipopolysaccharide, a major component of the outer wall of Gram-negative bacteria, is one of these endotoxins. The antibacterial activity was tested against *E. coli*, *S. aureus*, and pathogens of increased resistance—Vancomycin-resistant *Enterococci* and Methicillin-resistant *Staphylococcus aureus*. It was revealed that the polymeric derivative alone, when dissolved in water, does not exhibit antibacterial activity and thus the addition of the quaternary compound was

necessary. The results of the biocidal tests have shown that highly hydrophobic polymer was lethal not only to bacteria but also toxic to mammalian cells. On the other hand, highly hydrophilic polymer did not exhibit strong antibacterial properties but was not harmful to mammalian cells. Two compounds with adequate hydrophobicity and hydrogen bonding interactions exhibited effective antibacterial properties without any adverse effects to mammalian cells.

Uppu et al. (2016) presented an easy post-functionalization approach to develop maleic anhydride-based amphiphilic polymers. The synthesis allowed to adjust the amphiphilic properties of the resulting compounds by changing the side chains hydrophobicity. The substrate polymer and the synthesis steps were similar to the Author's previous work (Uppu and Haldar 2016). The four developed polymeric materials showed antibacterial activity against multi-drug resistant *Acinetobacter baumannii* biofilms on surfaces. Moreover, the bacteria did not gain any resistance to the polymeric materials, contrarily as to antibiotics.

Barman et al. (2019a) reported the studies about the activity of amino-acid conjugated polymers against drug-resistant *Acinetobacter baumannii*. Poly(isobutylene-*alt*-maleic anhydride) was used as the starting compound, similar as in the studies conducted by Uppu et al. (2016) and Uppu and Haldar (2016). The resulting materials had diverse activity against the pathogen due to the variation of the amino acid in the polymers. After optimization, the product demonstrated excellent properties against *A. baumannii* and caused the cell death in less than 2 min. Moreover, it showed the ability to remove the previously formed biofilm. No resistance towards the antimicrobial polymer after repeating the passage 14 times was displayed.

In other study, Barman et al. (2019b) developed membrane-active, amino-acid (glycine and L-alanine) conjugated polymers and combined them with a hydrophobic antibiotic—rifampicin. The material was tested against Gram-negative bacteria: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*. The products were similar to the ones obtained in the previous research and based on poly(isobutylene-*alt*-maleic anhydride) and various amino acids. When combined with the antibiotic, the materials exhibited a promising activity against drug-resistant bacteria strains. Also, they did not display any harmful nature towards mammalian cells.

4.3 Concerns About Using Maleic Anhydride Antimicrobial Polymers

The employment of maleic anhydride antimicrobial polymers delivers a great chance of fighting various pathogens including drug-resistant, deadly strains. The need for these materials grows increasingly, hence the amount of research has been and will be thriving as well. It must not be forgotten that the product applicability depends not only on its antibacterial activity but also on other properties that must be considered and evaluated. That includes toxicity against mammalian cells and possible

accumulation in the human body when it comes to drug-carriers systems. Along with that, the biodegradability and stability should be born in mind. In case of surfaces grafted or covered with protective layers of maleic anhydride antimicrobial polymers their abrasive properties need to be analyzed together with UV radiation resistance. The toxicity of these systems is also crucial. Moreover, the optimal adhesive properties of the layers are vital. One of the most important aspects of the material applicability and functionality is its processing technology which should be workable and the price of the final product which cannot be too high.

5 Conclusions

Despite the development of new technologies and the constant progress in medicine, antimicrobial infections are still one of the major threats to the human life. Usage of polymeric materials containing maleic anhydride could be one of the solutions of the problems related to pathogenic microbes and their interactions with people. The group of antimicrobial polymers based on maleic anhydride consists of:

- poly(styrene-maleic anhydride),
- poly(methyl methacrylate-*co*-maleic anhydride),
- poly(maleic anhydride-*alt*-acrylic acid),
- poly(maleic anhydride-*co*-vinyl acetate),
- N-vinyl amide/maleic anhydride copolymers,
- N-halamine polymeric compounds,
- polymers containing quaternary ammonium salts,
- derivatives of the abovementioned materials such as: poly[styrene-*alt*-(maleic acid, sodium salt)], poly(N-vinyl pyrrolidone-maleic anhydride), branched poly (ethylene imine) and styrene-maleic anhydride copolymer, poly(isobutylene-*alt*-N-(N′,N′-dimethylaminopropyl)-maleimide), poly(isobutylene-*alt*-maleic anhydride).

The polymers have been tested as antimicrobial coatings and drug delivery systems. They gave good results with potential applications in health care and in the food packaging industry. Most of the research however, was focused on the antibacterial action and only a few cases examined their antifungal and antiviral activity. Maleic anhydride polymers are promising antimicrobial agents and it can be assumed that the interest in their application will grow in the next years. Nonetheless, there are certain issues that still have to be addressed related to their mechanical properties and the adverse effects they can have in human.

References

Abd El-Rehim HA, El-Hag Ali A, Mostafa TB et al (2004) Anti-microbial activity of anhydride copolymers and their derivatives prepared by ionizing radiation. Eur Polym J 40:2203–2212. https://doi.org/10.1016/j.eurpolymj.2004.01.044

Ahamad A, Mary Lubi C, Mohan A et al (2001) Synthesis of unsaturated polyester resin - effect of anhydride composition. Des Monomers Polym 4:260–267. https://doi.org/10.1163/156855501750536242

Andersson JA, Fitts EC, Kirtley ML et al (2016) New role for FDA-approved drugs in combating antibiotic-resistant bacteria. Antimicrob Agents Chemother 60:3717–3729. https://doi.org/10.1128/AAC.00326-16

Ashland (2017) Product Stewardship Summary Maleic Anhydride. http://www.ashland.com/sustainability/product/product-stewardship. Accessed 10 Mar 2020

Atanasova KR, Yilmaz Ö (2015) Prelude to oral microbes and chronic diseases: past, present and future. Microbes Infect 17:473–483. https://doi.org/10.1016/j.micinf.2015.03.007

Barman S, Konai MM, Samaddar S et al (2019a) Amino acid conjugated polymers: antibacterial agents effective against drug-resistant Acinetobacter baumannii with no detectable resistance. ACS Appl Mater Interfaces 11:33559–33572. https://doi.org/10.1021/acsami.9b09016

Barman S, Mukherjee S, Ghosh S et al (2019b) Amino-acid-conjugated polymer-rifampicin combination: effective at tackling drug-resistant Gram-negative clinical isolates. ACS Appl Bio Mater 2:5404–5414. https://doi.org/10.1021/acsabm.9b00732

Bastarrachea LJ, Goddard JM (2015) Antimicrobial coatings with dual cationic and N-halamine character: characterization and biocidal efficacy. J Agric Food Chem 63:4243–4251. https://doi.org/10.1021/acs.jafc.5b00445

Bastarrachea LJ, Goddard JM (2016) Self-healing antimicrobial polymer coating with efficacy in the presence of organic matter. Appl Surf Sci 378:479–488. https://doi.org/10.1016/j.apsusc.2016.03.198

Ben Maamar S, Hu J, Hartmann EM (2020) Implications of indoor microbial ecology and evolution on antibiotic resistance. J Expo Sci Environ Epidemiol 30:1–15. https://doi.org/10.1038/s41370-019-0171-0

Benčina M, Mavrič T, Junkar I et al (2018) The importance of antibacterial surfaces in biomedical applications. Adv Biomembr Lipid Self Assembly 28:115–165. https://doi.org/10.1016/bs.abl.2018.05.001

Bielawski CW, Grubbs RH (2007) Living ring-opening metathesis polymerization. Prog Polym Sci 32:1–29. https://doi.org/10.1016/j.progpolymsci.2006.08.006

Bisen PS, Debnath M, Prasad GBKS (2012a) Human and microbial world. In: Microbes: concepts and applications, 1st edn. Wiley, Hoboken, pp 1–64

Bisen PS, Debnath M, Prasad GBKS (2012b) Microbes as a tool for industry and research. In: Microbes: concepts and applications, 1st edn. Wiley, Hoboken, pp 567–684

Bodnar A, Solymoss M, Szmercsanyi IV et al (1990) Method of preparation of unsaturated polyester resins from maleic acid/anhydride. United States Patent 4,902,773

Boruah M, Gogoi P, Adhikari B et al (2012) Preparation and characterization of Jatropha Curcas oil based alkyd resin suitable for surface coating. Prog Org Coat 74:596–602. https://doi.org/10.1016/j.porgcoat.2012.02.007

Brinkac L, Voorhies A, Gomez A et al (2017) The threat of antimicrobial resistance on the human microbiome. Microb Ecol 74:1001–1008. https://doi.org/10.1007/s00248-017-0985-z

Brown D (2015) Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void? Nat Rev Drug Discov 14:821–832. https://doi.org/10.1038/nrd4675

Can HK, Karakus G, Tuzcu N (2014) Synthesis, characterization and in vitro antibacterial assessments of a novel modified poly[maleic anhydride-alt-acrylic acid]/acriflavine conjugate. Polym Bull 71:2903–2921. https://doi.org/10.1007/s00289-014-1230-2

Cerkez I (2018) N-Halamine-based antimicrobial coatings. In: Handbook of antimicrobial coatings. Elsevier, London, pp 391–409

Chatterjee A, Abraham J (2018) Microbial contamination, prevention and early detection in food Industry. In: Microbial contamination and food degradation. Elsevier, London, pp 23–62
Chatterjee S, Raval IH (2019) Pathogenic microbial genetic diversity with reference to health. In: Microbial diversity in the genomic era. Elsevier, London, pp 559–577
Chlebicz A, Śliżewska K (2018) Campylobacteriosis, Salmonellosis, Yersiniosis, and Listeriosis as zoonotic foodborne diseases: a review. Int J Environ Res Public Health 15:1–28. https://doi.org/10.3390/ijerph15050863
Cloete WJ, Verwey L, Klumperman B (2013) Permanently antimicrobial waterborne coatings based on the dual role of modified poly(styrene-co-maleic anhydride). Eur Polym J 49:1080–1088. https://doi.org/10.1016/j.eurpolymj.2013.01.012
Croxen MA, Law RJ, Scholz R et al (2013) Recent advances in understanding enteric pathogenic Escherichia coli. Clin Microbiol Rev 26:822–880. https://doi.org/10.1128/CMR.00022-13
Den Boon S, Marston BJ, Nyenswah TG et al (2019) Ebola virus infection associated with transmission from survivors. Emerg Infect Dis 25:240–246. https://doi.org/10.3201/eid2502.181011
Dente M, Pierucci S, Tronconi E et al (2003) Selective oxidation of n-butane to maleic anhydride in fluid bed reactors: detailed kinetic investigation and reactor modelling. Chem Eng Sci 58:643–648. https://doi.org/10.1016/S0009-2509(02)00590-0
Dizman B, Elasri MO, Mathias LJ (2004) Synthesis and antimicrobial activities of new water-soluble bis-quaternary ammonium methacrylate polymers. J Appl Polym Sci 94:635–642. https://doi.org/10.1002/app.20872
Dodds WK, Whiles MR (2020) Microbes and plants. In: Freshwater ecology. Elsevier, London, pp 211–249
Dominic GJ, Yashoda MP, Ajith Kumar MP et al (2016) Process of making antimicrobial polymers from quaternary ammonium maleic di-ester surfmers and methyl methacrylate by emulsion polymerization. Macromol Symp 362:119–128. https://doi.org/10.1002/masy.201400264
Edwards RC (1985) United States Patent Number 4,515,904 Catalysts for the production of maleic anhydride by the oxidation of butane
Ergene C, Yasuhara K, Palermo EF (2018) Biomimetic antimicrobial polymers: recent advances in molecular design. Polym Chem 9:2407–2427. https://doi.org/10.1039/c8py00012c
Fang W, Cai Y, Chen X et al (2009) Poly(styrene-alt-maleic anhydride) derivatives as potent anti-HIV microbicide candidates. Bioorg Med Chem Lett 19:1903–1907. https://doi.org/10.1016/j.bmcl.2009.02.059
Ganewatta MS, Chen YP, Wang J et al (2014) Bio-inspired resin acid-derived materials as antibacterial resistance agents with unexpected activities. Chem Sci 5:2011–2016. https://doi.org/10.1039/c4sc00034j
Ganewatta MS, Miller KP, Singleton SP et al (2015) Antibacterial and biofilm-disrupting coatings from resin acid-derived materials. Biomacromolecules 16:3336–3344. https://doi.org/10.1021/acs.biomac.5b01005
Gascón J, Téllez C, Herguido J et al (2005) Fluidized bed reactors with two-zones for maleic anhydride production: different configurations and effect of scale. Ind Eng Chem Res 44:8945–8951. https://doi.org/10.1021/ie050638p
Gliścińska E, Gutarowska B, Brycki B et al (2013) Electrospun polyacrylonitrile nanofibers modified by quaternary ammonium salts. J Appl Polym Sci 128:767–775. https://doi.org/10.1002/app.38210
Gomes TAT, Elias WP, Scaletsky ICA et al (2016) Diarrheagenic Escherichia coli. Braz J Microbiol 47:3–30. https://doi.org/10.1016/j.bjm.2016.10.015
González LF, Joubert A, Andrès Y et al (2016) Filtration performances of HVAC filters for PM10 and microbial aerosols—influence of management in a lab-scale air handling unit. Aerosol Sci Technol 50:555–567. https://doi.org/10.1080/02786826.2016.1167833
Gooch JW (ed) (2007) Encyclopedic dictionary of polymers. Springer, New York
Grice EA, Segre JA (2012) The human microbiome: our second genome. Annu Rev Genomics Hum Genet 13:151–170. https://doi.org/10.1146/annurev-genom-090711-163814

Groneberg DA, Hilgenfeld R, Zabel P (2005) Molecular mechanisms of severe acute respiratory syndrome (SARS). Respir Res 6:1–16. https://doi.org/10.1186/1465-9921-6-8
Hacker J, Dobrindt U (2006) Pathogenomics: genome analysis of pathogenic microbes. Wiley, Hoboken
Hatti-Kaul R, Mamo G, Mattiasson B (2016) Anaerobes in biotechnology. In: Advances in biochemical engineering/biotechnology. Springer, Cham, pp 1–471
Hemalatha P, Veeraiah MK, Prasannakumar S et al (2014) Synthesis, characterisation and antibacterial activity of copolymer (N-vinylpyrrolidone – maleic anhydride) with N-diethylethanolamine. Int J Res Eng Technol 3:56–64. https://doi.org/10.15623/ijret.2014.0303011
Hernandez-Milian A, Payeras-Cifre A (2014) What is new in listeriosis? Biomed Res Int 2014:358051. https://doi.org/10.1155/2014/358051
Hernández-Moreno D, de la Casa RI, Soler-Rodríguez F (2014) Maleic anhydride. In: Encyclopedia of toxicology, 3rd edn. Elsevier, London, pp 138–141
Higgins R, Hutchings GJ (1980) Production of maleic anhydride. United States Patent 4,222,945
Hogg S (2005) Essential microbiology. Wiley, Hoboken
Huang J, Turner SR (2017) Recent advances in alternating copolymers: the synthesis, modification, and applications of precision polymers. Polymer 116:572–586. https://doi.org/10.1016/j.polymer.2017.01.020
Huang KS, Yang CH, Huang SL et al (2016) Recent advances in antimicrobial polymers: a mini-review. Int J Mol Sci 17:1578. https://doi.org/10.3390/ijms17091578
Institute of Medicine (2003) Microbial threats to health: emergence, detection, and response. National Academies Press, Washington DC
Jeong JH, Byoun YS, Ko SB et al (2001) Chemical modification of poly(styrene-alt-maleic anhydride) with antimicrobial 4-aminobenzoic acid and 4-hydroxybenzoic acid. J Ind Eng Chem 7:310–315
Jeong JH, Byoun YS, Lee YS (2002) Poly(styrene-alt-maleic anhydride)-4-aminophenol conjugate: synthesis and antibacterial activity. React Funct Polym 50:257–263. https://doi.org/10.1016/S1381-5148(01)00120-1
Jiang S, Wang L, Yu H et al (2006) Study on antibacterial behavior of insoluble quaternary ammonium. J Appl Polym Sci 99:2389–2394. https://doi.org/10.1002/app.22810
Jiao Y, Niu L, Ma S et al (2017) Quaternary ammonium-based biomedical materials: state-of-the-art, toxicological aspects and antimicrobial resistance. Prog Polym Sci 71:53–90. https://doi.org/10.1016/j.progpolymsci.2017.03.001
Kamaruzzaman NF, Tan LP, Hamdan RH et al (2019) Antimicrobial polymers: the potential replacement of existing antibiotics? Int J Mol Sci 20:112747. https://doi.org/10.3390/ijms20112747
Karakuş G (2016) Synthesis, structural characterization, and water solubility of a novel modified poly(maleic anhydride-co-vinyl acetate)/acriflavine conjugate. J Biol Chem 44:549–558. https://doi.org/10.15671/HJBC.2016.135
Kenawy ER, Abdel-Hay FI, El-Shanshoury AERR et al (2002) Biologically active polymers. V. Synthesis and antimicrobial activity of modified poly(glycidyl methacrylate-co-2-hydroxyethyl methacrylate) derivatives with quaternary ammonium and phosphonium salts. J Polym Sci Part A Polym Chem 40:2384–2393. https://doi.org/10.1002/pola.10325
Kenawy ER, Worley SD, Broughton R (2007) The chemistry and applications of antimicrobial polymers: a state-of-the-art review. Biomacromolecules 8:1359–1384. https://doi.org/10.1021/bm061150q
Khazaei A, Saednia S, Saien J et al (2013) Grafting amino drugs to poly(styrene-alt-maleic anhydride) as a potential method for drug release. J Braz Chem Soc 24:1109–1115. https://doi.org/10.5935/0103-5053.20130145
Kumar A, Chordia N (2017) Role of microbes in human health. Appl Microbiol Open Access 3:2. https://doi.org/10.4172/2471-9315.1000131

Lustgarten MS (2016) Classifying aging as a disease: the role of microbes. Front Genet 7:10–13. https://doi.org/10.3389/fgene.2016.00212
Majumdar P, Lee E, Gubbins N et al (2009) Synthesis and antimicrobial activity of quaternary ammonium-functionalized POSS (Q-POSS) and polysiloxane coatings containing Q-POSS. Polymer 50:1124–1133. https://doi.org/10.1016/j.polymer.2009.01.009
Mani S, Wierzba T, Walker RI (2016) Status of vaccine research and development for Shigella. Vaccine 34:2887–2894. https://doi.org/10.1016/j.vaccine.2016.02.075
Mcewen SA, Collignon PJ (2017) Antimicrobial resistance: a one health colloquium. Microbiol Spectr 6:1–26. https://doi.org/10.1128/microbiolspec.ARBA-0009-2017
Memarzadeh F, Olmsted RN, Bartley JM (2010) Applications of ultraviolet germicidal irradiation disinfection in health care facilities: effective adjunct, but not stand-alone technology. Am J Infect Control 38:S13–S24. https://doi.org/10.1016/j.ajic.2010.04.208
Miró-Canturri A, Ayerbe-Algaba R, Smani Y (2019) Drug repurposing for the treatment of bacterial and fungal infections. Front Microbiol 10:41. https://doi.org/10.3389/fmicb.2019.00041
Moghadam PN, Azaryan E, Zeynizade B (2010) Investigation of poly(styrene-alt-maleic anhydride) copolymer for controlled drug delivery of ceftriaxone antibiotic. J Macromol Sci Part A Pure Appl Chem 47:839–848. https://doi.org/10.1080/10601325.2010.492265
Möritz M, Peters H, Nipko B, Rüden H (2001) Capability of air filters to retain airborne bacteria and molds in heating, ventilating and air-conditioning (HVAC) systems. Int J Hyg Environ Health 203:401–409. https://doi.org/10.1078/1438-4639-00054
Morrison KR, Allen RA, Minbiole KPC et al (2019) More QACs, more questions: recent advances in structure activity relationships and hurdles in understanding resistance mechanisms. Tetrahedron Lett 60:150935. https://doi.org/10.1016/j.tetlet.2019.07.026
Musa OM (2016) Handbook of maleic anhydride based materials: syntheses, properties and applications. Springer, Cham
Musumeci T, Puglisi G (2013) Antimicrobial agents. In: Drug-biomembrane interaction studies: the application of calorimetric techniques. Woodhead Publishing Limited, Oxford, pp 305–333
Nagaraja A, Jalageri MD, Puttaiahgowda YM et al (2019) A review on various maleic anhydride antimicrobial polymers. J Microbiol Methods 163:105650. https://doi.org/10.1016/j.mimet.2019.105650
Nasirtabrizi MH, Ziaei ZM, Jadid AP et al (2013) Synthesis and chemical modification of maleic anhydride copolymers with phthalimide groups. Int J Ind Chem 4:11. https://doi.org/10.1186/2228-5547-4-11
National Academies of Sciences Engineering and Medicine (2017) Microbiomes of the built environment: a research agenda for indoor microbiology, human health, and buildings. The National Academies Press, Washington, DC
Nicolle LE (2011) Antimicrobial resistance. Eur Infect Dis 5:92–97. https://doi.org/10.4037/nci.0000000000000102
Noh H, Yu JS, Ko JS et al (2017) Preparation of poly(ethylene-co-acrylic acid) grafted with aliphatic quaternary ammonium salts as antibacterial polymers. Bull Kor Chem Soc 38:890–898. https://doi.org/10.1002/bkcs.11198
Noorbakhsh F, Abdolmohammadi K, Fatahi Y et al (2019) Zika virus infection, basic and clinical aspects: a review article. Iran J Public Health 48:20–31. https://doi.org/10.18502/ijph.v48i1.779
Nurdin N, Helary G, Sauvet G (1993) Biocidal polymers active by contact. II. Biological evaluation of polyurethane coatings with pendant quaternary ammonium salts. J Appl Polym Sci 50:663–670. https://doi.org/10.1002/app.1993.070500411
Parker SF, Wilson CC, Tomkinson J et al (2001) Structure and dynamics of maleic anhydride. J Phys Chem A 105:3064–3070. https://doi.org/10.1021/jp0038005
Patel H, Raval DA, Madamwar D et al (1997) Polymeric prodrugs. Synthesis, release study and antimicrobial properties of polymer-bound acriflavine. Die Angew Makromol Chem 245:1–8. https://doi.org/10.1016/j.ijpharm.2003.07.016
Patel H, Raval DA, Madamwar D et al (1998) Polymeric prodrug: synthesis, release study and antimicrobial property of poly(styrene-co-maleic anhydride)-bound acriflavine. Angew

Makromol Chem 263:25–30. https://doi.org/10.1002/(SICI)1522-9505(19981215)263:1<25::AID-APMC25>3.0.CO;2-9

Patel JS, Patel SV, Talpada NP et al (1999) Bioactive polymers: synthesis, release study and antimicrobial properties of polymer bound Ampicillin. Angew Makromol Chem 271:24–27. https://doi.org/10.1002/(SICI)1522-9505(19991101)271:1<24::AID-APMC24>3.0.CO;2-L

Pegues DA, Ohl ME, Miller SI (2006) Nontyphoidal Salmonellosis. Trop Infect Dis 1:241–254. https://doi.org/10.1016/B978-0-443-06668-9.50023-5

Pigłowski M (2019) Pathogenic and non-pathogenic microorganisms in the rapid alert system for food and feed. Int J Environ Res Public Health 16:1–19. https://doi.org/10.3390/ijerph16030477

Prasad R, Siddhardha B, Dyavaiah M (2020) Nanostructures for antimicrobial and antibiofilm applications. Springer International Publishing, Cham. ISBN 978-3-030-40336-2. https://www.springer.com/gp/book/9783030403362

Rani N, Sangwan P, Joshi M et al (2019) Wastewater treatment. In: Microbial wastewater treatment. Elsevier, London, pp 83–102

Reed NG (2010) The history of ultraviolet germicidal irradiation for air disinfection. Public Health Rep 125:15–27. https://doi.org/10.1177/003335491012500105

Rodríguez-Hernández J (2017) Polymers against microorganisms. Springer, New York

Rutala WA, Weber DJ (2019) Disinfection, sterilization, and antisepsis: an overview. Am J Infect Control 47:A3–A9. https://doi.org/10.1016/j.ajic.2019.01.018

Sauvet G, Fortuniak W, Kazmierski K et al (2003) Amphiphilic block and statistical siloxane copolymers with antimicrobial activity. J Polym Sci Part A Polym Chem 41:2939–2948. https://doi.org/10.1002/pola.10895

Schlagenhauf P, Poumerol G, Santos-O'Connor F (2017) Microbes on the move: prevention, required vaccinations, curtailment, outbreak. In: Peterson E, Chen LH, Schlagenhauf-Lawlor P (eds) Infectious diseases: a geographic guide, 2nd edn. Wiley, Hoboken, pp 45–54

Septimus EJ (2018) Antimicrobial resistance: an antimicrobial/diagnostic stewardship and infection prevention approach. Med Clin North Am 102:819–829. https://doi.org/10.1016/j.mcna.2018.04.005

Siedenbiedel F, Tiller JC (2012) Antimicrobial polymers in solution and on surfaces: overview and functional principles. Polymers 4:46–71. https://doi.org/10.3390/polym4010046

Singh SR, Krishnamurthy NB, Mathew BB (2014) A review on recent diseases caused by microbes. J Appl Environ Microbiol 2:106–115. https://doi.org/10.12691/JAEM-2-4-4

Smith M (2020) Microorganisms and microbiome. In: Gene environment interactions. Elsevier, London, pp 177–203

Stockwell RE, Ballard EL, O'Rourke P et al (2019) Indoor hospital air and the impact of ventilation on bioaerosols: a systematic review. J Hosp Infect 103:175–184. https://doi.org/10.1016/j.jhin.2019.06.016

Sun J, Chang EB (2014) Exploring gut microbes in human health and disease: pushing the envelope. Genes Dis 1:132–139. https://doi.org/10.1016/j.gendis.2014.08.001

Talu M, Uzluk E, Yüksel B (2010) Synthesis, characterization and bactericidal properties of poly (N-vinyl-2-pyrrolidone-co-maleic anhydride-co-N-isopropyl acrylamide). Macromol Symp 297:188–199. https://doi.org/10.1002/masy.200900140

Temiz A, Toğay SÖ, Şener A et al (2006) Antimicrobial poly(N-vinyl-2-pyrrolidone-alt-maleic anhydride)/ poly(ethylene imine) macrocomplexes. J Appl Polym Sci 102:5841–5847. https://doi.org/10.1002/app.24903

Tiller JC, Liao CJ, Lewis K et al (2001) Designing surfaces that kill bacteria on contact. Proc Natl Acad Sci U S A 98:5981–5985. https://doi.org/10.1073/pnas.111143098

Timofeeva L, Kleshcheva N (2011) Antimicrobial polymers: mechanism of action, factors of activity, and applications. Appl Microbiol Biotechnol 89:475–492. https://doi.org/10.1007/s00253-010-2920-9

Tiwari A, Chaturvedi A (2018) Antimicrobial coatings—technology advancement or scientific myth. In: Handbook of antimicrobial coatings. Elsevier, London, pp 1–5

Tseng CC, Li CS (2005) Inactivation of virus-containing aerosols by ultraviolet germicidal irradiation. Aerosol Sci Technol 39:1136–1142. https://doi.org/10.1080/02786820500428575

Uppu DSSM, Haldar J (2016) Lipopolysaccharide neutralization by cationic-amphiphilic polymers through pseudoaggregate formation. Biomacromolecules 17:862–873. https://doi.org/10.1021/acs.biomac.5b01567

Uppu DSSM, Samaddar S, Ghosh C et al (2016) Amide side chain amphiphilic polymers disrupt surface established bacterial bio-films and protect mice from chronic Acinetobacter baumannii infection. Biomaterials 74:131–143. https://doi.org/10.1016/j.biomaterials.2015.09.042

Vaydya UR, Nadkarni VM (1987) Unsaturated polyester resins from poly(ethylene terephthalate) waste. 1. Synthesis and characterisation. Ind Eng Chem Res 26:194–198. https://doi.org/10.1021/ie00062a003

Veron L, Revol M, Mandrand B et al (2001) Synthesis and characterization of poly(N-vinyl pyrrolidone-alt-maleic anhydride): conjugation with bovine serum albumin. J Appl Polym Sci 81:3327–3337. https://doi.org/10.1002/app.1789

Vicente AI, Campos J, Bordado JM et al (2008) Maleic anhydride modified ethylene-diene copolymers: synthesis and properties. React Funct Polym 68:519–526. https://doi.org/10.1016/j.reactfunctpolym.2007.10.026

Wang J, Chen YP, Yao K et al (2012) Robust antimicrobial compounds and polymers derived from natural resin acids. Chem Commun 48:916–918. https://doi.org/10.1039/c1cc16432e

Wang C, Hu X, Zhang Z (2019a) Airborne disinfection using microwave-based technology: energy efficient and distinct inactivation mechanism compared with waterborne disinfection. J Aerosol Sci 137:105437. https://doi.org/10.1016/j.jaerosci.2019.105437

Wang J, Sui M, Ma Z et al (2019b) Antibacterial performance of polymer quaternary ammonium salt-capped silver nanoparticles on: Bacillus subtilis in water. RSC Adv 9:25667–25676. https://doi.org/10.1039/c9ra05944j

Wang Q, Zhu X, Zhu P et al (2019c) N-halamine antibacterial cellulose fabrics functionalized with copoly(acrylamide-maleic anhydride). Fibers Polym 20:906–912. https://doi.org/10.1007/s12221-019-8865-4

Williamson DA, Carter GP, Howden BP (2017) Current and emerging topical antibacterial and antiseptics: agents, action, and resistance patterns. Clin Microbiol Rev 30:827–860. https://doi.org/10.1128/CMR.00112-16

World Health Organization (2015) Global action plan on antimicrobial resistance. Microbe Mag 10:354. https://doi.org/10.1128/microbe.10.354.1

Xue Y, Xiao H, Zhang Y (2015) Antimicrobial polymeric materials with quaternary ammonium and phosphonium salts. Int J Mol Sci 16:3626–3655. https://doi.org/10.3390/ijms16023626

Yang Y, Cai Z, Huang Z et al (2018) Antimicrobial cationic polymers: from structural design to functional control. Polym J 50:33–44. https://doi.org/10.1038/pj.2017.72

Zeng M, Xu J, Luo Q et al (2020) Constructing antibacterial polymer nanocapsules based on pyridine quaternary ammonium salt. Mater Sci Eng C 108:110383. https://doi.org/10.1016/j.msec.2019.110383

Zhang Z, Wagner VE (2017) Antimicrobial coatings and modifications on medical devices. Springer, New York

Zhang Z, Cheng G, Carr LR et al (2008) The hydrolysis of cationic polycarboxybetaine esters to zwitterionic polycarboxybetaines with controlled properties. Biomaterials 29:4719–4725. https://doi.org/10.1016/j.biomaterials.2008.08.030

Zhang A, Liu Q, Lei Y et al (2015) Synthesis and antimicrobial activities of acrylamide polymers containing quaternary ammonium salts on bacteria and phytopathogenic fungi. React Funct Polym 88:39–46. https://doi.org/10.1016/j.reactfunctpolym.2015.02.005

Zhong W, Dong C, Liuyang R et al (2017) Controllable synthesis and antimicrobial activities of acrylate polymers containing quaternary ammonium salts. React Funct Polym 121:110–118. https://doi.org/10.1016/j.reactfunctpolym.2017.10.010

Zhong Y, Godwin P, Jin Y et al (2020) Biodegradable polymers and green-based antimicrobial packaging materials: a mini-review. Adv Ind Eng Polym Res 3:27–35. https://doi.org/10.1016/j.aiepr.2019.11.002

Antimicrobial Magnetic Nanoparticles: A Potential Antibiotic Agent in the Era of Multi-Drug Resistance

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Abstract In the last few decades, microbes have evolved, having resistance to several drugs and antibiotics. Multiple-drug-resistant (MDR) strains have become a severe threat to human health that needs to be addressed immediately. In this context, research has led to a quest for new strategies in the development of novel antimicrobial therapies. The use of nanoparticles (NPs) has gained the attention of the research community working in the field of targeted delivery systems for drugs. Though NPs have proved their extraordinary antimicrobial activity against several disease-causing microbes, NPs with magnetic properties are found to be more efficient and effective. The unique physicochemical properties of magnetic nanoparticles (MNPs) have been proved to offer better antimicrobial activity when compared to the conventional forms. Moreover, magnetic nanoparticles have an extensive range of commercial and domestic applications in several fields, including environment, medicine, electronics, agriculture, and pharmaceuticals. This chapter provides aspects of the synthesis, use, and antimicrobial properties of MNPs along with a brief discussion of the probable mechanism involved. It also focuses on the characterization technique of MNPs, followed by the assessment strategies of antimicrobial activity. Overall, the chapter offers an insight into the antimicrobial activity of different MNPs while exploring the correlation of factors affecting the overall process.

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1 Introduction

Despite exceptional discoveries and achievements in the field of medical science, a few bacterial species have been a significant cause of chronic infections in humans that could lead to death. Antibiotics are an efficient and cost-effective solution and have been widely employed for the treatments of such diseases. However, in recent years, bacterial strains have evolved into a multi-drug-resistant (MDR) form that has become a global threat concerning severe health issues (Kruijshaar et al. 2008; Snell 2003). Moreover, only two new classes of antibiotics have been discovered and developed in the last few decades that have worsened the situation (De Vries et al. 2015). According to a report published by the World Health Organization (WHO), antibiotic resistance strains and biofilm associated infections will cost more than 300 million lives by 2050, along with the $100 trillion economic loss (Jose and Munita 2016). These severe concerns have accelerated the research towards finding and developing innovative strategies for microbial treatments (Arias and Murray 2009). An ideal antimicrobial agent should have excellent antimicrobial properties against a broader range of microbes while offering less or no toxic effect on the surrounding tissue. It should also be easy to synthesize and have no harm to the environment. Several materials have proved their potential while exhibiting antimicrobial activity against disease-causing strains. Among many, organic/inorganic polymers (nano/macroparticles), peptides, cationic surfactants (e.g., didodecyldimethylammonium bromide) have been assessed for their antimicrobial activities. Similarly, antibodies, phases, inhibitors (quorum sensitive), and antimicrobial NPs have been explored against several microbes in the recent past (Simões et al. 2016; Wang et al. 2017; Draper et al. 2015).

Generally, antimicrobial agents can be classified into two categories; organic and inorganic. Medicinal plants are organic agents that have proved their remarkable antimicrobial activities against numerous microbial strains, whereas NPs (usually less than 100 nm in diameter) belong to inorganic materials having superior antimicrobial activities against MDR strains (Kaviyarasu et al. 2017; Slavin et al. 2017). NPs seem to be an efficient and promising antimicrobial candidate against multi-drug resistance bacteria owing to their bio-mimicking properties similar to protein inhibitors. NPs show microbicidal nature where they confer similar size, geometries, and surface chemistry as biological agents. Typically, NPs can attack and directly affect the cell wall of bacteria without being penetrated into the cell cytoplasm that efficiently kills MDR strains. However, there are several other modes of action, including the release of toxic ions, generation of reactive oxygen species (ROS), interruption of electron transport, protein oxidation, and membrane collapse, which makes them a favorite antimicrobial candidate over others (Ali 2018). NPs have

shown antimicrobial effects against a broad spectrum of bacteria (Gram-positive and Gram-negative), mycobacteria, and fungi (Wang et al. 2017).

Moreover, magnetic nanoparticles (MNPs) offer superior features since they can be remotely monitored and directed using an external magnetic field to treat targeted sites, compared to their silica/carbon-based analogs signified for biopharmaceutical applications (Reddy et al. 2012). Additionally, magnetic fluid hyperthermia caused by MNPs enhances the overall antimicrobial effect where a fluctuating magnetic field of MNPs dissipates heat in the form of energy while elevating the local temperature around the targeted site (Laurent et al. 2011; López-Abarrategui et al. 2013). MNPs can exhibit unique physical properties allowing them to function at the cellular and molecular level and be efficiently established and employed in several pharmaceutical and biological applications (Reddy et al. 2012; Lu et al. 2007). Several metals, including zinc, silver, and copper, can be used to synthesize MNPs. Further, the nanoscale dimensions of these metals are inversely proportional to the antimicrobial activity (Seil and Webster 2012).

2 Microbial Resistance

Antimicrobial resistance in microorganisms is ancient and associated with the naturally produced antimicrobial compounds. Prolonged exposure and interactions between the microbes and antimicrobial compounds present in their natural surroundings can result in a resistant form. This type of microbes is known to be "intrinsically" resistant to one or more types of antimicrobial compounds. On the other hand, when a population of microbes becomes resistant that were initially susceptible to the antimicrobials, are known to have "acquired resistance." The following section focuses on the mechanisms of intrinsic/extrinsic factors that drive resistance at genetics/biochemistry level in bacteria, against antimicrobials.

2.1 Genetics at the DNA Level

Bacteria exhibit remarkable genetic adaptivity that helps them survive under a wide range of stressful environments. The presence of antibiotic molecules in the surrounding is a significant threat to bacteria and may trigger genetic modifications leading to an antibiotic-resistant form. Bacteria sharing the same environment as antimicrobial compound producing-strain can push them to withstand the impact of harmful antibiotic compounds, considering the intrinsic resistance that ultimately allows them to flourish in the presence of antimicrobials (Jose and Munita 2016). To survive and adapt to the antibiotic attack, bacteria can evolve through two major routes of genetic modifications. Spontaneous mutation of existing/exogenous gene (s) often allied with the action mechanics of the antimicrobial compounds representing the intrinsic resistance of bacteria, whereas acquired resistance causes

mutations through the acquisition of foreign code of DNA exercising horizontal gene transfer (HGT). The rise of multi-drug-resistant strains, in particular, is a consequence of the acquired resistance where the acquisition of multiple drug-resistance genes occurs in the same bacterial cell (Aung et al. 2016). Typically, bacteria can acquire external genetic composition via three routes: (1) incorporation of naked DNA via transformation, (2) bacterial sex via conjugation, and (3) phage mediated transduction. Further, the acquired resistance can be spread and transferred among bacteria through integrons, transposons, and plasmids (Coetzee et al. 2016; Tsutsui et al. 2015; Moghaddam et al. 2015).

2.2 Biochemistry at the Protein Level

Apart from genetic adjustments, certain antimicrobial resistance in bacteria could be a result of alterations in specific types of proteins present inside and on the surface of the cell. There are several possible mechanisms studied to assess the modifications of protein biochemistry. The resistance can be obtained by (1) altering of the target molecule that interacts with antibiotic molecule; (2) adding specific chemical moieties to the antibiotic molecule that ultimately hinders the molecule interaction with its target; (3) forming passivated/inactivated enzymes; (4) forming biofilms (Andersson et al. 2016); (5) employing activated efflux pump systems (Daury et al. 2016; Lytvynenko et al. 2016); (6) preventing antibiotic permeation inside the cell; and (7) eliminating specific proteins (e.g., KatG/BamA28) that are involved in the infection mechanism (Noinaj et al. 2013). Moreover, two or more mechanisms can be observed in one type of cell where resistance can be attained by (8) increasing production of a counteracting inhibitor that competes with the antibiotic and (9) preventing antibiotics through several metabolic pathways (Khameneh et al. 2016).

Pre-NP era, mainly three strategies were used to be employed to tackle the antibiotic-resistant microbes or MDR, including the development of novel antibiotics/drugs, high dosage of antibiotics/drugs (Huh and Kwon 2011), and combination of multiple antibiotic/drug compounds (Koul et al. 2011; Yount and Yeaman 2012). However, the identification and production of novel antibiotics could not keep up with the continuous evolution of bacteria through mutations. Moreover, the high dosage and application of combined drugs (two or more antibiotics) led to the intolerable toxicity that ultimately evolved highly multidrug-resistant strains than before. Therefore, NPs as an antibiotic agent can be employed to fight against resistant strains and must be explored for the possible enhancements in the field, considering their extraordinary physicochemical properties.

3 Mode of Action of Magnetic Nanoparticles

Increased usage of NPs in medicinal applications has initiated many investigations examining potential antibacterial mechanisms of NPs (Huh and Kwon 2011). The ability of NPs to eliminate bacteria to cure several types of diseases has led researchers to explore the possible mechanism involved in the process. NPs own unique chemical, physical, and biological properties along with electronic, electrical, mechanical, thermal, dielectric, optical, and magnetic properties. Metal oxide NPs have proved their great potential considering unique electronic, optical, and magnetic properties. NPs offer electrostatic interactions with negatively charged bacteria surface where they quickly get penetrated through the membrane. Moreover, a strong positive zeta potential of NPs can promote surface interactions leading to disruption of bacterial cell membrane along with enhanced flocculation with reduced viability. However, the exact mechanisms of NPs showing antimicrobial activity are yet to be entirely understood. According to prior reports, NPs can generate toxicity in several ways, including cell membrane damage, the release of toxic ions, interruption of electron transport, protein oxidation, and membrane collapse. Also, the generation of ROS (reactive oxygen species) can confer antimicrobial activity to NPs. Possible mechanisms supporting the antimicrobial activity of NPs and MNPs are discussed in this section.

3.1 Cell Membrane Deterioration

NPs can interact with bacterial cell membrane via electrostatic attractions (Li et al. 2015), Van der Waals forces (Armentano et al. 2014), and receptor–ligand hydrophobic interactions (Gao et al. 2014; Luan et al. 2016). These interactions between NPs and cell membranes may yield toxic effects on bacterial cells (Thill et al. 2006). However, the involvement of polymyxins in the process is not yet profoundly established. Reports suggest that polymyxin antibiotics can attack cell membrane that is responsible for furnishing a protecting shell around the bacterial cell (Aruguete et al. 2013). NPs can positively alter the permeability of the cell membrane that ultimately brings toxic effects to them. Several researchers suggested that pore/hole formation on the cell membrane can damage the cell where explicit evidence of cell damage has surfaced (Leroueil et al. 2007); however, the mechanics of the same demands more clarification. Nevertheless, a literal hole in the bilayer membrane can promote the absolute destruction of the plasma membrane that eventually causes the death of the cell (Niskanen et al. 2010).

3.2 Discharge of Toxic Ions

Different types of ions (e.g., Ag^+, Zn^{2+}, and Cd^{2+}) have demonstrated their ability to react with various groups of proteins present in the bacterial cell. Among many possible mechanisms, formation and accumulation of soluble salts in the cytoplasm due to the reaction of Ag^+ ions have been widely accepted for the antimicrobial effect of silver NPs. Such accumulated salts in the cytoplasm can inhibit respiration in the affected cell. For instance, silver chloride precipitation induced by chloride ions can kill the cell by hindering its essential metabolic activities. Similarly, silver NPs can also show antibiotic activity against several Gram-negative bacterial species, including *E. coli*. Silver NPs not only offer a toxic effect by delivering silver ions but also get penetrated through the cell membrane while hindering the metabolic activities of the cell (Niskanen et al. 2010). Further, Ag^+ ions have been reported to damage DNA by blocking the replication process that ultimately leads to the death of the cell. Similarly, Zn^+ and Cd^+ ions also have shown antibiotic activity against several bacterial species through binding to sulfur-containing surface proteins. These surface proteins mainly prevent external molecules from penetrating through the cell membrane. The NP-surface protein interactions make NPs easily penetrate the cell, which is necessary to cause an adverse effect on the regular metabolic activities of the cell. Additionally, the concentration of ions required to attain the bactericidal action is evidently less and therefore makes the NPs a favorable candidate over others.

3.3 Interruption of Protein Oxidation, Electron Transport, and Membrane Collapse

Positively charged NPs can evidently interact with the negatively charged cell membrane of a bacterial cell that awards antimicrobial activity to NPs. Despite the lack of establishment of a defined mechanism of the same, it was found that ions can alter the membrane-bound respiratory enzymes via oxidation. Further, it can also influence the efflux bombs of ions leading to the death of the cell (Allaker 2010). Contact of NPs with cell membranes can also trigger a cascade reaction that inactivates crucial enzymes involved in metabolic pathways. Typically, NPs coming with the contact of bacterial cells initiate possible oxidation of respiratory enzymes along with the production of reactive oxygen and radical species that ultimately alter the physiology of the cell while promoting DNA degradation (Spacciapoli et al. 2001; Xia et al. 2008).

3.4 ROS (Reactive Oxygen Species) Generation

Despite being a potent oxidant agent and acceptor of electrons during cellular respiration, oxygen could be fatal to some bacterial species. Oxygen in its singlet (O_2) or triplet ($3O_2$) form can be toxic to the cell. Singlet (O_2) is a strong reagent that can promote undesirable and spontaneous peroxidation of several cellular components, including lipids and proteins (Bronshteint et al. 2006). H_2O_2 formed during respiration consumes O_2 while producing free hydroxy radicals that evidently lead to oxidation of lipids, proteins, and DNA (Bronshteint et al. 2006). ROS affects the cell membranes by hindering their adhesion to the surface while unable to maintain communication with nearby bacterial cells hindering their functions and efficiency. Nevertheless, several bacterial species can fight back to neutralize oxidative stress by employing enzymes (e.g., superoxide dismutase). Further, they can cope up with the oxidative stress by responding to superoxide (SoxRS) and hydrogen peroxide (OxyR) while effectively repairing damaged cell constituents (Aruguete et al. 2013; Allaker 2010).

3.5 Magnetic Fluid Hyperthermia

Under the application of a high frequency and amplitude of the alternating magnetic field, MNPs can absorb electromagnetic radiation and converts the magnetic energy to localized heat, often referred to as magnetic fluid hyperthermia (Laurent et al. 2011; López-Abarrategui et al. 2013). The MNPs induced hyperthermia is highly useful to control infectious diseases while increasing antibiotics efficacy along with biofilm detachment (Xu et al. 2019). Ibelli et al. (2018) have shown that the magnetic hypothermia process increases the membrane permeability at elevated temperature (>45 °C), where most of the bacterial pathogens become vulnerable. Rodrigues et al. (2013) also derived a similar conclusion stating, at 45 °C, bacterial morphology, mechanical properties, and the viability of *P. fluorescens* was significantly influenced. The detailed study showed that by applying an external magnetic field, the viability of both biofilm cells and planktonic decreases with an increase in temperature. Also, hypothermia caused by MNPs has more significant destruction of the bacterial biofilms in comparison to the direct heating method. Kim et al. (2013) have further investigated the antimicrobial effectiveness of magnetic hypothermia against *S. aureus* and reported 80% efficiency of antibody-modified MNPs under the alternating magnetic field.

To intensify the antibody interactions (immobilization) at conjugation sites, antibodies conjugated with MNPs surface have been employed in the separation and selective targeting of several bacteria (Kim et al. 2016). For the separation of *Salmonella typhimurium*, MNPs were functionalized with O-or H-antibodies. The polysorbate 80-coated MNPs (PCMNC) were prepared in two steps. Firstly, the hydrophobic ligands (oleic acid) coated MNPs were synthesized by thermal

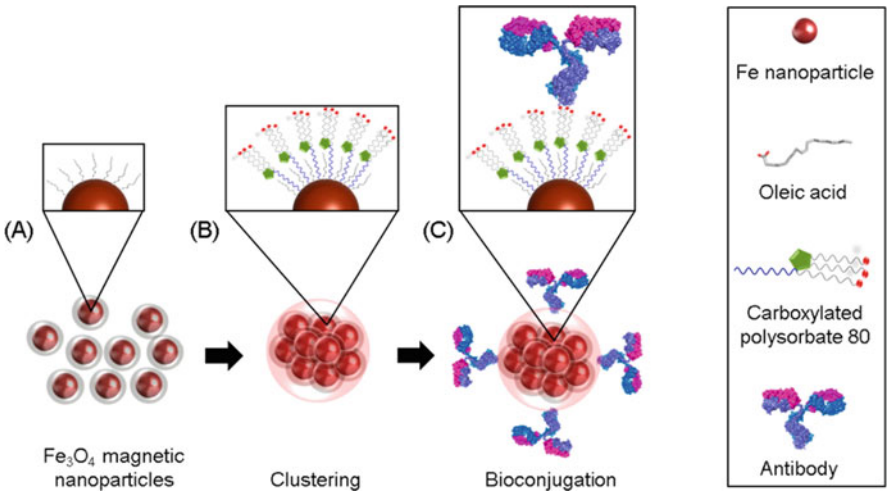

Fig. 1 Schematic of preparation of bioconjugated MNPs with antibodies (Copyright © 2016, American Chemical Society, All rights reserved, reprinted with permission) (Kim et al. 2016)

decomposition of iron (III) acetyloacetonate and oleic acid in benzyl ether (Fig. 1a). The surface of prepared material was then modified by using carboxyl group containing polysorbate 80 (Fig. 1b). The prepared PCMNC was then conjugated with amine group of antibodies to get magnetically separable nanocomposite (Fig. 1c). The MNPs nanocluster showed an effective capturing of *S. typhimurium* with 57 and 99% cell separation efficiency of H- and O-antibody modified MNPs nanocluster, respectively. The transmission electron microscopic (TEM) analysis of the *S. typhimurium* decorated MNPs cluster showed that O-antibody modified nanocluster is accumulated in flagella while H-antibody modified nanocluster is accumulated in salmonella body (Fig. 2).

Furthermore, modification of MNPs with cationic polymers or antibiotics can increase the antimicrobial activity due to the supporting action of magnetic hypothermia (Wang et al. 2018a; Pu et al. 2016; Nguyen et al. 2015; Zomorodian et al. 2018). Nguyen et al. (2015) have studied the combined effect of hypothermia induced due to MNPs along with gentamicin, against the biofilm formed by *P. aeruginosa.* Poly ((oligo (ethylene glycol) methyl ether acrylate)-*block*-poly (monoacryloxy ethyl phosphate)-stabilized iron oxide NPs (POEGA-*b*-PMAEP@IONPs) can produce local heating in biofilms when exposed to the magnetic field while promoting the detachment of biofilm cell. The combined treatments of nanocomposite, along with gentamicin, showed an increase in the efficacy against planktonic and biofilm in comparison to gentamicin alone. Fang et al. (2017) have combined the magnetic hypothermia with vancomycin to see the bacterial killing efficiency against *S. aureus*. The MNPs conjugates were heated (up to 75 °C) under the exposure of external magnetic field, which ultimately enhanced the antibacterial efficacy of vancomycin. Similarly, Chudzik et al.

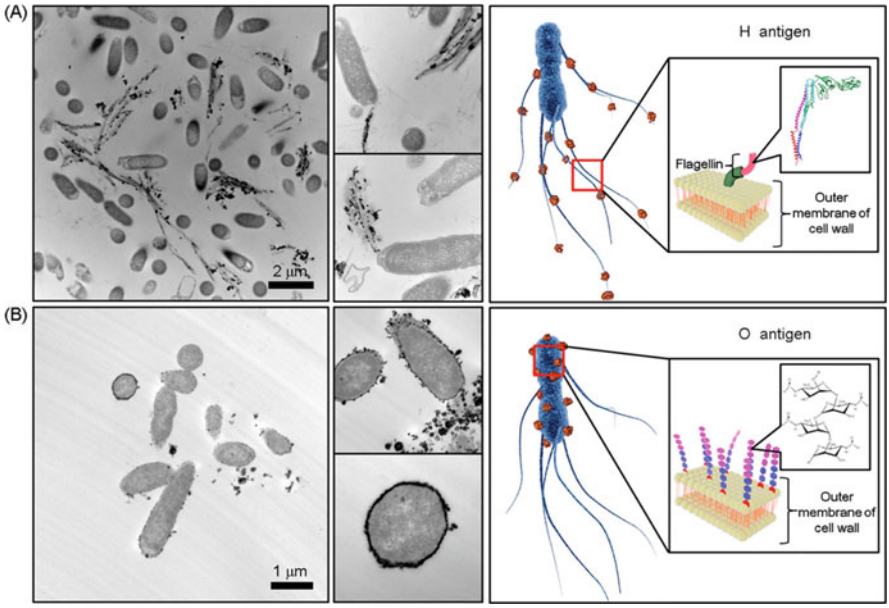

Fig. 2 Selective binding of *Salmonella typhimurium* for different antigens (Copyright © 2016, American Chemical Society, All rights reserved, reprinted with permission) (Kim et al. 2016)

(2016) have described the antifungal activity of magnetic fluid hyperthermia against *C. albicans*. The composite material was prepared by functionalizing antimicrobials (anti-*C. albican*) on Meso-2,3-dimercaptosuccinic acid (DMSA) coated MNPs. The hyperthermia-induced under the exposure of external magnetic field with DMSA coated MNPs and functionalized MNPs have shown higher toxicity against the *C. albicans* cells in comparison to the static heating.

4 Synthesis of Magnetic Nanoparticles

The specific activity of the nanomaterials is the function of the structure, and the phase it exists in. The selectivity, antimicrobial activity, and overall performance of these nanomaterials are often correlated with their structure (Zhou et al. 2018). The effect of different precursors and methods of preparation results in varied activity, shape, size, and distribution of NPs. In a bottom-up approach, several methods are reported for the synthesis of NPs, which can be broadly categorized into conventional, green, and advanced synthesis.

4.1 Conventional Methods

In a typical nanoparticle synthesis, the metal precursor is reduced to the metal nanoparticle, either physically or chemically (Park 2014). In a physical method, high temperature is used to breakdown the precursor. This method gives uniform distribution and shape, though it takes a long time with harmful operating conditions. On the other hand, chemical synthesis is the most widely practiced method, which involves the use of three main components: a metal precursor, organic/inorganic reducing agents, and stabilizing agent. The most common reducing agents are sodium borohydride and hydrazine hydrate. Chemical synthesis methods are further categorized into the microemulsion, photo-induced reduction, UV-assisted photoreduction, electrochemical reduction, and different irradiation methods. The chemical methods have the upper hand in terms of the yield of NPs compared to physical methods (Fernando et al. 2018).

4.2 Green Methods

Recently, the paradigm of using chemical reducing agents has shifted to green and sustainable methods (Park 2014). The biological synthesis methods offer an excellent solution to develop environment-friendly methods. The ability of bacteria, fungi, and plants to biosynthesize the metal NPs by an environmentally friendly process offers an exciting prospect (Prasad et al. 2016, 2018). In this method, the plant extract is utilized to reduce the metal precursor to obtain NPs (Park 2014; Rafique et al. 2017; Prasad 2014; Joshi et al. 2018). The plant extract, as a reducing agent coming from multiple parts of the plant (e.g., leaves, flowers, bark, root fruits, etc.) is used. The antimicrobial property of such NPs can be correlated to their enhanced stability. Thus, cationic and anionic surfactants are employed to stabilize the NPs (Andersson et al. 2016).

4.3 Advanced Synthesis Methods for Functionalization of Nanoparticles

The physical properties and the stability of each metal vary concerning the structure, activity, and application. This demands the development of new strategies to synthesize advanced functional materials. Several metal NPs, including Ag, Cu, Zn, Ti, Au, and carbon-based, have been investigated for their antimicrobial activity. Among others, silver NPs have shown a broad spectrum of applications, and several methods are reported for the synthesis of Ag NPs. Ag NPs supported on SiO_2 were prepared using the co-condensation method to enhance the antimicrobial activity (Tian et al. 2014). Multi-functional nanocomposite supported on graphene oxide was prepared by the co-precipitation method. The graphene as support helps to grow the

NPs and gives them stability. Functionalized gold particles with antimicrobial activity can be obtained by chemical processes such as Turkevic, brust, and seeded growth. Similarly, the biological method can also be employed where functionalization can be obtained using plant extracts, microorganisms, and biomolecules (Shah et al. 2014).

Some of the advanced methods for the synthesis of antibacterial MNPs are mentioned below. Ag NPs with antimicrobial activity were incorporated with iron oxide to provide magnetic properties. One-pot hydrothermal synthesis of porous core–shell structure was developed by embedding the Ag in Fe_3O_4 shell. The synthesized structure helped the sustained release of silver ions that prolonged the antibacterial activity (Fang et al. 2014). Moosavi et al. (2015) have prepared the magnetic nanocomposite made of Fe_3O_4 as a core, the graphene oxide as a shell, and Ag as supported metal. The graphene oxide sheet was first incorporated with iron oxide to provide magnetic properties. This magnetic graphene sheet was then supported with silver NPs using cinnamon extract (Moosavi et al. 2015). Recyclable MNPs were prepared by inducing a controlled living radical polymerization technique wherein the Fe_3O_4 NPs' surface was functionalized with the atom transfer radical polymerization (ATRP) (Dong et al. 2011). The synthesis consists of multiple steps, and the resulting material showed excellent reusability with sustained antimicrobial activity for eight multiple cycles (Dong et al. 2011). In another example, silver MNPs were prepared by forming a silver ring and the magnetic core with ligand sandwiched in between, which facilitated a promising increase in antibacterial properties of the material (Mahmoudi and Serpooshan 2012). Multifunctional polyester fabric with antibacterial and magnetic properties was prepared by in-situ grafting of Fe_3O_4 NPs on the surface of a fabric. Chloride and sulfate precursor of Fe in specific ratios were used to treat the polyester fabric by the co-precipitation method using NaOH as a base (Harifi and Montazer 2014). The pulsed laser ablation technique synthesized Fe_3O_4 NPs by dispersing iron target in dimethylformamide and sodium dodecyl sulfate (SDS) solution (Ismail et al. 2015). Bomila et al. (2018) have prepared La-doped ZnO MNPs by the wet chemical method, which showed a varied antibacterial activity with different doping concentrations. The various methods for the preparation of antibacterial nanomaterials are summarized in Table 1.

5 Characterization of Magnetic Nanocomposites

The characterization of prepared nanocomposites can be divided into two parts. The physical and chemical properties of prepared MNPs can elaborate on the advancements in the field. On the other hand, the antimicrobial assessment of synthesized MNPs can help in assessing the biological responses associated with their physicochemical properties.

Table 1 Methods for the preparation of antibacterial magnetic nanomaterials

Sr. No.	Magnetic nanoparticles	Method of preparation	Antibacterial activity	Reference
1.	Ag and Fe core shell	Solvothermal	*Escherichia coli* and *Bacillus subtilis*	Fang et al. (2014)
2.	Ag, Fe, graphene oxide	Co-precipitation and ultra-sonication	*E. coli* and *S. aureus*	Moosavi et al. (2015)
3.	Fe	Co-precipitation	*E. coli*	Dong et al. (2011)
4.	Au and Fe core shell	Chemical reduction	Pathogens	Mahmoudi and Serpooshan (2012)
5.	Fe	In-situ co-precipitation on fabric	*S. aureus*	Harifi and Montazer (2014)
6.	Fe	Pulsed laser ablation	*S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens*	Ismail et al. (2015)
7.	La-doped Zn	Co-precipitation	Gram-positive: *Bacillus subtilis*, *S. aureus*, Gram-negative: *Proteus mirabilis*, *Salmonella typhi*	Bomila et al. (2018)

5.1 Physicochemical Techniques

Several methods and techniques are proposed to understand the physical and chemical structure of MNPs and nanomaterials.

5.1.1 Microscopy

The stability and magnetic properties of nanocomposites mainly depend on their shape and size (Allafchian and Hosseini 2019). The several microscopic techniques used include scanning electron microscopy (SEM), field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), and HRTEM. The detailed microscopic characterization gives the information on shape, aggregate state, size, and core–shell structure of NPs (Ali et al. 2016; Hurley et al. 2015; Ansari et al. 2019). FESEM and HRTEM usually analyze the NPs of less than 20 nm in size. Moreover, atomic force microscopy (AFM) provides information about shape heterogeneity, dispersion for a wide range of analyzing conditions such as liquid, air, or vacuum. Besides, AFM is useful for the simultaneous analysis of a biological system to gather data on their morphology, elasticity, deformation, energy dissipation, and adhesion (Ansari et al. 2019).

5.1.2 Spectroscopy

Spectroscopy techniques such as Raman, Fourier Transform Infrared (FTIR), Energy dispersive X-ray (EDS), UV-visible (UV-Vis), X-ray photoelectron (XPS) are used for the structural confirmation of NPs (Ali et al. 2016; Hurley et al. 2015; Ansari et al. 2019; Arakha et al. 2019). Raman spectra can confirm the formation of a certain material phase in the sample. FTIR investigates the surface chemical group of samples and various chemical bonds formed. EDS provides the electron mapping of the sample and hence give information on the composition of the nanomaterial. UV-vis spectroscopy provides information on the optical absorption rate of suspension. XPS examines the surface layer, which is generally highly oxidized that helps to assess the chemical state of the components.

5.1.3 Magnetometric Techniques

The magnetic properties of prepared MNPs and composites can be analyzed using magnetometers such as superconducting quantum interference device (SQUID) and vibrating sample magnetometer (VSM). The critical magnetic parameters of MNPs, such as coercive field, remnant magnetization, and saturation magnetization, are measured using the above-mentioned magnetometers (Tarantash et al. 2018; Ghazanfari et al. 2016). The SQUID is considered as standard magnetization measurement technique due to its better sensitivity (up to 10^{-10} emu) in comparison to VSM (up to 10^{-6} emu) and offers the analysis of samples in various forms (Ali et al. 2016).

5.1.4 Other Conventional Techniques

Apart from the techniques mentioned above, other relevant methods, such as X-ray diffraction (XRD), contact angle measurement, and zeta potential, are employed. XRD helps to identify the phase of the NPs, crystallinity of the sample while verifying the chemical composition (Talpade et al. 2019; Tiwari et al. 2017). The surface wettability of NPs can be monitored using contact angle measurement and thus can be used for the quantitative analysis of hydrophobicity and hydrophilicity of the surface of a material (Allafchian and Hosseini 2019). Zeta potential measures the colloidal stability of NPs. The high value of zeta potential for small enough dispersed particles would resist their tendency to aggregate. The dispersed NPs having zeta potential magnitude more than 30 mV are found to be stable (Hatamie et al. 2015).

5.2 *Antimicrobial Activity Test*

Understanding the impact of antimicrobial agents on the viability of a microbial cell is an essential factor for the development of next-generation antimicrobial agents. Here, a brief overview of conventional methods for testing antimicrobial property of NPs is provided. The details regarding all these methods can be found in the published literature along with their limitations (Webster and Seil 2012; Hoseinzadeh et al. 2017).

5.2.1 Disk-Diffusion Method

In this method, a disc containing antimicrobial agents is placed on the microbes inoculated agar (Mueller-Hinton agar (pH 7.2–7.4). After an incubation period of 24 h, if the examined agent inhibits the growth of the microbes, a clear zone of inhibition will form around the disc. The common factors affecting the size of the inhibition zone are nanoparticle size, agars' porosity, the diffusion rate of NPs, and possible interaction between agar and antimicrobial agent (Vega-Jiménez et al. 2019).

5.2.2 Dilution Methods

Two types of processes, agar or broth dilution method, are employed to measure the antimicrobial activity against microbes (Webster and Seil 2012). Also, the dilution methods are more appropriate to determine the minimum inhibitory concentration (MIC) value. The broth dilution method is less laborious and gives better results in comparison to agar dilution, and hence is a preferable method of testing (Baker et al. 1991).

5.2.3 Minimum Inhibitory Concentration (MIC)

The MIC refers to the minimum concentration of antimicrobial agent that completely inhibits the growth of microbes and is a well-documented method to determine the antimicrobial potential of NPs (Hoseinzadeh et al. 2017). Moreover, the calorimetric methods based on the use of dye reagents are developed to determine the MIC endpoint (Balouiri et al. 2016). The most common dyes used are Tetrazolium salts, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 2,3-bis {2-methoxy-4-nitro-5-[(sulfenylamino) carbonyl]-2Htetrazolium-hydroxide} (XTT) are utilized to determine MIC endpoint in both antifungal and antibacterial assays (Balouiri et al. 2016; Liang et al. 2012; Al-Bakri and Afifi 2007; Monteiro et al. 2012).

5.2.4 Minimum Lethal Concentration (MLC)

Minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFC) refers to the lowest concentration of antimicrobial agents needed to kill 99.9% of bacteria or fungi (Allafchian and Hosseini 2019). MLC testing compares the germ-killing activity of the different antimicrobial agents in single experiments (Hoseinzadeh et al. 2017).

5.2.5 Time-Kill Method

The time-kill test provides the time-dependent or concentration-dependent antimicrobial effect and is a robust tool to determine the interaction between microbial strain and antimicrobial agents (Hoseinzadeh et al. 2017, 2012, 2014; Lara et al. 2010). This method is more frequently used to assess the antimicrobial activity of NPs.

5.2.6 Flow Cytofluorometric Method

In the flow cytofluorometric technique, a fluorescent dye is used to determine the cell viability after exposure to drugs or pathogenic organisms (Hoseinzadeh et al. 2017). Propidium iodide (PI), a red fluorescent nucleic acid dye, is mostly used as a DNA staining agent.

6 Applications of MNPs

6.1 MNPs as Antimicrobials

The toxicity can be influenced by the intrinsic properties of NPs, along with the composition and surface modifications. Moreover, the type of bacterial species also affects the extent of the antibacterial effect generated by NPs. In comparison to several MNPs, iron oxide NPs (IONPs) have found great importance in biomedical applications owing to their ease of preparation, surface modification, and low toxicity (Liu et al. 2013). Prucek et al. (2011) have synthesized two different types of MNPs, one having the ultra-small Ag NPs (~5 nm) supported on Fe_3O_4 (~70 nm) as a magnetic core ($Ag@Fe_3O_4$). The second form of MNPs (α-$Fe_2O_3@Ag$) was prepared by taking silver NPs (20–40 nm) as a core and surrounded by the ultra-small α-Fe_2O_3. The prepared NPs have shown vital antimicrobial activities against different bacterial strains. These MNPs are found to be useful for the transportation of targeted antimicrobial agents to the specific target while offering convenient removal of particles by applying the external magnetic field. Several parameters,

including size, shape, surface features, and functionalization play a crucial role in producing overall antimicrobial effect.

6.1.1 Size

The small size of the NPs has been a responsible factor conferring potent antimicrobial activity to these particles. IONPs (66 nm in size) were tested against different bacterial strains and found to have better antimicrobial activity against Gram-positive bacteria in comparison to Gram-negative bacteria (Behera et al. 2012). However, the prepared particles were not coated and adversely affected the antimicrobial efficacy and stability of MNPs. The antimicrobial activity of NPs is mainly due to their active surface area, which increases with a decrease in size and increase in numbers (Allafchian and Hosseini 2019). Auffan et al. (2008) have synthesized the iron-based NPs and studied their antibacterial activity against *E. coli*. The results showed that the NPs exhibited a size-dependent inhibitory effect. Gao et al. (2016) described the antimicrobial activity of MNPs in combination with H_2O_2 as an effective method to kill bacteria (*S. mutans*), causing dental caries. The catalytic nanoparticle, along with H_2O_2, has shown a high antibacterial effect (>99.9% killing in 5 min) against the biofilm. Therefore, the excellent activity of the system can be correlated with the small size of IONPs.

6.1.2 Shape/Composite

Core and shell-type of magnetic nanocomposite (Fe_3O_4@SiO_2/CTMP NPs) having a core of magnetic Fe_3O_4, silica as the middle layer, and antibacterial N-calamine as the outer components were prepared (Yao et al. 2016). The prepared material showed a strong antimicrobial effect against two bacterial strains (*E. coli* and *S. aureus*) while killing bacterial cells in 20 min (100% kill rate) with an oxidative concentration of Cl^+ (0.58%). Thukkaram et al. (2014) have studied the effect of IONPs on biofilm structure while assessing them with different surfaces and biomaterials. The MNPs found to have the potent antimicrobial activity against *S. aureus*, *P. aeruginosa*, and *E. coli*, while showing a significant decline in the biofilm growth for all bacterial species. The formation of biofilm results in a decrease in the effectiveness of antibiotics; hence suitable anti-biofilm therapies have been put forward using NPs (Taylor et al. 2014). In this context, Grumezescu et al. (2015) have reported the synthesis of core and shell structure of MNPs loaded with an antibiotic (as an antibiotic adsorption shell) assembled by matrix-assisted pulsed laser evaporation. The novel anti-biofilm nano-coatings consist of magnetic core (Fe_3O_4), sodium lauryl sulfate (SLS) as a shell, and encumbered with cephalosporin (cefotaxime (CTX) and cefrom (CEF)) as antibiotics. The prepared MNPs have been tested against *E. coli*, *S. aureus*, and *P. aeruginosa* and showed a significant decrease in biofilm growth. This study also revealed that the amount of MNPs required is

relatively less since iron NPs at 0.15 mg/mL showed the highest reduction in biofilm formation.

6.1.3 Surface Features

Apart from the size of the nanoparticle, surface features also play an essential role in the efficiency of antimicrobial agents. Javanbkht et al. (2016) have evaluated the interaction of superparamagnetic iron oxide NPs (SPIONs) on the bacterial biofilm (*S. mutans*) based on their surface feature. Two different SPIONs, one with a positive charge and second with a negative charge, were prepared and tested to show that surface feature determines the diffusion of nanoparticle through biofilm. The positive charged SPIONs showed better activity in killing bacteria than negative charged MNPs. Arakha et al. (2015) have also studied the effect of the surface potential of MNPs on their antimicrobial activity against *E. coli* and *Bacillus subtilis*. The results showed that MNPs with negative surface potentials have significant antimicrobial activity against both the Gram-negative and Gram-positive bacteria. Bhosle et al. (2018) have prepared the $NiFe_2O_4$ NPs by two different methods. The prepared NPs were tested against different bacterial strain and fungal species. The antimicrobial activity of prepared NPs was mainly controlled by the surface properties such as lesser agglomeration leading to high crystalline structure formation. Similarly, Konwar et al. (2016) have described the antimicrobial activity of graphene oxide coated iron oxide nanomaterial with the chitosan matrix. The prepared nanocomposites have shown substantial antimicrobial activity against *Candida albicans* along with different bacterial strains due to the specific surface properties of MNPs. The above results confirmed that the surface characteristic of NPs is one such parameter that needs to be tuned in order to enhance the overall efficiency of antimicrobial agents.

6.1.4 Surface Functionalization

The surface functionalization of MNPs also results in enhanced antimicrobial activity. Glycerol-iron oxide NPs with an average size of ~4.2 nm were prepared by the co-precipitation method (Iconaru et al. 2013). The prepared MNPs have shown the inhibitory effect against the biofilm formation of *P. aeruginosa* at a lower concentration (ranging from 0.01 to 0.625 mg/mL). In recent, Farouk et al. (2020) have used an aqueous extract of *Citrullus colocynth* (CTC) to produce MNPs with enhanced antimicrobial activity. The produced MNPs showed a comparable antimicrobial activity against two Gram-positive (i.e., *B. subtilis* and *S. aureus*) and two Gram-negative (*E. coli* and *P. aeruginosa*) bacteria along with yeast (*Candida albicans*). Sandhya and Kalaiselvam (2020) have also reported a similar kind of result where the MNPs were synthesized using the seed coat extract of *Borassus flabellifer*. The prepared MNPs have shown enhanced microbial activity against *E. coli*, *B. subtilis*, *Shigella*, *S. aureus*, *A. niger*, and *Candida albicans*. Khan et al. (2020) have

synthesized the citric acid-functionalized MNPs with different concentrations of citric acid. The prepared functionalized MNPs showed an increase in the antibacterial activity against *E. coli and B. subtilis*, in comparison to the native form of MNPs. Cyanoethyl cellulose (CEC)/Fe_3O_4 composite was prepared by in-situ blending techniques (Dacrory et al. 2020). The prepared nanocomposite found to have significant antimicrobial properties against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria, yeast (*C. albicans*), and fungus (*Aspergillus niger*). The prepared particles have shown higher antimicrobial activity in comparison to CEC alone. The Fe_3O_4 particle produced ROS that ultimately is responsible for the antimicrobial activity of MNPs.

Further antifungal nano therapies based on the MNPs were also studied (Konwar et al. 2016; Chifiriuc et al. 2012; Anghel et al. 2013; Franco et al. 2016). Parveen et al. (2018) have prepared the IONPs using tannic acid as a reducing and capping agent. The prepared MNPs have shown significant antifungal activity against several fungal species. Citric acid-modified $MnFeO_4$ NPs of 5 nm diameter in size were tested against *C. albicans*, *S. aureus*, and *E. coli* (Franco et al. 2016). The results showed that the prepared MNPs have an inhibitory effect on the growth of *C. albicans* but were not effective against the tested bacterial strains. The results also showed that the antimicrobial action of these MNPs is specific to a yeast cell mainly due to the electrostatic connection among yeast plasma membrane and MNPs.

However, the bare iron oxide NPs can lead to an increase in bacterial growth. The MNPs of different sizes showed no inhibition against the biofilm growth of *P. aeruginosa* (Haney et al. 2012). The MNPs of smaller size (2 nm) were found to be responsible for an increase in the formation of biofilm significantly in comparison to the larger NPs (540 nm) (Balouiri et al. 2016). The hypothesis behind the increase in bacterial growth could be associated with the release of Fe^{3+} ions from MNPs that help in the growth of bacteria. Haney et al. (2012) have also reported that similar results for three different sets of MNPs assessed against *P. aeruginosa* biofilm growth. The concentration of MNPs up to 200 μg/mL was found to have no inhibition ability against the biofilm formation that supported the hypothesis mentioned above.

6.2 MNP-Based Antibiotic Delivery Systems

MNPs of different structures have shown excellent antibacterial activity to kill bacterial species of wide range, including multidrug-resistance bacteria and bacterial biofilms (Dacrory et al. 2020). Various antibiotics such as vancomycin, gentamycin, methicillin, and cephalexin (Lai and Chen 2013; Bhattacharya and Neogi 2017; Geilich et al. 2017; Rayegan et al. 2018) supported on MNPs and their derivatives (Co-doped, cationic polymer-modified, Au coated, or Ag coated) have been widely investigated to explore their potential to penetrate biofilms and inactivate

antibiotic-resistant strains (Pu et al. 2016; Zomorodian et al. 2018; Dhanakotti et al. 2015; Car et al. 2014; Chen et al. 2016).

MNPs have also been used as a vehicle for the controlled release of a different drug (López-Abarrategui et al. 2013). MNPs based drug delivery system has a primary aim of drug accumulation in a specific organ or tissues using drug loaded on the magnetic carrier while applying an external magnetic field (Chomoucka et al. 2010; Wu et al. 2016; Rodrigues et al. 2019). The use of MNPs based drug delivery system minimizes the systemic side effects since it requires relatively less drug concentration to be administrated. The low activity, stability, and inhibitory effect of drugs is mainly due to the hindrance that occurred during drug transportation across cellular membranes. This has promoted research towards the quest for novel strategies to enhance the overall antimicrobial effect (López-Abarrategui et al. 2013; Chudzik et al. 2016; Ulbrich et al. 2016). The use of NPs as a drug carrier can be one of the possible solutions for the existing shortcomings. The various materials like mesoporous silica and polymers (chitosan, PAA, PEG, etc.) can be used as a coating material for bare MNPs before employing in drug delivery (Wu et al. 2008, 2016). The choice of coating material is a crucial factor and depends on the release behavior and tailored drug loading.

To increase the antimicrobial properties of different molecules, they can be chemically and physically bonded with MNPs (Rodrigues et al. 2019; Ragelle et al. 2017). Several studies have demonstrated the enhanced antimicrobial activity of antimicrobial peptides (AMP) and antibiotics in conjugation with MNPs (Chudzik et al. 2016; Franco et al. 2016; Rodrigues et al. 2019). Zhang et al. (2012) have covalently immobilized bacitracin on the Fe_3O_4 NPs via Click chemistry and investigated its antimicrobial activity against both Gram-positive and Gram-negative microorganisms. The conjugated NPs showed higher activity in comparison to bacitracin itself against all tested microorganisms. The enhanced microbial activity of the magnetic nanocomposite conferred high drug efficacy while reducing the side effects largely caused by an excess dosage of antibiotics. Niemirowicz et al. (2015) have prepared core and shell-type MNPs (MNP-CSA-13) with ceragenin CSA-13 as a shell linked with iron oxide as a core through amine linkage. The pH control system was used to release the CSA-13 from the prepared nanocomposite and showed potent antibacterial activity in comparison to soluble ceragenin in killing of *P. aeruginosa*.

Similarly, MNPs based drug delivery system has been tested against fungi, bacteria (MDR), and biofilm of *S. aureus* and *P. aeruginosa* (Nguyen et al. 2015; Niemirowicz et al. 2016a). Niemirowicz et al. (2016a) have studied the effect of MNPs on the activity of AMP, i.e., cathelicidin, synthetic ceragenins, and antibiotics (colistin and vancomycin) against methicillin-resistant microorganisms. Three different core and shell structure MNPs, i.e., gold-coated (MNP@Au), amino silane coated (MNP@NH_2), and quaternary ammonium derivatives coated (MNP@PQAS) NPs were synthesized and tested as combined therapy against the microorganisms. The results were calculated based on the fractional inhibitory concentration index and fractional bactericidal concentration index using the microdilution method. In most cases, a synergistic effect of the combination of MNPs with AMP or classical

antibiotics was observed. The core–shell MNPs, along with antibacterial agents, also found to restrict biofilm formation. The prepared MNPs interact with cellular membrane or bacterial cell wall, which enhances the antimicrobial molecule penetration resulting in an increased activity of the combined system. The similar type of synergistic effect of combining MNPs and antibiotics (polypeptides, B-lactams, aminoglycosides, and macrolides) have been reported (Istrate et al. 2014). The prepared nanosystem increases the interaction of antibiotics with the cellular membrane by increasing the membrane fluidity. Grumezescu et al. (2014) have also reported the 5 and 8-fold MIC reduction of amoxicillin against *S. aureus* and *E. coli*, respectively, when combined with MNPs. Geilich et al. (2017) conducted a similar study of anti-biofilm activity assay of biocompatible multicomponent nanocarrier made up of superparamagnetic iron oxide coated with methicillin and obtained identical results. The penetration depth and antibacterial property of MNPs loaded with methicillin against bacterial biofilm was also studied by using a laser scanning confocal microscopy. Wang et al. (2018b) have investigated the antibacterial activity of the MNPs based material coated with multilayer films containing antibiotic gentamicin, tannic acid, and silver nanoparticle. Further biodegradable hyaluronic acid was capped on the outer surface as a responsive shell to improve biocompatibility while getting control over drug release. The prepared nanocomposites have shown satisfactory antibacterial capacities against Gram-positive *S. aureus* and Gram-negative *E. coli*. The probable mechanism of biofilm treatment was presented based on the confocal laser scanning microscopy (CLSM-3D) images of the biofilms (Fig. 3). With the application of a magnetic field, a selective and fast penetration in a biofilm of *S. aureus* was achieved. In the absence of the magnetic field, the nanocomposites showed an insufficient antibacterial activity due to their incapability to penetrate the dense and intact biofilm (Fig. 4). Though the treatment with nanocarrier increased the number of dead bacteria, in absence of a magnetic field, a high number of live bacteria were observed. However, the application of the magnetic field showed a dramatic decrease in viable bacteria and biofilm thickness. The results confirmed that the use of MNPs based drug delivery system could help to attain deep penetration while delivering high concentrations of antibiotics into the targeted multilayers of biofilms.

Streptomycin-coated chitosan MNPs (Strep-CS-MNP) released a 100% antibiotic over 350 min (Hussein-Al-Ali et al. 2014a). The prepared nanocomposite showed an enhanced antibacterial activity against *S. aureus*. The results confirmed that the nanocomposites activity depends on the antibiotic only, as the bare MNPs have no antimicrobial activity at all (Hussein-Al-Ali et al. 2014a). Hussein-Al-Ali et al. (2014b) have studied the antibacterial and antifungal activity of nystatin incorporated on the chitosan-coated MNPs (Nyst-CS-MNP). The prepared nanocomposites released a 100% Nyst in 1800 min. The prepared nanocomposites showed high activity against *Candida albicans*, *P. aeruginosa*, and *E. coli* while showing a weak activity against *S. aureus*. In another study, Niemirowicz et al. (2016b) have prepared polyene (amphotericin (AMF) and nystatin (NYS)) attached to the surface of MNPs and used against the clinical isolates of Candida species. The synthesized nanosystem showed a synergistic activity due to a combination of NPs and polyene

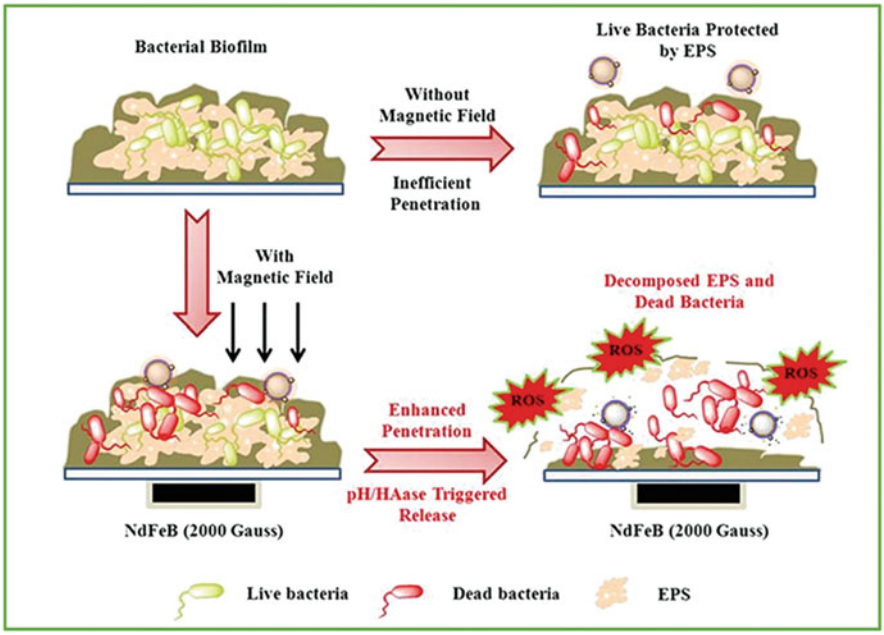

Fig. 3 Illustration for inactivation of embedded bacteria using MNPs nanocomposite (MNPs@Ag@HA) under magnetic field (Copyright © 2018, American Chemical Society, All rights reserved, reprinted with permission) (Wang et al. 2018b)

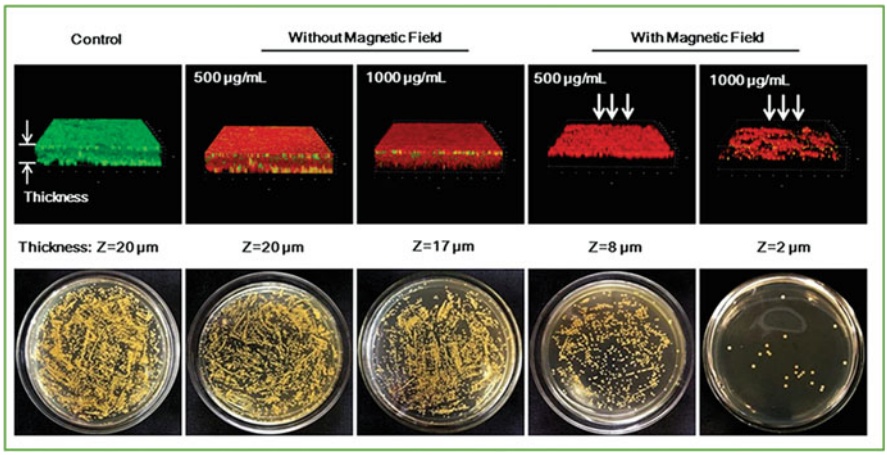

Fig. 4 Live/dead staining of 3D reconstructions of biofilm of *S. aureus* and bacterial colonies of surviving *S. aureus* in biofilms after treatment of MNPs@Ag@HA with and without applied magnetic field, respectively (Copyright © 2018, American Chemical Society, All rights reserved, reprinted with permission) (Wang et al. 2018b)

against all tested candida strains in comparison to unbound AMF and NYS. Similarly, Saldanha et al. (2018) have prepared the nanocomposite consisting of amphotericin B drug loaded on the MNPs. The prepared nanocomposite showed an enhanced antifungal activity against *Paracoccidioides brasiliensis*.

Nevertheless, the use of MNPs does not always have a positive effect on the antimicrobial activity, and some uncertainty has been observed associated with the delivery systems of antimicrobial agents (Amirnasr et al. 2012; Masadeh et al. 2015). Borcherding et al. (2014) have studied the synergistic effect on antimicrobial activity of a combination of antimicrobial molecules (lactoferrin, lysozyme, and human neutrophil peptide (HNP) 1 and 2), in the presence of MNPs of different diameter ($2 \pm 1, 43 \pm 6, 85 \pm 25$, and 540 ± 90 nm). The experiments conducted for one-hour incubation of antimicrobial peptides (AMP) mixture at 37 °C in the presence of different MNPs, followed by centrifugation to separate the soluble molecules. Further, a soluble medium was used for the antimicrobial activity assessment. The small NPs were found to have high adsorption capacity of antimicrobial polypeptides and resulted in a decrease in the activity of AMP. The antimicrobial activity of ciprofloxacin was studied in combination with cerium oxide (CeO_2) and iron oxide (Fe_2O_3) NPs (average diameter of 45 nm) on a panel of Gram-positive and Gram-negative bacteria (Masadeh et al. 2015). The minimal inhibitory concentration (MIC) of antibiotics against different bacteria was compared between MICs of NPs (CeO_2 and Fe_2O_3) with and without ciprofloxacin. The results showed that the presence of NPs resulted in a decrease in the activity of antibiotics, whereas the NPs alone failed to inhibit bacterial growth and biofilm.

In general, the results showed that the MNPs based drug delivery system could deepen the drug penetration along with high antibiotic concentration delivery into the biofilm. This could result in high activity, unlike bare antibiotics that cannot penetrate the biofilm while only able to control the planktonic bacteria. The use of MNPs, a drug delivery platform, allows the use of the low amount of drug in comparison to traditional drug therapies while decreasing the adverse effects caused by drug toxicity. Moreover, the use of MNPs with antimicrobial molecules has a synergistic effect on the activity of prepared nanocomposite, which can be associated with the inherent antimicrobial properties of MNPs.

7 Limitations of the Current Research and Future Prospects

Understanding the precise mechanism of antimicrobial activity is still in its infant stage. Although several reports confirmed the antimicrobial activity by MNPs, the shortage of standard experimental parameters to assess the antimicrobial activity is a concerning issue. Moreover, the research also lacks a uniform method that meets all the required conditions to collect data concerning the antibacterial mechanisms of NPs. Since the efficiency of antimicrobial activity shown by different types of MNPs

varies, a general hypothesis is often suggested. Despite being employed as an antibiotic agent, an explicit mechanism of MNPs is still unclear. Many reports indicate that ROS driven oxidative stress is a primary reason for antimicrobial activity of MNPs, whereas other studies could not confirm the same. For instance, the role of MgO NPs showing antimicrobial activity could not be associated with the regulation of bacterial metabolism, unlike most of the reports. Therefore, it demands more research to understand the mechanisms involved in MNPs antimicrobial activities that could lead the research to the next level. Further, in vitro studies to assess the antimicrobial effect of MNPs have not been much practical since the in vitro model organism cannot entirely simulate the in vivo state. In vitro bacterial models may differently interact with MNPs that questions the assessment of antimicrobial activity of MNPs being considered for in vivo application.

The clarity on nano-neurotoxicity is yet to be established where several questions are open. Research in the field has not able to prove that how NPs can cross the membrane of a bacterial cell that is mainly a barrier regulating in/out movements of molecules. Typically, Gram-negative bacterial cells can allow the transport of a molecule through porins, with a specific size (up to 600 Da). However, several reports surfaced stating that porins can facilitate the transport of NPs, ranging from 1 to 9 nm diameter (Neal 2008). Though the endocytosis, a natural process that can engulf large molecules can facilitate the transport of such NPs through the bacterial cell membrane (Lai et al. 2015), an evident report on the same is yet to be reported.

Nevertheless, the most acceptable and rational explanation for antimicrobial activities of NPs could be associated with a mechanism, where NPs exposure to the bacterial cell causes damage to the cell membrane. During the NPs exposure, the entire disintegration of the cells, along with the release of the lipopolysaccharides layer, occurs in the form of vesicles. NPs present in the surrounding can interact and bind with these vesicles and enter into the cell by electrostatic attraction. However, more research should be carried in the field. Additionally, there are several limitations associated with the synthesis of MNPs. The antimicrobial activity of the metal NPs is the function of the structure. A slight deviation in the preparation method may result in loss of the activity and lead to toxicity. Extensive research has committed to developing advanced materials with enhanced stability and antimicrobial activity. However, most of the processes limit the scalable approach. To summarize, more studies should be carried out assessing the mechanisms associated with the intracellular inhibitory actions of MNPs while overcoming synthesis related challenges. Moreover, interactions of NPs with gene/protein level along with its overall effect on metabolic activities of bacterial cells deserve more consideration.

8 Conclusion

MNPs have established themselves as an efficient candidate considering the magnetic properties that make them superior to NPs. MNPs have demonstrated antimicrobial activity while having varying sizes, shapes, and surface coatings. Also,

several engineering advancements in the biomedical field have improved MNP's features, including size distribution and crystallinity, along with superior magnetic properties. Magnetic properties of NPs make them easily target specific sites that are generally difficult to address. Additionally, the synthesis of MNPs is a cost-efficient process that also offers high versatility when compared to other existing options. Moreover, the optimal physicochemical properties of MNPs have paved new opportunities in clinical research to innovate efficient ways of drug administration. However, more research should be focused on understanding the explicit mechanism of MNP's role in antibiotic activities that are essential to developing a more efficient MNPs as an antibiotic agent. Nevertheless, MNPs are promising agents offering a significant antimicrobial approach to fight against MDR and antibiotic-resistant strains causing obstacles in treating infectious diseases in humans.

References

Al-Bakri AG, Afifi FU (2007) Evaluation of antimicrobial activity of selected plant extracts by rapid XTT colorimetry and bacterial enumeration. J Microbiol Methods 68:19–25

Ali M (2018) Application of nanomaterials as antimicrobial agents: a review. Arch Nanomed Open Access J 1:59–64. https://doi.org/10.32474/anoaj.2018.01.000114

Ali A, Zafar H, Zia M, Ul Haq I, Phull AR, Ali JS, Hussain A (2016) Synthesis, characterization, applications, and challenges of iron oxide nanoparticles. Nanotechnol Sci Appl 9:49–67. https://doi.org/10.2147/NSA.S99986

Allafchian A, Hosseini SS (2019) Antibacterial magnetic nanoparticles for therapeutics: a review. IET Nanobiotechnol 13:786–799. https://doi.org/10.1049/iet-nbt.2019.0146

Allaker RP (2010) The use of nanoparticles to control oral biofilm formation. J Dent Res 89:1175–1186. https://doi.org/10.1177/0022034510377794

Amirnasr A, Emtiazi G, Abasi S, Yaaghoobi M (2012) Adsorption of hemoglobin, fatty acid and glucose to iron nanoparticles as a mean for drug delivery. J Biochem Technol 3:280–283

Andersson DI, Hughes D, Kubicek-Sutherland JZ (2016) Mechanisms and consequences of bacterial resistance to antimicrobial peptides. Drug Resist Updat 26:43–57. https://doi.org/10.1016/j.drup.2016.04.002

Anghel I, Grumezescu A, Holban A, Ficai A, Anghel A, Chifiriuc M (2013) Biohybrid nanostructured iron oxide nanoparticles and satureja hortensis to prevent fungal biofilm development. Int J Mol Sci 14:18110–18123. https://doi.org/10.3390/ijms140918110

Ansari S, Ficiarà E, Ruffinatti F, Stura I, Argenziano M, Abollino O, Cavalli R, Guiot C, D'Agata F (2019) Magnetic iron oxide nanoparticles: synthesis, characterization and functionalization for biomedical applications in the central nervous system. Materials 12:465. https://doi.org/10.3390/ma12030465

Arakha M, Pal S, Samantarrai D, Panigrahi TK, Mallick BC, Pramanik K, Mallick B, Jha S (2015) Antimicrobial activity of iron oxide nanoparticle upon modulation of nanoparticle-bacteria interface. Sci Rep 5:14813. https://doi.org/10.1038/srep14813

Arakha M, Mallick BC, Jha S (2019) Magnetic nanoparticle interface with an antimicrobial propensity. In: Magnetic nanostructures. Springer, Cham, pp 287–300. https://doi.org/10.1007/978-3-030-16439-3_15

Arias CA, Murray BE (2009) Antibiotic-resistant bugs in the 21st century - a clinical super-challenge. N Engl J Med 360:439–443. https://doi.org/10.1056/NEJMp0804651

Armentano I, Arciola CR, Fortunati E, Ferrari D, Mattioli S, Amoroso CF, Rizzo J, Kenny JM, Imbriani M, Visai L (2014) The interaction of bacteria with engineered nanostructured polymeric materials: a review. Sci World J 41:423. https://doi.org/10.1155/2014/410423

Aruguete DM, Kim B, Hochella MF, Ma Y, Cheng Y, Hoegh A, Liu J, Pruden A (2013) Antimicrobial nanotechnology: its potential for the effective management of microbial drug resistance and implications for research needs in microbial nanotoxicology. Environ Sci Process Impacts 15:93–102. https://doi.org/10.1039/c2em30692a

Auffan M, Achouak W, Rose J, Roncato M-A, Chanéac C, Waite DT, Masion A, Woicik JC, Wiesner MR, Bottero J-Y (2008) Relation between the redox state of iron-based nanoparticles and their cytotoxicity toward Escherichia coli. Environ Sci Technol 42:6730–6735. https://doi.org/10.1021/es800086f

Aung MS, Zi H, Nwe KM, Maw WW, Aung MT, Min WW, Nyein N, Kawaguchiya M, Urushibara N, Sumi A, Kobayashi N (2016) Drug resistance and genetic characteristics of clinical isolates of staphylococci in Myanmar: high prevalence of PVL among methicillin-susceptible Staphylococcus aureus belonging to various sequence types. N Microb N Infect 10:58–65. https://doi.org/10.1016/j.nmni.2015.12.007

Baker CN, Stocker SA, Culver DH, Thornsberry C (1991) Comparison of the E Test to agar dilution, broth microdilution, and agar diffusion susceptibility testing techniques by using a special challenge set of bacteria. J Clin Microbiol 29:533–538

Balouiri M, Sadiki M, Ibnsouda SK (2016) Methods for in vitro evaluating antimicrobial activity: a review. J Pharm Anal 6:71–79. https://doi.org/10.1016/j.jpha.2015.11.005

Behera SS, Patra JK, Pramanik K, Panda N, Thatoi H (2012) Characterization and evaluation of antibacterial activities of chemically synthesized iron oxide nanoparticles. World J Nano Sci Eng 2:196–200. https://doi.org/10.4236/wjnse.2012.24026

Bhattacharya P, Neogi S (2017) Gentamicin coated iron oxide nanoparticles as novel antibacterial agents. Mater Res Exp 4:095005. https://doi.org/10.1088/2053-1591/aa8652

Bhosale SV, Ekambe PS, Bhoraskar SV, Mathe VL (2018) Effect of surface properties of NiFe2O4 nanoparticles synthesized by dc thermal plasma route on antimicrobial activity. Appl Surf Sci 441:724–733. https://doi.org/10.1016/j.apsusc.2018.01.220

Bomila R, Srinivasan S, Gunasekaran S, Manikandan A (2018) Enhanced photocatalytic degradation of methylene blue dye, opto-magnetic and antibacterial behaviour of pure and la-doped ZnO nanoparticles. J Supercond Nov Magn 31:855–864. https://doi.org/10.1007/s10948-017-4261-8

Borcherding J, Baltrusaitis J, Chen H, Stebounova L, Wu C-M, Rubasinghege G, Mudunkotuwa IA, Caraballo JC, Zabner J, Grassian VH, Comellas AP (2014) Iron oxide nanoparticles induce Pseudomonas aeruginosa growth, induce biofilm formation, and inhibit antimicrobial peptide function. Environ Sci Nano 1:123. https://doi.org/10.1039/c3en00029j

Bronshteint I, Aulova S, Juzeniene A, Iani V, Ma L-W, Smith KM, Malik Z, Moan J, Ehrenberg B (2006) In vitro and in vivo photosensitization by protoporphyrins possessing different lipophilicities and vertical localization in the membrane. Photochem Photobiol 82:1319–1325. https://doi.org/10.1562/2006-04-02-RA-865

Car H, Niemirowicz K, Swiecicka I, Wilczewska A, Bienias K, Bucki R, Misztalewska I, Kalska-Szostko B (2014) Gold-functionalized magnetic nanoparticles restrict growth of Pseudomonas aeruginosa. Int J Nanomedicine 2014:2217. https://doi.org/10.2147/IJN.S56588

Chen X, Hu B, Xiang Q, Yong C, Liu Z, Xing X (2016) Magnetic nanoparticles modified with quaternarized N -halamine based polymer and their antibacterial properties. J Biomater Sci Polym Ed 27:1187–1199. https://doi.org/10.1080/09205063.2016.1188471

Chifiriuc C, Grumezescu V, Grumezescu A, Saviuc C, Lazăr V, Andronescu E (2012) Hybrid magnetite nanoparticles/Rosmarinus officinalis essential oil nanobiosystem with antibiofilm activity. Nanoscale Res Lett 7:209. https://doi.org/10.1186/1556-276X-7-209

Chomoucka J, Drbohlavova J, Huska D, Adam V, Kizek R, Hubalek J (2010) Magnetic nanoparticles and targeted drug delivering. Pharmacol Res 62:144–149. https://doi.org/10.1016/j.phrs.2010.01.014

Chudzik B, Miaskowski A, Surowiec Z, Czernel G, Duluk T, Marczuk A, Gagoś M (2016) Effectiveness of magnetic fluid hyperthermia against Candida albicans cells. Int J Hyperth 32:842–857. https://doi.org/10.1080/02656736.2016.1212277

Coetzee J, Corcoran C, Prentice E, Moodley M, Mendelson M, Poirel L, Nordmann P, Brink AJ (2016) Emergence of plasmid-mediated colistin resistance (MCR-1) among Escherichia coli isolated from South African patients. S Afr Med J 106:449–450. https://doi.org/10.7196/SAMJ.2016.v106i5.10710

Dacrory S, Moussa M, Turky G, Kamel S (2020) In situ synthesis of Fe3O4@ cyanoethyl cellulose composite as antimicrobial and semiconducting film. Carbohydr Polym 236:116032. https://doi.org/10.1016/j.carbpol.2020.116032

Daury L, Orange F, Taveau JC, Verchère A, Monlezun L, Gounou C, Marreddy RKR, Picard M, Broutin I, Pos KM, Lambert O (2016) Tripartite assembly of RND multidrug efflux pumps. Nat Commun 7:10731. https://doi.org/10.1038/ncomms10731

De Vries R, Andrade CAS, Bakuzis AF, Mandal SM, Franco OL (2015) Next-generation nanoantibacterial tools developed from peptides. Nanomedicine 10:1643–1661. https://doi.org/10.2217/nnm.15.9

Dhanakotti RB, Kaliyamoorthy V, Mane Prabhu KB, Ravi S, Radhakrishnan V, Saminathan M, Pandurangan A, Mukannan A, Yasuhiro H (2015) Structural and magnetic properties of cobalt-doped iron oxide nanoparticles prepared by solution combustion method for biomedical applications. Int J Nanomedicine 2015:189. https://doi.org/10.2147/IJN.S82210

Dong H, Huang J, Koepsel RR, Ye P, Russell AJ, Matyjaszewski K (2011) Recyclable antibacterial magnetic nanoparticles grafted with quaternized poly(2-(dimethylamino)ethyl methacrylate) brushes. Biomacromolecules 12:1305–1311. https://doi.org/10.1021/bm200031v

Draper LA, Cotter PD, Hill C, Ross RP (2015) Lantibiotic resistance. Microbiol Mol Biol Rev 79:171–191. https://doi.org/10.1128/MMBR.00051-14

Fang W, Fang W, Zheng J, Chen C, Zhang H, Lu Y, Ma L, Chen G (2014) One-pot synthesis of porous Fe3O4 shell/silver core nanocomposites used as recyclable magnetic antibacterial agents. J Magn Magn Mater 357:1–6. https://doi.org/10.1016/j.jmmm.2014.01.024

Fang C-H, Tsai P-I, Huang S-W, Sun J-S, Chang JZ-C, Shen H-H, Chen S-Y, Lin FH, Hsu L-T, Chen Y-C (2017) Magnetic hyperthermia enhance the treatment efficacy of peri-implant osteomyelitis. BMC Infect Dis 17:516. https://doi.org/10.1186/s12879-017-2621-4

Farouk F, Abdelmageed M, Azam Ansari M, Azzazy HME (2020) Synthesis of magnetic iron oxide nanoparticles using pulp and seed aqueous extract of Citrullus colocynth and evaluation of their antimicrobial activity. Biotechnol Lett 42:231–240. https://doi.org/10.1007/s10529-019-02762-7

Fernando S, Gunasekara T, Holton J (2018) Antimicrobial Nanoparticles: applications and mechanisms of action. Sri Lankan J Infect Dis 8:2. https://doi.org/10.4038/sljid.v8i1.8167

Franco O, Lopez-Abarrategui C, Figueroa-Espi V, Lugo-Alvarez M, Pereira C, Garay H, Barbosa J, Jimenez-Hernandez L, Estevez-Hernandez O, Reguera-Ruiz E, Dias S, Otero-Gonzalez A, Falcao R (2016) The intrinsic antimicrobial activity of citric acid-coated manganese ferrite nanoparticles is enhanced after conjugation with the antifungal peptide Cm-p5. Int J Nanomedicine 11:3849–3857. https://doi.org/10.2147/IJN.S107561

Gao W, Thamphiwatana S, Angsantikul P, Zhang L (2014) Nanoparticle approaches against bacterial infections. Wiley Interdiscip Rev Nanomed Nanobiotechnol 6:532–547. https://doi.org/10.1002/wnan.1282

Gao L, Liu Y, Kim D, Li Y, Hwang G, Naha PC, Cormode DP, Koo H (2016) Nanocatalysts promote Streptococcus mutans biofilm matrix degradation and enhance bacterial killing to suppress dental caries in vivo. Biomaterials 101:272–284. https://doi.org/10.1016/j.biomaterials.2016.05.051

Geilich BM, Gelfat I, Sridhar S, van de Ven AL, Webster TJ (2017) Superparamagnetic iron oxide-encapsulating polymersome nanocarriers for biofilm eradication. Biomaterials 119:78–85. https://doi.org/10.1016/j.biomaterials.2016.12.011

Ghazanfari MR, Kashefi M, Shams SF, Jaafari MR (2016) Perspective of Fe3O4 nanoparticles role in biomedical applications. Biochem Res Int 2016:7840161. https://doi.org/10.1155/2016/7840161

Grumezescu A, Gestal M, Holban A, Grumezescu V, Vasile B, Mogoantă L, Iordache F, Bleotu C, Mogoşanu G (2014) Biocompatible Fe3O4 increases the efficacy of amoxicillin delivery against gram-positive and gram-negative bacteria. Molecules 19:5013–5027. https://doi.org/10.3390/molecules19045013

Grumezescu AM, Cristescu R, Chifiriuc MC, Dorcioman G, Socol G, Mihailescu IN, Mihaiescu DE, Ficai A, Vasile OR, Enculescu M, Chrisey DB (2015) Fabrication of magnetite-based core–shell coated nanoparticles with antibacterial properties. Biofabrication 7:015014. https://doi.org/10.1088/1758-5090/7/1/015014

Haney C, Rowe JJ, Robinson JB (2012) Spions increase biofilm formation by Pseudomonas aeruginosa. J Biomater Nanobiotechnol 3:508

Harifi T, Montazer M (2014) In situ synthesis of iron oxide nanoparticles on polyester fabric utilizing color, magnetic, antibacterial and sono-Fenton catalytic properties. J Mater Chem B 2:272–282. https://doi.org/10.1039/c3tb21445a

Hatamie A, Khan A, Golabi M, Turner APF, Beni V, Mak WC, Sadollahkhani A, Alnoor H, Zargar B, Bano S, Nur O, Willander M (2015) Zinc oxide nanostructure-modified textile and its application to biosensing, photocatalysis, and as antibacterial material. Langmuir 31:10913–10921. https://doi.org/10.1021/acs.langmuir.5b02341

Hoseinzadeh E, Samargandi MR, Alikhani MY, Roshanaei G, Asgari G (2012) Antimicrobial efficacy of zinc oxide nanoparticles suspension against Gram negative and Gram positive bacteria. Iran J Health Environ 5:331–342

Hoseinzadeh E, Alikhani M-Y, Samarghandi M-R, Shirzad-Siboni M (2014) Antimicrobial potential of synthesized zinc oxide nanoparticles against gram positive and gram negative bacteria. Desalin Water Treat 52:4969–4976

Hoseinzadeh E, Makhdoumi P, Taha P, Hossini H, Pirsaheb M, Omid Rastegar S, Stelling J (2017) A review of available techniques for determination of nano-antimicrobials activity. Toxin Rev 36:18–32. https://doi.org/10.1080/15569543.2016.1237527

Huh AJ, Kwon YJ (2011) "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release 156:128–145. https://doi.org/10.1016/j.jconrel.2011.07.002

Hurley KR, Ring HL, Kang H, Klein ND, Haynes CL (2015) Characterization of magnetic nanoparticles in biological matrices. Anal Chem 87:11611–11619. https://doi.org/10.1021/acs.analchem.5b02229

Hussein-Al-Ali SH, El Zowalaty ME, Hussein MZ, Ismail M, Webster TJ (2014a) Synthesis, characterization, controlled release, and antibacterial studies of a novel streptomycin chitosan magnetic nanoantibiotic. Int J Nanomedicine 9:549–557. https://doi.org/10.2147/IJN.S53079

Hussein-Al-Ali SH, El Zowalaty ME, Kura AU, Geilich B, Fakurazi S, Webster TJ, Hussein MZ (2014b) Antimicrobial and controlled release studies of a novel nystatin conjugated iron oxide nanocomposite. Biomed Res Int 2014:1–13. https://doi.org/10.1155/2014/651831

Ibelli T, Templeton S, Levi-Polyachenko N (2018) Progress on utilizing hyperthermia for mitigating bacterial infections. Int J Hyperth 34:144–156. https://doi.org/10.1080/02656736.2017.1369173

Iconaru SL, Prodan AM, Le Coustumer P, Predoi D (2013) Synthesis and antibacterial and antibiofilm activity of iron oxide glycerol nanoparticles obtained by coprecipitation method. J Chem 2013:1–6. https://doi.org/10.1155/2013/412079

Ismail RA, Sulaiman GM, Abdulrahman SA, Marzoog TR (2015) Antibacterial activity of magnetic iron oxide nanoparticles synthesized by laser ablation in liquid. Mater Sci Eng C 53:286–297. https://doi.org/10.1016/j.msec.2015.04.047

Istrate CM, Holban AM, Grumezescu AM, Mogoantă L, Mogoşanu GD, Savopol T, Moisescu M, Iordache M, Vasile BS, Kovacs E (2014) Iron oxide nanoparticles modulate the interaction of different antibiotics with cellular membranes. Romanian J Morphol Embryol 55:849–856

Javanbakht T, Laurent S, Stanicki D, Wilkinson KJ (2016) Relating the surface properties of superparamagnetic iron oxide nanoparticles (SPIONs) to their bactericidal effect towards a biofilm of Streptococcus mutans. PLoS One 11:e0154445. https://doi.org/10.1371/journal.pone.0154445

Jose CAA, Munita M (2016) Mechanisms of antibiotic resistance. Microbiol Spectr 4:16. https://doi.org/10.1128/microbiolspec.vmbf-0016-2015

Joshi N, Jain N, Pathak A, Singh J, Prasad R, Upadhyaya CP (2018) Biosynthesis of silver nanoparticles using *Carissa carandas* berries and its potential antibacterial activities. J Sol-Gel Sci Technol 86(3):682–689. https://doi.org/10.1007/s10971-018-4666-2

Kaviyarasu K, Maria Magdalane C, Kanimozhi K, Kennedy J, Siddhardha B, Subba Reddy E, Rotte NK, Sharma CS, Thema FT, Letsholathebe D, Mola GT, Maaza M (2017) Elucidation of photocatalysis, photoluminescence and antibacterial studies of ZnO thin films by spin coating method. J Photochem Photobiol B Biol 173:466–475. https://doi.org/10.1016/j.jphotobiol.2017.06.026

Khameneh B, Diab R, Ghazvini K, Fazly Bazzaz BS (2016) Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. Microb Pathog 95:32–42. https://doi.org/10.1016/j.micpath.2016.02.009

Khan S, Shah ZH, Riaz S, Ahmad N, Islam S, Raza MA, Naseem S (2020) Antimicrobial activity of citric acid functionalized iron oxide nanoparticles –superparamagnetic effect. Ceram Int 1:109. https://doi.org/10.1016/j.ceramint.2020.01.109

Kim M-H, Yamayoshi I, Mathew S, Lin H, Nayfach J, Simon SI (2013) Magnetic nanoparticle targeted hyperthermia of cutaneous staphylococcus aureus infection. Ann Biomed Eng 41:598–609. https://doi.org/10.1007/s10439-012-0698-x

Kim Y-T, Kim K-H, Kang ES, Jo G, Ahn SY, Park SH, Il Kim S, Mun S, Baek K, Kim B, Lee K, Yun WS, Kim YH (2016) Synergistic effect of detection and separation for pathogen using magnetic clusters. Bioconjug Chem 27:59–65. https://doi.org/10.1021/acs.bioconjchem.5b00681

Konwar A, Kalita S, Kotoky J, Chowdhury D (2016) Chitosan–iron oxide coated graphene oxide nanocomposite hydrogel: a robust and soft antimicrobial biofilm. ACS Appl Mater Interfaces 8:20625–20634. https://doi.org/10.1021/acsami.6b07510

Koul A, Arnoult E, Lounis N, Guillemont J, Andries K (2011) The challenge of new drug discovery for tuberculosis. Nature 469:483–490. https://doi.org/10.1038/nature09657

Kruijshaar ME, Watson JM, Drobniewski F, Anderson C, Brown TJ, Magee JG, Smith EG, Story A, Abubakar I (2008) Increasing antituberculosis drug resistance in the United Kingdom: analysis of national surveillance data. BMJ 336:1231–1234. https://doi.org/10.1136/bmj.39546.573067.25

Lai B-H, Chen D-H (2013) Vancomycin-modified LaB6@SiO2/Fe3O4 composite nanoparticles for near-infrared photothermal ablation of bacteria. Acta Biomater 9:7573–7579. https://doi.org/10.1016/j.actbio.2013.03.023

Lai HZ, Chen WY, Wu CY, Chen YC (2015) Potent antibacterial nanoparticles for pathogenic bacteria. ACS Appl Mater Interfaces 7:2046–2054. https://doi.org/10.1021/am507919m

Lara HH, Ayala-Núñez NV, del Turrent L, Padilla CR (2010) Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. World J Microbiol Biotechnol 26:615–621

Laurent S, Dutz S, Häfeli UO, Mahmoudi M (2011) Magnetic fluid hyperthermia: Focus on superparamagnetic iron oxide nanoparticles. Adv Colloid Interf Sci 166:8–23. https://doi.org/10.1016/j.cis.2011.04.003

Leroueil PR, Hong S, Mecke A, Baker JR, Orr BG, Holl MMB (2007) Nanoparticle interaction with biological membranes: does nanotechnology present a janus face? Acc Chem Res 40:335–342. https://doi.org/10.1021/ar600012y

Li H, Chen Q, Zhao J, Urmila K (2015) Enhancing the antimicrobial activity of natural extraction using the synthetic ultrasmall metal nanoparticles. Sci Rep 5:11033. https://doi.org/10.1038/srep11033

Liang H, Xing Y, Chen J, Zhang D, Guo S, Wang C (2012) Antimicrobial activities of endophytic fungi isolated from Ophiopogon japonicus (Liliaceae). BMC Complement Altern Med 12:238

Liu G, Gao J, Ai H, Chen X (2013) Applications and potential toxicity of magnetic iron oxide nanoparticles. Small 9:1533–1545. https://doi.org/10.1002/smll.201201531

López-Abarrategui C, Figueroa-Espí V, Reyes-Acosta O, Reguera E, Otero-Gonzalez AJ (2013) Magnetic nanoparticles: new players in antimicrobial peptide therapeutics. Curr Protein Pept Sci 14:595–606. https://doi.org/10.2174/1389203711209070682

Lu AH, Salabas EL, Schüth F (2007) Magnetic nanoparticles: synthesis, protection, functionalization, and application. Angew Chem Int Ed 46:1222–1244. https://doi.org/10.1002/anie.200602866

Luan B, Huynh T, Zhou R (2016) Complete wetting of graphene by biological lipids. Nanoscale 8:5750–5754. https://doi.org/10.1039/c6nr00202a

Lytvynenko I, Brill S, Oswald C, Pos KM (2016) Molecular basis of polyspecificity of the small multidrug resistance efflux pump AbeS from Acinetobacter baumannii. J Mol Biol 428:644–657. https://doi.org/10.1016/j.jmb.2015.12.006

Mahmoudi M, Serpooshan V (2012) Silver-coated engineered magnetic nanoparticles are promising for the success in the fight against antibacterial resistance threat. ACS Nano 6:2656–2664. https://doi.org/10.1021/nn300042m

Masadeh MM, Karasneh GA, Al-Akhras MA, Albiss BA, Aljarah KM, Al-azzam SI, Alzoubi KH (2015) Cerium oxide and iron oxide nanoparticles abolish the antibacterial activity of ciprofloxacin against gram positive and gram negative biofilm bacteria. Cytotechnology 67:427–435. https://doi.org/10.1007/s10616-014-9701-8

Moghaddam MJM, Mirbagheri AA, Salehi Z, Habibzade SM (2015) Prevalence of class 1 integrons and extended spectrum beta lactamases among multi-drug resistant Escherichia coli isolates from north of Iran. Iran Biomed J 19:233–239. https://doi.org/10.7508/ibj.2015.04.007

Monteiro MC, de la Cruz M, Cantizani J, Moreno C, Tormo JR, Mellado E, De Lucas JR, Asensio F, Valiante V, Brakhage AA (2012) A new approach to drug discovery: high-throughput screening of microbial natural extracts against Aspergillus fumigatus using resazurin. J Biomol Screen 17:542–549

Moosavi R, Ramanathan S, Lee YY, Siew Ling KC, Afkhami A, Archunan G, Padmanabhan P, Gulyás B, Kakran M, Selvan ST (2015) Synthesis of antibacterial and magnetic nanocomposites by decorating graphene oxide surface with metal nanoparticles. RSC Adv 5:76442–76450. https://doi.org/10.1039/c5ra15578a

Neal AL (2008) What can be inferred from bacterium-nanoparticle interactions about the potential consequences of environmental exposure to nanoparticles? Ecotoxicology 17:362–371. https://doi.org/10.1007/s10646-008-0217-x

Nguyen T-K, Duong HTT, Selvanayagam R, Boyer C, Barraud N (2015) Iron oxide nanoparticle-mediated hyperthermia stimulates dispersal in bacterial biofilms and enhances antibiotic efficacy. Sci Rep 5:18385. https://doi.org/10.1038/srep18385

Niemirowicz K, Surel U, Wilczewska AZ, Mystkowska J, Piktel E, Gu X, Namiot Z, Kułakowska A, Savage PB, Bucki R (2015) Bactericidal activity and biocompatibility of ceragenin-coated magnetic nanoparticles. J Nanobiotechnol 13:32. https://doi.org/10.1186/s12951-015-0093-5

Niemirowicz K, Piktel E, Wilczewska A, Markiewicz K, Durnaś B, Wątek M, Puszkarz I, Wróblewska M, Niklińska W, Savage P, Bucki R (2016a) Core–shell magnetic nanoparticles display synergistic antibacterial effects against Pseudomonas aeruginosa and Staphylococcus aureus when combined with cathelicidin LL-37 or selected ceragenins. Int J Nanomedicine 11:5443–5455. https://doi.org/10.2147/IJN.S113706

Niemirowicz K, Durnaś B, Tokajuk G, Głuszek K, Wilczewska AZ, Misztalewska I, Mystkowska J, Michalak G, Sodo A, Wątek M, Kiziewicz B, Góźdź S, Głuszek S, Bucki R (2016b) Magnetic nanoparticles as a drug delivery system that enhance fungicidal activity of polyene antibiotics. Nanomedicine 12:2395–2404. https://doi.org/10.1016/j.nano.2016.07.006

Niskanen J, Shan J, Tenhu H, Jiang H, Kauppinen E, Barranco V, Picó F, Yliniemi K, Kontturi K (2010) Synthesis of copolymer-stabilized silver nanoparticles for coating materials. Colloid Polym Sci 288:543–553. https://doi.org/10.1007/s00396-009-2178-x

Noinaj N, Kuszak AJ, Gumbart JC, Lukacik P, Chang H, Easley NC, Lithgow T, Buchanan SK (2013) Structural insight into the biogenesis of β-barrel membrane proteins. Nature 501:385–390. https://doi.org/10.1038/nature12521

Park Y (2014) A new paradigm shift for the green synthesis of antibacterial silver nanoparticles utilizing plant extracts. Toxicol Res 30:169–178. https://doi.org/10.5487/TR.2014.30.3.169

Parveen S, Wani AH, Shah MA, Devi HS, Bhat MY, Koka JA (2018) Preparation, characterization and antifungal activity of iron oxide nanoparticles. Microb Pathog 115:287–292. https://doi.org/10.1016/j.micpath.2017.12.068

Prasad R (2014) Synthesis of silver nanoparticles in photosynthetic plants. J Nanopart, Article ID: 963961. https://doi.org/10.1155/2014/963961

Prasad R, Jha A, Prasad K (2018) Exploring the realms of nature for nanosynthesis. Springer International Publishing, Cham. ISBN 978-3-319-99570-0. https://www.springer.com/978-3-319-99570-0

Prasad R, Pandey R, Barman I (2016) Engineering tailored nanoparticles with microbes: quo vadis. WIREs Nanomed Nanobiotechnol 8:316–330. https://doi.org/10.1002/wnan.1363

Prucek R, Tuček J, Kilianová M, Panáček A, Kvítek L, Filip J, Kolář M, Tománková K, Zbořil R (2011) The targeted antibacterial and antifungal properties of magnetic nanocomposite of iron oxide and silver nanoparticles. Biomaterials 32:4704–4713. https://doi.org/10.1016/j.biomaterials.2011.03.039

Pu L, Xu J, Sun Y, Fang Z, Chan-Park MB, Duan H (2016) Cationic polycarbonate-grafted superparamagnetic nanoparticles with synergistic dual-modality antimicrobial activity. Biomater Sci 4:871–879. https://doi.org/10.1039/C5BM00545K

Rafique M, Sadaf I, Rafique MS, Tahir MB (2017) A review on green synthesis of silver nanoparticles and their applications. Artif Cells Nanomed Biotechnol 45:1272–1291. https://doi.org/10.1080/21691401.2016.1241792

Ragelle H, Danhier F, Préat V, Langer R, Anderson DG (2017) Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opin Drug Deliv 14:851–864. https://doi.org/10.1080/17425247.2016.1244187

Rayegan A, Allafchian A, Abdolhosseini Sarsari I, Kameli P (2018) Synthesis and characterization of basil seed mucilage coated Fe3O4 magnetic nanoparticles as a drug carrier for the controlled delivery of cephalexin. Int J Biol Macromol 113:317–328. https://doi.org/10.1016/j.ijbiomac.2018.02.134

Reddy LH, Arias JL, Nicolas J, Couvreur P (2012) Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications. Chem Rev 112:5818–5878. https://doi.org/10.1021/cr300068p

Rodrigues D, Bañobre-López M, Espiña B, Rivas J, Azeredo J (2013) Effect of magnetic hyperthermia on the structure of biofilm and cellular viability of a food spoilage bacterium. Biofouling 29:1225–1232. https://doi.org/10.1080/08927014.2013.834893

Rodrigues GR, López-Abarrategui C, de la Serna Gómez I, Dias SC, Otero-González AJ, Franco OL (2019) Antimicrobial magnetic nanoparticles based-therapies for controlling infectious diseases. Int J Pharm 555:356–367. https://doi.org/10.1016/j.ijpharm.2018.11.043

Sandhya J, Kalaiselvam S (2020) Biogenic synthesis of magnetic iron oxide nanoparticles using inedible Borassus flabellifer seed coat: characterization, antimicrobial, antioxidant activity and in vitro cytotoxicity analysis. Mater Res Exp 7:015045. https://doi.org/10.1088/2053-1591/ab6642

Seil JT, Webster TJ (2012) Antimicrobial applications of nanotechnology: methods and literature. Int J Nanomedicine 7:2767–2781. https://doi.org/10.2147/IJN.S24805

Shah M, Badwaik V, Kherde Y, Waghwani HK, Modi T, Aguilar ZP, Rodgers H, Hamilton W, Marutharaj T, Webb C, Lawrenz MB, Dakshinamurthy R (2014) Gold nanoparticles: various

methods of synthesis and antibacterial applications. Front Biosci Landmark 19:1320–1344. https://doi.org/10.2741/4284

Simões NG, Bettencourt AF, Monge N, Ribeiro IAC (2016) Novel antibacterial agents: an emergent need to win the battle against infections. Mini Rev Med Chem 17:1364–1376. https://doi.org/10.2174/1389557516666160907151454

Slavin YN, Asnis J, Häfeli UO, Bach H (2017) Metal nanoparticles: understanding the mechanisms behind antibacterial activity. J Nanobiotechnol 15:65. https://doi.org/10.1186/s12951-017-0308-z

Snell NJC (2003) Examining unmet needs in infectious disease. Drug Discov Today 8:22–30. https://doi.org/10.1016/s1359644602025412

Spacciapoli P, Buxton D, Rothstein D, Friden P (2001) Antimicrobial activity of silver nitrate against periodontal pathogens. J Periodontal Res 36:108–113. https://doi.org/10.1034/j.1600-0765.2001.360207.x

Talpade AD, Tiwari MS, Yadav GD (2019) Selective hydrogenation of bio-based 5-hydroxymethyl furfural to 2, 5-dimethylfuran over magnetically separable Fe-Pd/C bimetallic nanocatalyst. Mol Catal 465:1–15

Tarantash M, Nosrati H, Kheiri Manjili H, Baradar Khoshfetrat A (2018) Preparation, characterization and in vitro anticancer activity of paclitaxel conjugated magnetic nanoparticles. Drug Dev Ind Pharm 44:1895–1903

Taylor PK, Yeung ATY, Hancock REW (2014) Antibiotic resistance in Pseudomonas aeruginosa biofilms: towards the development of novel anti-biofilm therapies. J Biotechnol 191:121–130. https://doi.org/10.1016/j.jbiotec.2014.09.003

Thill A, Zeyons O, Spalla O, Chauvat F, Rose J, Auffan M, Flank AM (2006) Cytotoxicity of CeO2 nanoparticles for Escherichia coli. Physico-chemical insight of the cytotoxicity mechanism. Environ Sci Technol 40:6151–6156. https://doi.org/10.1021/es060999b

Thukkaram M, Sitaram S, Kumar Kannaiyan S, Subbiahdoss G (2014) Antibacterial efficacy of iron-oxide nanoparticles against biofilms on different biomaterial surfaces. Int J Biomater 2014:1–6. https://doi.org/10.1155/2014/716080

Tian Y, Qi J, Zhang W, Cai Q, Jiang X (2014) Facile, one-pot synthesis, and antibacterial activity of mesoporous silica nanoparticles decorated with well-dispersed silver nanoparticles. ACS Appl Mater Interfaces 6:12038–12045. https://doi.org/10.1021/am5026424

Tiwari MS, Gawade AB, Yadav GD (2017) Magnetically separable sulfated zirconia as highly active acidic catalysts for selective synthesis of ethyl levulinate from furfuryl alcohol. Green Chem 19(4):963–976

Tsutsui M, Kawakubo H, Hayashida T, Fukuda K, Nakamura R, Takahashi T, Wada N, Saikawa Y, Omori T, Takeuchi H, Kitagawa Y (2015) Comprehensive screening of genes resistant to an anticancer drug in esophageal squamous cell carcinoma. Int J Oncol 47:867–874. https://doi.org/10.3892/ijo.2015.3085

Ulbrich K, Holá K, Šubr V, Bakandritsos A, Tuček J, Zbořil R (2016) Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies. Chem Rev 116:5338–5431. https://doi.org/10.1021/acs.chemrev.5b00589

Vega-Jiménez AL, Vázquez-Olmos AR, Acosta-Gío E, Antonio Álvarez-Pérez M (2019) In vitro antimicrobial activity evaluation of metal oxide nanoparticles. In: Nanoemulsions - prop. fabr. appl. IntechOpen, London. https://doi.org/10.5772/intechopen.84369

Wang L, Hu C, Shao L (2017) The antimicrobial activity of nanoparticles: present situation and prospects for the future. Int J Nanomedicine 12:1227–1249. https://doi.org/10.2147/IJN.S121956

Wang X, Deng A, Cao W, Li Q, Wang L, Zhou J, Hu B, Xing X (2018a) Synthesis of chitosan/poly (ethylene glycol)-modified magnetic nanoparticles for antibiotic delivery and their enhanced anti-biofilm activity in the presence of magnetic field. J Mater Sci 53:6433–6449. https://doi.org/10.1007/s10853-018-1998-9

Wang X, Wu J, Li P, Wang L, Zhou J, Zhang G, Li X, Hu B, Xing X (2018b) Microenvironment-responsive magnetic nanocomposites based on silver nanoparticles/gentamicin for enhanced

biofilm disruption by magnetic field. ACS Appl Mater Interfaces 10:34905–34915. https://doi.org/10.1021/acsami.8b10972

Webster TJ, Seil I (2012) Antimicrobial applications of nanotechnology: methods and literature. Int J Nanomedicine 7:2767. https://doi.org/10.2147/IJN.S24805

Wu W, He Q, Jiang C (2008) Magnetic iron oxide nanoparticles: synthesis and surface functionalization strategies. Nanoscale Res Lett 3:397–415. https://doi.org/10.1007/s11671-008-9174-9

Wu W, Jiang CZ, Roy VAL (2016) Designed synthesis and surface engineering strategies of magnetic iron oxide nanoparticles for biomedical applications. Nanoscale 8:19421–19474. https://doi.org/10.1039/C6NR07542H

Xia T, Kovochich M, Liong M, Mädler L, Gilbert B, Shi H, Yeh JI, Zink JI, Nel AE (2008) Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties. ACS Nano 2:2121–2134. https://doi.org/10.1021/nn800511k

Xu C, Akakuru OU, Zheng J, Wu A (2019) Applications of iron oxide-based magnetic nanoparticles in the diagnosis and treatment of bacterial infections. Front Bioeng Biotechnol 7:141. https://doi.org/10.3389/fbioe.2019.00141

Yao Q, Gao Y, Gao T, Zhang Y, Harnoode C, Dong A, Liu Y, Xiao L (2016) Surface arming magnetic nanoparticles with amine N-halamines as recyclable antibacterial agents: construction and evaluation. Colloids Surf B Biointerfaces 144:319–326. https://doi.org/10.1016/j.colsurfb.2016.04.024

Yount NY, Yeaman MR (2012) Emerging themes and therapeutic prospects for anti-infective peptides. Annu Rev Pharmacol Toxicol 52:337–360. https://doi.org/10.1146/annurev-pharmtox-010611-134535

Zhang W, Shi X, Huang J, Zhang Y, Wu Z, Xian Y (2012) Bacitracin-conjugated superparamagnetic iron oxide nanoparticles: synthesis, characterization and antibacterial activity. ChemPhysChem 13:3388–3396. https://doi.org/10.1002/cphc.201200161

Zhou Y, Jin C, Li Y, Shen W (2018) Dynamic behavior of metal nanoparticles for catalysis. Nano Today 20:101–120. https://doi.org/10.1016/j.nantod.2018.04.005

Zomorodian K, Veisi H, Mousavi M, Ataabadi M, Yazdanpanah S, Bagheri MJ, Mehr A, Hemmati S, Veisi H (2018) Modified magnetic nanoparticles by PEG-400-immobilized Ag nanoparticles (Fe3O4@PEG–Ag) as a core/shell nanocomposite and evaluation of its antimicrobial activity. Int J Nanomedicine 13:3965–3973. https://doi.org/10.2147/IJN.S161002

Antifungal, Antimycotoxigenic, and Antioxidant Activity of Essential Oils and Medicinal Plant Extracts

Aminallah Tahmasebi and Akbar Karami

Abstract Fungi are among the most devastating pathogens which their infections can cause food spoilage and mycotoxin production. These detrimental effects caused by fungi can negatively impact foodstuffs, economics and health. Another harmful factor is oxidation process, which causes food degradation. Antioxidants inhibit or delay the substrate oxidation. In order to avoid food spoilage, contamination, destruction, and oxidation and minimize the harmful effects of synthetic food preservatives, there is a growing interest to apply plant-based materials in food industry. It has been established that plants possess antifungal, antimycotoxigenic, and antioxidant activities as they contain various bioactive compounds. The essential oils (EOs) and plant extracts have been shown to act against fungal pathogens. Therefore, EOs and plant extracts are considered as natural, safe and effective agents to preserve foodstuffs and safeguard health.

Keywords Antifungal · Antimycotoxigenic · Antioxidant · Essential oils · Plant extracts

1 Introduction

Medicinal plants have been used in traditional medicine to cure diseases (Karunamoorthi et al. 2013). The antioxidant and antimicrobial properties of aromatic plants have been well studied (Stanković et al. 2016). Plants include various types of bioactive compounds with antifungal, antimycotoxigenic, and antioxidant activities. Fungi are considered as major threats which affect foodstuffs either by

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lowering nutritional values or producing mycotoxins (Arya and Perelló 2010). Grains are infected by fungi including *Aspergillus parasiticus*, *Aspergillus flavus,* and *Fusarium verticillioides* in the field or during storage which cause economic losses with reducing of quality and quantity of foods and producing mycotoxins (Makun 2013). There is an increasing concern regarding fungal mycotoxins which may endanger public health (Wagacha and Muthomi 2008). It has been estimated that mycotoxins contaminate about 25% of harvested crops worldwide (Marin et al. 2013). Most pathogen control measurements are heavily dependent on the chemical applications (Waard et al. 1993). Synthetic fungicides are considered as primary way against fungi with hazardous effects which cause environmental problems and fungal resistance (El-Ghaouth 1997). It has been shown that plant-based secondary metabolites are capable of acting against fungal pathogens with great advantages including target specificity and biodegradable potential (Ribera and Zuñiga 2012).

Therefore, there is a growing trend to apply safe and natural products in food and agricultural industry (Muzzalupo 2013). Interests toward using natural plant compounds are increasing (Da Silva and Rodrigues 2014).

Most plants contain bioactive metabolites produced either in growth stages or in response to stresses (Isah 2019). Plant extracts and essential oils (EOs) are used as green agents to control fungi growth and their toxins (Jiménez-Reyes et al. 2019). Moreover, EOs as bioactive secondary metabolites have been shown less fungal resistance compared to synthetic fungicides (Daferera et al. 2003). Additionally, a number of plants contain efficient and important sources of natural antioxidants (El-Ghorab et al. 2007). Antioxidants prevent or retard the oxidation of the substrate which leads to food preservation and human health via protection from coronary heart disease and cancer (Halliwell and Gutteridge 2015). Plant-based natural antioxidants as safe and effective compounds minimize the side effects compared to synthetic antioxidants (Augustyniak et al. 2010). The carcinogenic effects of the synthetic antioxidants such as butylated hydroxyanisole have been reported before (Ito et al. 1983). Therefore, this chapter contains a detailed consideration of the application of EOs and plant extracts with their antifungal, antimycotoxigenic, and antioxidant activities.

2 The EOs and Medicinal Plant Extracts Antifungal Activity

Plant products have demonstrated strong capacity against fungi (Soković et al. 2013). EOs disrupt the function of fungal enzymes by decreasing the synthesis of key compounds like proteins, denaturing enzymes and preventing the germination of amino acids (Nychas 1995). Some plant constituents including limonene as a monoterpenes were found to inhibit pectin methylesterase in fungi, which plays a role in building of cell wall (Marei et al. 2012).

Table 1 Strong antifungal activity of some essential oils and plant extracts

Plant species	Essential oil/plant extract	Fungus species	Reference
Trachyspermum ammi	Essential oil	*Aspergillus flavus*	Dwivedi and Dubey (1993)
Cymbopogon citratus	Essential oil	*Aspergillus flavus*	Mishra and Dubey (1994)
Origanum compactum	Essential oil	*Botrytis cinerea*	Bouchra et al. (2003)
Thymus glandulosus	Essential oil	*Botrytis cinerea*	Bouchra et al. (2003)
Eucalyptus globulus	Essential oil	*Aspergillus parasiticus*, *Fusarium moniliforme*	López-Meneses et al. (2015)
Thymus capitatus	Essential oil	*Aspergillus parasiticus*, *Fusarium moniliforme*	López-Meneses et al. (2015)
Thymus daenensis	Essential oil, ethanol extract	*Aspergillus flavus*	Gorran et al. (2013)
Satureja khozistanica	Essential oil, ethanol extract	*Aspergillus flavus*	Gorran et al. (2013)
Rosmarinus officinalis	Essential oil	*Aspergillus flavus*	Moghtader et al. (2011)

The strong activity of a number of strong EOs and plant extracts has been shown against fungi in Table 1. The antifungal activity of the EO of a number of plants including *Daucus carota*, *Carum carvi*, *Trachyspermum ammi*, *Cuminum cyminum*, *Anethum graveolens*, *Seseli indicum* was assessed against *A. flavus.* The *T. ammi* EO showed the highest antifungal activity. Other plants except *Coriandrum sativum* and *S. indicum* revealed the 100% protection against *A. flavus* at the concentration of 3000 ppm (Dwivedi and Dubey 1993). Another study revealed that the EO of *Cymbopogon citratus* could inhibit *A. flavus* growth and acts as a strong antifungal agent (Mishra and Dubey 1994). Furthermore, the evaluation of 37 EOs against eight fungi showed that *Cymbopogon martini*, *Syzygium aromaticum*, *Cymbopogon nardus*, *Pimenta racemosa*, and *Chenopodium ambrosioides* cause the highest antifungal activity (Delespaul et al. 2000). In addition, the antifungal activity of *Caesulia axillaris* EO and its major component γ-asarone showed that compared to EO, γ-asarone had higher antifungal activity at the 500-ppm concentration (Varma et al. 2002). Moreover, the effectivity of clove (*S. aromaticum*) EO has been shown against the fungi including *A. parasiticus* and *Fusarium moniliforme* (Juglal et al. 2002). In another study, the EO of 12 plants revealed that thyme (*Thymus vulgaris*), anise (*Illicium verum*), spearmint (*Mentha spicata*), and cinnamon (*Cinnamomum Verum*) were more effective against fungi including *A. flavus*, *F.moniliforme*, *Aspergillus ochraceus* and *A. parasiticus. A. flavus*, *A. ochraceus*, *A. parasiticus,* and *F. moniliforme* and inhibited mycotoxin production (Soliman and Badeaa 2002).

Antifungal activity of seven Labiatae plants showed that *Origanum compactum* and *Thymus glandulosus* could inhibit the complete growth of *Botrytis cinerea*. Carvacrol and thymol as main constituents of the EOs demonstrated the highest

antifungal activity at the 100 ppm concentration (Bouchra et al. 2003). The efficacy of a number of plant EOs including thyme, sage (*Salvia officinalis*), nutmeg (*Myristica fragrans*), eucalyptus (*Eucalyptus globulus*), and cassia showed that cassia acts with higher potential to control postharvest fungi of fruits and vegetables (Feng and Zheng 2007). The EO of eucalyptus and thymus significantly decreased spore germination of *A. parasiticus.* In addition, the EOs showed a remarkable effect on *F. moniliforme* and *A. parasiticus* growth (López-Meneses et al. 2015).

The EOs and extracts of *Satureja macrosiphonia, Thymus daenensis,* and *Satureja khozistanica* were assessed against *A. flavus* growth. *T. daenensis* and *S. khozistanica* EOs and their extracts could completely inhibit *Aspergillus* growth (Gorran et al. 2013).

The effect of different extracts of *Scrophularia striata* was studied for inhibiting *A. flavus* mycelial growth. The findings showed that the aqueous extract could suppress *A. flavus* growth (Moradi et al. 2016).

The antifungal activity of clove, summer savory (*Satureja hortensis*), and thyme EOs revealed that thyme and summer savory EOs contained the highest activity against *A. flavus* in tomato paste (Omidbeygi et al. 2007).

The EO of *C. citratus* inhibited growth, spore production, germ tube length, and germination of fungi including *Rhizopus stolonifer, Colletotrichum coccodes*, *Aspergillus niger, Cladosporium herbarum,* and *B. cinerea* (Tzortzakis and Economakis 2007). The EO of *Origanum acutidens* could inhibit mycelial growth of 17 phytopathogenic fungi. In addition, thymol and carvacrol (the major constituents of the EO) showed inhibition against the growth of the fungi (Kordali et al. 2008). Leaf extracts and EO of *Nandina domestica* revealed antifungal activity against *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Rhizoctonia solani*, *Phytophthora capsici*, *B. cinerea*, *Colletotrichum capsici,* and *Fusarium solani* (Bajpai et al. 2009a, b).

EOs of black caraway (*Nigella Sativa*) and fennel (*Foeniculum vulgare*) inhibited the growth of *B. cinerea.* In vivo study showed that fennel and black caraway EOs protected plum fruits against *B. cinerea* and enhanced their shelf life (Aminifard and Mohammadi 2013). Also, the EOs of lemongrass (*C. citratus*), clove, thyme, and oregano (*Origanum vulgare*) demonstrated strong antifungal activity (Božik et al. 2017).

EOs of *Sclerorhachis platyrachis* and *Sclerorhachis leptoclada* were evaluated against *A. flavus* and *F. verticilloides.* The findings showed that the EOs could reduce dry mycelium weight and hyphal radial growth of the fungi (Tahmasebi et al. 2012). Another study demonstrated a reduction in the growth of *A. flavus*, *F. verticillioides,* and *A. parasiticus* in response to star anise EO (Aly et al. 2016). Furthermore, the EO of *Boswellia serrata* showed antifungal activity against 15 various fungi (Venkatesh et al. 2017). The rosemary (*Rosmarinus officinalis*) EO showed strong activity against *A. flavus*. The antifungal activities of rosemary oil are related with its main compound, α-pinene of monoterpenes (Moghtader et al. 2011).

The findings showed that medicinal plant extracts, EOs, and their constituents could act as strong inhibitor of fungal growth. Also, a number of EOs have been

tested in vivo condition and prove that EO could work efficiently in natural systems. The high potential of plant products offers them as green alternative to synthetic chemicals in the control of fungal infections.

3 The EOs and Medicinal Plant Extracts Antimycotoxigenic Activity

Mycotoxins as secondary toxic metabolites are produced by fungi including *Aspergillus*, *Penicillium*, *Trichothecium*, *Trichoderma,* and *Fusarium* (Penugonda et al. 2010). Mycotoxins contaminate foodstuffs which endanger public health. Mycotoxins are considered as serious problems in the tropical regions (Kumar et al. 2008). Fumonisins and aflatoxins are regarded as the secondary metabolites with the high toxicity secreted by *Aspergillus* and *Fusarium* species. *A. flavus* and *F. verticillioides* are two important mycotoxigenic fungi that colonize various grains (Greeff-Laubscher et al. 2019).

The major mycotoxins infecting foodstuffs are aflatoxin, ochratoxin, citrinin, patulin, zearalenone, fumonisin, trichothecene, and deoxynivalenol. *Aspergillus* species produce patulin, sterigmatocystin, and terreic acid, whereas *Fusarium* species secret nivalenol, diacetoxyscripenol, deoxynivalenol, fusarinone-X, HT-2 toxins zearalenone and neosolaniol. *Penicillium griseofulvum* produces cyclopiazonic acid. In addition, *Trichothecium roseum* produces trichothecin, while *Trichoderma viride* secretes trichodermin and gliotoxin mycotoxins (Penugonda et al. 2010). Due to these adverse effects, there is a growing trend to find natural products, which may tackle mycotoxin contamination. The strong antimycotoxigenic activity of some EOs and medicinal plant extracts has been presented in Table 2.

The EO of clove and cinnamon could inhibit the production of aflatoxin B_1 and ochratoxin (Patkar et al. 1994). It has been shown that eugenol as a major component of clove EO is able to prevent aflatoxin biosynthesis resulting in antiaflatoxigenic process (Jayashree and Subramanyam 1999). The EO of *C. citratus* showed antiaflatoxigenic activity and its activity was increased by higher concentrations. The value of 0.2 mg ml^{-1} and higher concentrations suppressed aflatoxin B1 production (Paranagama et al. 2003). The EO of *Thymus eriocalyx* and *Thymus X-porlock* was evaluated to determine their antiaflatoxigenic activity. The EO of both species showed strong property at the concentration of 250 ppm in inhibiting aflatoxin production. The EO of *T. eriocalyx* was more effective compared to that in *T. X-porlock* (Rasooli and Owlia 2005). *C. citratus* EO inhibited completely the aflatoxin B1 production (Helal et al. 2007). The combination of *Cinnamomum camphora* and *Alpinia galanga* EOs suppressed the complete production of aflatoxin B1 and showed stronger activity in comparison to individual EO treatment (Srivastava et al. 2008). The EO of *Ocimum basilicum* inhibited the biosynthesis of aflatoxin B_1 and G_1 (Atanda et al. 2007). Moreover, the EO of *C. ambrosioides*

Table 2 Strong antimycotoxigenic activity of some essential oils and plant extracts

Plant species	Essential oil/plant extract	Mycotoxin	Reference
Thymus eriocalyx	Essential oil	Aflatoxin	Rasooli and Owlia (2005)
Thymus X-porlock	Essential oil	Aflatoxin	Rasooli and Owlia (2005)
Cymbopogon citratus	Essential oil	Aflatoxin	Helal et al. (2007)
Rosmarinus officinalis	Essential oil	Aflatoxin	Rasooli et al. (2008)
Trachyspermum copticum	Essential oil	Aflatoxin	Rasooli et al. (2008)
Hibiscus sabdariffa	Extract	Aflatoxin	El-Nagerabi et al. (2012)
Illicium verum	Essential oil	Aflatoxin, Fumonisin	Aly et al. (2016)
Boswellia serrata	Essential oil	Aflatoxin, Fumonisin	Venkatesh et al. (2017)
Thymus daenensis	Extract	Aflatoxin	Gorran et al. (2013)
Scrophularia striata	Extract	Aflatoxin	Moradi et al. (2016)
Allium sativum	Extract	Aflatoxin	Reddy et al. (2009)
Ocimum sanctum	Extract	Aflatoxin	Reddy et al. (2009)
Curcuma longa	Extract	Aflatoxin	Reddy et al. (2009)
Syzygium aromaticum	Extract	Aflatoxin	Reddy et al. (2009)

suppressed the production of aflatoxin B_1 secreted by *A. flavus* (Kumar et al. 2007). The EOs of *R. officinalis* and *Trachyspermum copticum* could inhibit 100 and 90.28% of aflatoxin biosynthesis, respectively (Rasooli et al. 2008). In addition, the EOs of *T. vulgaris*, *Citrus aurantifolia,* and *C. carvi* inhibited the production of aflatoxin B1 and G1 (Razzaghi-Abyaneh et al. 2009). The combination of various plant extracts including *Citrullus colocynthis* + *Commiphora wightii* + *C. nardus* and *C. colocynthis* + *C. wightii* + *Curcuma longa* inhibited 100% of aflatoxin B_1 production. Moreover, plant extracts combination showed the higher activity compared to individual extract (Sidhu et al. 2009). Aqueous extract of ajowan (*T. ammi*) seed degraded aflatoxin G1 (Velazhahan et al. 2010). Methyl syringate as a compound of *Betula alba* suppressed the production of aflatoxin in *A. flavus* and *A. parasiticus.* It has been demonstrated that methyl syringate has decreased the expression of genes involved in aflatoxin biosynthesis (Jermnak et al. 2012). The extract of *Hibiscus sabdariffa* could decrease the aflatoxin B1 production of *A. parasiticus* and *A. flavus* (El-Nagerabi et al. 2012). The production of mycotoxins including fumonisin B1 and aflatoxin B1 was suppressed 100% at the concentration of 100 and 200 ppm of the EO of star anise, respectively (Aly et al. 2016). Thymus and eucalyptus EOs reduced the production of aflatoxin (4%) and fumonisin (31%), respectively (López-Meneses et al. 2015). Furthermore, the fumonisin B1 and aflatoxin B1 production was inhibited 100% by the EO of *B. serrata* (Venkatesh et al. 2017).

The EOs and extracts of *T. daenensis*, *S. macrosiphonia,* and *S. khozistanica* were assessed for evaluating their effects against aflatoxin B1 level in *A. flavus*. Ethanol extracts of all three plants and their EOs inhibited (51–87%) production of aflatoxin B1 and showed strong anti-aflatoxin biosynthesis activity. On the other hand, the EOs and ethanol extracts showed no potential to degrade aflatoxin B1, while the aqueous extracts were able to degrade aflatoxin B1. The *T. daenensis* aqueous extract reduced 97% of aflatoxin B1 level, while the extracts of *S. macrosiphonia* and *S. khozistanica* decreased the content of aflatoxin B1 up to 15% (Gorran et al. 2013).

The effect of extracts of *S. striata* was studied for reducing aflatoxin B1 level. Ethyl acetate, methanol, and aqueous extracts could inhibit (92–100%) the production of aflatoxin. The aqueous and methanolic extracts degraded the aflatoxin, 33.7 and 29.2%, respectively (Moradi et al. 2016).

The EOs of sage, melissa, bay leaves, fenugreek, mint, and cumin showed a higher impact compared to extracts on the ochratoxin A production. The levels of reduction varied depending on the EO type which were 80% for melissa and 25% for sage at 5 μL mL^{-1} concentration. While these levels were 69% for mint and 13% for thyme extracts. Thus, the EOs and extracts were able to reduce ochratoxin A production in *Aspergillus carbonarius* (El Khoury et al. 2017).

The extracts of *S. aromaticum*, *Allium sativum*, *C. longa,* and *Ocimum sanctum* effectively inhibited aflatoxin production (Reddy et al. 2009).

It has been indicated that EOs of lemon, grapefruit, eucalyptus, and palmarosa could degrade the zearalenone toxin (Perczak et al. 2016). Some factors including temperature, pH, the concentration of EO and toxin, and time affected the degradation of zearalenone (Perczak et al. 2016).

The literature suggests that plant products have shown a promising alternative to inhibit or degrade mycotoxins. Therefore, plant-based products as natural choice might be applied in food industry to control mycotoxin contamination.

4 The EOs and Medicinal Plant Extracts Antioxidant Activity

Antioxidants act as reducing agents against free radical activity. Free radicals cause oxidative stress involved in the development of diseases including diabetes and cancer (Đilas et al. 2012; Bakırel et al. 2008). Therefore, antioxidant substances inhibit the diseases by scavenging free radicals (Kapadiya et al. 2016). In addition, antioxidants decrease the impacts of mycotoxins in foodstuffs (Abdel-Razek et al. 2017). A number of techniques are used to evaluate the antioxidant activity. The common methods used frequently in the studies include 1,1-diphenyl-2-picrylhydrazine (DPPH) radical scavenging assay (Candan et al. 2003), OH radicals scavenging activity (Mimica-Dukic et al. 2004), *beta*-carotene linoleic acid bleaching assay (Kulisic et al. 2004), thiobarbituric acid reactive species (TBARS)

(Damien Dorman et al. 1995), and ABTS+cation bleaching assay (Re et al. 1999). Many plant substances including polyphenolic compounds have been found to have antioxidant property (Shehata et al. 2017). The antioxidant activity of plants makes them as appropriate source in food preservative and therapeutic abilities (Al-Sereiti et al. 1999). The strong antioxidant property of *R. officinalis* makes it effective to apply as natural food preservative and therapeutic agent (Rafie et al. 2017). Phenolic diterpenes including carnosic acid and carnosol have been known as the strongest antioxidants in rosemary (Loussouarn et al. 2017). The EO and extract of rosemary scavenge and inhibit free radicals (Žegura et al. 2011; Rašković et al. 2014). In addition, rosemary prevents lipid peroxidation process induced by oxidative stress (Bulbul et al. 2012; Al-Sereiti et al. 1999). Also, it has been shown that rosemary increases the activity of antioxidant enzymes (Afonso et al. 2013). All these activities caused by rosemary in suppressing harmful free radicals highlight rosemary EO and extract as promising alternative with its therapeutic potential to replace synthetic antioxidants.

The assessment of nutmeg, thyme, monarda, geranium, and oregano EOs highlighted the antioxidant activity of these EOs. The degree of antioxidant activity varied among them according to various assay systems (Damien Dorman et al. 1995). The EO of *N. sativa* seed indicated effective antioxidant activity (Burits and Bucar 2000). Furthermore, *Achillea millefolium* the EO potently reduced the DPPH radical, showed hydroxyl radical scavenging effect, and inhibited the lipid peroxidation (Candan et al. 2003). Another study assessed the antioxidant activity of *Thymus mastichina*, *Thymus caespititius,* and *Thymus camphoratus.* The results showed the *T. caespititius* oil with the highest capacity compared to *T. mastichina* and *T. camphoratus* (Miguel et al. 2004). The evaluation of antioxidant activity among 43 plants demonstrated that *Gymnema inodorum*, *Piper sarmentosum,* and *Mentha arvensis* contained the highest antioxidant amounts. The findings concluded that the highest antioxidant capacity of the tested plants is attributed to vitamin C, vitamin E, carotenoids, and phenolic compounds (Chanwitheesuk et al. 2005). Solvent extracts affect the level of antioxidant activity. Aqueous methanol extract of *Salvia tomentosa* showed the strongest antioxidant capacity compared to various tested solvent extracts (Tepe et al. 2005). The EO of parsley (*Petroselinum crispum*) exhibited antioxidant activity. Apiol was reported as a major compound to contribute the antioxidant activity of parsley EO (Zhang et al. 2006). Various parts of a plant show different antioxidant amounts. Bamboo (*Sasa palmata*) parts including leaf, stem, rhizome, and root were compared regarding their antioxidant activity. Leaf extract contained the highest antioxidant content in comparison to other plant parts (Kurosumi et al. 2007). Also, the EOs of the leaves and flower parts of *Bidens pilosa* were found to have strong antioxidant capacity (Deba et al. 2008). Antioxidant activity of EO and ethyl acetate extract of *Magnolia liliiflora* revealed the highest antioxidant contents, respectively (Bajpai et al. 2009a, b). Significant variation was observed in antioxidant properties of *Hemerocallis fulva* during maturity stages including bud developing, flower opening, and fully flower opening. Flower opening stage showed the highest antioxidant activity, which contained the most values of phenolic compounds (Fu et al. 2009). Geographic and climatic factors influence the

antioxidant activity of plants. The EOs of *R. officinalis* var. *typicus* and var. *troglodytorum* collected at different regions showed various levels of antioxidant activity. The EO of var. *troglodytorum* indicated potent antioxidant capacity compared to var. *typicus* (Zaouali et al. 2010). The antioxidant activity of plant EO and extract might show various degrees depending on the special compounds involved in antioxidant activity. The antioxidant capacity of methanolic extract and EO of *Salvia eremophila* was evaluated. The EO revealed weak antioxidant activity, whereas the methanolic extract showed strong capacity (Ebrahimabadi et al. 2010). Also, the antioxidant activity of EO and methanolic extract of *Semenovia tragioides* was assessed. Methanolic extract of *S. tragioides* showed considerable activity, while the EO revealed poor antioxidant capacity (Bamoniri et al. 2010). In another study, the ethyl acetate extract of *Rhizoma homalomenae* showed considerable antioxidant activity, whereas the EO exhibited only weak or moderate capacity (Zeng et al. 2011). In the other study the EO and the methanolic extracts antioxidant activity of *Oliveria decumbens* Vent. were investigated in the phenological stages. The findings of this study showed that the EOs and extracts obtained at the flowering stage have remarkable antioxidant activity (Esmaeili et al. 2018).

The type of plant cultivars could affect the antioxidant activity. The ethanolic extract of fruits of ten cultivars of litchi (*Litchi chinensis*) was checked. Nuomici cultivar showed the highest antioxidant capacity compared to other cultivars (Wang et al. 2011). The antioxidant activity of nineteen commonly consumed spices was assessed in China. In this study, *Alpinia galanga* revealed the highest antioxidant activity in comparison to other spices (Lu et al. 2011). The antioxidant activity of EO of *Piper betle* showed strong capacity, which was close to ascorbic acid and more than synthetic antioxidant, BHT (Prakash et al. 2010). Thus, the EO of this species has potential to apply as natural antioxidant in food industry.

The literature emphasizes the efficiency of plant antioxidants, which may apply as natural and safe antioxidants for various purposes in food and pharmaceutical industries.

5 Conclusion

Plant EOs and extracts could be used as strong sources of natural products with antifungal, antimycotoxigenic, and antioxidant activities. Special constituents, their amount and the interaction among compounds determine the biological activities of a plant species. Plant EOs and extracts could be applied as food preservatives and therapeutic agents in food, pharmaceutical, and agricultural industries. There is an increasing trend for natural substances to the synthetic chemicals used frequently in various industries. It has been shown that, in some cases the antifungal activity of plant compounds is stronger than synthetics to control fungi. Therefore, the application of plant EOs and extracts may inhibit the adverse effects of synthetic chemicals on human and animal health and environment.

References

Abdel-Razek AG, Badr AN, Shehata MG (2017) Characterization of olive oil By-products: antioxidant activity, its ability to reduce aflatoxigenic fungi hazard and its aflatoxins. Annu Res Rev Biol 14:1–14

Afonso MS, de Silva AM, Carvalho EB, Rivelli DP, Barros SB, Rogero MM, Mancini-Filho J (2013) Phenolic compounds from rosemary (Rosmarinus officinalis L.) attenuate oxidative stress and reduce blood cholesterol concentrations in diet-induced hypercholesterolemic rats. Nutr Metab 10(1):19

Al-Sereiti MR, Abu-Amer KM, Sena P (1999) Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol 37:124–131

Aly SE, Sabry BA, Shaheen MS, Hathout AS (2016) Assessment of antimycotoxigenic and antioxidant activity of star anise (Illicium verum) in vitro. J Saudi Soc Agric Sci 15(1):20–27

Aminifard MH, Mohammadi S (2013) Essential oils to control Botrytis cinerea in vitro and in vivo on plum fruits. J Sci Food Agric 93(2):348–353

Arya A, Perelló AE (eds) (2010) Management of fungal plant pathogens. CABI, Wallingford, p 375

Atanda OO, Akpan I, Oluwafemi F (2007) The potential of some spice essential oils in the control of A. parasiticus CFR 223 and aflatoxin production. Food Control 18(5):601–607

Augustyniak A, Bartosz G, Čipak A, Duburs G, Horáková LU, Łuczaj W, Stefek M (2010) Natural and synthetic antioxidants: an updated overview. Free Radic Res 44(10):1216–1262

Bajpai VK, Lee TJ, Kang SC (2009a) Chemical composition and in vitro control of agricultural plant pathogens by the essential oil and various extracts of Nandina domestica Thunb. J Sci Food Agric 89(1):109–116

Bajpai VK, Yoon JI, Kang SC (2009b) Antioxidant and antidermatophytic activities of essential oil and extracts of Magnolia liliflora Desr. Food Chem Toxicol 47(10):2606–2612

Bakırel T, Bakırel U, Keleş OÜ, Ülgen SG, Yardibi H (2008) In vivo assessment of antidiabetic and antioxidant activities of rosemary (Rosmarinus officinalis) in alloxan-diabetic rabbits. J Ethnopharmacol 116(1):64–73

Bamoniri A, Ebrahimabadi AH, Mazoochi A, Behpour M, Kashi FJ, Batooli H (2010) Antioxidant and antimicrobial activity evaluation and essential oil analysis of Semenovia tragioides Boiss. from Iran. Food Chem 122(3):553–558

Bouchra C, Achouri M, Hassani LI, Hmamouchi M (2003) Chemical composition and antifungal activity of essential oils of seven Moroccan Labiatae against Botrytis cinerea Pers: Fr. J Ethnopharmacol 89(1):165–169

Božik M, Císarová M, Tančinová D, Kouřimská L, Hleba L, Klouček P (2017) Selected essential oil vapours inhibit growth of Aspergillus spp. in oats with improved consumer acceptability. Ind Crop Prod 98:146–152

Bulbul A, Bulbul T, Biricik H, Yesilbag D, Gezen SS (2012) Effects of various levels of rosemary and oregano volatile oil mixture on oxidative stress parameters in quails. Afr J Biotechnol 11 (8):1800–1805

Burits M, Bucar F (2000) Antioxidant activity of Nigella sativa essential oil. Phytother Res 14 (5):323–328

Candan F, Unlu M, Tepe B, Daferera D, Polissiou M, Sökmen A, Akpulat HA (2003) Antioxidant and antimicrobial activity of the essential oil and methanol extracts of Achillea millefolium subsp. Millefolium Afan. (Asteraceae). J Ethnopharmacol 87(2–3):215–220

Chanwitheesuk A, Teerawutgulrag A, Rakariyatham N (2005) Screening of antioxidant activity and antioxidant compounds of some edible plants of Thailand. Food Chem 92(3):491–497

Da Silva VC, Rodrigues CM (2014) Natural products: an extraordinary source of value-added compounds from diverse biomasses in Brazil. Chem Biol Technol Agric 1(1):14

Daferera DJ, Ziogas BN, Polissiou MG (2003) The effectiveness of plant essential oils on the growth of Botrytis cinerea, Fusarium sp. and Clavibacter michiganensis subsp. michiganensis. Crop Prot 22(1):39–44

Damien Dorman HJ, Deans SG, Noble RC, Surai P (1995) Evaluation in vitro of plant essential oils as natural antioxidants. J Essent Oil Res 7(6):645–651

Deba F, Xuan TD, Yasuda M, Tawata S (2008) Chemical composition and antioxidant, antibacterial and antifungal activities of the essential oils from Bidens pilosa Linn. var. Radiata. Food Control 19(4):346–352

Delespaul Q, de Billerbeck VG, Roques CG, Michel G, Marquier-Viñuales C, Bessière JM (2000) The antifungal activity of essential oils as determined by different screening methods. J Essent Oil Res 12(2):256–266

Đilas S, Knez Ž, Četojević-Simin D, Tumbas V, Škerget M, Čanadanović-Brunet J, Ćetković G (2012) In vitro antioxidant and antiproliferative activity of three rosemary (Rosmarinus officinalis L.) extract formulations. Int J Food Sci Technol 47(10):2052–2062

Dwivedi SK, Dubey NK (1993) Potential use of the essential oil of Trachyspermum ammi against seed-borne fungi of Guar (Cyamopsis tetragonoloba L. (Taub.)). Mycopathologia 121(2):101–104

Ebrahimabadi AH, Mazoochi A, Kashi FJ, Djafari-Bidgoli Z, Batooli H (2010) Essential oil composition and antioxidant and antimicrobial properties of the aerial parts of Salvia eremophila Boiss. from Iran. Food Chem Toxicol 48(5):1371–1376

El Khoury R, Atoui A, Mathieu F, Kawtharani H, El Khoury A, Maroun RG, El Khoury A (2017) Antifungal and antiochratoxigenic activities of essential oils and total phenolic extracts: a comparative study. Antioxidants 6(3):44

El-Ghaouth A (1997) Biologically-based alternatives to synthetic fungicides for the control of postharvest diseases. J Ind Microbiol Biotechnol 19(3):160–162

El-Ghorab A, Shibamoto T, Özcan MM (2007) Chemical composition and antioxidant activities of buds and leaves of capers (Capparis ovata Desf. var. Canescens) cultivated in Turkey. J Essent Oil Res 19(1):72–77

El-Nagerabi SA, Al-Bahry SN, Elshafie AE, AlHilali S (2012) Effect of Hibiscus sabdariffa extract and Nigella sativa oil on the growth and aflatoxin B1 production of Aspergillus flavus and Aspergillus parasiticus strains. Food Control 25(1):59–63

Esmaeili H, Karami A, Maggi F (2018) Essential oil composition, total phenolic and flavonoids contents, and antioxidant activity of Oliveria decumbens Vent. (Apiaceae) at different phenological stages. J Clean Prod 198:91–95

Feng W, Zheng X (2007) Essential oils to control Alternaria alternata in vitro and in vivo. Food Control 18(9):1126–1130

Fu M, He Z, Zhao Y, Yang J, Mao L (2009) Antioxidant properties and involved compounds of daylily flowers in relation to maturity. Food Chem 114(4):1192–1197

Gorran A, Farzaneh M, Shivazad M, Rezaeian M, Ghassempour A (2013) Aflatoxin B1-reduction of Aspergillus flavus by three medicinal plants (Lamiaceae). Food Control 31(1):218–223

Greeff-Laubscher MR, Beukes I, Marais GJ, Jacobs K (2019) Mycotoxin production by three different toxigenic fungi genera on formulated abalone feed and the effect of an aquatic environment on fumonisins. Mycology 11:1–13

Halliwell B, Gutteridge JM (2015) Free radicals in biology and medicine. Oxford University Press, Cambridge

Helal GA, Sarhan MM, Abu Shahla ANK, Abou El-Khair EK (2007) Effects of Cymbopogon citratus L. essential oil on the growth, morphogenesis and aflatoxin production of Aspergillus flavus ML2-strain. J Basic Microbiol 47(1):5–15

Isah T (2019) Stress and defense responses in plant secondary metabolites production. Biol Res 52 (1):39

Ito N, Fukushima S, Haqlwara A, Shibata M, Ogiso T (1983) Carcinogenicity of butylated hydroxyanisole in F344 rats. J Natl Cancer Inst 70(2):343–352

Jayashree T, Subramanyam C (1999) Antiaflatoxigenic activity of eugenol is due to inhibition of lipid peroxidation. Lett Appl Microbiol 28(3):179–183

Jermnak U, Yoshinari T, Sugiyama Y, Tsuyuki R, Nagasawa H, Sakuda S (2012) Isolation of methyl syringate as a specific aflatoxin production inhibitor from the essential oil of Betula alba

and aflatoxin production inhibitory activities of its related compounds. Int J Food Microbiol 153 (3):339–344
Jiménez-Reyes MF, Carrasco H, Olea AF, Silva-Moreno E (2019) Natural compounds: a sustainable alternative to the phytopathogen control. J Chil Chem Soc 64(2):4459–4465
Juglal S, Govinden R, Odhav B (2002) Spice oils for the control of co-occurring mycotoxin-producing fungi. J Food Prot 65(4):683–687
Kapadiya DB, Dabhi BK, Aparnathi KD (2016) Spices and herbs as a source of natural antioxidants for food. Int J Curr Microbiol App Sci 5(7):280–288
Karunamoorthi K, Jegajeevanram K, Vijayalakshmi J, Mengistie E (2013) Traditional medicinal plants: a source of phytotherapeutic modality in resource-constrained health care settings. J Evid Based Complementary Alternat Med 18(1):67–74
Kordali S, Cakir A, Ozer H, Cakmakci R, Kesdek M, Mete E (2008) Antifungal, phytotoxic and insecticidal properties of essential oil isolated from Turkish Origanum acutidens and its three components, carvacrol, thymol and p-cymene. Bioresour Technol 99(18):8788–8795
Kulisic T, Radonic A, Katalinic V, Milos M (2004) Use of different methods for testing antioxidative activity of oregano essential oil. Food Chem 85(4):633–640
Kumar R, Mishra AK, Dubey NK, Tripathi YB (2007) Evaluation of Chenopodium ambrosioides oil as a potential source of antifungal, antiaflatoxigenic and antioxidant activity. Int J Food Microbiol 115(2):159–164
Kumar V, Basu MS, Rajendran TP (2008) Mycotoxin research and mycoflora in some commercially important agricultural commodities. Crop Prot 27(6):891–905
Kurosumi A, Sasaki C, Kumada K, Kobayashi F, Mtui G, Nakamura Y (2007) Novel extraction method of antioxidant compounds from Sasa palmata (Bean) Nakai using steam explosion. Process Biochem 42(10):1449–1453
López-Meneses AK, Plascencia-Jatomea M, Lizardi-Mendoza J, Rosas-Burgos EC, Luque-Alcaraz AG, Cortez-Rocha MO (2015) Antifungal and antimycotoxigenic activity of essential oils from Eucalyptus globulus, Thymus capitatus and Schinus molle. Food Sci Technol 35(4):664–671
Loussouarn M, Krieger-Liszkay A, Svilar L, Bily A, Birtić S, Havaux M (2017) Carnosic acid and carnosol, two major antioxidants of rosemary, act through different mechanisms. Plant Physiol 175(3):1381–1394
Lu M, Yuan B, Zeng M, Chen J (2011) Antioxidant capacity and major phenolic compounds of spices commonly consumed in China. Food Res Int 44(2):530–536
Makun H (ed) (2013) Mycotoxin and food safety in developing countries. BoD–Books on Demand, Norderstedt, p 268
Marei GIK, Rasoul MAA, Abdelgaleil SA (2012) Comparative antifungal activities and biochemical effects of monoterpenes on plant pathogenic fungi. Pestic Biochem Physiol 103(1):56–61
Marin S, Ramos AJ, Cano-Sancho G, Sanchis V (2013) Mycotoxins: occurrence, toxicology, and exposure assessment. Food Chem Toxicol 60:218–237
Miguel G, Simoes M, Figueiredo AC, Barroso JG, Pedro LG, Carvalho L (2004) Composition and antioxidant activities of the essential oils of Thymus caespititius, Thymus camphoratus and Thymus mastichina. Food Chem 86(2):183–188
Mimica-Dukic N, Bozin B, Sokovic M, Simin N (2004) Antimicrobial and antioxidant activities of Melissa officinalis L. (Lamiaceae) essential oil. J Agric Food Chem 52(9):2485–2489
Mishra AK, Dubey NK (1994) Evaluation of some essential oils for their toxicity against fungi causing deterioration of stored food commodities. Appl Environ Microbiol 60(4):1101–1105
Moghtader M, Salari H, Farahmand A (2011) Evaluation of the antifungal effects of rosemary oil and comparison with synthetic born essential oil and fungicide on the growth of Aspergillus flavus. J Ecol Nat Environ 3(6):210–214
Moradi L, Jafari Z, Farzaneh M (2016) Effects of various extractions of Scrophularia striata to reduce Aflatoxin B1 from Aspergillus flavus on pistachio nut. Biol Control Pests Plant Dis 5 (2):201–209
Muzzalupo I (ed) (2013) Food industry. BoD–Books on Demand, Norderstedt, p 748

Nychas GJE (1995) Natural antimicrobials from plants. In: New methods of food preservation. Springer, Boston, pp 58–89

Omidbeygi M, Barzegar M, Hamidi Z, Naghdibadi H (2007) Antifungal activity of thyme, summer savory and clove essential oils against Aspergillus flavus in liquid medium and tomato paste. Food Control 18(12):1518–1523

Paranagama PA, Abeysekera KHT, Abeywickrama K, Nugaliyadde L (2003) Fungicidal and anti-aflatoxigenic effects of the essential oil of Cymbopogon citratus (DC.) Stapf. (lemongrass) against Aspergillus flavus Link. isolated from stored rice. Lett Appl Microbiol 37(1):86–90

Patkar KL, Usha CM, Shetty HS, Paster N, Lacey J (1994) Effects of spice oil treatment of rice on moulding and mycotoxin contamination. Crop Prot 13(7):519–524

Penugonda S, Girisham S, Reddy S (2010) Elaboration of mycotoxins by seed-borne fungi of finger millet (Eleusine coracana L.). Int J Biotechnol Mol Biol Res 1:62–64

Perczak A, Juś K, Marchwińska K, Gwiazdowska D, Waśkiewicz A, Goliński P (2016) Degradation of zearalenone by essential oils under in vitro conditions. Front Microbiol 7:1224

Prakash B, Shukla R, Singh P, Kumar A, Mishra PK, Dubey NK (2010) Efficacy of chemically characterized Piper betle L. essential oil against fungal and aflatoxin contamination of some edible commodities and its antioxidant activity. Int J Food Microbiol 142(1–2):114–119

Rafie H, Soheila H, Grant E (2017) Rosmarinus officinalis (Rosemary): a novel therapeutic agent for antioxidant, antimicrobial, anticancer, antidiabetic, antidepressant, neuroprotective, anti-inflammatory and anti-obesity treatment. J Herbal Med 3(2):8

Rašković A, Milanović I, Pavlović N, Ćebović T, Vukmirović S, Mikov M (2014) Antioxidant activity of rosemary (Rosmarinus officinalis L.) essential oil and its hepatoprotective potential. BMC Complement Altern Med 14(1):225

Rasooli I, Owlia P (2005) Chemoprevention by thyme oils of Aspergillus parasiticus growth and aflatoxin production. Phytochemistry 66(24):2851–2856

Rasooli I, Fakoor MH, Yadegarinia D, Gachkar L, Allameh A, Rezaei MB (2008) Antimycotoxigenic characteristics of Rosmarinus officinalis and Trachyspermum copticum L. essential oils. Int J Food Microbiol 122(1–2):135–139

Razzaghi-Abyaneh M, Shams-Ghahfarokhi M, Rezaee MB, Jaimand K, Alinezhad S, Saberi R, Yoshinari T (2009) Chemical composition and antiaflatoxigenic activity of Carum carvi L., Thymus vulgaris and Citrus aurantifolia essential oils. Food Control 20(11):1018–1024

Re R, Pellegrini N, Proteggente A, Pannala A, Yang M, Rice-Evans C (1999) Antioxidant activity applying an improved ABTS radical cation decolorization assay. Free Radic Biol Med 26 (9-10):1231–1237

Reddy KRN, Reddy CS, Muralidharan K (2009) Potential of botanicals and biocontrol agents on growth and aflatoxin production by Aspergillus flavus infecting rice grains. Food Control 20 (2):173–178

Ribera AE, Zuñiga G (2012) Induced plant secondary metabolites for phytopatogenic fungi control: a review. J Soil Sci Plant Nutr 12(4):893–911

Shehata MG, Badr AN, Abdel-Razek AG, Hassanein MM, Amra HA (2017) Oil-bioactive films as an antifungal application to save post-harvest food crops. Annu Res Rev Biol 16:1–16

Sidhu OP, Chandra H, Behl HM (2009) Occurrence of aflatoxins in mahua (Madhuca indica Gmel.) seeds: synergistic effect of plant extracts on inhibition of Aspergillus flavus growth and aflatoxin production. Food Chem Toxicol 47(4):774–777

Soković MD, Glamočlija JM, Ćirić AD (2013) Natural products from plants and fungi as fungicides. In: Fungicides-showcases of integrated plant disease management from around the world. InTech, London, pp 185–232

Soliman KM, Badeaa RI (2002) Effect of oil extracted from some medicinal plants on different mycotoxigenic fungi. Food Chem Toxicol 40(11):1669–1675

Srivastava B, Singh P, Shukla R, Dubey NK (2008) A novel combination of the essential oils of Cinnamomum camphora and Alpinia galanga in checking aflatoxin B1 production by a toxigenic strain of Aspergillus flavus. World J Microbiol Biotechnol 24(5):693–697

Stanković N, Mihajilov-Krstev T, Zlatković B, Stankov-Jovanović V, Mitić V, Jović J, Bernstein N (2016) Antibacterial and antioxidant activity of traditional medicinal plants from the Balkan Peninsula. NJAS - Wageningen J Life Sci 78:21–28

Tahmasebi A, Andi SA, Ahmadi MR, Alavi BG (2012) Inhibitory effect of essential oils of Sclerorhachis platyrachis and Sclerorhachis leptoclada on phytopathogenic fungi. Int J Agric Sci 2(1):48–53

Tepe B, Daferera D, Sokmen A, Sokmen M, Polissiou M (2005) Antimicrobial and antioxidant activities of the essential oil and various extracts of Salvia tomentosa Miller (Lamiaceae). Food Chem 90(3):333–340

Tzortzakis NG, Economakis CD (2007) Antifungal activity of lemongrass (Cympopogon citratus L.) essential oil against key postharvest pathogens. Innov Food Sci Emerg Technol 8(2):253–258

Varma J, Tripathi M, Ram VJ, Pandey VB, Dubey NK (2002) γ-Asarone–the fungitoxic principle of the essential oil of Caesulia axillaris. World J Microbiol Biotechnol 18(3):277–279

Velazhahan R, Vijayanandraj S, Vijayasamundeeswari A, Paranidharan V, Samiyappan R, Iwamoto T et al (2010) Detoxification of aflatoxins by seed extracts of the medicinal plant, Trachyspermum ammi (L.) Sprague ex Turrill–structural analysis and biological toxicity of degradation product of aflatoxin G1. Food Control 21(5):719–725

Venkatesh HN, Sudharshana TN, Abhishek RU, Thippeswamy S, Manjunath K, Mohana DC (2017) Antifungal and antimycotoxigenic properties of chemically characterised essential oil of Boswellia serrata Roxb. ex Colebr. Int J Food Prop 20(Suppl 2):1856–1868

Waard MA, Gessential Oilrgopoulos SG, Hollomon DW, Ishii H, Leroux P, Ragsdale NN, Schwinn FJ (1993) Chemical control of plant diseases: problems and prospects. Annu Rev Phytopathol 31(1):403–421

Wagacha JM, Muthomi JW (2008) Mycotoxin problem in Africa: current status, implications to food safety and health and possible management strategies. Int J Food Microbiol 124(1):1–12

Wang HC, Hu ZQ, Wang Y, Chen HB, Huang XM (2011) Phenolic compounds and the antioxidant activities in litchi pericarp: difference among cultivars. Sci Hortic 129(4):784–789

Zaouali Y, Bouzaine T, Boussaid M (2010) Essential oil composition in two Rosmarinus officinalis L. varieties and incidence for antimicrobial and antioxidant activities. Food Chem Toxicol 48 (11):3144–3152

Žegura B, Dobnik D, Niderl MH, Filipič M (2011) Antioxidant and antigenotoxic effects of rosemary (Rosmarinus officinalis L.) extracts in Salmonella typhimurium TA98 and HepG2 cells. Environ Toxicol Pharmacol 32(2):296–305

Zeng LB, Zhang ZR, Luo ZH, Zhu JX (2011) Antioxidant activity and chemical constituents of essential oil and extracts of Rhizoma homalomenae. Food Chem 125(2):456–463

Zhang H, Chen F, Wang X, Yao HY (2006) Evaluation of antioxidant activity of parsley (Petroselinum crispum) essential oil and identification of its antioxidant constituents. Food Res Int 39(8):833–839

Antibacterial Electrospun Nanofibres

Wazed Ali, Rahul Gadkari, Sanchi Arora, Viraj Somkuwar, and Anupam Chowdhury

Abstract Several methods are available for the production of nanofibres, such as rotary jet spinning, melt fibrillation, electrospinning, sol-gel method, phase separation, gas-jet technique, self-assembly and template synthesis. However, electrospinning surpasses all of them in terms of efficiency and effectiveness. Electrospinning enables the production of continuous nanofibres from a wide range of materials. It also facilitates precise control over several fibre/membrane properties like diameter, morphology, composition, porosity, etc., that too by using simple equipment and even simpler procedure. Nanofibres produced from electrospinning technique exhibit diverse features, such as high porosity, high surface area-to-volume ratio, small pore size, low weight and good mechanical properties. Considering these favourable characteristics, electrospun membranes are extensively used to fabricate bioactive products for application in various areas like healthcare, energy harvesting and storage, biomedical, environmental engineering, defence and security. This chapter focuses on the potential use of various natural, synthetic, functionalised, encapsulated and composite electrospun nanofibrous membranes for antibacterial bioactive applications.

Keywords Nanofibres · Electrospinning · Antibacterial · Plant extract · Composite nanofibres

1 Introduction

Nanotechnology is an interesting interdisciplinary area with potential applications in almost all fields of science and technology: healthcare, material science, energy studies, environmental studies, mechanics, optics, electronics, plastics, aerospace

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and so on. Some typical morphologies of nanomaterials that have been researched upon extensively are nanofibres, nanowires, nanorods, nanotubes, nanoparticles, etc. Among these, nanofibres have recently gained substantial interest of the research community owing to their large surface area-to-volume ratio, feasibility of generating diverse surface functionalities and superior mechanical properties that render them suitable for use in myriad applications. Out of the numerous existing techniques for spinning nanofibres, electrospinning has emerged as most potent of producing continuous nanofibres from a variety of natural as well as synthetic polymers (Panthi et al. 2015; Joshi et al. 2008).

Over the years, bioactive and antibacterial/antimicrobial materials are gaining rising importance not only in healthcare sector but also in other applications like, sportswear, defence clothing, protective and industrial textiles, geomembranes, etc. These are important for creating a healthy and hygienic atmosphere at home, workplace and in general environment. In order to tackle bacterial infections, composite nanofibres, i.e. nanofibres integrated with powerful antibacterial agents such as silver, copper, copper oxide (CuO), zinc oxide (ZnO) in the form of nanoparticles are being developed (Ditaranto et al. 2018; Gadkari et al. 2017a; Saquing et al. 2009). In general, fabrication of antibacterial nanofibres via electrospinning technique involves integration of biocides in fibres. This can be achieved by various methods, such as using a homogenous blend of antibacterial agent in the polymer solution as feed for electrospinning, adding nanostructures of antibacterial substance(s) in feed solution for electrospinning fibres embedded with nanostructures, enclosing an antibacterial agent in the core of nanocomposite fibre by a sheath of other polymer, treating the electrospun nanofibres with antibacterial agent(s), etc. (Xue et al. 2017). However, the rising concern related to the adverse effects of synthetic antibacterial agents on the health of the human population and on the environment has driven the research on development of electrospun antibacterial fibres towards usage of natural plant extracts and essential oils having bactericidal property. The present chapter presents an overview of some significant studies focused upon the electrospinning of such antibacterial nanofibres or nanofibrous membranes.

2 Electrospinning Process

Electrospinning is the most popular and vastly used technology for making nanoscale fibres from both natural and synthetic polymers. Traditionally, synthetic fibres are obtained via melt spinning, which results in fibre diameter ranging between 5 μm to 200 μm, whereas the diameter of electrospun fibres falls within a range of several nanometres (Brown et al. 2016; Bhardwaj and Kundu 2010; Stankus et al. 2006). Moreover, production of polymeric fibres via melt spinning uses mechanical force to extract the melt polymer through spinnerets, whereas electrospinning is an electrohydrodynamic process that uses electric potential to draw polymer solution into fibres. The electrospinning phenomenon was first observed way back in 1600

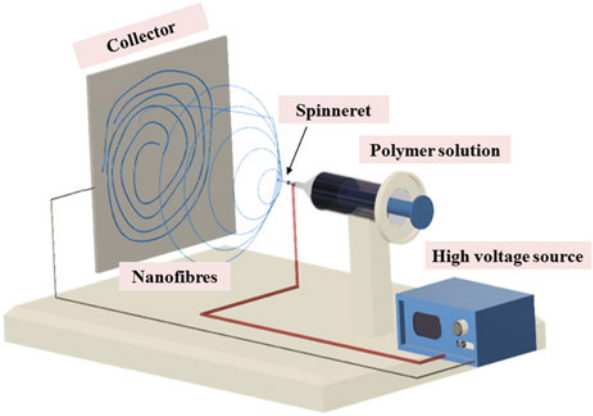

Fig. 1 Schematic depiction of a horizontal electrospinning set-up

century by W. Gilbert, an English Physicist. He observed a water droplet placed over a dry surface reshaping in a conical form on being brought into proximity of a piece of rubbed amber (Brown et al. 2016). In 1749, Nollet demonstrated separation of water drops from charged water jet falling into a collector set at different electric potential. Later, Rayleigh (1897), Zeleny (1914) and Formhals (1934) also observed electrospraying effect (Bhardwaj and Kundu 2010). All of these studies became the basis for Antonin Formhals in 1934 to fabricate the first system for producing electrospun yarn using a voltage of 57 kV, whereafter a thorough research on electrospinning gained momentum.

Typically, an electrospinning set-up consists of three basic units: a variable high DC voltage supply, a metallic spinneret (syringe) with a very fine orifice and a collector plate with some conductive element (Fig. 1). The granules of polymer to be electrospun are generally dissolved in some solvent to prepare a solution with requisite viscosity. A very high voltage is applied between the drop of polymer (held inside the spinneret tip by its surface tension) and a collector plate or target electrode placed at certain distance from the spinneret tip. Application of high voltage results in development of an electrostatic force on the polymer drop, which deforms the polymer drop into a conical shape called Taylor cone. When this electrostatic force reaches a critical value, it overcomes the surface tension, resulting in ejection of a charged jet from Taylor cone towards the collector plate. The solvent evaporates leaving behind the solid polymer in fibrous form, which gets deposited onto the collector forming nonwoven fibrous webs or mats (Persano et al. 2013; Balamurugan et al. 2011; Zhang et al. 2005; Zaikov 2016; Baker et al. 2006; Tamura and Kawakami 2010). Besides, during the stretching of polymer stream and simultaneous evaporation of solvent, the size of polymeric strand can be drastically decreased (up to six orders of magnitude), resulting in nano-sized fibres (Tamura and Kawakami 2010). The continuous deposition of fibres generates 2D nanofibrous web of very high porosity (even 90%), thus making them suitable for use in high efficiency filters, scaffolds for tissue engineering, artificial implants, wound dressings, masks, etc. Other than these applications, electrospun nanofibres are also used

in energy harvesting and storage devices for smart textiles, solar cells, fuel cells, chemical and biological protection sensors, etc. (Ramakrishna et al. 2006; Riboldi et al. 2005; Reneker and Chun 1996; Reneker et al. 2000; Rho et al. 2006).

Conventional electrospinning set-ups are horizontal or vertical (Bhardwaj and Kundu 2010; Persano et al. 2013; Balamurugan et al. 2011), though some researchers have also reported designing typical systems for the production of complex nanofibrous structures to suit specific requirements and applications. Balamurugan et al. (2011) reported a system combining electrospinning and electrospraying techniques for the fabrication of nanocomposite membranes. Stankus et al. (2006) also combined electrospraying with electrospinning to integrate smooth muscle cells into biodegradable fibre matrix. Baker et al. (2006) used a circular mandrel to produce 3D electrospun polystyrene scaffolds which could be used for cell growth and cell to cell interaction. Numerous other studies about modification of electrospinning set-ups like development of coaxial electrospinning system for highly concentrated solutions (Yu et al. 2011), combination of melt electrospinning and solution electrospinning for hybrid electrospinning of scaffolds (Il Yoon et al. 2013), using differently profiled collectors for creating different alignment of fibres (Stocco et al. 2017; Levitt et al. 2017), etc. are also available.

3 Bioactive Antibacterial Electrospun Nanofibres

For any antibacterial material to function efficiently, the bacteria should essentially have good contact with it. Thus, the high surface area-to-volume ratio of electrospun nanofibres enhances the bactericidal effect of materials developed from them (Li et al. 2015). Moreover, the fibrous mats developed by electrospinning can be easily tailored for different applications during or after the generation of fibres. In addition, various strategies such as doping of antimicrobial agent(s) in precursor solution, surface functionalisation (Su et al. 2012; Schiffman and Elimelech 2011), solution blending (Charernsriwilaiwat et al. 2012), coaxial spinning (Khalf and Madihally 2017; Liu et al. 2011), coating of antibacterial/antimicrobial agents on nanofibrous mat (Rieger et al. 2016; Kang et al. 2009) can also be easily adopted as per required applications.

3.1 Natural Polymer Based Nanofibres

Natural polymer based electrospun nanofibres have been extensively used for various medical applications, like wound healing, artificial tissues, medical implants and drug delivery. Natural polymers are chosen over synthetic ones due to better biocompatibility, biodegradability, poor immunogenicity and enhanced cell proliferation (Bhattarai et al. 2005; Wang et al. 2016). However, it is difficult to spin natural polymers in their pure form. For instance, in case of pure alginate, fibre

formation is not possible for less concentrated solutions due to occurrence of gelation. On the other hand, at higher concentration, the solution becomes too viscous to be extruded through spinneret (Bhattarai et al. 2006). Similarly, electrospinning of pure chitosan solution poses problems due to its polycationicity, rigid chemical structure and typical inter- and intra-molecular interactions (Pakravan et al. 2011). Hence, natural polymers are often either blended with synthetic copolymers or chemically modified to be electrospun into nanofibres.

3.1.1 Chitosan Based Nanofibres

Chitosan is a deacetylated derivative of chitin, which is a natural polysaccharide found in crustaceans, insects and some fungi exoskeletons. Chitosan derivatives, nanoparticles and nanofibres exhibit antibacterial activity against several fungi, viruses and bacteria (Gadkari et al. 2017b). However, as already mentioned, it is difficult to electrospin it. Many researchers have reported combining chitosan with other polymers to enhance its spinnability. Jung et al. (2007) dissolved poly(ethylene terephthalate) (PET) and chitosan in trifluoroacetic acid and electrospun this polymeric blend solution to make PET/chitosan nanofibrous mats having fibres with 500–800 nm diameter. Homayoni et al. (2009) suggested that the difficulty associated with electrospinning of pure chitosan due to its high viscosity can be resolved using alkaline treatment for hydrolysing its polymer chains, and thus decreasing its molecular weight. They demonstrated successful production of chitosan nanofibres of appropriate quality and processing stability by electrospinning a solution of alkaline treated chitosan in aqueous acetic acid. They also reported an increase in the mean diameter of the chitosan nanofibres upon decreasing the acetic acid concentration in the solvent.

Nguyen et al. (2011) manufactured core/shell structured poly(lactic acid)(PLA)/chitosan fibres through coaxial electrospinning process at different core feed rates of 1 μL/min, 2 μL/min and 4 μL/min. The antibacterial performance of the nanofibrous mats thus produced against *E. coli* bacterium was found to be 99–100% for a bacterial concentration of 10^3 CFU/mL. Ahmed et al. (2018) fabricated electrospun fibrous mats from polyvinyl alcohol (PVA)/chitosan blend and PVA/chitosan/ZnO nanoparticles blend. On assessing them for their antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus* by disc diffusion method, they were found to create zone of inhibitions with average diameter of 14.1 ± 0.8 mm, 15.8 ± 1.0 mm, 13.0 ± 0.7 mm and 5.4 ± 0.5 mm, respectively, in case of PVA/chitosan mats and 20.2 ± 1.0 mm, 21.8 ± 1.5 mm, 15.5 ± 0.8 mm and 21.5 ± 0.5 mm, respectively, in case of PVA/chitosan/ZnO mats.

3.1.2 Protein Based Nanofibres

A protein is a linear polymer of amino acids and is known to exhibit miscellaneous functions. Over the years, researchers have been increasingly exploiting the

structural and functional qualities of fibrous proteins in order to enhance the efficiency of synthetic biomaterials. A variety of proteins and their blends with other polymer(s) have been electrospun by several researchers. This section highlights the use of various protein fibres for application in antibacterial materials.

Lin et al. (2012) prepared electrospun fibrous mats from pure collagen, pure zein and their blend using 40% (w/v) solutions of these polymeric polymers in 70% (v/v) aqueous acetic acid. Though they could not process pure collagen into micro- or nanofibres, pure zein and collagen/zein blend could be efficiently electrospun into bead-free fibrous mats. Besides, they also observed an increase in average fibre diameter from 423 nm to 910 nm on increasing zein weight fraction in collagen/zein blend from 0.33 to 0.67. In order to impart an inherent bactericidal effect, the authors also incorporated berberine drug in the feed solution while electrospinning collagen/zein membrane. In a similar study, Wongkanya et al. (2017) electrospun sodium alginate (SA) and soy protein isolated (SPI) blend fibres with poly(ethylene oxide) (PEO) polymer using different weight percentages of SA, SPI and PEO. They also added vancomycin (Van) drug (0.1 wt.% of polymer), which resists Gram-positive type bacteria, to the feed solution. The zone of inhibition created by Van-loaded SA/PEO/SPI fibres against *S. aureus* bacteria was found to be 21–22.8 mm.

Zhou et al. (2017) used 10:1 (v/v) mixture of 8% collagen solution in hexafluoroisopropanol and bioactive glass (BG) precursor solution to electrospin collagen/BG nanofibres with 494 ± 153 nm average diameter, good thermal stability and hydrophilicity. These fibres were also found to inhibit adhesion and proliferation of *S. aureus* bacterium due to release of Ca, P and Si ions. Khajavi et al. (2016) explored the feasibility of electrospinning nanofibrous scaffolds from different blend compositions of keratin (extracted from quail feather wastes), PVA and silver nanoparticles (Ag-NPs) at 20 kV voltage, 15 cm tip to collector distance and 1 mL/h feed rate. Increase in process efficiency was reflected in formation of uniform nanofibres with fewer beads upon increase in proteinaceous or keratin content. Besides, these mats showed 93–98% antibacterial activity against *S. aureus* (higher for higher keratin content), and almost 100% against *E. coli*.

3.1.3 Cellulose Based Nanofibres

Cellulose is a biocompatible and biodegradable polysaccharide consisting of linear chains of β(1→4) linked d-glucose monomer units. Cellulose based electrospun nanostructures and their derivatives find enormous applications in pharmaceutical industry. This section presents examples of studies conducted on production of antibacterial nanofibres from different derivatives of cellulose.

Carboxymethyl cellulose (CMC) is a classic derivative of cellulose and is non-toxic, biodegradable, biocompatible, water soluble, and has reported usage in variety of biomedical applications, food, detergents, etc. However, alike other natural polymers, it is not suitable to electrospin it in its pure form and needs blending with synthetic copolymers. Shi et al. (2016) developed CMC/PEO membrane by electrospinning an aqueous solution of CMC and PEO in equal amount, at

22 kV with a solution feed rate of 2 mL/h. Subsequent to this, they immersed the membrane in $AgNO_3$ solution for 2 h, followed by irradiation under ultraviolet (UV) lamp for deposition of silver nanoparticles (Ag-NPs) on fibres. The scanning electron micrographs of the membranes thus developed using $AgNO_3$ solutions of different concentrations showed presence of several Ag-NPs on their surface as well as in between the adjacent nanofibres. Treatment with 0.10 mol/L $AgNO_3$ solution was observed to facilitate uniform growth of Ag-NPs on membrane surface, as well as preserved the integrity of 3D membranous structure unlike $AgNO_3$ solutions with concentration lower or higher than this. Besides, this membrane was also found to exhibit 100% activity against both *S. aureus* and *E. coli* bacteria.

Cellulose acetate (CA) is the only derivative of cellulose that can be processed in an electrospinning set-up in its pure form itself. Several studies are available demonstrating increasing interest in electrospinning CA based antibacterial nanofibres using various antibacterial compounds. In one such study, Sultana et al. (2016) electrospun CA nanofibrous from differently concentrated solutions of CA in acetic acid/acetone. Lower concentration of CA (10% w/v) yielded nanofibres with many beads, whereas bead-free nanofibres were obtained when concentration of CA was increased to 14% (w/v). In case of feed solution loaded with 2% (w/v) tetracycline hydrochloride drug, clear area of inhibition was observed against *B. cereus* and *E. coli* bacteria, unlike pure CA membrane that exhibited no inhibition zone.

Cyclodextrin (CD), another derivative of cellulose, has attracted attention of the research community for the development of antimicrobial nanofibres. Celebioglu et al. (2014) electrospun nanofibres from extremely concentrated (160%) aqueous suspensions of cyclodextrin inclusion complexes (CD-IC) loaded with an antibacterial agent triclosan, using two forms of chemically modified CD, namely hydroxypropyl-beta-cyclodextrin (HPβCD) and hydroxypropyl-gamma-cyclodextrin (HPγCD). Bead-free membranes were obtained with average fibre diameter as 520 ± 250 nm and 1100 ± 660 nm, corresponding to former and latter forms of CD, which also showed very good antibacterial effect against both *E. coli* and *S. aureus*.

3.2 Nanofibres Encapsulating Bioactive Plant Extract

Plants are sources of numerous chemical compounds that display antibacterial activity against a range of bacteria. For thousands of years, plant oils and extracts have been in use for a wide range of purposes (Hammer et al. 1999), antimicrobial functionality being the most popular. Additionally, the over-rising concerns about the hazardous side effects of conventionally used synthetic compounds in medication and nourishment industry, as well as the escalating resistance of pathogens to antibiotics have led to a growing interest among the research community to integrate natural extracts with polymers to electrospin nanofibres for various applications like wound dressings, scaffolds for tissue engineering, drug delivery and active food packaging systems (Sridhar et al. 2015; Khan and Shi Xiangyang 2018; Zhang et al. 2017a). Crude extracts can be easily obtained from fresh plants or from milled dried

plants via organic solvent extraction. Numerous extracts of crude plants, for example *Garcinia mangostana*, *grewia mollis*, *aloe vera*, *centella asiatica*, *tecomella undulata*, *baicalein*, *chamomile*, *memecylon edule*, *Indigofera aspalathoides and Azadirachta indica*, have been reported to be successfully encapsulated in electrospun fibres (Motealleh et al. 2014; Suganya et al. 2011; Chan et al. 2017; Charernsriwilaiwat et al. 2013; Agnes Mary and Giri Dev 2015; Al-Youssef et al. 2013).

Ganesan et al. (Ganesan and Pradeepa 2017) electrospun 108–519 nm diameter fibres from a blend of 80% PVA and 20% tridax daisy (or *Tridax procumbens*) leaves extract. The developed nanofibrous mat created 45 mm and 36 mm zone of inhibition for *S. aureus* and *E. coli*, respectively, demonstrating strong resistivity against both bacteria. Yao et al. (2017) prepared an electrospun membrane from a mixture of 17% gelatin solution (in formic acid) and aqueous PVA, also containing gotu kola or *centella asiatica* extract and demonstrated it to be biodegradable, facilitate dermal wound healing and exhibit antibacterial activity against *S. aureus*, *E. coli* and *P. aeruginosa* with minimum inhibitory concentration (MIC) of 6.25 mg/mL for *S. aureus* and 25 mg/mL for both *E. coli* and *P. aeruginosa*. Yousefi et al. (2017) fabricated 90/10 chitosan/PEO nanofibrous mat loaded with Henna (*Lawsonia inermis*) leaves extract. Though Henna extract did not affect the electrospinnability of the precursor blend solution, but the fibre diameter was affected by its concentration. It was also observed that on increasing Henna extract loading from 1 to 2 wt%, the zone of inhibition against *E. coli* increased from 16 mm to 25 mm and from 14 mm to 18 mm for *S. aureus*, as seen in Fig. 2.

Radusin et al. (2019) electrospun films from pure PLA solution and PLA solution loaded with 10 wt.% wild garlic or *Allium ursinum L* (AU) extract at 2000 μL/h flow rate and 14 kV applied voltage. After annealing the films under hydraulic press at 135 °C, without pressure for 5 ± 1 s, followed by air-cooling at room temperature, PVA and AU were observed to exhibit 'island-and-sea' morphology, indicating successful encapsulation of AU droplets of size 2.3 ± 0.5 μm in the PLA matrix (Fig. 3). The PVA/AU film was found to exhibit high antibacterial activity against *E. coli*, but just reasonable against *S. aureus*. Zeyohanness and Zulkifli (2018) successfully electrospun bead-free nanofibres from 10% PVA solution loaded with rose myrtle or *Rhodomyrtus tomentosa* extract (RTE) in different proportions (0.25%, 0.5%, 1.5% and 2.5%). The concentration of RTE was observed to affect the average fibre diameter as well as the antibacterial activity of the fibres against *B. subtilis*, *E. coli*, *P. aeruginosa and E. faecalis* bacteria.

Essential oils (EOs) are usually derived from aromatic plants and are mixtures of various chemical compounds like linalool, pinene, eugenol and cymene, etc. They can be biosynthesised from various plant organs, including flowers, herbs, buds, leaves, fruits, bark, seeds, wood and roots (El Asbahani et al. 2015). EOs, for example *cinnamon*, *lemongrass*, *candeia*, *tea tree*, *lavender* and *thyme* have been extensively explored for integration of antibacterial property in electrospun fibrous mats. Zhang et al. (2017b) electrospun PLA solution loaded with different concentrations of tea tree and manuka oils at a flow rate of 2 mL/h, applied voltage of 18.5 kV and needle to collector distance of 15 cm to form antibacterial nanofibres.

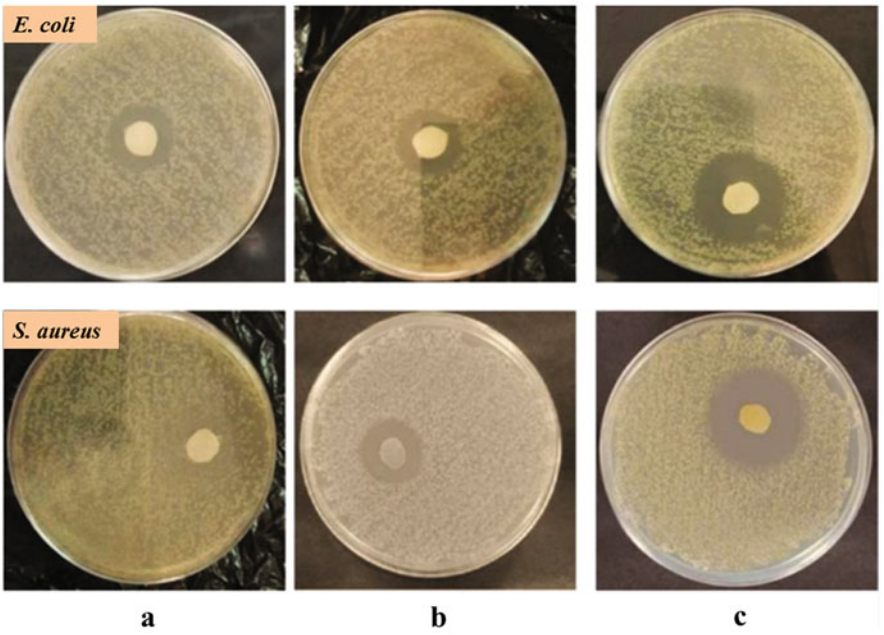

Fig. 2 Antibacterial activity of electrospun nonwoven mats of chitosan/PEO/Henna extract: (**a**) chitosan/PEO (0 wt.% Henna extract), (**b**) 1 wt.% Henna extract loading and (**c**) 2 wt.% Henna extract loading (Yousefi et al. 2017)

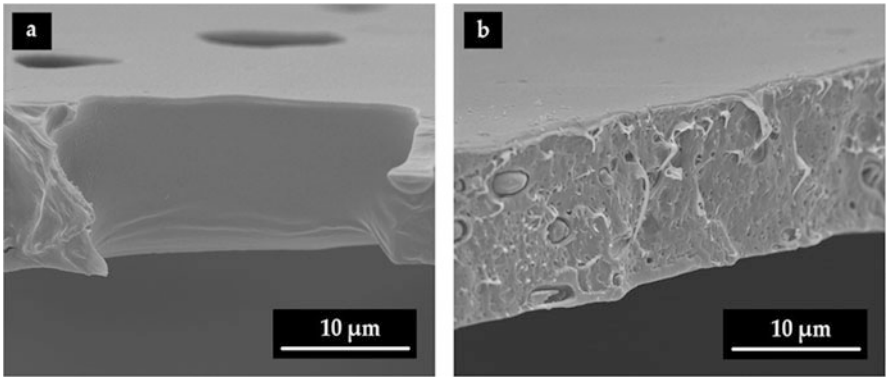

Fig. 3 Scanning electron micrographs of cross-section of electrospun films of (**a**) neat PLA, (**b**) PLA/AU (Radusin et al. 2019)

The used EOs not only improved the antibacterial activity of PLA fibres, but also their mechanical properties, i.e. elongation at break and tensile strength. The bactericidal action of EOs was attributed to the partition of hydrocarbons into the bacterial membrane, further causing damage to the cytoplasmic membranes, thus disrupting their functions and ultimately causing cell lysis. Jung et al. (2020) developed

Table 1 Antibacterial effect of nanofibrous membranes containing cinnamon oil (Jung et al. 2020)

Bacteria	Contact time (h)	Number of bacterial colonies (CFU/mL)		Bacterial reduction (%)
		Control	Nanofibrous membranes containing cinnamon oil	
S. aureus	0	2.5×10^5	2.5×10^5	–
	24	1.3×10^5	9.0×10^5	99.9
K. pneumoniae	0	2.1×10^5	2.1×10^5	–
	24	1.7×10^5	3.0×10^5	0

membranes of core/sheath nanofibres of cinnamon oil (4.9 wt.%)/PVA by emulsion electrospinning. Upon evaluation of their antibacterial activity against *S. aureus* under dynamic contact condition, a reduction of 99.9% in the number of bacterial colonies was observed in comparison with the inoculated buffer solution (Table 1). However, the same nanofibrous membranes did not exhibit any inhibitory effect against *K. pneumonia* because of more complex cell wall structure of this bacteria. Unalan et al. (2019) manufactured peppermint essential oil (PEP) loaded poly(-ε-caprolactone) (PCL) electrospun fibrous mats with a smooth, uniform and bead-free morphology; and with average fibre diameter reducing from 1.6 μm to 0.9 μm with increase in concentration of PEP from 1.5 to 6% (v/v). Other than bringing reduction in fibre diameter, higher PEP concentrations also led to reduction in bacterial viability for *S. aureus* and *E. coli* strains. However, as *E. coli* consists of a double membrane with the outer membrane having a layer of lipopolysaccharide that prevents the penetration of certain antibacterial compounds (Burt and Reinders 2003), the PEP loaded fibrous mats were less effective against *E. coli*.

Sofi et al. (2019) fabricated composite nanofibres consisting of polyurethane (PU) loaded with different concentrations of lavender oil (0%, 5%, 10%, 15% and 20%) and Ag-NPs (0%, 1%, 2%, 5% and 7%). As seen in Fig. 4, the growth of *E. coli* and *S. aureus* strains was not inhibited by pure PU fibrous mats. However, all the mats containing fibres loaded with Ag-NPs and lavender oil were effective in suppressing the bacterial growth.

3.3 Composite Nanofibres

Numerous polymers have been electrospun into nanofibres over the past few decades. However, these single-component electrospun nanofibres typically have limited properties and cannot perform multiple functions (Gao et al. 2019; Sahay et al. 2012; Yang et al. 2014). Of late, many researchers have focused their work around inclusion of other nanoscaled structures in the nanofibres to create composite nanofibres with added functionalities. This section comprises studies related to functionalisation of electrospun nanofibres by incorporation of nanoparticles to improve their antibacterial activity.

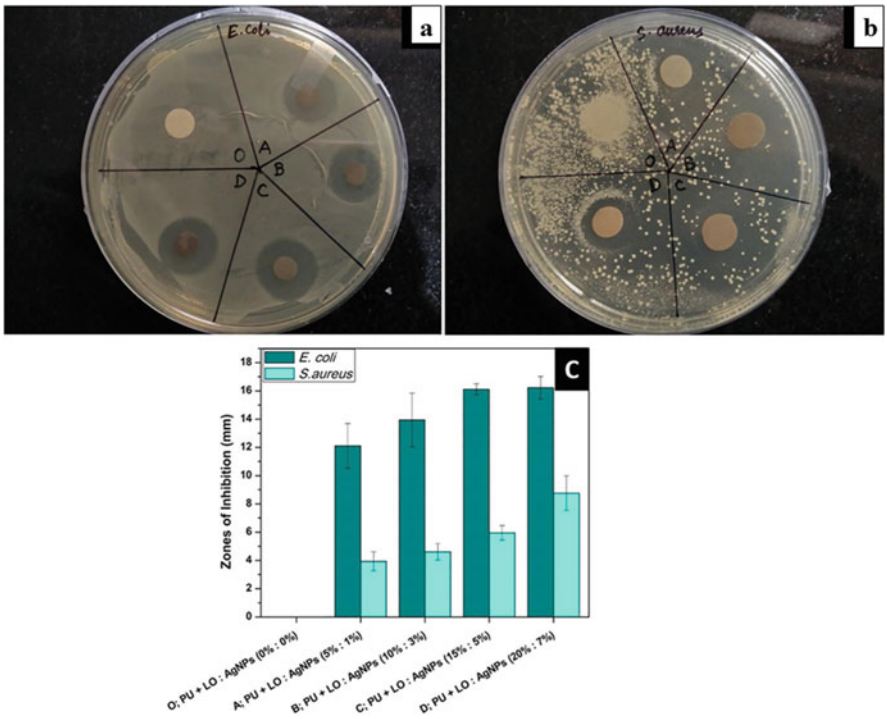

Fig. 4 Zone of inhibition of pure PU fibre and PU/lavender oil/Ag-NPs composite fibre mats against *E. coli and S. aureus*; (**a**, **b**) Photos of agar plates from antibacterial testing; (**c**) average diameter of zone of inhibition (Sofi et al. 2019)

Augustine et al. (2014) added ZnO nanoparticles of size ~60 nm in polycaprolactone (PCL) solution, in varying proportions, to electrospin PCL/ZnO nanocomposite membrane. For higher concentration of ZnO nanoparticles, fibre diameter was less than that of pure PCL fibres (2500 nm), and roughening of fibre surface was observed due to their agglomeration. The antibacterial activity assessment of these membrane revealed that membranes with less than 5 wt.% ZnO nanoparticles showed no activity against both bacteria. Notably, the bactericidal effect of ZnO nanoparticles activates only when they come in direct contact with the walls of the bacterial cells. At lower concentrations, most of the nanoparticles were trapped inside the polymer only, with very few superficial nanoparticles being able to make direct contact with bacterial cell wall.

Zhang et al. (2016) electrospun PVA/Ag-NPs composite nanofibrous membranes with varying concentration of embedded Ag-NPs (1–5%). The antibacterial activity of these nanofibres against *S. aureus* and *E. coli*, as evaluated via UV absorption method, has been depicted in Fig. 5 through the variation curves between UV–vis absorbance intensity and PVA/Ag-NPs nanofibres with different Ag-NPs content.

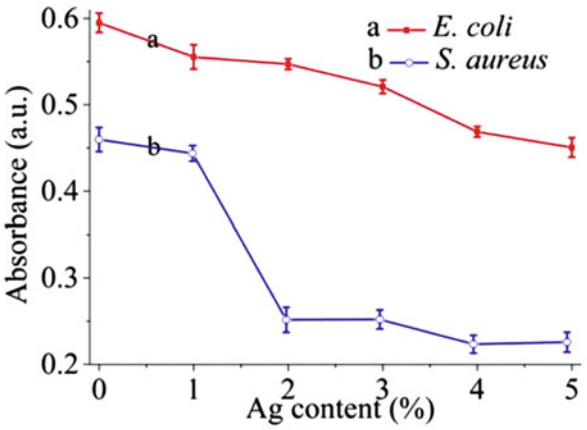

Fig. 5 Variation curves between UV–vis absorbance and PVA/Ag-NPs nanofibres with different Ag-NPs content against (**a**) *E. coli* and (**b**) and *S. aureus* (Zhang et al. 2016)

The solution of bacterial suspension without any antibacterial agent in the broth medium was observed to be very turbid after incubation, supporting high UV-vis absorption. Besides, the UV–vis absorbance of PVA/Ag-NPs nanofibres was found to decrease with increase in concentration of Ag-NPs, for both bacteria. It was also observed that antibacterial activity of these fibres was better against *S. aureus* than against *E. coli*.

Tijing et al. (2012) electrospun mats from pure PU nanofibres and composite nanofibres of PU incorporated with tourmaline nanoparticles (TM-NPs) in varying proportion. Pure PU nanofibrous mat showed no zone of inhibition, i.e. absence of any antibacterial activity, against both *E. coli* and *Streptococci* bacterial strains. On the other hand, PU/TM-NPs composite mats showed distinct inhibition zone, with increasing average diameter corresponding to increasing TM-NPs content. It is important to note here that TU-NPs decrease the membrane fluidity of *E. coli*, leading to increase in cell membrane permeability, and subsequent cell death. Moreover, TM-NPs possess piezoelectric and pyroelectric effects, which facilitate in killing Gram-positive *Streptococci* bacterium.

4 Summary

The key attributes of electrospun nanofibres, such as high surface area-to-volume ratio, tuneable mechanical and physical properties, excellent porosity make them a popular choice for various applications. The last decade has seen an increased number of publications involving electrospinning of natural and synthetic nanofibres with bactericidal property. This number is, in fact, expected to rise even further in the upcoming years to fulfil the growing need for improvement in materials for wound dressings, dressings for dermal bacterial infections, artificial skin, implants and scaffolds for tissue engineering, membranes for air/water purification, protective

masks, sportswear, food packaging material, etc. There is still a tremendous scope for quality enhancement by exploring new antibacterial materials and finding ways to make their electrospinning feasible. Besides, a lot can be done to upscale the electrospinning set-ups for mass production of nanofibrous webs, as well as to make the process cost-effective and the final products affordable.

References

Agnes Mary S, Giri Dev VR (2015) Electrospun herbal nanofibrous wound dressings for skin tissue engineering. J Text Inst 106:886–895. https://doi.org/10.1080/00405000.2014.951247

Ahmed R, Tariq M, Ali I, Asghar R, Noorunnisa Khanam P, Augustine R, Hasan A (2018) Novel electrospun chitosan/polyvinyl alcohol/zinc oxide nanofibrous mats with antibacterial and antioxidant properties for diabetic wound healing. Int J Biol Macromol 120:385–393. https://doi.org/10.1016/j.ijbiomac.2018.08.057

Al-Youssef HM, Amina M, Hassan S, Amna T, Jeong JW, Nam KT, Kim HY (2013) Herbal drug loaded poly(D,L-lactide-co-glycolide) ultrafine fibers: interaction with pathogenic bacteria. Macromol Res 21:589–598. https://doi.org/10.1007/s13233-013-1062-1

Augustine R, Malik HN, Singhal DK, Mukherjee A, Malakar D, Kalarikkal N, Thomas S (2014) Electrospun polycaprolactone/ZnO nanocomposite membranes as biomaterials with antibacterial and cell adhesion properties. J Polym Res 21:6. https://doi.org/10.1007/s10965-013-0347-6

Baker SC, Atkin N, Gunning PA, Granville N, Wilson K, Wilson D, Southgate J (2006) Characterisation of electrospun polystyrene scaffolds for three-dimensional in vitro biological studies. Biomaterials 27:3136–3146. https://doi.org/10.1016/j.biomaterials.2006.01.026

Balamurugan R, Sundarrajan S, Ramakrishna S (2011) Recent trends in nanofibrous membranes and their suitability for air and water filtrations. Membranes 1:232–248. https://doi.org/10.3390/membranes1030232

Bhardwaj N, Kundu SC (2010) Electrospinning: a fascinating fiber fabrication technique. Biotechnol Adv 28:325–347. https://doi.org/10.1016/j.biotechadv.2010.01.004

Bhattarai N, Edmondson D, Veiseh O, Matsen FA, Zhang M (2005) Electrospun chitosan-based nanofibers and their cellular compatibility. Biomaterials 26:6176–6184. https://doi.org/10.1016/j.biomaterials.2005.03.027

Bhattarai N, Li Z, Edmondson D, Zhang M (2006) Alginate-based nanofibrous scaffolds: structural, mechanical, and biological properties. Adv Mater 18:1463–1467. https://doi.org/10.1002/adma.200502537

Brown TD, Dalton PD, Hutmacher DW (2016) Melt electrospinning today: an opportune time for an emerging polymer process. Prog Polym Sci 56:116–166. https://doi.org/10.1016/j.progpolymsci.2016.01.001

Burt SA, Reinders RD (2003) Antibacterial activity of selected plant essential oils against Escherichia coli O157:H7. Lett Appl Microbiol 36:162–167. https://doi.org/10.1046/j.1472-765X.2003.01285.x

Celebioglu A, Umu OCO, Tekinay T, Uyar T (2014) Antibacterial electrospun nanofibers from triclosan/cyclodextrin inclusion complexes. Colloids Surf B Biointerfaces 116:612–619. https://doi.org/10.1016/j.colsurfb.2013.10.029

Chan WP, Huang KC, Bai MY (2017) Silk fibroin protein-based nonwoven mats incorporating baicalein Chinese herbal extract: preparation, characterizations, and in vivo evaluation. J Biomed Mater Res 105:420–430. https://doi.org/10.1002/jbm.b.33560

Charernsriwilaiwat N, Opanasopit P, Rojanarata T, Ngawhirunpat T (2012) Lysozyme-loaded, electrospun chitosan-based nanofiber mats for wound healing. Int J Pharm 427:379–384. https://doi.org/10.1016/j.ijpharm.2012.02.010

Charernsriwilaiwat N, Rojanarata T, Ngawhirunpat T, Sukma M, Opanasopit P (2013) Electrospun chitosan-based nanofiber mats loaded with Garcinia mangostana extracts. Int J Pharm 452:333–343. https://doi.org/10.1016/j.ijpharm.2013.05.012

Ditaranto N, Basoli F, Trombetta M, Cioffi N, Rainer A (2018) Electrospun nanomaterials implementing antibacterial inorganic nanophases. Appl Sci 8:91643. https://doi.org/10.3390/app8091643

El Asbahani A, Miladi K, Badri W, Sala M, Addi EHA, Casabianca H, El Mousadik A, Hartmann D, Jilale A, Renaud FNR, Elaissari A (2015) Essential oils: from extraction to encapsulation. Int J Pharm 483:220–243. https://doi.org/10.1016/j.ijpharm.2014.12.069

Gadkari RR, Ali SW, Alagirusamy R, Das A (2017a) Silver nanoparticles in water purification: opportunities and challenges. In: Modern age environmental problems and their remediation. Springer, Cham, pp 229–237. https://doi.org/10.1007/978-3-319-64501-8_13

Gadkari R, Ali W, Das A, Alagirusamy R (2017b) Scope of electrospun chitosan nanofibrous web for its potential application in water filtration. In: Chitosan. Wiley, Hoboken, pp 431–451. https://doi.org/10.1002/9781119364849.ch16

Ganesan P, Pradeepa P (2017) Development and characterization of nanofibrous mat from PVA/Tridax Procumbens (TP) leaves extracts. Wound Med 19:15–22. https://doi.org/10.1016/j.wndm.2017.09.004

Gao X, Han S, Zhang R, Liu G, Wu J (2019) Progress in electrospun composite nanofibers: Composition, performance and applications for tissue engineering. J Mater Chem B 7:7075–7089. https://doi.org/10.1039/c9tb01730e

Hammer KA, Carson CF, Riley TV (1999) Antimicrobial activity of essential oils and other plant extracts. J Appl Microbiol 86:985–990. https://doi.org/10.1046/j.1365-2672.1999.00780.x

Homayoni H, Ravandi SAH, Valizadeh M (2009) Electrospinning of chitosan nanofibers: processing optimization. Carbohydr Polym 77:656–661. https://doi.org/10.1016/j.carbpol.2009.02.008

Il Yoon Y, Park KE, Lee SJ, Park WH (2013) Fabrication of microfibrous and nano-/microfibrous scaffolds: Melt and hybrid electrospinning and surface modification of poly(L-lactic acid) with plasticizer. Biomed Res Int 2013:309048. https://doi.org/10.1155/2013/309048

Joshi M, Bhattacharyya A, Ali SW (2008) Characterization techniques for nanotechnology applications in textiles. Indian J Fibre Text Res 33:304–317

Jung KH, Huh MW, Meng W, Yuan J, Hyun SH, Bae JS, Hudson SM, Kang IK (2007) Preparation and antibacterial activity of PET/chitosan nanofibrous mats using an electrospinning technique. J Appl Polym Sci 105:2816–2823. https://doi.org/10.1002/app.25594

Jung Y, Yang H, Lee IY, Yong TS, Lee S (2020) Core/sheath-structured composite nanofibers containing cinnamon oil: Their antibacterial and antifungal properties and acaricidal effect against house dust mites. Polymers 12:1–18. https://doi.org/10.3390/polym12010243

Kang YO, Yoon I-S, Lee SY, Kim D-D, Lee SJ, Park WH, Hudson SM (2009) Chitosan-coated poly(vinyl alcohol) nanofibers for wound dressings. J Biomed Mater Res Pt B Appl Biomater 9999:31554. https://doi.org/10.1002/jbm.b.31554

Khajavi R, Rahimi MK, Abbasipour M, Brendjchi AH (2016) Antibacterial nanofibrous scaffolds with lowered cytotoxicity using keratin extracted from quail feathers. J Bioact Compat Polym 31:60–71. https://doi.org/10.1177/0883911515598793

Khalf A, Madihally SV (2017) Recent advances in multiaxial electrospinning for drug delivery. Eur J Pharm Biopharm 112:1–17. https://doi.org/10.1016/j.ejpb.2016.11.010

Khan AR, Shi Xiangyang XM (2018) Electrospinning of crude plant extracts for antibacterial and wound healing applications: a review. J Biomed Eng 4:1–8

Levitt AS, Knittel CE, Vallett R, Koerner M, Dion G, Schauer CL (2017) Investigation of nanoyarn preparation by modified electrospinning setup. J Appl Polym Sci 134:1–7. https://doi.org/10.1002/app.44813

Li R, Jiang Q, Ren X, Xie Z, Huang TS (2015) Electrospun non-leaching biocombatible antimicrobial cellulose acetate nanofibrous mats. J Ind Eng Chem 27:315–321. https://doi.org/10.1016/j.jiec.2015.01.006

Lin J, Li C, Zhao Y, Hu J, Zhang LM (2012) Co-electrospun nanofibrous membranes of collagen and zein for wound healing. ACS Appl Mater Interfaces 4:1050–1057. https://doi.org/10.1021/am201669z

Liu J, Wang C, Wang J, Ruan H, Fan C (2011) Peripheral nerve regeneration using composite poly (lactic acid-caprolactone)/nerve growth factor conduits prepared by coaxial electrospinning. J Biomed Mater Res Part A 96A:13–20. https://doi.org/10.1002/JBM.A.32946

Motealleh B, Zahedi P, Rezaeian I, Moghimi M, Abdolghaffari AH, Zarandi MA (2014) Morphology, drug release, antibacterial, cell proliferation, and histology studies of chamomile-loaded wound dressing mats based on electrospun nanofibrous poly(ε-caprolactone)/polystyrene blends. J Biomed Mater Res 102:977–987. https://doi.org/10.1002/jbm.b.33078

Nguyen TTT, Chung OH, Park JS (2011) Coaxial electrospun poly(lactic acid)/chitosan (core/shell) composite nanofibers and their antibacterial activity. Carbohydr Polym 86:1799–1806. https://doi.org/10.1016/j.carbpol.2011.07.014

Pakravan M, Heuzey MC, Ajji A (2011) A fundamental study of chitosan/PEO electrospinning. Polymer 52:4813–4824. https://doi.org/10.1016/j.polymer.2011.08.034

Panthi G, Park M, Kim HY, Park SJ (2015) Electrospun polymeric nanofibers encapsulated with nanostructured materials and their applications: a review. J Ind Eng Chem 24:1–13. https://doi.org/10.1016/j.jiec.2014.09.011

Persano L, Camposeo A, Tekmen C, Pisignano D (2013) Industrial upscaling of electrospinning and applications of polymer nanofibers: a review. Macromol Mater Eng 298:504–520. https://doi.org/10.1002/mame.201200290

Radusin T, Torres-Giner S, Stupar A, Ristic I, Miletic A, Novakovic A, Lagaron JM (2019) Preparation, characterization and antimicrobial properties of electrospun polylactide films containing Allium ursinum L. extract. Food Packag Shelf Life 21:100357. https://doi.org/10.1016/j.fpsl.2019.100357

Ramakrishna S, Fujihara K, Teo WE, Yong T, Ma Z, Ramaseshan R (2006) Electrospun nanofibers: solving global issues. Mater Today 9:40–50. https://doi.org/10.1016/S1369-7021(06)71389-X

Reneker DH, Chun I (1996) Nanometre diameter fibres of polymer, produced by electrospinning. Nanotechnology 7:216–223. https://doi.org/10.1088/0957-4484/7/3/009

Reneker DH, Yarin AL, Fong H, Koombhongse S (2000) Bending instability of electrically charged liquid jets of polymer solutions in electrospinning. J Appl Phys 87:4531–4547. https://doi.org/10.1063/1.373532

Rho KS, Jeong L, Lee G, Seo BM, Park YJ, Hong SD, Roh S, Cho JJ, Park WH, Min BM (2006) Electrospinning of collagen nanofibers: effects on the behavior of normal human keratinocytes and early-stage wound healing. Biomaterials 27:1452–1461. https://doi.org/10.1016/j.biomaterials.2005.08.004

Riboldi SA, Sampaolesi M, Neuenschwander P, Cossu G, Mantero S (2005) Electrospun degradable polyesterurethane membranes: potential scaffolds for skeletal muscle tissue engineering. Biomaterials 26:4606–4615. https://doi.org/10.1016/j.biomaterials.2004.11.035

Rieger KA, Porter M, Schiffman JD (2016) Polyelectrolyte-functionalized nanofiber mats control the collection and inactivation of Escherichia coli. Materials 9:297. https://doi.org/10.3390/ma9040297

Sahay R, Kumar PS, Sridhar R, Sundaramurthy J, Venugopal J, Mhaisalkar SG, Ramakrishna S (2012) Electrospun composite nanofibers and their multifaceted applications. J Mater Chem 22:12953–12971. https://doi.org/10.1039/c2jm30966a

Saquing CD, Manasco JL, Khan SA (2009) Electrospun nanoparticle-nanofiber composites via a one-step synthesis. Small 5:944–951. https://doi.org/10.1002/smll.200801273

Schiffman JD, Elimelech M (2011) Antibacterial activity of electrospun polymer mats with incorporated narrow diameter single-walled carbon nanotubes. ACS Appl Mater Interfaces 3:462–468. https://doi.org/10.1021/am101043y

Shi D, Wang F, Lan T, Zhang Y, Shao Z (2016) Convenient fabrication of carboxymethyl cellulose electrospun nanofibers functionalized with silver nanoparticles. Cellulose 23:1899–1909. https://doi.org/10.1007/s10570-016-0918-x

Sofi HS, Akram T, Tamboli AH, Majeed A, Shabir N, Sheikh FA (2019) Novel lavender oil and silver nanoparticles simultaneously loaded onto polyurethane nanofibers for wound-healing applications. Int J Pharm 569:118590. https://doi.org/10.1016/j.ijpharm.2019.118590

Sridhar R, Lakshminarayanan R, Madhaiyan K, Barathi VA, Limh KHC, Ramakrishna S (2015) Electrosprayed nanoparticles and electrospun nanofibers based on natural materials: Applications in tissue regeneration, drug delivery and pharmaceuticals. Chem Soc Rev 44:790–814. https://doi.org/10.1039/c4cs00226a

Stankus JJ, Guan J, Fujimoto K, Wagner WR (2006) Microintegrating smooth muscle cells into a biodegradable, elastomeric fiber matrix. Biomaterials 27:735–744. https://doi.org/10.1016/j.biomaterials.2005.06.020

Stocco TD, Rodrigues BVM, Marciano FR, Lobo AO (2017) Design of a novel electrospinning setup for the fabrication of biomimetic scaffolds for meniscus tissue engineering applications. Mater Lett 196:221–224. https://doi.org/10.1016/j.matlet.2017.03.055

Su Y, Su Q, Liu W, Jin G, Mo X, Ramakrishn S (2012) Dual-drug encapsulation and release from core-shell nanofibers. J Biomater Sci Polym Ed 23:861–871. https://doi.org/10.1163/092050611X564137

Suganya S, Senthil Ram T, Lakshmi BS, Giridev VR (2011) Herbal drug incorporated antibacterial nanofibrous mat fabricated by electrospinning: an excellent matrix for wound dressings. J Appl Polym Sci 121:2893–2899. https://doi.org/10.1002/app.33915

Sultana N, Zainal A (2016) Cellulose acetate electrospun nanofibrous membrane: fabrication, characterization, drug loading and antibacterial properties. Bull Mater Sci 39:337–343. https://doi.org/10.1007/s12034-016-1162-6

Tamura T, Kawakami H (2010) Aligned electrospun nanofiber composite membranes for fuel cell electrolytes. Nano Lett 10:1324–1328. https://doi.org/10.1021/nl1007079

Tijing LD, Ruelo MTG, Amarjargal A, Pant HR, Park CH, Kim DW, Kim CS (2012) Antibacterial and superhydrophilic electrospun polyurethane nanocomposite fibers containing tourmaline nanoparticles. Chem Eng J 197:41–48. https://doi.org/10.1016/j.cej.2012.05.005

Unalan I, Slavik B, Buettner A, Goldmann WH, Frank G, Boccaccini AR (2019) Physical and antibacterial properties of peppermint essential oil loaded poly (ε-caprolactone) (PCL) electrospun fiber mats for wound healing. Front Bioeng Biotechnol 7:1–11. https://doi.org/10.3389/fbioe.2019.00346

Wang Y, Li P, Xiang P, Lu J, Yuan J, Shen J (2016) Electrospun polyurethane/keratin/AgNP biocomposite mats for biocompatible and antibacterial wound dressings. J Mater Chem B 4:635–648. https://doi.org/10.1039/c5tb02358k

Wongkanya R, Chuysinuan P, Pengsuk C, Techasakul S, Lirdprapamongkol K, Svasti J, Nooeaid P (2017) Electrospinning of alginate/soy protein isolated nanofibers and their release characteristics for biomedical applications. J Sci Adv Mater Dev 2:309–316. https://doi.org/10.1016/j.jsamd.2017.05.010

Xue J, Xie J, Liu W, Xia Y (2017) Electrospun nanofibers: new concepts, materials, and applications. Acc Chem Res 50:1976–1987. https://doi.org/10.1021/acs.accounts.7b00218

Yang H, Gao PF, Wu WB, Yang XX, Zeng QL, Li C, Huang CZ (2014) Antibacterials loaded electrospun composite nanofibers: release profile and sustained antibacterial efficacy. Polym Chem 5:1965–1975. https://doi.org/10.1039/c3py01335a

Yao CH, Yeh JY, Chen YS, Li MH, Huang CH (2017) Wound-healing effect of electrospun gelatin nanofibres containing Centella asiatica extract in a rat model. J Tissue Eng Regen Med 11:905–915. https://doi.org/10.1002/term.1992

Yousefi I, Pakravan M, Rahimi H, Bahador A, Farshadzadeh Z, Haririan I (2017) An investigation of electrospun Henna leaves extract-loaded chitosan based nanofibrous mats for skin tissue engineering. Mater Sci Eng C 75:433–444. https://doi.org/10.1016/j.msec.2017.02.076

Yu DG, Branford-White C, White K, Chatterton NP, Zhu LM, Huang LY, Wang B (2011) A modified coaxial electrospinning for preparing fibers from a high concentration polymer solution. Express Polym Lett 5:732–741. https://doi.org/10.3144/expresspolymlett.2011.71

Zaikov GE (2016) Nanostructured fibers via electrospinning (part I). Appl Nanotechnol Mater Appl 2016:253–280. https://doi.org/10.1201/9781315366333

Zeyohanness SS, Abd Hamid H, Zulkifli FH (2018) Poly(vinyl alcohol) electrospun nanofibers containing antimicrobial Rhodomyrtus tomentosa extract. J Bioact Compat Polym 33:585–596. https://doi.org/10.1177/0883911518801040

Zhang Y, Ouyang H, Chwee TL, Ramakrishna S, Huang ZM (2005) Electrospinning of gelatin fibers and gelatin/PCL composite fibrous scaffolds. J Biomed Mater Res 72:156–165. https://doi.org/10.1002/jbm.b.30128

Zhang Z, Wu Y, Wang Z, Zou X, Zhao Y, Sun L (2016) Fabrication of silver nanoparticles embedded into polyvinyl alcohol (Ag/PVA) composite nanofibrous films through electrospinning for antibacterial and surface-enhanced Raman scattering (SERS) activities. Mater Sci Eng C 69:462–469. https://doi.org/10.1016/j.msec.2016.07.015

Zhang W, Ronca S, Mele E (2017a) Electrospun nanofibres containing antimicrobial plant extracts. Nanomaterials 7:1–17. https://doi.org/10.3390/nano7020042

Zhang W, Huang C, Kusmartseva O, Thomas NL, Mele E (2017b) Electrospinning of polylactic acid fibres containing tea tree and manuka oil. React Funct Polym 117:106–111. https://doi.org/10.1016/j.reactfunctpolym.2017.06.013

Zhou T, Sui B, Mo X, Sun J (2017) Multifunctional and biomimetic fish collagen/bioactive glass nanofibers: fabrication, antibacterial activity and inducing skin regeneration in vitro and in vivo. Int J Nanomedicine 12:3495–3507. https://doi.org/10.2147/IJN.S132459

Plant Extracts: Antimicrobial Properties, Mechanisms of Action and Applications

Tuyen C. Kha and Linh T. P. Le

Abstract It is generally agreed that bioactive compounds derived from plants play an important role in human health. Therefore, it is desirable to understand antimicrobial properties and mechanism of action of bioactive compounds from plants. This chapter presents a general overview of the plant extract sources, chemical structures, and antimicrobial properties. Particularly, understanding of the chemical structures of bioactives is of importance for more in-depth understanding of the mechanisms of the antimicrobial actions. The evaluation techniques for antimicrobial activity of the bioactive compounds, broadly classified as diffusion and dilution methods, are also presented in terms of principles, applications, affecting factors, advantages, and drawbacks. Furthermore, applications of plant bioactive compounds as antimicrobial preservatives in foods are also discussed.

Keywords Antimicrobials · Bioactive compound · Mechanism of action · Plant material

1 Introduction

Nowadays, the increasing demand for natural bioactive compounds has been the trend of healthier diets and reduced food spoilages and foodborne diseases that are a growing public health problem worldwide. Plant bioactive compounds used as natural antimicrobials are currently under investigation in many laboratories and industries. Valuable natural compound extracts from plants are widely used as drugs, functional food ingredients or nutraceuticals, especially antimicrobial activity due to consumer growing interest in health food products (Prasad et al. 2008). Accordingly, the biologically active compounds from the plant sources, their chemical structures and their antimicrobial properties are an area of importance to academia and industry.

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A large number of complex and structurally diverse bioactive compounds from plant materials exhibiting potential antimicrobial activities is of great interest. It is desirable to develop an in-depth understanding of the current mechanisms of antimicrobial actions for their applications in foods. Therefore, this chapter provides theoretical background and several practical evidences on the mechanisms of action of the bioactive compounds and the different evaluation techniques for screening and quantifying antimicrobial activity. Furthermore, some applications of plant extracts as antimicrobial preservative in foods are also presented.

2 Plant Extract Sources

Throughout the centuries, plants have been known as a source of bioactive compounds which have been used broadly as crude extracts and/or pure compounds. Found on their chemical structures, those bioactive compounds could be classified into three major categories: (a) phenolic compounds (~8000 types), (b) alkaloids (~12,000 types), and (c) terpenes and terpenoids (~25,000 types). General structures of different bioactive compound categories are given in Fig. 1. The most essential compounds from different chemical classes have been classified in Tables 1 and 2.

2.1 Alkaloid

Alkaloids are a nitrogen atom group of naturally existing chemical compounds. Major source of alkaloid is flowering plants. The important methods used for alkaloid extraction are ultrasound-assisted method, microwave assisted method, and supercritical carbon dioxide extraction methods with aqueous or acidic water, alcoholic solvent, chloroform, benzene, ether or lipophilic organic solvent, and the combination of ultrasound and surfactants for the extraction of alkaloids (Roy 2017; Shang et al. 2002; Yubin et al. 2014).

Piperine, a piperidine-type alkaloid, isolated from present in amounts of 1.7–8% in the fruit outer and in the black, white, green, and red peppers (*Piper nigrum* and *Piper longum*) seeds (Gutiérrez et al. 2013). Berberine is predominant compound of an isoquinoline alkaloid which could be extracted from roots and stem bark of *Berberis*, *Coptis,* and *Hydrastis* species, *Rhizoma coptidis*, *Cortex phellodendri* and it has been extensively applied in traditional medicine that is commercially available to consumers (Khameneh et al. 2019).

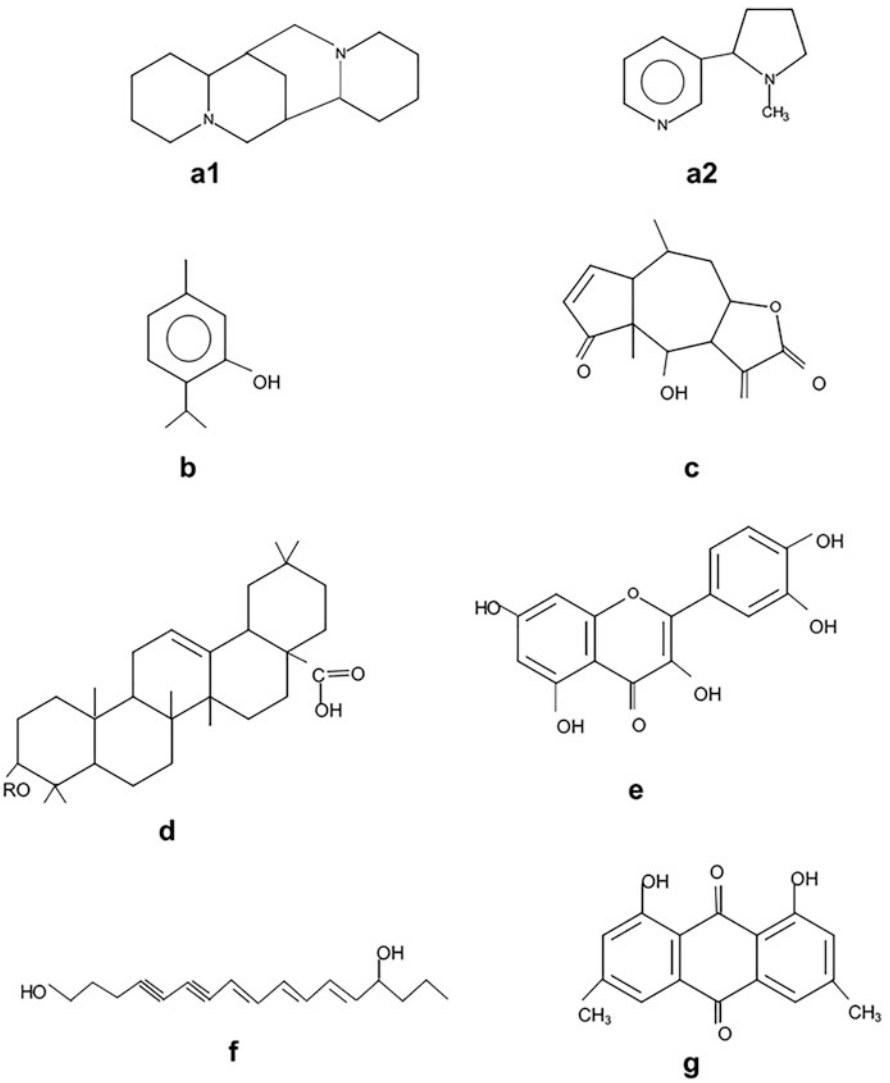

Fig. 1 General structures of different classifications of plant bioactive compounds (alkaloids (**a1**, **a2**), monoterpenes (**b**), sesquiterpenes (**c**), triterpenes, saponins, steroid (**d**), flavonoids (**e**), polyacetylenes (**f**), polyketides (**g**)) (adapted from Azmir et al. 2013)

2.2 Phenolics

Phenolics are ubiquitous compounds found in all plants as their secondary metabolites consisting flavonoids, phenolics acids, tannins, and the less ordinary lignans and stilbenes, which are available in many plant materials, such as fruits, vegetables, seeds, legumes, and cereal.

Table 1 Bioactive compounds in different plant materials and solvents used for extraction

Class	Compound	Plant products	Solvents used for active component extraction
Alkaloids	Berberine	Barberry, goldenseal, oregon grape, goldenseal	Ether
	Piperine	Black pepper	
	Others	Red beet, glory lily, papaya, periwinkle, peyote, poppy, quinine	
Phenolics	Anthocyanins	Apple, peach, berries, red, grape, red cabbage, carrot	Water Ethanol Methanol Chloroform Ether Acetone
	Anthemic acid	Chamomile	
	Apigenin	Carrot, parsley, celery	
	Caffeic acid	Thyme	
	Catechin	Green tea, apple, purple/red grapes peach, berries, apricot	
	Phenolic acids	Hops	
	Coumarins	Tonka bean, mullein, vanilla grass, caraway, chaparral, woodruff	
	Gallic acid	Blackberry, mango, cherry, purple/red grapes, henna	
	Glabrol	Licorice	
	Quercetin	Oak, apple, citrus fruits, apricot, onions, berries	
	Tannins	Cascara sagrada, eucalyptus, oak, burdock, Ceylon cinnamon, sainfoin, tarragon, thyme, willow, wintergreen	
	Thymol	Thyme	
	Salicylic acids	Cashew	
	Anthemic acid	Chamomile	
	Saponins	Ginseng	
Terpenes and terpenoids	Eugenol	All spices, betel pepper	Water Chloroform Dichloromethanol Ether
	Ajoene	Garlic, coca	
	Allicin	Garlic, onion	
	Curcumin	Turmeric	
	Essential oil	Bael tree, basil, bay, buchu, burdock, Ceylon cinnamon, chili peppers, paprika, dill, lemon verbena, rosemary, tansy, valerian	
	Terpenoids	Clove, Brazilian pepper tree, eucalyptus, gotu kola, grapefruit peel, hops, horseradish, hyssop, orange peel, pau d'arco, papaya, peppermint, savory, thyme	

(continued)

Table 1 (continued)

Class	Compound	Plant products	Solvents used for active component extraction
Others	Lignan	Banana, orange, cranberry, broccoli, peach, chaparral	–
	Steroids	Apples, banana, cruciferous Vegetables, onions, asparagus	–
	Turmeric oil	Turmeric	Chloroform Dichloromethanol Ether

Adapted from Cowan (1999), Khameneh et al. (2019)

Table 2 Common solvents for the extraction of bioactive compounds from plants

Polarity	Solvent used	Products
Apolar	Cyclohexane, hexane, toluene, benzene, ether, chloroform, ethyl acetate	Alkaloids, terpenoids, coumarins, fatty acids, flavonoids, terpenoids
Polar	Acetone, acetonitrile, butanol, propanol, ethanol, methanol	Flavanols, lectins, alkaloids, quassinoids, flavones, polyphenols, tannins, saponins

According to the oxidation state of the central C ring, flavonoids are subdivided into flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins. Some of the most common flavonoids include quercetin, catechin, and anthocyanin. Quercetin is a flavonol existing in large amount in apple, broccoli, and onion. Catechin is identified most in tea and certain kinds of fruits. Anthocyanin is found abundant in berry species as blackberry, raspberry, black currant, etc. Phenolic acids could be subdivided into two classes, for instance, cinnamic acid derivatives as coumaric; and benzoic acid derivatives as gallic acid, which is the most abundant in herbs, chaparral, woodruff, blackberry, mango, cherry, purple/red grapes, and henna. Another main polyphenol group in plant is tannins. This component is usually classified into two groups as hydrolysable tannins and condensed tannins found in medical plants and vegetables.

Plant samples in fresh, dried or frozen forms can be utilized to extract phenolic compounds. The solubility of these compounds is affected by the chemical nature of the plant sample, as well as the polarity of the solvents used. Ethanol, methanol, acetone, ethyl acetate, or their combinations with/without different proportions of water have been used as solvent for phenolic extraction from materials. Particularly, low molecular weight polyphenols have been typically obtained more methodically throughout methanol extraction while aqueous acetone was given better extraction of the higher molecular weight flavanols. Additionally, ethanol has been explained as a better choice of good solvent for polyphenol extraction that is safe for human consumption. Most of studies were began with maceration and Soxhlet extraction, however, it has revealed low efficiency. As results, numerous methods following trendy “green extraction methods” have been developed to replace conventional treatments as microwave, ultrasound-assisted extractions, accelerated solvent

extraction (ASE), pressurized fluid extraction (PFE), supercritical fluid extraction (SFE), or subcritical water extraction (SWE). In addition to extraction solvents, enzyme-assisted extraction involves pectinase, cellulase, and hemicellulase enzymes which hydrolyzed the linkage of the cell walls and decrease phenols extraction to support the extraction of polyphenolic compounds from a plant material (Dai and Mumper 2010; Stagos 2020). Techniques for extraction and isolation of bioactive compounds from plant materials have been thoroughly reviewed by Kha and Nguyen (2015).

2.3 Terpenes and Terpenoids

Terpenes comprise a large group of distinct natural metabolites, many of which were discovered in plants and have been utilized widely in foods, cosmetics, pharmaceuticals, and in various biotechnological applications. In plants, minority of terpenes and terpenoids (oxygenated forms of terpenes) are consisted in primary metabolism. Majority of structurally terpene derivatives have been typified as secondary metabolites in plants. Terpenes and terpenoids were obtained considerable amounts in extracts of the plant material parts as seeds, flowers, fruits, leaves, and roots. Particularly, terpenes contribute less than terpenoids to the flavor and aroma of the oil (Azmir et al. 2013; Caputi and Aprea 2011; Zwenger and Basu 2008).

Physical procedure for separation of natural terpenes and terpenoids involved distillation or solvent extraction. Polar solvents such as cyclohexane, hexane, toluene, benzene, ether, chloroform, ethyl acetate have been studied to propose as suitable solvent for terpenes and terpenoids extraction. For instance, the ratio of hexane: ethyl acetate could be modified depending on the polarity of the terpene sought. Usually a higher proportion of hexane would draw out more non-polar terpenes, whereas higher ratio of ethyl acetate extracted more polar terpenes (Jiang et al. 2016). Diversely, in the area of extraction techniques, compared to Soxhlet extraction and ultrasonically assisted extraction, terpenoids extraction by accelerated solvent extraction (ASE) had given a consideration booster process and less solvent usage (Shen and Shao 2005).

3 Antimicrobial Properties of Plant Extract

Even though synthetic antimicrobial substances have been now accepted for the food industry in numerous nations, yet the utilization of natural compounds that are derivative from plants are in purposes of numerous investigations. These compounds have been shown auspicious results in solving the difficulty of antibiotic resistance in microbial pathogens as well as demonstrating the beneficial advantages in terms of antimicrobial activities as antibacteria, antifungi, and anti-virus. For instance, some of the plants and/or plant components which containing antimicrobial abilities are illustrated in Table 3. According to their chemical structures, bioactive

Table 3 Selected antimicrobial activity of plant extracts

Plant sources	Extraction methods	Active against	Antimicrobial activity
15 Mediterranean medicinal plants	Ethanol: water (80: 20)	Antibacteria	Lowest MIC values (mg/mL): 0.35–1.67
Achyranthes aspera, *Cynodon dactylon*, *Lantana camara,* and *Tagetes patula*	Ethanol	Antibacteria	MIC (mg/mL): 25–125
Apple peel	Ethanol	Antibacteria	Inhibition concentration: 2–20 μg/disk Inhibition haloes: 6–14 mm
Apple phenolic fractions	Acetone: ethanol (1: 3), solid phase extraction	Antibacteria	Inhibition concentration: 10–5000 μg/disk Inhibition haloes (mm): 3.7–17.6
Apple pomace	Ethyl acetate	Antibacteria	MIC (mg/mL): 1.25–2.50
Bayberry	Ethanol	Antibacteria	Inhibition haloes (mm): 13.3–22.9
Black grape pomace, apple and pitahaya residues	10% ethanol after enzyme-aided extraction	Antibacteria	MICs: from 12.5 to $\geq$ 100 mg/mL
Blackberry and blueberry pomaces	10% methanol, 10% ethanol	Antibacteria	MIC (mg/mL GAE): 0.4–0.6 MBC (mg/mL GAE): 0.5–0.8
Blueberry puree	75% ethanol	Antibacteria	MIC (mg/mL): 300–1200
Cinnamomum zeylanicum	Hydrodistillation	Antifungal and anti-mycotoxigenic activity	
Cinnamon bark and Ajowan fruit	Acetone, ethanol	Antibacteria	MIC (μg/mL): Ethanol extract 32–64 MIC (μg/mL): Acetone extracts 16–128
Citrus aurantifolia/ limon/sinensis/latifolia	Hydrodistillation steam distillation	Antifungi	
Eucalyptus citriodora/ gillii	Hydrodistillation	Antimicrobial properties	
Ginger rhizomes	Aqueous, ethanol, n-hexane	Antibacteria	Inhibition concentration: 10 μg/mL Inhibition haloes (mm): 0.8–18.3
Grape marc waste	Aqueous extraction and Amberlite FPX-66 purification	Antibacteria	MBC (%, w/v): 0.125–2

(continued)

Table 3 (continued)

Plant sources	Extraction methods	Active against	Antimicrobial activity
Grape pomace	50% methanol, 50% ethanol	Antiyeast	Inhibition concentration: 1 mg/disk Inhibition haloes (mm):12–13
Grape residues	Ultrasound-assisted extraction, methanol: acetone: water: acetic acid (30:42:27.5:0.5)	Antibacteria Antifungi Antiyeast	Inhibition concentration: 30 μg/disk Inhibition haloes (mm): 12.1–19.7
Marsilea minuta leaf	Methanol Hexane: methanol	Antibacteria	MICs: from 125 to 250 μg/mL
Mentha viridis leaves *Mentha spicata* leaves *Mentha villosa* leaves	Hydrodistillation	Antibacteria Antiyeast Antifungi	MIC (μL/mL): 3.75–15
Murraya koenigii leaves	Ethyl acetate extraction	Antibacteria	MIC (μL/mL): 31.25
Pelargonium sidoides DC.	Methanol (85%), acetone (80%)	Antibacteria Antiyeast	Inhibition haloes (mm): 8–36
Piper sarmentosum	Methanolic extraction	Antibacteria	MIC (mg/mL): 7.5 mg/mL
Punica granatum L. var. *pleniflora* flowers	Ethanol	Antibacteria	Inhibition concentration: 50 mg/well Inhibition haloes (mm): 22–32
Red and white grape pomaces	Acetone	Antibacteria	MBC (mg/mL): 9.38 to >250
Red wine grape pomace	70% acetone/0.1% HCl/29.9% water (v/v/v)	Antibacteria	Merlot-pomace and skin MIC: 8–9%
Roselle, rosemary, clove and thyme	Aqueous and ethanol	Antibacteria Antiyeast	MICs: from 0.313 to 20% (w/v)
Ruta chalepensis	Methanol	Antibacteria	Inhibition concentration: 10 mg/disk Inhibition haloes (mm): 7.7–17.7
Syzygium polyanthum L. leaves	Ethanol	Antibacteria	MICs (mg/mL): 0.63–1.25 MBCs (mg/mL): 0.63–2.5 mg/mL
Ziziphus and *eucalyptus* leaves	Aqueous and ethanol	Antibacteria	Inhibition concentration: 50–100 mg/mL Inhibition haloes (mm): 9–18

components could be classified into considerable major groups including alkaloids, sulfur-containing compounds, terpenoids, and polyphenols. Among those, the most important phytocompounds from different chemical groups are detailed in Table 4.

3.1 Antibacterial Properties

The antibacterial ability of the plant extract was known for many years and is well-documented (Table 3). Bioactive compounds in plants have been generally extracted by hydroethanolic or combination of other methods to increase the efficiency. Most of the plant extracts were reported the bacterially inhibitory activity more than bactericidal properties. *Mentha viridis* essential oil obtained using hydrodistillation showed the antibacterial activity with important bactericidal action against *Staphylococcus aureus* and *Listeria monocytogenes* (MIC = MBC = 0.25%) (Bouyahya et al. 2020). With same target Gram-positive bacteria, acetone extract from red and white grapes gave a value of MBC at 9.38 mg/mL against *L. monocytogenes* and *S. aureus*, but not against *E. coli* O157:H7 and *S. typhimurium*. Among those, *L. monocytogenes* was more impressionable than *S. aureus* (Xu et al. 2016). It has been achieved by numerous researches that the weaker antibacterial activity against the Gram-negative bacteria compared to Gram-positive ones was explained by the presence of hydrophilic polysaccharides chains at outer membrane which played a role of a rigid barrier for hydrophobic essential oils. On the other hand, the mixture of different solvents reinforced bioactive compound extraction better than single solvent usage. Blackberry extracted by mixture of solvents: water, 10% (v/v) ethanol, and 10% (v/v) methanol significantly compressed the growth of *C. jejuni* with MBC value at 0.8 mg/mL GAE (Salaheen et al. 2014). The extract by ethyl acetate from *Murraya koenigii* leaves (Indian curry leaves) gave the lowest MIC value at 15.63 μg/mL against *S. aureus*, *E. coli* 0157:H7, *V. alginolyticus*, *V. parahaemolyticus,* and *Y. enterocolitica*. In a group of the tested compounds, myricetin and quercetin revealed the best activities against *Y. enterocolitica* (ATCC 23715) with a least MIC value of 31.25 μg/mL (Abuga et al. 2020). In different circumstances, it was possible to enhance the antimicrobial activity of plant extracts by different extraction systems. The solvent combination of methanol, acetone, water, and acetic acid in system of ultrasound-assisted extraction provided extract against strongly both Gram-negative and Gram-positive illustrated the halo inhibition diameter of 12.1–19.7 mm (Radovanović et al. 2019). The extract from grape marc waste was treated by aqueous extraction and Amberlite FPX-66 purification to capture, recovery, and purification of bioactive molecules. As a result, the extract gave a bactericidal activity at MBC 0.125–2%, w/v against both *E. coli* and *S. aureus* (Olejar et al. 2019).

Several reports examined the antibacterial activities of a small number of secondary metabolites usually present in plant-food products, such as tannins, terpenoids, alkaloids, and phenolics, etc. (Table 3). Phenolic compounds, which are especially rich plant flavonoid extracts, had antibacterial activity against a scope of

Table 4 Antimicrobial activity of bioactive compounds, some examples

Class of naturally compound	Compounds	Antimicrobial activity (MIC/MBC)	Active against	References
Alkaloids	Reserpine	100 mg/L	*Staphylococcus* sp., *Streptococcus* sp., *Micrococcus* sp.	Sridevi et al. (2017)
	Piperine	100 μg/mL	*Staphylococcus aureus* (MRSA) *Staphylococcus aureus*	
	Berberine	4 mM	*Escherichia coli* *Candida albicans*	Khameneh et al. (2015)
	Solasodine	32 μg/mL	*Candida albicans*	
	Conessine	20 mg/L	*Pseudomonas aeruginosa*	Boberek et al. (2010)
Organosulfur	Allicin	–	*Staphylococcus epidermidis*, *P. aeruginosa*, *Streptococcus agalactiae*	Zorić et al. (2017)
	Ajoene	5–160 μg/mL	*Aspergillus flavus*, *Aspergillus niger*, *Cryptococcus neoformans*, *Alternaria alternata*, *Streproproteus*, *Staphylococcus* sp., *E. coli*	
	Isothiocyanates	2–32 μg/mL	*Helicobacter pylori*	Chang et al. (2017)
		0.016–0.256 mg/mL	*Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Salmonella typhimurium*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli.*	
Phenolic compounds	Gallic acid Catechin Curcumin	2.5–15 mg/100 μL 43.2–49.8 μg/mL	*Escherichia coli* *Herpes Simplex* Virus type 1 (HSV-1)	Siriyong et al. (2017)
	Flavonoids	0.5–39.2 μg/mL	*P. vulgaris*, *P. mirabilis*, Methicillin-resistant *Staphylococcus aureus*, Methicillin-sensitive *S. aureus*, *Enterococcus spp.*, *P. aeruginosa*, *K. pneumonia*, *S. aureus*, *S. typhi*, *S. pyogenes*, *B. cereus*, *L. monocytogenes*, *S. aureus*, *S. epidermidis*, *M. tuberculosis*, *C. freundii*,	

(continued)

Table 4 (continued)

Class of naturally compound	Compounds	Antimicrobial activity (MIC/MBC)	Active against	References
			S. dysenteriae, *S. faecalis*, *E. aerogenes*, *E. cloacae*, *E. faecalis*, *E. faecium*	
	Phenolic acids	1000 μg/mL	*E. coli*, *P. aeruginosa*, *L. monocytogenes*, *S. aureus*, *L. monocytogenes*, *Lactobacillus* spp., *P. aeruginosa*, *C. albicans. S. epidermidis*, *Corynebacterium xerosis*, *Micrococcus luteus*	Reiter et al. (2017)
	Tannins	–	*S. aureus*, *MRSA*, *MRSA*, *S. epidermidis*, *S. flexneri*, *Bacillus pumilus*, *B. subtilis*, *B. cereus*, *Aeromonas hydrophila*, *Proteus mirabilis*, *E. faecalis*, *S. pyogen*, *E. coli*, *Neisseria gonorrhoeae*, *S. typhi*, *K. pneumonia*, *V. cholera*, *Pseudomonas* spp., *Enterobacter* sp., *Cryptococcus neoformans*, *Candida albican*, *Candida tropicalis*, *Trichoderma viride*, *A. niger*, *A. fumigatus*, *A. flavus*, *Penicillium verrucosum*, *Aureobasidium pullulans*, *Mucor* spp.	
	Stilbenes and lignans	1–128 μg/mL	*Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *S. aureus*, *S. aureus* (*MRSA*) *Shigella dysenteriae*, *E. coli*, *Salmonella typhi*, *Bacillus cereus*, *Bacillus subtilis*, *Cryptococcus neoformans*, *Enterococcus faecalis*, *Candida albicans*, *Blastoschizomyces*, *Aspergillus fumigatus*, *Aspergillus flavus*, Influenza virus, H1N1 and H9N2	Nakamoto et al. (2020)
Coumarin		0.625–1024 μg/mL	*Salmonella enterica* serovar Typhi, *Salmonella infantis*, *Salmonella Typhimurium*, *Enterobacter aerogenes*, *Escherichia coli*, *Enterobacter cloacae* *S. aureus*, *MSSA*, *H. pylori*,	

(continued)

Table 4 (continued)

Class of naturally compound	Compounds	Antimicrobial activity (MIC/MBC)	Active against	References
			B. subtilis, *K. pneumonia*, *Botrytis cinerea*	
Terpene	Thymol Carvacrol Eugenol	1–900 mg/mL	*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Yersinia enterocolitica*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus* sp., *Micrococcus* sp., *Bacillus* sp., *Enterobacter* sp., *Enterococcus faecalis*, *Cladosporium* spp., *Aspergillus* spp, *Fusarium oxysporum*, *Botrytis cinerea*, *Penicillium* spp., *Alternaria alternate*, *Rhizopus oryzae*	Lawal et al. (2012)

pathogenic microorganisms. It demonstrated that both Gram-positive and Gram-negative were against by gallic acid, catechin, curcumin, flavonoids, phenolic acids, tannins, stilbenes, and lignans with the MIC values ranged from 0.5 to 1000 μg/mL (Díaz-Gómez et al. 2014; El-Toumy et al. 2018; Górniak et al. 2019; Guil-Guerrero et al. 2016; Mulat et al. 2020; Tsopmo et al. 2013). Compared to other researchers, Górniak et al. (2019) have revealed that flavonoids had better antibacterial activities with low minimum inhibition concentration at the range of 0.5–39.2 μg/mL as well as against a wide range of bacteria, even against methicillin-resistant *S. aureus*. Ajani and Nwinyi (2010) reported synthesis of substituted coumarins showed good activity against *S. aureus*, *E. coli,* and *B. subtilis*. Following the research, Takó et al. (2020) and Khameneh et al. (2019) extracted coumarin from plant and came out with the MIC value lowering down at the range of 0.625–1024 μg/mL against to *Salmonella* spp., *Enterobacter* spp., *Staphylococcus* spp., *Bacillus* spp., and *Klebsiella*. Especially, few natural products have testified antimicrobial activity against *H. pylori*, which is classified as a microaerophilic bacterium specifically colonizing the gastric mucosa and affecting more than half of the world's community. There were 21 extracts from different natural products by hydroalcoholic extract demonstrating the anti-*H. pylori* activity in both in vitro and in vivo studies (Bonifácio et al. 2014).

Furthermore, over the most recent couple of decades, there have been expanded findings of the specific antimicrobial impacts of these EOs. A few ongoing studies have concentrated on late reports of the foodborne pathogenic bacteria against by spices and herbs or essential oil. Main compound group in extracted essential oil have been known as terpene involving thymol, carvacrol, and eugenol. Both

pathogenic and spoilage bacteria being *E. coli*, *P. aeruginosa*, *S. typhimurium*, *Y. enterocolitica*, *E. faecalis*, *L. monocytogenes*, *Staphylococcus* sp., *Micrococcus* sp., *Bacillus* sp., *Enterobacter* sp., *E. faecalis* were inhibited by terpene at moderate MIC from 1 to 900 mg/mL (Abbaszadeh et al. 2014; Metsämuuronen and Siren 2014).

3.2 Antifungal Properties

Various essential oils (EO) which are secondary metabolites highly enriched in compounds as terpenes have been applied for antifungal effects (Tables 4, 5, and 6). Numerous studies have been reported in this field during recently. *Aspergillus* and *Fusarium* are the fungal genera most commonly tested with EOs and plant extracts, followed by *Penicillium* and other phytopathogenic species. *Mentha viridis* essential oil obtained using hydrodistillation method presented remarkably the antifungal activity with important inhibitions of *T. mentagrophytes*, *T. tonsurans,* and *T. violaceum* (Bouyahya et al. 2020). In addition, steam-distilled essential oils from different types of *Mentha spicata* (spearmint) and *Mentha villosa* (crawling mint) could dormant the possibly decay yeasts *C. albicans*, *C. tropicalis*, *P. anomala*, and *S. cerevisiae* in pineapple, cashew, guava, and mango juice kept under refrigeration. The individual usage of extracted oils at different concentrations resulted in more than 5-log decrease in total colony counts of four tested yeasts in Sabouraud dextrose broth likewise in food samples (da Cruz Almeida et al. 2018). In the same field, Zorić et al. (2017) proved that the MICs of eugenol and thymol in a range of 100–500 mg/mL for different fungal isolates as *Cladosporium* spp., *Aspergillus* spp., *Fusarium oxysporum*, *Botrytis cinerea*, *Penicillium* spp., *Alternaria alternata,* and *Rhizopus oryzae*. The increased concentrations of eugenol and thymol led to stronger inhibition of fungal development. In a while, at higher concentrations, the carvacrol compound had significantly fungicidal activity. A higher antifungal activity due to an increase in concentration of bioactive compounds was figured out from *Moringa oleifera* (drumstick tree) leave and seed extracts. Those extracts revealed the presence of various bioactive compounds being glycosides, flavonoids, alkaloids, tannins, saponins, phenols, and hydrolysable tannins. Methanol leave extract at concentration of 100 mg/mL gave wider inhibition zones for the *Aspergillus* species, for instance 18.33-mm zone against *A. flavus* and 17.17 mm-zone against *A. niger*, than that of the seed extract (16.50-mm zone against *A. flavus* and 16.33-mm zone against *A. niger*) (Ayirezang et al. 2020). In addition to zone of growth inhibition, plant extracts also control the production of mycotoxin from fungi. Turmeric, *Curcuma longa L.*, had either antimicrobial, antioxidant or antifungal properties. Ferreira et al. (2013) reported the anti-aflatoxigenic activities of the essential oil of *C. longa and curcumin*. All doses of the essential oil that inhibited the aflatoxin production had a greater than 96% inhibitory effect with the levels of aflatoxin B1 (AFB1) production at 1.0 μg/mL. Furthermore, the 70% ethanol *Equisetum arvense* extract and a mixture 1:1 of *Equisetum arvense–Stevia*

Table 5 Recent studies on antibiofilm activity of plant extracts against food pathogen microorganisms, from 2017 to 2020

Source/residue	Solvent of extraction	Target biofilm	Percent biofilm inhibition
Black cardamom	80% ethanol	*S. aureus*, *S. Typhimurium*, *P. aeruginosa*	45.2–51.9%
Propolis and bud poplar resins	85% ethanol	*P. aeruginosa*	50–60%
Butia odorata	Acetone	*S. aureus*	99.9%
Onion	Methanol	*P. aeruginosa*, *S. aureus*	27.3–61.5%
Olive leaves	Methanol	*P. aeruginosa*, Methicillin-resistant *S. aureus* (MRSA), *S. aureus*, *B. subtilis*, *E. coli*, *E. faecalis*, *C. albicans*	29.3–98%
Populus nigra and *Populus alba* bud	Methanol	MRSA, *S. aureus*	>70% for *P. nigra*, >50% for *P. alba*
Opuntia ficus-indica cladodes	80% methanol	*S. aureus*	71–85%
Eugenia and *Syzygium* leaf	Acetone	*P. aeruginosa*, *S.* Typhimurium, *S. aureus*, *E. faecalis*, *E. coli*, *B. cereus*	>50% for several samples
Potentilla visianii	Methanol, ethyl acetate	*S. enterica*, *E. coli*, *S. aureus*, *B. subtilis*	>50%
Gentiana asclepiadea	Water, ethanol, acetone	*S. aureus*, *P. aeruginosa*, *P. mirabilis*	>50%

Takó et al. (2020)

rebaudiana might be effective for the inhibition of both growth of *A. flavus* and aflatoxin production.

3.3 Antiviral Properties

The extract from different parts of burdock, caraway, cascara sagrada, chamomile, eucalyptus, green tea, hemp, hops, hyssop, tarragon, lemon palm, woodruff, thyme, and yarrow have been studied recently to prove the antiviral activity (Cowan 1999). For instance, the chloroformic plant extracts from *Moringa oleifera* showed potent antiviral activity ($p < 0.05$), while *Azadirachta indica* extract showed significant antiviral activity in the range of 1–50 μg/mL and 12–100 μg/mL, respectively, against foot and mouth disease virus (Younus et al. 2016). The dichloromethane: methanol (1:1) extract of *Baccharis gaudichaudiana* and *Baccharis spicata* were active against poliovirus type 2 and vesicular stomatitis virus (Jaime et al. 2013). The crude methanolic extract and its organic solvent fractions of *Aloe sinana* root and

Table 6 Antibiofilm activities of the bioactive compounds found in plant

Phenolic compound	Name of bacteria	Antibiofilm activity
Anthocyanins	*K. pneumoniae*	Inhibited biofilm formation Inhibited EPS production
Coumarins	*E. coli* *S. aureus* *V. anguillarum* *E. tarda* *P. aeruginosa*	Inhibited biofilm formation Reductions in biofilm formation
Flavonoids	*S. mutans* *S. aureus* *E. coli* *V. Harvey* *S. mutans* *E. coli (UPEC)*	Sortase-specific oral biofilm inhibition Inhibited biofilm formation Inhibited motility In vitro and in vivo antibiofilm efficacy Reduced pathogenic biofilm
Tannins	*P. aeruginosa* *E. coli* *S. mutans* *S. epidermidis* *P. gingivalis*	Inhibited biofilm formation Inactivated bacteria

Slobodníková et al. (2016)

leaf latex were tested in vitro for antiviral activity against influenza A and B viruses, Picornavirus including Rhinovirus, Coxsackievirus, Enterovirus, and Denguevirus. Methanol, n-hexane, and ethyl acetate extracts of root and chloroform extract of leaf latex significantly inhibited influenza A and B viruses. n-butanol extract of root exhibited a strong activity against Enterovirus. All of extracts from root and leaf latex significantly inhibited DENV-2 production at higher concentrations (Jaime et al. 2013).

Various natural compounds including herbal products and plant extracts have been researched their antiviral activities against several viruses. Antiviral activity of coumarin (which is available in Tonka bean, mullein, vanilla grass, caraway, chaparral, woodruff) and its derivatives has been observed against a wide range of viruses such as influenza viruses, HIV, Enterovirus 71 (EV71), coxsackievirus A16 (CVA16), dengue virus, and chikungunya virus (Mishra et al. 2020). Lignans and their derivatives possess their antiviral properties that have been reported recently. The antiviral extract containing lignans was used to treat Hepatitis B and C virus, Dengue virus, West Nile virus, Influenza A viruses, Herpes simplex virus, Human Papilloma virus, Human immunodeficiency virus type 1, Human cytomegalovirus, and SARS-Corona virus (Cui et al. 2020). Flavonoids from plants have been investigated as potential antiviral substances against RNA and DNA viruses which were active against non-picornaviruses and picornaviruses (Lalani and Poh 2020).

3.4 Antibiofilm Properties

Certain foodborne pathogens could suffer under unfavorable environmental factors, for example, cool, heat, acidic, and high salt conditions, and have the ability to produce biofilms on biotic or abiotic surfaces. Biofilms comprise microbial companies stuck on surfaces and embedded in a slimy of extracellular matrix composed of extracellular polymeric substances (EPS) conglomerating extracellular polysaccharides, lipids, proteins, and nucleic acids.

In current ages, investigations on the antibiofilm activity of essential oils have been intensified. Bazargani and Rohloff (2016) had summarized that the antibiofilm activity of essential oils has been described against *S. aureus* by *Nigella sativa* L. seed oil, lemongrass oil, oregano oil, carvacrol and thymol, oregano oil, red thyme essential oils, tea tree oil, and melissa oil. Potential antibiofilm effect against *E. coli* has been shown for tea tree, lavender, melissa oil, cinnamon oil, and cinnamaldehyde, eugenol, and carvacrol. Compared to the previous findings, Bazargani and Rohloff (2016) proved that hydrodistillation of essential oil of coriander extracts showed in vitro stronger antibiofilm activity through inhibition of bacteria cell attachment of *E. coli* and *S. aureus* with inhibitory concentration at 0.8 and 1.6 μL/mL, respectively. In further study, 3-day ethanol leaf of *Piper betle L.* extract showed the active against Gram-negative bacteria than Gram-positive bacteria with bactericidal concentration 2.08–8.33 mg/mL, respectively, in both planktonic and biofilm form. *P. betle* extract acts as a potent antibiofilm agent with dual actions, preventing and eradicating the biofilm (Teanpaisan et al. 2017). Considerations of solvents of extraction, acetone gave the *Butia odorata* extract achieved 99.9% of *S. aureus* biofilm inhibition while other ethanol and methanol extracts just inhibited greater 50% biofilm formation from *P. aeruginosa*, *Methicillin-resistant S. aureus* (MRSA), *S. aureus*, *B. subtilis*, *E. coli*, *E. faecalis*, *C. albicans* due to the properties of solvents and bioactive compounds in plant extracts.

4 Mechanism of Action

It is noteworthy that plant extracts contain different types of bioactive compounds with antimicrobial activity for the utilization in food preservation (refer to Sects. 2 and 3). Different bioactives have different mechanisms of antimicrobial action due to their structure, their concentration, the feature of targeted microorganisms and processing conditions. In order to select the best extracts from different plant sources for food applications, understanding mechanisms of action of several bioactive compounds is highly desirable.

It is generally agreed that antimicrobial activity could be linked to more than two mechanisms of action. This is because the natural food extracts or products are complex mixtures of several or numerous bioactive compounds which have different chemical composition, resulting in different modes of action. As a result, it is

desirable to use at least two methods for evaluating antimicrobial activity (refer to Sect. 5). Furthermore, growing condition, harvest time, pre-treatment and extraction method may also contribute to mechanism of action for antimicrobial activity due to chemical composition, chemical structure, and amount of specific compounds. In order to clarify possible mechanisms of antimicrobial action of different bioactives, it is desirable to comprehend characteristics of target microbial cells (bacteria, yeast or mold cell, Gram-positive and Gram-negative bacteria) and structure of bioactives (particularly active groups), and to control environment conditions, where antimicrobial action can be affected, including temperature, pH, water activity, and redox potential. It is also recommended that antibiotics should be applied to inhibit unexpected microbial infections.

For chemical composition of bioactive compounds, it is well-known that molecular structure of the compounds is strongly related to antimicrobial activity. It is interesting that both hydrophobic and hydrophilic characteristics of functional groups in hydrocarbon skeleton play important role in the antimicrobial activity. The ascending order of the antimicrobial activities related to several functional groups was reported to be hydrocarbons, ethers, alcohols, ketones, aldehydes, and phenols. The highest antimicrobial action of phenols could be explained by the fact that the hydroxyl functional group connects to an enzyme active center by a hydrogen bond (Kalemba and Kunicka 2003), resulting inactivating enzyme activity.

The presence of several specific functional groups plays important role in preventing or slowing the growth of microbials. Kuete (2010) illustrated that the compounds acquired such as angusticornin B and bartericin A by hydroxylation of the prenyl groups of stipulin resulted in an excellent antimicrobial action including Gram-positive and Gram-negative bacteria as well as yeast. Similarly, the antimicrobial action of limonene and *p*-cymene and other components including thymol and carvacrol were found to be contributed by the alkyl group and hydroxyl groups, respectively (Nazzaro et al. 2013). In addition, the aldehyde group in various plant materials has been proven to have antimicrobial activity against numerous bacterial strains. Many studies confirmed that that aldehyde groups exhibited extraordinary antimicrobial activity as they can react and form with DNA and protein by covalent bonds. This reaction is due to the functional nature of aldehyde group, consisting of the carbon double bonded to oxygen. Consequently, the normal functions of DNA and proteins are probably limited or inhibited (Fitzgerald et al. 2005). In this view, it is desirable to investigate the structure of bioactives to fully understand mechanisms of antimicrobial action. This step is basically important to facilitate the use of bioactive compounds from plants as natural food preservatives. More information on chemical structures of bioactives in plant materials is presented in Sect. 2.

Since there are many factors affecting antimicrobial mechanism of bioactives, understanding of the features of microorganisms is highly recommended in order to apply appropriate bioactive compounds for antimicrobial purposes in foods. For the cell structure, the cell wall of Gram-positive bacteria is smooth and single-layered, composing of multiple layers of peptidoglycan linked to other molecules such as teichoic acid and proteins. Whereas the cell wall of Gram-negative bacteria is a wavy

and double-layered, consisting of an outer membrane (composed of lipoproteins, phospholipids, and lipopolysaccharides) and several layers of peptidoglycan (lacks of teichoic acid). The peptidoglycan stays interact to lipoproteins of the outer membrane that is positioned in the fluid-like periplasm between the plasma membrane and the outer membrane. The periplasm, comprised of proteins (porins) and degrading enzymes, supports to deliver molecules such as nutrient, water, and iron. Exotoxins are generated by both Gram-positive and Gram-negative bacteria, whereas endotoxins are produced by only Gram-negative bacteria.

Due to thicker outer layers of peptidoglycan, lipophilic molecules easily go through the cell walls of Gram-positive bacteria and react with either the cell or the cytoplasm. As a result, Gram-positive bacteria are more susceptible to antibacterial agents including natural extracts rich in bioactives than Gram-negative bacteria. In general, the essential oil extract containing phenolics shows more effective in antimicrobial action against Gram-positive bacteria (Nazzaro et al. 2013). However, Gram-negative shows more resistant to hydrophobic molecules due to natural structure of their cell wall that peptidoglycan is covered by an outer membrane functioned as hydrophilic transmembrane channels.

Yeast and molds, both known as Eukaryotic microorganisms, are types of fungi. Yeast is a single cell organism, which is usually a thread and filamentous in shape, whereas molds are multicellular, appearing round or oval shape. The cell walls of yeast and molds are mainly composed of chitin (acetylglucosamine polymers), glucans, polysaccharides, and mucopolysaccharides, waxes, and pigments. Therefore, it is important to better understand the cell wall structure of target yeast and molds in order to apply appropriate antifungal agent throughout understanding mechanisms of action. Similar to Gram-positive bacteria, the action of bioactive compounds destroys fungal cell wall and cytoplasmic membrane, resulting in disintegration of the cytoplasm and its coagulation (Kalemba and Kunicka 2003).

There are many reports on mechanisms of action for plant extracts' antimicrobial activity, some of which overlap. Diverse mechanisms of action for the antimicrobial activity of plant bioactives include mainly cell wall damage, cytoplasm coagulation, hydrolysis of ATP, rate of cell permeability, modification of proton motive force, and membrane protein destruction. Generally, the cell envelop protects the cell protoplast from physical, chemical, and mechanical damages in microorganisms' surviving environment. It is well-known that the structure, integrity, permeability or functionality of the cell wall and the outer membrane arrangement can be influenced by the functional groups of the bioactive compounds. The effect of the bioactive compounds is predicted to occur in more than one way, and a consequence of other activities. Both hydrophobic and hydrophilic groups presented in the bioactive compounds can affect the cell wall, mainly react on lipid and protein of the cell membrane, inhibiting cell division in microorganisms. The cell wall is disrupted by interaction with the functional groups, resulting in pore creation and destruction of membrane entirety. Afterward, an outflow of intracellular components and clotting of cytoplasm occur and lead to cell death.

In general, it is clear that the cell membrane entirety is requisite for the survival of microorganisms because it is the basic component that ensures the biological

activities occurring in the cell. The permeability of the cell membrane plays important role in the transport of molecules and ions and the integrity of the cell membrane protects microorganisms from environment surrounding. When antimicrobial compounds such as phenolics are added to environment surrounding microorganisms, they can deviate the permeability and the cell membrane functions via the phospholipid bilayer of the cell walls, resulting in the impairment of molecules and ions transport within microbial cells. According to Nazzaro et al. (2013), the antimicrobial activity of bioactive components could be explained by several biochemical and structural mechanisms at different sites inside the cell and on the surface of the cell. This phenomenon is due to the different molecules presented in the natural extract. Consequently, the cell membrane, cytoplasm, enzymes, and proteins are chemically modified, resulting in the sustained loss of metabolites and thus cell death.

The mechanism of antimicrobial action of bioactives can be directly related to DNA/RNA/protein synthesis. In general, thiosulfinate is a functional group consisting of the linkage of R_1-S(O)S-R_2, readily reacts with free-SH group of intercellular enzymes. Alliin (S-allyl-I-cysteine-sulfoxide) and allicin (2-propenyl-2-propenethiol sulfinate), the main active principles of thiosulfinates, are found to inhibit and delay DNA, RNA, and protein synthesis. Similarly, DNA/RNA/protein synthesis are also affected by the flavonoids such as apigenin, quercetin, epigallocatechin gallate, epicatechin gallate, and 3-O-octanoyl-(+)-catechin (Radulovic et al. 2013).

Quorum sensing is known as communication between bacterial cells (including Gram-positive and Gram-negative) regulating the production and detection of diffusible chemical signal molecules that is called autoinducers. Communication within and among species is vital for microorganisms' survival and interaction in natural environment. Gram-positive bacteria employ processed oligo-peptides to communicate, while Gram-negative bacteria use acylated homoserine lactones as autoinducers (Miller and Bassler 2001). It is interesting that one of the early steps in the multicellular development is the evolution of quorum sensing systems in bacteria. There is a need to investigate quorum sensing inhibitor to stop the growth of the cells. Fortunately, several natural extracts (i.e. bean sprout, carrot, and garlic) are found to contain different quorum sensing inhibitors in an amount-dependent way and with competitive binding of a structure activity relationship (Radulovic et al. 2013). As a result, it is recommended that the antimicrobial action of new bioactive compounds should be investigated based on information gained from studies of quorum sensing.

It is worthily noted that synergistic effect should be taken into account for antimicrobial activity of the bioactives if the results of an antimicrobial assays cannot fully understood. Since the plant extract consists of lead bioactive compound and several compounds, the interactions may occur within the extract. As such, it is recommended that quantitative analysis of the bioactive compounds and their structure are highly desirable to obtain valuable insight into the specific mechanisms of antimicrobial action. However, investigation on this area may be extremely complex. Several methodologies have been employed such as bioassay-guided fractionation and synergy-directed fractionation, also known as synergy testing

that identified amount of a known bioactive component from the crude extract is added to the resultant fractions and the antimicrobial activity is then examined. For those assays, several processes such as extraction, isolation, separation, and/or fractionation of pure compounds are sometimes needed. Furthermore, prediction and correlation of the metabolomic profile of the resultant extracts and their bioactivities using statistical and mathematical modeling, is known as biochemometric assay, are recently developed. This method allows to comprehend the relationship between the bioactive compounds and their activity (Santos et al. 2019).

5 Evaluation Methods for Antimicrobial Activity

It is desirable to determine if the bioactive compounds in the plant extracts can be then applied in the food industry as natural antimicrobial preservatives. As presented in Sect. 4, there are several mechanisms of antimicrobial activity, the use of different in vitro methods for assessing antimicrobial activity of the bioactive extracts is of great importance. Broadly, the evaluation techniques for antimicrobial activity can be classified into diffusion and dilution methods. Several methods employed for screening antimicrobial activity of plant extracts, known as diffusion method, include agar disk diffusion, agar well diffusion, cross streak method, poisoned food method, gradient method (E-test), and bioautographic (thin layer chromatography). The dilution techniques are broth (micro or macro) dilution and agar dilution methods. The diffusion methods are known as qualitative techniques, while dilution methods are quantitative assays.

5.1 Diffusion Methods

Agar diffusion method is the most widely used for antimicrobial activity evaluation. Briefly, agar plates are injected with a standardized inoculum of the test microorganism. Afterward, filter paper discs (approximately 6 mm in diameter), comprising the tested bioactive compound at different concentrations, are introduced on the agar surface. The petri dishes are incubated under the most appropriate conditions for the multiplication of the tested microorganism. The antimicrobial compound diffuses into the agar and retards the germination and the growth of the tested microorganism and afterward the diameters of inhibition growth zones are visually or instrumentally determined. The effectiveness of bioactive compound is evaluated by the size of the inhibition zone of microorganism surrounding the disc, and it is reported as the diameter of this zone (in mm or cm). The results can be expressed to be 0, +, ++, etc.

The principle of agar well diffusion is similar to that of agar disk diffusion method, the agar plate surface is injected by spreading a volume of the microbial inoculum over the whole agar surface. Afterward, an amount of the extract (about 20–100 mL) at the determined concentration is placed into the well through a hole

(6 to 8 mm in diameter) that is aseptically made. Then, agar plates are incubated under the appropriately controlled conditions depending upon the growing conditions of the test microorganism. The antimicrobial compound diffuses in the agar medium and prevents the development of the tested microorganism. More details about the other diffusion methods including cross streak method, poisoned food method, gradient method (E-test), and bioautographic are found in the report by Balouiri et al. (2016).

Since there are many factors affecting the experimental results of the assays, it is highly recommended to strictly control the key parameters including culture, type, and concentration of bioactive compound, incubation time, and temperature. For the culture, the tested microorganisms are often obtained from globally recognized pure culture porfolios, however, isolated microorganisms from natural resources such as food products may also be used in some cases, for example, there is a lack of the pure culture. It is also important to note that there is a need to determine the most suitable growth phase and the defined amount of microorganism cells. In addition, it is considered to use the negative and positive control cultures. For the negative control cultures, the bioactive compound is replaced by the appropriate solvent or water. The positive control culture, that a proper amount of standard antibiotic is often added, is frequently carried out to evaluate the sensitivity of tested microorganism.

Compared to other methods, there are superior benefits, in terms of simplicity, low cost, the ability to examine different types of microorganisms and bioactive compounds and easy interpretation of the obtained results, when the diffusion method is employed. Accordingly, the diffusion method is commonly applied to screen the antimicrobial activity of the plant bioactive compounds. However, one of the drawbacks of this method, particularly Agar disk diffusion method, is inappropriate to find out the minimum inhibitory concentration (MIC), as the concentration of bioactive compound widely spread into the agar medium is difficult to be quantified. As such, an appropriate MIC can be estimated for several microorganisms and antibiotics by comparing the inhibition zones with the stored algorithms (Balouiri et al. 2016). Furthermore, it is not recommended to use the agar diffusion method for evaluating the antimicrobial activity of water insoluble compounds such as essential oil. This is because the evaporation and poorly diffusion in agar broth of volatile components during incubation time lead to the limit of diffusion method. Nevertheless, this method is still commonly applied for evaluation of antimicrobial activity due to its above-mentioned advantages. For those reasons, it is highly recommended the use of the diffusion methods to pre-screen antimicrobial activity of a larger number of the plant extracts containing oil soluble compounds. After that, further evaluation using more complicated techniques can be applied for a better understanding of the antimicrobial activity.

5.2 Dilution Methods

In order to determine MIC values, dilutions methods are widely employed because the amount of the tested bioactive compound in the agar (agar dilution method) or broth medium (broth micro- or macro-dilution method) can be approximately calculated. The methods are commonly applied to quantitatively measure the antimicrobial activity. In brief, cultures of Agar broth are conducted in Petri dishes or tubes or wells, whereas cultures of liquid broth for tested molds are grown in conical flasks added with about 100 ml medium (for test molds) or test tubes added with a range of 2.5–5 ml medium (for test bacteria and molds). The inhibitory effect of the bioactive compound extract in the test tubes cultures or microtitre plates is determined by turbidimetric method or the count plate method. The results can be expressed in GII (growth inhibitory index), MIC (minimal inhibitory concentration), or MLC (minimal lethal concentration). In addition, the antimicrobial activity is also studied by analysis of sporulation inhibition and toxin productivity.

Several definitions of common terms used for the expressed results of the antimicrobial activity are as follows:

- GII (%) is calculated by comparing to the control growth culture without bioactive compound.
- MIC (μg/ ml or mg/L or %) is determined as the lowest content of the assayed bioactive compound in the broth that completely prevents the visible growth of the tested microorganism. For lethality evaluation of the bioactive compound, the tested microorganism in the liquid or agar broth is moved and then incubated into a new broth medium. It is important to note that non-growth of the microorganism should be observed.
- MLC (μg/ ml or mg/L or %) is calculated as the minimal content of the bioactive compound needed to kill 99.9% microorganism inoculum number after incubation under the optimized conditions. MLC is sometimes known as MBC (minimal bactericidal concentration) for bacteria and MFC (minimal fungicidal concentration) for fungi.

Since the testing results rely mostly on the type of the evaluation method, it is desirable to select an appropriate method to assess the antimicrobial activity of the extract. One of the important criteria to choose the method is the final application of the extract, for example, food preservative. It is well-known that a number of factors affecting the testing results of the antimicrobial evaluation method, i.e. MIC values, including the inoculum size, the type of growth medium, the incubation time, and temperature and the inoculum preparation. Similar to the diffusion methods, the origin of microorganism is carefully chosen according to standard guideline. Furthermore, the concentration of the bioactive compound, dispersing solvent, inhibition parameter, and origin of the bioactive compounds (including extraction methods used) should be taken into account in the dilution methods. It is also known that all procedures for the evaluation of the antimicrobial activity should follow approved

standards, such as CLSI (the Clinical and Laboratory Standards Institute) and EUCAST (the European Committee on Antimicrobial Susceptibility Testing).

6 Applications of Plant Extracts

There are many food preservation methods, including pasteurization, sterilization, salting, acidification, and drying, applied in the industry in order to inhibit development of spoilage and pathogen microorganisms in food products, prolonging the shelf life. Recently, the use of the natural antimicrobials from plant materials to prevent growth of microorganisms in foods is of great interest. The antimicrobial compounds can be applied in foods in different ways, including directly added product formulation, and surface coated packaging and incorporated packaging. Depending on the types of foods, and processing and storage conditions, an appropriate application of antimicrobials is selected.

Numerous reports have confirmed the efficacy of the use of natural bioactive extracts from plants against spoilage and pathogen microorganisms. Those studies on applications of natural antimicrobials in the minimally processed products are an example and can be easily found in the literature (Quinto et al. 2019). Several techniques including dipping, impregnation, coating, and spraying are used when applying bioactive compounds in fresh-cut fruit and vegetables; among them, the application of plant bioactives using coating methods for prolonged shelf life of ready-to-eat fruits and vegetables is found to be the most popular (Del Nobile et al. 2012). For this kind of applications, most of bioactive compounds are essential oils. The sensorial quality of the coated products is one of the limiting factors due to undesired smell of volatile compounds which the natural flavor of fruits and vegetable are masked. For this reason, it is important to study an appropriate type and dose of essential oil or a use of masking agents as a promising alternative. It is highly recommended to apply different preservation methods, known as hurdle technology, that can enhance their advantages while decreasing the amount of antimicrobial substances used. As such, the applications of moderate heat treatment in combination with refrigeration storage conditions should be performed. In addition, natural antimicrobials can be also applied in other foodstuffs such as dairy, meat-based, fish-based, and cereal-based products (Del Nobile et al. 2012).

Although, the natural antimicrobial from the plant extracts have shown to be effective in many food applications in both the laboratory and industry, several limitations in the food industry should overcome, such as risk of toxicity and cost of natural bioactive compounds. Other issues including legal aspects, regulations of labeling, and the maximum amount are also taken into account.

In general, many studies show that the plant bioactive compounds such as essential oils are more active in the in vitro testing matrix for the antimicrobial activity than that in situ, e.g. in foods. Sometimes, the results of the antimicrobial activity in the food systems are supported by laboratory in vitro studies (Kalemba and Kunicka 2003). As a result, there is a need to evaluate the bioactives being used

as food preservatives in foods, the practical experiments in specific foods should be carried out. In addition, a smaller number of research groups have move forward to investigate the in vivo effectiveness of the bioactive compounds from the well demonstrated in vitro research results. However, it is scarcely to conduct this kind of study due to more complex and costly activity. Studies on mammalian cell toxicity and allergic reactions also need to be considered. Until now, the use of essential oils against human skin infections is the most common in vivo investigation, and the following of standard clinical trial protocols it is recommended.

7 Conclusions

In conclusion, the use of the antimicrobials from plant materials as natural food preservatives in the industry is of great importance due to health care needs. In this chapter, different bioactive compounds from plant materials, and their antimicrobial properties are presented. It is highly desirable to understand the relationships between the bioactive compounds and their properties. The antimicrobial activity of the bioactive compounds is strongly related to bioactive structure, especially functional groups. Diverse mechanisms of action for the antimicrobial activity of plant bioactives including cell wall damage, cytoplasm coagulation, hydrolysis of ATP, rate of cell permeability, modification of proton motive force, and membrane protein destruction are also discussed. Feature of microorganisms plays important role in more in-depth understanding of the mechanisms of the antimicrobial actions for the plant bioactive compounds. Afterward, the principles of the two main evaluation methods of the antimicrobial activity, diffusion and dilution methods, are discussed in this chapter. Several advantages and limitations of those methods are also mentioned. Finally, the published works on the applications of the plant extract as natural antimicrobials in the food industry and some recommendations are also given.

References

Abbaszadeh S, Sharifzadeh A, Shokri H, Khosravi A, Abbaszadeh A (2014) Antifungal efficacy of thymol, carvacrol, eugenol and menthol as alternative agents to control the growth of food-relevant fungi. J Mycol Med 24(2):e51–e56

Abuga I, Sulaiman SF, Abdul Wahab R, Ooi KL, Abdull Rasad MSB (2020) In vitro antibacterial effect of the leaf extract of Murraya koenigii on cell membrane destruction against pathogenic bacteria and phenolic compounds identification. Eur J Integrat Med 33:101010

Ajani OO, Nwinyi OC (2010) Microwave-assisted synthesis and evaluation of antimicrobial activity of 3-{3-(s-aryl and s-heteroaromatic) acryloyl}-2H-chromen-2-one derivatives. J Heterocyclic Chem 47(1):179–187

Ayirezang FA, Azumah BK, Achio S (2020) Effects of Moringa oleifera leaves and seeds extracts against food spoilage fungi. Adv Microbiol 10(1):27–38

Azmir J, Zaidul I, Rahman M, Sharif K, Mohamed A, Sahena F, Jahurul M, Ghafoor K, Norulaini N, Omar A (2013) Techniques for extraction of bioactive compounds from plant materials: a review. J Food Eng 117(4):426–436

Balouiri M, Sadiki M, Ibnsouda SK (2016) Methods for in vitro evaluating antimicrobial activity: a review. J Pharm Anal 6(2):71–79

Bazargani MM, Rohloff J (2016) Antibiofilm activity of essential oils and plant extracts against Staphylococcus aureus and Escherichia coli biofilms. Food Control 61:156–164

Beevi SS, Mangamoori LN, Dhand V, Ramakrishna DS (2009) Isothiocyanate profile and selective antibacterial activity of root, stem, and leaf extracts derived from Raphanus sativus L. Foodborne Pathog Dis 6(1):129–136

Boberek JM, Stach J, Good L (2010) Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. PLoS One 5(10):e13745

Bonifácio BV, dos Santos Ramos MA, da Silva PB, Bauab TM (2014) Antimicrobial activity of natural products against Helicobacter pylori: a review. Ann Clin Microbiol Antimicrob 13(1):54

Bouyahya A, Lagrouh F, El Omari N, Bourais I, El Jemli M, Marmouzi I, Salhi N, Faouzi MEA, Belmehdi O, Dakka N, Bakri Y (2020) Essential oils of Mentha viridis rich phenolic compounds show important antioxidant, antidiabetic, dermatoprotective, antidermatophyte and antibacterial properties. Biocatal Agric Biotechnol 23:101471

Caputi L, Aprea E (2011) Use of terpenoids as natural flavouring compounds in food industry. Recent Pat Food Nutr Agric 3(1):9–16

Chang W, Li Y, Zhang M, Zheng S, Li Y, Lou H (2017) Solasodine-3-O-β-d-glucopyranoside kills Candida albicans by disrupting the intracellular vacuole. Food Chem Toxicol 106:139–146

Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582

Cui Q, Du R, Liu M, Rong L (2020) Lignans and their derivatives from plants as antivirals. Molecules 25(1):183

da Cruz Almeida ET, de Medeiros Barbosa I, Tavares JF, Barbosa-Filho JM, Magnani M, de Souza EL (2018) Inactivation of spoilage yeasts by Mentha spicata L. and M.× villosa huds. Essential oils in cashew, guava, mango, and pineapple juices. Front Microbiol 9:1111

Dai J, Mumper RJ (2010) Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules 15(10):7313–7352

Del Nobile MA, Lucera A, Costa C, Conte A (2012) Food applications of natural antimicrobial compounds. Front Microbiol 3(287):1–13

Díaz-Gómez R, Toledo-Araya H, López-Solís R, Obreque-Slier E (2014) Combined effect of gallic acid and catechin against Escherichia coli. LWT Food Sci Technol 59(2):896–900

El-Toumy SA, Salib JY, El-Kashak WA, Marty C, Bedoux G, Bourgougnon N (2018) Antiviral effect of polyphenol rich plant extracts on herpes simplex virus type 1. Food Sci Human Wellness 7(1):91–101

Ferreira FD, Kemmelmeier C, Arrotéia CC, da Costa CL, Mallmann CA, Janeiro V, Ferreira FMD, Mossini SAG, Silva EL, Machinski M Jr (2013) Inhibitory effect of the essential oil of Curcuma longa L. and curcumin on aflatoxin production by Aspergillus flavus Link. Food Chem 136 (2):789–793

Fitzgerald DJ, Stratford M, Gasson MJ, Narbad A (2005) Structure−function analysis of the vanillin molecule and its antifungal properties. J Agric Food Chem 53(5):1769–1775

Górniak I, Bartoszewski R, Króliczewski J (2019) Comprehensive review of antimicrobial activities of plant flavonoids. Phytochem Rev 18(1):241–272

Guil-Guerrero J, Ramos L, Moreno C, Zúñiga-Paredes J, Carlosama-Yepez M, Ruales P (2016) Antimicrobial activity of plant-food by-products: a review focusing on the tropics. Livest Sci 189:32–49

Gutiérrez RMP, Gonzalez AMN, Hoyo-Vadillo C (2013) Alkaloids from piper: a review of its phytochemistry and pharmacology. Mini Rev Med Chem 13(2):163–193

Jaime MFV, Redko F, Muschietti LV, Campos RH, Martino VS, Cavallaro LV (2013) In vitro antiviral activity of plant extracts from Asteraceae medicinal plants. Virol J 10(1):245

Jiang Z, Kempinski C, Chappell J (2016) Extraction and analysis of terpenes/terpenoids. Curr Protocols Plant Biol 1(2):345–358
Kalemba D, Kunicka A (2003) Antibacterial and antifungal properties of essential oils. Curr Med Chem 10(10):813–829
Kha TC, Nguyen MH (2015) Extraction and isolation of plant bioactives. In: Scarlett C, Vuong QV (eds) Plant bioactive compounds for pancreatic cancer prevention and treatment. Nova Science Publishers, Inc., New York, pp 117–144
Khameneh B, Iranshahy M, Ghandadi M, Ghoochi Atashbeyk D, Fazly Bazzaz BS, Iranshahi M (2015) Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant Staphylococcus aureus. Drug Dev Ind Pharm 41(6):989–994
Khameneh B, Iranshahy M, Soheili V, Bazzaz BSF (2019) Review on plant antimicrobials: a mechanistic viewpoint. Antimicrob Resist Infect Control 8(1):118
Kuete V (2010) Potential of Cameroonian plants and derived products against microbial infections: a review. Planta Med 76(14):1479–1491
Lalani S, Poh CL (2020) Flavonoids as antiviral agents for Enterovirus A71 (EV-A71). Viruses 12 (2):184
Lawal TO, Soni KK, Saxena R, Adeniyi BA, Mahady GB (2012) Anti-Helicobacter pylori activities of compounds of natural origin bioactive natural products: opportunities and challenges in medicinal chemistry. World Scientific, Singapore, pp 475–497
Metsämuuronen S, Siren H (2014) Antibacterial compounds in predominant trees in Finland: review. J Bioprocess Biotechnol 4(167):2
Miller MB, Bassler BL (2001) Quorum sensing in bacteria. Annu Rev Microbiol 55(1):165–199
Mishra S, Pandey A, Manvati S (2020) Coumarin: an emerging antiviral agent. Heliyon 6(1): e03217
Mulat M, Khan F, Muluneh G, Pandita A (2020) Phytochemical profile and antimicrobial effects of different medicinal plant: current knowledge and future perspectives. Curr Tradit Med 6 (1):24–42
Nakamoto M, Kunimura K, Suzuki JI, Kodera Y (2020) Antimicrobial properties of hydrophobic compounds in garlic: Allicin, vinyldithiin, ajoene and diallyl polysulfides. Exp Ther Med 19:1550
Nazzaro F, Fratianni F, De Martino L, Coppola R, De Feo V (2013) Effect of essential oils on pathogenic bacteria. Pharmaceuticals 6(12):1451–1474
Olejar KJ, Ricci A, Swift S, Zujovic Z, Gordon KC, Fedrizzi B, Versari A, Kilmartin PA (2019) Characterization of an antioxidant and antimicrobial extract from cool climate, white grape marc. Antioxidants 8(7):232
Prasad R, Sharma M, Kamal S, Rai MK, Rawat AKS, Pushpangdan P, Varma A (2008) Interaction of *Piriformospora indica* with medicinal plants. In: Varma A (ed) Mycorrhiza. Springer-Verlag, Berlin, pp 655–678
Quinto EJ, Caro I, Villalobos-Delgado LH, Mateo J, De-Mateo-Silleras B, Redondo-Del-Río MP (2019) Food safety through natural antimicrobials. Antibiotics 8(4):208
Radovanović V, Andjelković M, Arsić B, Radovanović A, Gojković-Bukarica L (2019) Cost-effective ultrasonic extraction of bioactive polyphenols from vine and wine waste in Serbia. S Afr J Enol Viticulture 40(2):1–1
Radulovic NS, Blagojevic PD, Stojanovic-Radic ZZ, Stojanovic NM (2013) Antimicrobial plant metabolites: structural diversity and mechanism of action. Curr Med Chem 20(7):932–952
Reiter J, Levina N, Van der Linden M, Gruhlke M, Martin C, Slusarenko AJ (2017) Diallylthiosulfinate (Allicin), a volatile antimicrobial from garlic (Allium sativum), kills human lung pathogenic bacteria, including MDR strains, as a vapor. Molecules 22(10):1711
Roy A (2017) A review on the alkaloids an important therapeutic compound from plants. IJPB 3 (2):1–9

Salaheen S, Nguyen C, Hewes D, Biswas D (2014) Cheap extraction of antibacterial compounds of berry pomace and their mode of action against the pathogen Campylobacter jejuni. Food Control 46:174–181

Santos SAO, Martins C, Pereira C, Silvestre AJD, Rocha SM (2019) Current challenges and perspectives for the use of aqueous plant extracts in the management of bacterial infections: the case-study of salmonella enterica serovars. Int J Mol Sci 20(4):1–17

Shang Z, Li S, Xiao L (2002) Review on extraction technology of alkaloids from plants. Mod Chem Ind 1:56–59

Shen J, Shao X (2005) A comparison of accelerated solvent extraction, Soxhlet extraction, and ultrasonic-assisted extraction for analysis of terpenoids and sterols in tobacco. Anal Bioanal Chem 383(6):1003–1008

Siriyong T, Srimanote P, Chusri S, Yingyongnarongkul B-E, Suaisom C, Tipmanee V, Voravuthikunchai SP (2017) Conessine as a novel inhibitor of multidrug efflux pump systems in Pseudomonas aeruginosa. BMC Complement Altern Med 17(1):405

Slobodníková L, Fialová S, Rendeková K, Kováč J, Mučaji P (2016) Antibiofilm activity of plant polyphenols. Molecules 21(12):1717

Sridevi D, Shankar C, Prakash P, Park JH, Thamaraiselvi K (2017) Inhibitory effects of reserpine against efflux pump activity of antibiotic resistance bacteria. Chem Biol Lett 4(2):69–72

Stagos D (2020) Antioxidant activity of polyphenolic plant extracts. Multidisciplinary Digital Publishing Institute, Basel

Takó M, Kerekes EB, Zambrano C, Kotogán A, Papp T, Krisch J, Vágvölgyi C (2020) Plant phenolics and phenolic-enriched extracts as antimicrobial agents against food-contaminating microorganisms. Antioxidants 9(2):165

Teanpaisan R, Kawsud P, Pahumunto N, Puripattanavong J (2017) Screening for antibacterial and antibiofilm activity in Thai medicinal plant extracts against oral microorganisms. J Tradit Complement Med 7(2):172–177

Tsopmo A, Awah FM, Kuete V (2013) Lignans and stilbenes from African medicinal plants medicinal plant research in Africa. Elsevier, London, pp 435–478

Xu Y, Burton S, Kim C, Sismour E (2016) Phenolic compounds, antioxidant, and antibacterial properties of pomace extracts from four Virginia-grown grape varieties. Food Sci Nutr 4 (1):125–133

Younus I, Siddiq A, Ishaq H, Anwer L, Badar S, Ashraf M (2016) Evaluation of antiviral activity of plant extracts against foot and mouth disease virus in vitro. Pak J Pharm Sci 29(4):1263–1268

Yubin J, Miao Y, Bing W, Yao Z (2014) The extraction, separation and purification of alkaloids in the natural medicine. J Chem Pharm Res 6(1):338–345

Zorić N, Kosalec I, Tomić S, Bobnjarić I, Jug M, Vlainić T, Vlainić J (2017) Membrane of Candida albicans as a target of berberine. BMC Complement Altern Med 17(1):268

Zwenger S, Basu C (2008) Plant terpenoids: applications and future potentials. Biotechnol Mol Biol Rev 3(1):1–7

Antimicrobial Materials for Local Drug Delivery

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Abstract In a vast number of medical treatments, the local drug delivery is of prime importance to achieve a favorable therapeutic effect since it enhances drug bioavailability. These systems provide biological and chemical protection for drugs, reduce toxicity, increase the concentration at the site of interest, and avoid systemic exposure. The development of local systems is of great interest in both prophylactics and intensive therapies, and their formulation will depend on the characteristics of the drug and motives for actions pursued. This chapter describes the use of carrier systems, routes of administration, release mechanisms and methods, and site of action.

Keywords Local drug delivery · Antimicrobial · Stimuli sensitive polymers · Liposome · Micelle

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1 Introduction

Controlled drug delivery systems can be designed for temporal control, local control, or both. The first consists of continuous drug release in therapeutic doses without reaching maximum levels, thus avoiding the side effects produced by large drug discharges. These systems represent an advantage for substances, which are quickly metabolized or eliminated by the body, and for therapies that need the release of drug at a controlled concentration for long periods. On another hand, local drug delivery systems allow drug release in a specific place of the organism or target side, which has the advantages of decreasing drug toxicity, and increasing drug effectiveness because these provide a high concentration where is required and avoid systemic exposure (Alt et al. 2015). Localized release of antimicrobial drugs can help overcome some of the drawbacks of systemic therapy, such as low concentrations at the target site of the injured tissue, and administration to avascular sites. Most bacterial infections in the body tend to form biofilms, which lead to persistent and extremely resistant to antimicrobials infections, mainly due to the difficulty of penetrating the barrier of polysaccharides that cover them. The use of release systems allows greater penetration into the biofilm and increasing drug efficiency (Berlanga and Guerrero 2016; Prasad et al. 2020).

2 Mechanisms of Drug Delivery

Drug delivery can be controlled by various mechanisms such as dissolution, diffusion, osmosis, swelling, and erosion; this depends on the composition of the system, the loading drug, and the use environment. Delivery systems may show different release mechanisms simultaneously, but usually, one mechanism is predominant. For example, most of the release systems present a dissolution mechanism, nevertheless it rarely constitutes the main mechanism. The most studied mechanisms for local drug delivery are diffusion control, solvent control, and chemical control (Anand et al. 2020; Prasad et al. 2017).

2.1 Diffusion-Controlled Systems

Diffusion is a mass transport phenomenon, fundamental for many natural processes. It is defined as the movement of a solute from a region of higher concentration to an adjacent region of lower concentration. In 1855, Adolf Eugen Fick presented the quantitative description of this phenomenon. He considered the unidirectionality of diffusion and related the diffusion flux with the gradient in solute concentration (Fick's First Law), according to the equation:

$$J = -D\frac{\partial c}{\partial x} \tag{1}$$

where the diffusion flux (J) is the amount of substance per unit area, per unit time; $\frac{\partial c}{\partial x}$ is the concentration gradient with distance; D is the diffusion coefficient, which is a measure of the mobility of the individual molecules of solute in a dissolvent; and the negative sign indicates that the flow direction is against the concentration gradient (Bruschi 2015).

In diffusion-controlled systems, the release occurs by permeation of the drug from inside the device to the medium, and the release rate is controlled by the diffusion rate. Although the diffusion occurs in all release mechanisms, it predominates when other processes are not involved in the control of drug release or their contribution is negligible. There are two types of diffusion devices, deposit and matrix systems.

2.1.1 Deposit or Reserve Systems

Deposit systems consist of drugs encapsulated in permeable membranes (thin or porous), where the release is given by the diffusion of the drug towards the outside of the membrane by affinity with the solvent, under the influence of a concentration gradient, following Fick's first law. These systems are one of the most used to date and ensure a relatively constant release rate, but present difficulty to deliver high-molecular-weight compounds and are expensive, due to requiring strict control in the thickness and the membrane area, because a failure could produce a massive release and overdose poisoning. Reserve systems can be classified for having either a nonconstant activity source or constant activity source. In the first case, drug concentration in the reservoir is less than its solubility, so released drug molecules are not replaced, and the reservoir's drug concentration decreases with time. Otherwise, in a constant activity source system, the depot is loaded whit an excess of drug that allows replacing the drug released and maintaining a constant concentration for more time (Yang and Pierstorff 2012), Fig. 1 shows a diagram of types of deposit systems.

2.1.2 Matrix or Monolithic Systems

In monolithic systems, the drug is evenly distributed in the polymer matrix and the migration occurs by diffusion of the drug through the support (Fig. 2). The release depends on the drug load concentration, the nature of components, and the geometry of the matrix. There are two types of monolithic systems: solutions and dispersions, in the first case, drugs are dissolved in the matrix; while in the second case, drugs are insoluble in the matrix and found as dispersed particles (Siepmann et al. 2012).

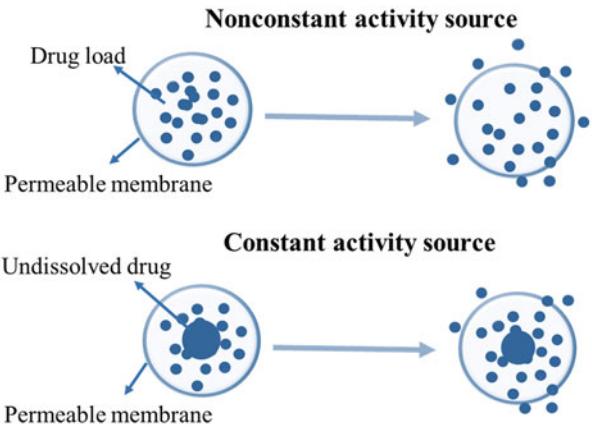

Fig. 1 Deposit systems with nonconstant activity and constant activity source

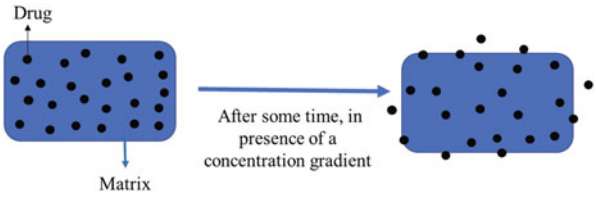

Fig. 2 Monolithic systems

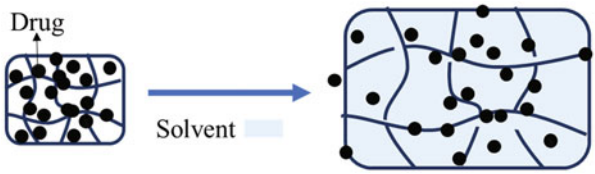

Fig. 3 Solvent controlled systems

2.2 Swelling Controlled Systems

In swelling controlled systems, the matrix, generally polymeric, absorbs solvent from the medium and swells affecting the release kinetics. The solvent enters the polymer and produces an expansion of volume and more space between polymeric chains, which is used to control the release (Fig. 3). The swelling mechanism is presented by sensitive polymers that change their swelling properties as a response to external conditions. The degree of swelling of the polymer depends on its hydrophilic/hydrophobic ratio, crosslinking grade, charge, and the ionic strength of the medium. The driving force for the swelling process is generally a balance of the osmotic and electrostatic forces favored by the entropy of the polymer in the solvent (Bruschi 2015).

2.3 Chemical Control Systems

Chemical control systems show active participation of the matrix in the release process because of the release occurs by matrix erosion as a result of a chemical reaction. This rupture or eventual formation of a weak bond or its ionization can occur by hydrolysis or enzymatic action, and the release rate will depend on the chemical characteristics of the bond and the conditions of the medium. The immobilization of the drug can be physical or chemical (Fig. 4). For physical immobilization, the drug is embedded in the matrix and released after its erosion. On the other hand, in chemical immobilization, the drug is chemically linked at the matrix´s structure and form part of its, so the drug is released when it erodes. An advantage of these systems is that do not need to be retrieval after full drug released because they are biodegradable and easily assimilated by the organism (Rezk et al. 2019).

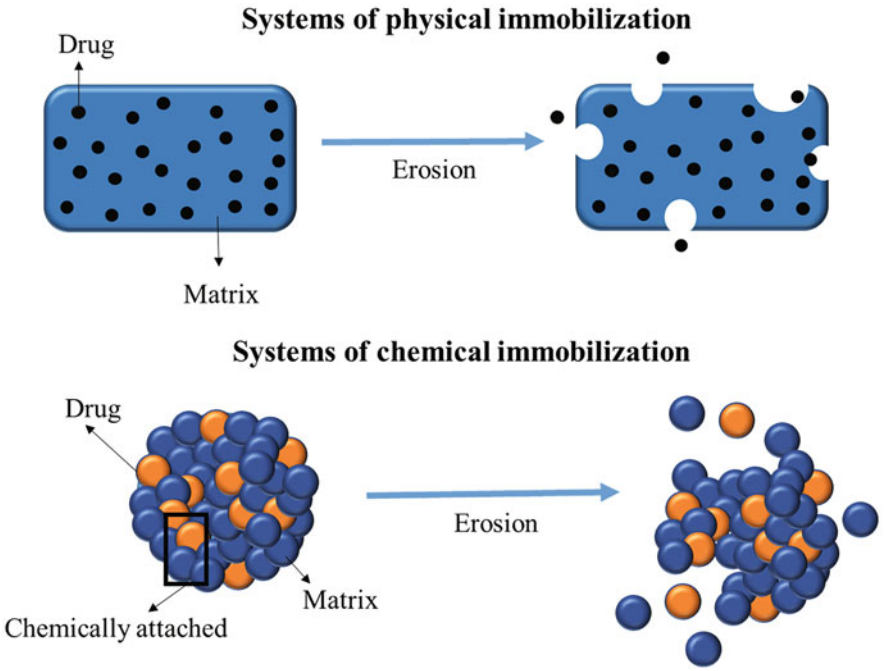

Fig. 4 Chemical controlled systems

3 Antimicrobial Drugs: Antibiotics

Antibiotics are antimicrobial agents, considered the most important drugs against bacterial infections. There is a wide variety of antibiotics among which stand out β-lactams, aminoglycosides, azoles, fluoroquinolones, macrolides, sulfonamides, and tetracyclines, which depending on their origin can be natural or synthetic (Figs. 5 and 6). This section describes general information about the chemical structure, mechanisms of action, and examples of active principles of these drugs.

3.1 β-lactams

β-lactams are cyclic amides of low molecular weight, with activity against Gram-positive and some Gram-negative bacteria. There is a wide range of antimicrobials as penicillin, cephalothin, clavulanic acid, and carbapenem types. Some bacteria strains can develop resistance against this class of compounds by enzyme synthesis, specifically a β-lactamase (Bush and Bradford 2016). Carbapenem is a sub-group

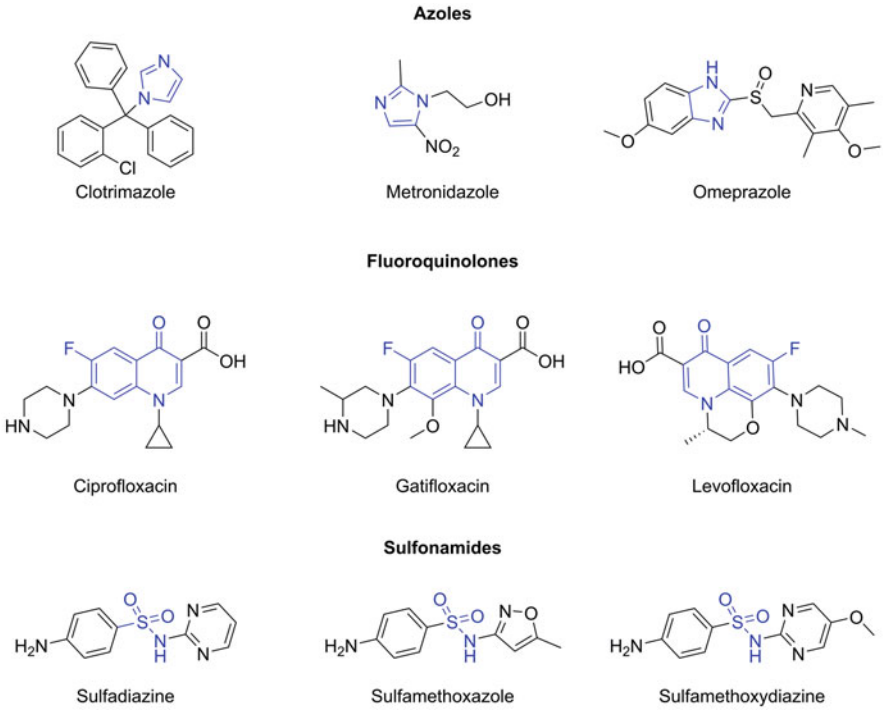

Fig. 5 Examples of synthetic antibiotics

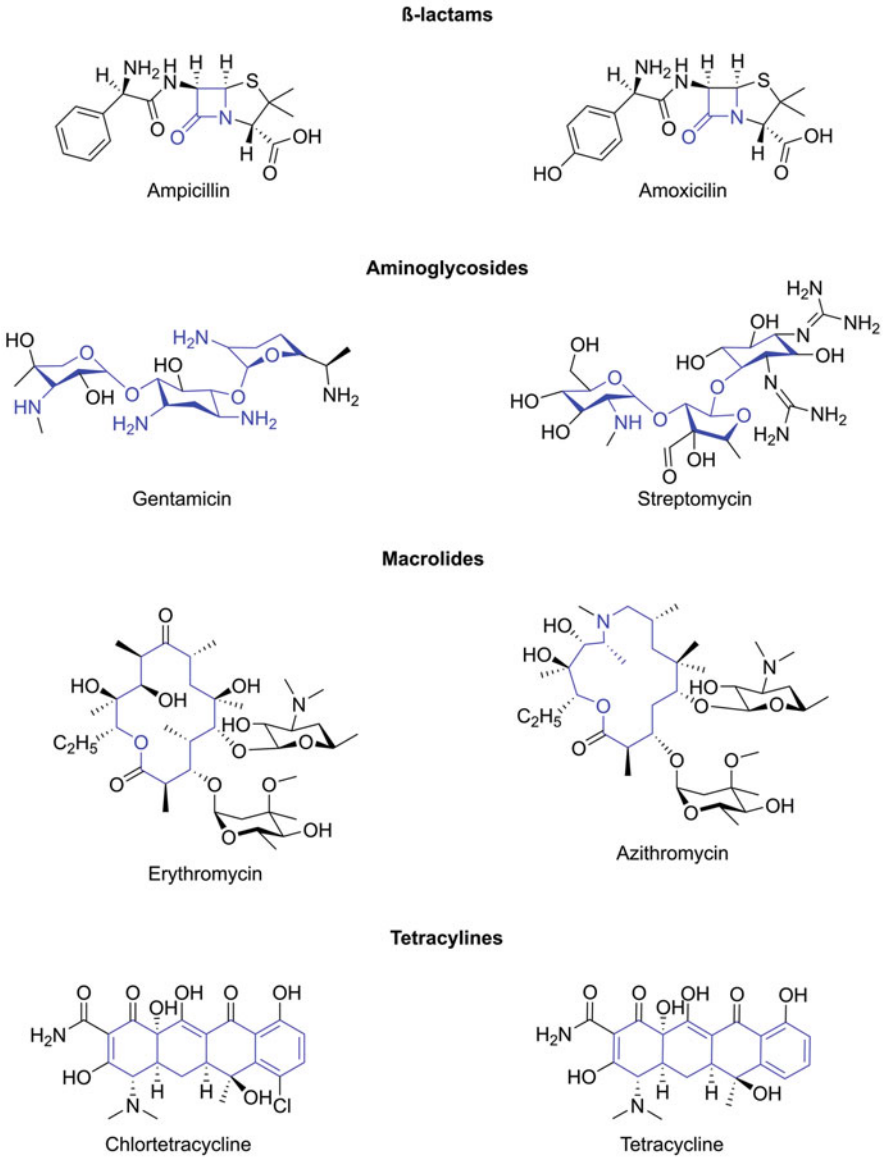

Fig. 6 Some examples of natural antibiotics

of broad-spectrum antibiotics with bactericidal activity characterized by their high resistance to beta-lactamases (Zhanel et al. 2007). The relatively low toxicity of β-lactams still makes them a good option.

3.2 Aminoglycosides

Aminoglycosides are natural origin antibiotics that are isolated from *Streptomyces* strains and contain in their structures two or more amino sugars. Some aminoglycosides of extending use are gentamicin, streptomycin, and neomycins. These are prescribed for the treatment of aerobic Gram-negative *Bacillus*, *Staphylococcus*, and *Mycobacterium tuberculosis*. Their mechanism of action includes protein synthesis inhibition (Kotra et al. 2000). A disadvantage of these antibiotics is that high drug concentrations are required to reach inhibition, and it is necessary to be careful with the dose because there is a small difference between a toxic dose and therapeutic effect dose. Another limitation of aminoglycosides is the administration, which must be via injection, otherwise, the body does not carry out a correct absorption.

3.3 Azoles

Azoles are compounds of low and medium molecular weight, which chemical structure contains one five-membered heterocyclic ring with one N and also another S, O, or N atoms. There is a vast number of bioactive molecules in this class of heterocyclic compounds, such as imidazoles, thiazoles, oxazoles, pyrazoles, isoxazoles, isothiazoles, etc. Some of those azoles can act as enzymatic inhibitors of cytochrome P-450 or through mechanisms involving reactive oxygen species (ROS) (Francois et al. 2006), the most important drugs of this class are mentioned below. The first example is the albendazole, an anti-parasitic drug, useful against giardiasis, trichuriasis, filariasis, neurocysticercosis or ascariasis, microsporidiosis, etcetera (Horton 2000). Another drug is metronidazole that is active against a wide range of microorganisms as *Bacteroides*, *Fusobacteria*, *Giardia lamblia*, *Clostridia*, *Eubacteria*, *Gardnerella vaginalis*, *Trichomonas*, *Entamoeba histolytica*, or *Balantidium* (Freeman et al. 1997). While, the omeprazole and its derivatives, including lansoprazole and pantoprazole, are used against nosocomial opportunistic bacteria like Gram-negative *Helicobacter pylori*, the bioactivity of these compounds is through a selective mechanism of proton-pump inhibition. Nonetheless, another group of azoles is mainly used in the treatment of fungal infections as tinea, chromomycosis, paracoccidioidomycosis, or cutaneous candidiasis. The most important commercial antifungal azoles are ketoconazole, fluconazole, voriconazole, clotrimazole, and itraconazole, which are effective against pathogenic fungi *Candida*, *Histoplasma*, *Coccidioides*, and *Blastomyces* (Mast et al. 2013).

3.4 Fluoroquinolones

These molecules are fluoroquinolones substituted with low molecular weight. These compounds are effective against Gram-negative bacteria. Mechanisms of action propose inhibition at DNA level, first- and second-generation quinolones act as inhibitors of the bacterial DNA gyrase, also the third- and fourth-generation quinolones act through a similar mechanism but more selective to the enzyme domain topoisomerase IV and can inhibit the growth of some Gram-positive bacteria (Hooper 1999). Some active principles are ofloxacin, moxifloxacin, levofloxacin, enoxacin, norfloxacin, gatifloxacin, and ciprofloxacin. Unfortunately, this group of drugs is contraindicated to patients with epileptic antecedents and limited for children and women during pregnancy.

3.5 Lincosamides

Lincosamides are a class of antibiotics that have in their molecular structure amides link to thio-sugars by peptide bonds. The first lincosamide, the lincomycin, was from a natural origin, but currently, it has been replaced by semi-synthetic derivatives as clindamycin and pirlimycin. These antibiotics show a bacteriostatic activity at low concentrations, but bactericidal activity at higher concentrations. Their action mechanism is the inhibition of protein synthesis of the 50S ribosomal subunit of the bacterial ribosome (Spížek and Řezanka 2017). And their range of use is against Gram-positive *Staphylococci* and *Streptococci*. Nevertheless, some bacteria strains can develop lincosamide-resistant, the most important type is the so-called MLS_B resistance, which consists of a monomethylation or dimethylation at an enzymatic level in the N6 exocyclic amino group of A_{2058} by a specific ribosome.

3.6 Macrolides

The first compounds of this kind were isolated from natural sources (e.g., erythromycin and azithromycin). Their general structure includes a macrocyclic lactone ring bonded to hexoses. Macrolides belong to a class of natural products named polyketides, and are mainly effective against Gram-positive bacteria genus as *Streptococci*, *Pneumococci*, *Staphylococci*, or *Enterococci*; Gram-negative as *Chlamydia*, *Bordetella pertussis*, *Haemophilus influenzae*, or *Legionella pneumophila*; and are used in the treatment of infections caused by *Mycoplasma pneumoniae*. The role of macrolides as antibiotics is inhibiting P-glycoprotein in bacterial protein synthesis during the translation process. Pathogen microorganisms are particularly susceptible to macrolide action during the replication process. Examples of synthetic macrolides are roxithromycin and clarithromycin drugs. Just as to other types of

antibiotics, microorganisms develop resistance to macrolides through enzymatic modification or the efflux pump mechanism.

3.7 Sulfonamides

It is a synthetic group of molecules derived from sulfanilamide, which show different pharmacokinetics and pharmacodynamics as well as a different mechanism of action, depending on the changes in their chemical structure that interact with different receptors (Hassanein 2019). Some sulfonamides show broad-spectrum activity inhibiting the metabolic cycles of the bacteria like *Streptococci* and *Bacilli*. Sulfonamides are indicated to treat urinary tract, eye, ear, intestinal, and lung infections. However, one part of the population becomes photosensitive after treatment or present an allergic reaction. Common antibiotic sulfonamides are sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfasalazine, and sulfamethoxydiazine. Due to sulfonamides are selective to the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway, bacteria strains can mutate and develop resistance that way the sulfonamides lose their effectiveness (Sköld 2000).

3.8 Tetracyclines

This class of molecules has a polycyclic structure of four six-membered rings linearly fused, and functionalized with oxo, hydroxyl, and amine groups; some tetracyclines also contain halide, methyl, or amide groups. First tetracyclines were isolated from *Streptomyces* but currently, semi-synthetic derivatives are more used. Tetracyclines show bacteriostatic and bactericidal activity, through mechanisms of protein synthesis inhibition, and are easily absorbed via oral. Also, some of these broad-spectrum antibiotics such as tetracycline, chlortetracycline, oxytetracycline, minocycline, and doxycycline show also activity against protozoan parasites. Bacteria strains develop resistance by many paths as efflux pump, site mutation in RNA, or ribosomal protection.

4 Antimicrobial Pharmacokinetics and Pharmacodynamics

The interaction between antimicrobial drugs and the body produces different effects at the local and systemic levels. The reactions and action mechanisms of drugs from administration until eliminate are explained by their pharmacokinetics and pharmacodynamics parameters. The following provides information about each stage concerning these processes and the use of antibiotics.

Pharmacokinetics studies the movement of the drug within the body and the changes until it leaves the body. Pharmacokinetics has four phases: (a) absorption, (b) distribution, (c) metabolism, and (d) excretion (Levison and Levison 2009).

a. Absorption comprises the drug passage from the administration to the systemic circulation. Absorption depends on the concentration and the lipid-soluble/water-soluble equilibria at the molecular level. Drug transport in biological membranes may be direct (used for lipid-soluble antimicrobial), through pores (used for water-soluble antimicrobials) or by passive and active diffusion. Passive diffusion does not need expenditure of energy; on the other hand, active transport goes to counter-gradient and energy is required, this energy is obtained from the hydrolysis of ATP. Both facilitated diffusion and active diffusion use a transport protein to pass through the cell membrane. Finally, pinocytosis is another way in which high-molecular-weight antimicrobials penetrate the bacterial membrane, in this mechanism the antimicrobial is deposited in vesicles.
b. In the case of the drug distribution, the antimicrobial is already in the bloodstream and from there it is distributed to the target organ, at this stage, drugs may be free or protein-bound, acidic drugs often bond to albumin, and alkaline drugs to β-lipoprotein and acidic α1-glycoprotein. The free antimicrobial is the only one with an activity that is capable of diffusing into the target organ, while the protein-bounded antimicrobial is unable to pass to the target organ and acts as a reservoir. The antimicrobial-cell bond is reversible in a dynamic equilibrium, where liposoluble antimicrobials have the greatest opportunity to reach both extracellular and intracellular bacterial targets. Useful pharmacokinetic parameters for local dosage are (1) volume of distribution (Eq. (2)), (2) loading dose, (3) maintenance dose, (4) steady-state volume of distribution (Weiss 1984).

$$Vd = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} \tag{2}$$

c. In the phase of metabolism occurs the biotransformation of the drug, through a sequence of chemical reactions by enzymatic action. The purpose of this step is to turn the antimicrobial into a more water-soluble metabolite to be retained in the target organ. Metabolism takes place in organs such as the lung, kidney, digestive system, bloodstream, but is in the liver where most drugs are metabolized. The drugs metabolize in phases I and II reactions (Gibson and Skett 1996). In the phase I reactions or non-synthetic reactions (oxidation, reduction, hydrolysis, decarboxylation), metabolites can be active, inactive, or toxic; normally, a phase I metabolism may be necessary to form a prodrug (metabolized active drug). In phase II or synthetic reactions (acetylation, ethylation, methylation, conjugation), the drug or its phase I metabolite is combined with an endogenous substance, producing usually inactive metabolites. The second objective of metabolism reactions is to transform the drug into a more water-soluble substance

to continue the cycle in the process of urinary elimination by filtering through the kidney, through cytochrome CYP P450 mechanisms (White 2000).

d. Excretion is the elimination of drugs or their metabolites from the body (Kok-Yong and Lawrence 2015). The main liquid excretion is through the kidney and comprises three processes glomerular filtration, tubular secretion, and passive tubular reabsorption. The second route of elimination is hepatobiliary that is used to eliminate high-molecular-weight drugs or metabolites, which is produced by active transport and on some occasions, it is useful to treat biliary infections, in this case, the drugs are eliminated through the feces. Another route of excretion is pulmonary excretion, where the inhaled drugs are eliminated. Finally, the excretion maybe by secondary routes as sweat, salivary, or lacrimal. The capacity of an organ to eliminate a drug is variable, in general, the factors that alternate the renal or hepatic capacity have repercussions in the velocity of excretion drug interfere in the effect of the drug.

Pharmacodynamics studies the interaction of the drug with cellular receptors and the mechanisms of action through which it acts. Drugs may be classified as agonists (produce a response) and antagonists (block a response). Receptors, which are macromolecules responsible for chemical signaling between and within cells, play a principal role in antimicrobial activity. If the antimicrobial bonding a receptor (chemical target) occurs a change in its cellular function, this interaction may be reversible or irreversible, the response that receptor triggers may be changing in ion flux, enzyme activity, and protein production and structure. Antimicrobial efficacy and potency (minimum inhibitory concentration and minimum bactericidal concentration) are indicators of activity (Dafale et al. 2016). Overall, the efficacy is the capability of a drug to modify response processes and produce a biological response after binding to a receptor. In the case of antimicrobial efficacy, it is defined as the capability to inhibit proliferation or kill the pathogenic microorganism. The potency is a measure of drug activity; it is defined as the amount necessary to achieve an effect. Extrapolating to antimicrobials is the amount necessary (dose) to achieve the bacteriostatic or bactericidal effect.

5 Antibiotic Administration Routes

Antibiotic administration comprises enteral (oral), parenteral (intravenous and intramuscular), topical, ophthalmic, and ototopical routes. The correct choice of drug administration is as important as the choice of the antibiotic, being these factors to fight successfully against infections caused by microorganisms such as bacteria, fungi, protozoa, viruses, and other pathogens, which are responsible for various diseases that unbalance the homeostasis in the human body. Even when any person is susceptible to become afflicted by pathogens, the vulnerable groups such as children, major adults, and immunocompromised people are who have a higher risk to develop an infection and posteriorly to get sepsis, this can eventually diminish

Table 1 Advantages and disadvantages of drug administration routes

Route	Advantages	Disadvantages
Oral	Administration and dosage is easily controlled Controlled release	Effect and delivery are not achieved as fast as with other routes Unpredictable absorption Drug resistance developed faster
Intravenous	Delivery at the systemic circulation immediately	Preparation requires special cares and specialized personal Cannulae are prone to infection Drugs may cause local reactions.
Intramuscular	Fast delivery and effect Good absorption	Preparation requires special cares Injections hurt causing bruises
Topical	Localized delivery Non-invasive	Irritation Slow absorption Penetration limited
Ophthalmic	Localized delivery Fast delivery and effect	Irritation Penetration limited Limited drug available
Ototopical	Localized delivery No systemic side effects	Limited drug available May cause local sensitivity reactions

the quality of life and in the worst scenario to be fatal. Opportune therapy is critical to enhancing the chances of recovery because when the antibiotic is administered in time, it may be controlled and stopped the bacterial proliferation. Nevertheless, the use of antibiotics must be prudent and discretional to avoid or minimize complications and side effects. A therapy must focus on how antibiotics are administrated to perform the more effective, selective, and localized drug delivery. Table 1 shows the most important advantages and disadvantages of each route of administration.

5.1 Oral

The oral route is the most known and widely used. The antibiotic ingested by oral route pass to the intestinal system where it is posteriorly absorbed to the target organ. There are some therapeutics advantages such as easy ingestion, do not require previous care or cleaning in the zone of administration, and preparation and dosage can be well-regulated. Oral administration is mainly used in respiratory, gastrointestinal, dermatological, and genitourinary infections. This route has good penetration to almost any organ. Some bactericidal compounds show a good activity when they are administrated via oral, examples are lincosamides as lincomycin and clindamycin; macrolides as erythromycin; sulfonamides as sulfamethoxazole; or first-generation cephalosporins as cephalexin. However, some studies in mice have suggested that oral administration has a higher effect on antibiotic resistance amplification and development in gut microbiota (Zhang et al. 2013). Drugs coat with polymer or embedded in a matrix can protect and avoid the gastric release. For

example, plant-based polysaccharides have been used for the oral administration of colonic drugs for the treatment of infections. The colonic microflora secretes a series of enzymes capable of hydrolyzing the glycosidic bonds of the polysaccharides, which allows a localized release, by the erosion of the matrix (Paderni et al. 2012; Wilson 2013).

5.2 Parenteral

Parenteral drug administration is defined as any reconstituted powder, suspension, emulsion, or solution formulation supplied to the body by injection, which can be subcutaneous, intramuscular, and intravenous. Occasionally, parenteral dosage forms can also be administered by intrathecally, intracisternal, intraspinal, and intraepidermal injection to achieve a local effect (Birrer et al. 2001). This route is the most common for drug administration since it allows close interaction between the delivery system and the body. In the case of antibiotics administration, intravenous and intramuscular injections are preferred (Osmani et al. 2014).

5.2.1 Intravenous

The intravenous is the fastest way to reach the target, where a direct inoculation of the antibiotic is dosage by a needle into the bloodstream. The intravenous route is very useful for infections in the nervous system such as meningitis, myopathies, or osteotendinous system because practically the intravenous route targets any infected organ since it has a systemic effect on the human body (Harper et al. 2018). A prompt antibiotics administration through this route is adequate to counter bacterial proliferation and reducing the probabilities of sepsis. It is highly recommended to commence antibiotic therapy within the first hours after the diagnosis of sepsis and septic shock (Brown and Semler 2019). Nevertheless, a previous preparation and application by specialized personal must be effectuated, besides a meticulous and well-controlled dosage, rate, and composition must be watched out during all the therapy. Otherwise, an overdose or incorrect dosage may cause adverse consequences. Drugs such as carbapenems (include imipenem), lincosamides, second-generation cephalosporins as ceftriaxone, amikacin and gentamicin, and metronidazole, whose properties are not only antibacterial but also antifungal, are some examples of drug administrated by this route.

5.2.2 Intramuscular

The intramuscular route consists of the direct inoculation of the drug directly in muscle tissue. It is used to combat primary and secondary pathologies (Gordetsky et al. 2018). Antibiotics available for intramuscular injection are considered an

economical alternative to intravenous injections (under appropriate conditions) because the absorption of antibiotics through intramuscular is fast besides a previous preparation in the zone of application require less care as by intravenous (Milkovich and Piazza 1991). However, given the anatomical proximity to the neurovascular bundles, the connections with nerves and blood vessels may get damaged, possibly causing hematomas at the puncture site and even necrotic tissue.

Examples of infections that may be treated by intramuscular injection are from the bacterial origin Gram-positive bacteria like *Staphylococcus aureus*, responsible for abscesses and gastroenteritis; or *Streptococcus pneumonia* that causes pneumonia; and Gram-negative such as *Neisseria gonorrhoeae* responsible of gonorrhea and *Escherichia coli* associated with urinary infections. Also, the intramuscular route is used in treatment for diseases of the respiratory, skeletal, circulatory, and genitourinary systems. In general, this route of administration is prescribed in the body zone with good penetration of the active substance and with adequate irrigation at the site of inoculation. Using this route of administration, third-generation cephalosporins are dosed to treat pseudomonas infections, including folliculitis skin, tissue infections, or pneumonia.

Parenteral drug delivery systems offer an easy administration and if they are in situ, the number of applications may be decreased, at a lower dose, and minimizing side effects. Therefore, the development and improvement of new injectable systems have received much attention in recent years. For example, in the use of micelle (lipid nanoparticles) solutions for the administration of antibiotics and anticancer drugs (Lu et al. 2008); the injection of thermoplastic matrices that allow a local drug administration in the sites of surgical interventions (Schwach-Abdellaoui et al. 2002); or in the use of liposomes for controlled release such as liposomal amphotericin B, which is used for the treatment of fungal infection, being the first licensed liposomal formulation (Patel and Patel 2010).

5.3 Topical

The topical route of administration consists of applying the antimicrobial drug directly on integuments, in such a way that a local effect is produced only in the zone. It is mainly used for dermatological diseases as abscesses, cutaneous infections, or cellulite. Via the topical route, the drug can be absorbed for longer periods and in and controlled way, which is sometimes more convenient, especially for patients who are incapable to take drugs via oral. Thus, comparing the administration through the topical route with the oral and parenteral routes, the topical is the lesser invasive and decreasing the risk caused by ingestion. Most of the topical antimicrobials act with a bacteriostatic effect as 50S ribosomal subunit inhibitors such as fusidic acid, metronidazole, or clindamycin. Also, other common antimicrobials as neomycin, bacitracin, silver sulfadiazine, mupirocin, or polymyxin are applied topically (Thornton Spann et al. 2004). Another advantage of topical administration is that combo drugs with analgesics may be incorporated in the same medicine,

achieving a local effect, and without compromising the integrity of the patient. For example, topical administration of analgesics lidocaine or capsaicin (patches or cream), or antidepressants as selegiline (patches) act locally as receptors of ion channels (Leppert et al. 2018).

5.4 *Ophthalmic*

The ophthalmic administration aims to reach the receptors of the eye when occurs an ocular infection. Antibiotics are delivered in the form of eye drops, directly applied in the ocular globe, but also it is possible to find ophthalmic antibiotics in ointment or hydrogel. Ocular diseases, such as conjunctivitis, caused by the Gram-negative bacteria *Haemophilus influenzae* may be treated using erythromycin ophthalmic ointment or gentamicin ophthalmic solution. Although, it is estimated that only 5–10% of ophthalmic antibiotics cross the corneal barriers (Dubald et al. 2018), drug delivery by ocular route produces a better bioavailability in the target than via the oral route. Regarding ophtalmic administration, the chloramphenicol works through the inhibition of the 50S ribosomal subunit in bacteria strains as *Escherichia coli*, *Staphylococcus aureus*, or *Streptococcus pneumoniae*.

5.5 *Ototopical*

The otic route has a local effect on the area to be treated and no systemic side effects. The antimicrobial is placed on the ear canal producing bacteriostatic or bactericidal activity depending on the antibiotic type and dose administered. It is mainly used as an adjunct in pathologies such as acute otitis media that is associated with the etiological agents *Moraxella Catarrhalis*, *Streptococcus Pneumoniae*, and *Haemophilus Influenzae*. An example of antimicrobials administrated via this localized route is broad-spectrum fluoroquinolones such as ciprofloxacin (Mosges et al. 2011). However, many antibiotics are contraindicated via this route because can damage the ears. Ototoxic drugs include antibiotics as gentamicin, neomycin, streptomycin, and vancomycin.

6 Methods to Local Controlled Release

The release mechanism will depend on the release system, which is determined by the therapeutic requirements of the application and the objective of the drug, focusing on maximizing drug effectiveness and stability, and decreasing its toxicity and the manifestation of side effects. Localized release concentrates drug at the site of action instead of dispersing throughout the body, which improves the

effectiveness of the therapy. Many materials allow formulating this type of systems, among which stand out liposomes, micelles, stimulus sensitive polymers, and their combination.

6.1 Liposomes and Micelles

Liposomes are spherical vesicles constitute by a lipid bilayer, which is composed of cholesterol and natural phospholipids, due to which presents biocompatibility, biodegradability, and low toxicity, besides allows encapsulating hydrophobic and hydrophilic agents (drugs, nucleotides, proteins). Figure 7 shows the general structure of a liposome where each phospholipid presents a hydrophilic part, "head," consisting of a phosphate group, and two hydrophobic "tails" of fatty acids. The properties of the liposome will depend on its lipid composition, size, surface charge, and preparation processes. In general, unsaturated lipids with greater hydrophilic character produce more permeable and less stable bilayers, and hydrophobic saturated lipid's bilayers are rigid and impermeable (Akbarzadeh et al. 2013). For their high compatibility and versatility, the liposomes are widely used as a carrier in cosmetic, food, farming, and pharmaceutical industry, especially as a way to manage unstable molecules (Sercombe et al. 2015). Besides, liposomes can be functionalized to respond to specific chemical markers and external stimuli.

There are many methods for liposome preparation but all of them involve four stages. First, separation of lipids from an organic solvent, then dispersion the lipid in

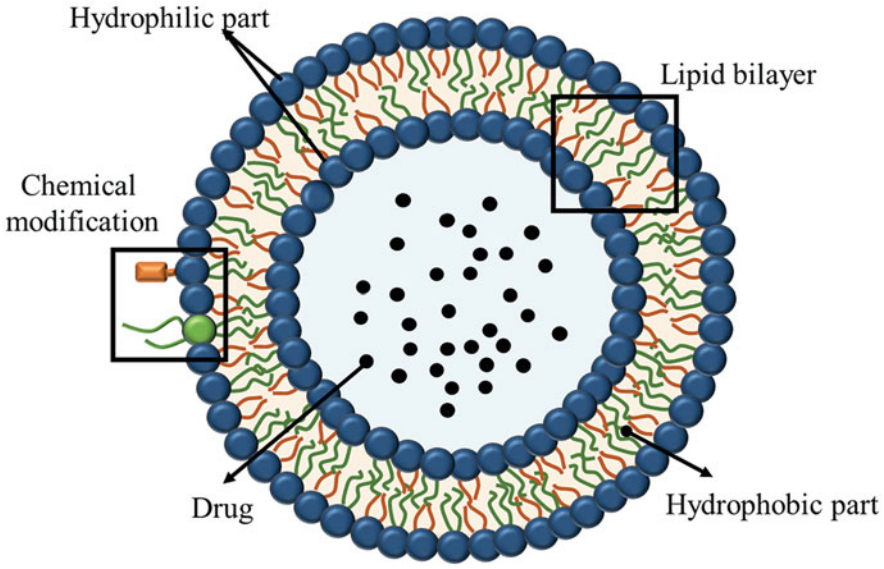

Fig. 7 Structure of a liposome

aqueous media, and finally, the purification and characterization of the product. Depending on the method, the liposome diameter can vary from 25 nm to 2.5 μm, and they may have unilamellar (single phospholipid bilayer) or multilamellar (onion structure) assembly. These parameters affect the durability and drug loading capacity of the liposome. Two ways are known for drug loading in liposomes: passive load, in which the drug is incorporated at liposome during its formation, and active load, where load occurs after liposome formation. The passive process is used for hydrophobic drugs, like amphotericin B taxol or annamycin, two antibiotics that have no permeability across the membrane (Daraee et al. 2016).

Some strong antibiotics need to be released into the cytoplasm or cell nucleus to have a greater effect. However, many of them have low permeability in the cell membrane making it difficult to admire. The release of these drugs through liposomes is a very attractive possibility, since allowing a direct attack to the site of interest. Kunisawa et al. developed fusogenic liposomes, which are conventional liposomes, functionalized with an inactive virus, in this case, Sendai virus, giving it the ability to release nanoparticles in the cell cytoplasm through the mechanism of fusion of the virus, which increases the concentration of nanoparticles in the cytoplasm compared to administration with conventional liposome, in in vitro tests. This type of gene functionalization of liposomes opens the way for devices capable of regulating intracellular pharmacokinetics and more effective carriers (Kunisawa et al. 2005). Liposomes are good alternatives as carriers since their interaction with cells occurs naturally, and they easily access it because of the similarity of their membranes. Although achieving cell differentiation is difficult, current researches are being advanced using a stimulus sensitive functionalization to control the site of release. Cancer or bacterial and fungal advanced infections therapies can be very toxic, and treatment efficiency is limited by low concentration of drugs that can be achieved without produce severe side effects. This is the case of doxorubicin HCl and amphotericin, two very toxic drugs that have shown good results to be administered with liposomes as carriers (Lopez-Berestein et al. 1985; Olusanya et al. 2018).

There are three types of liposomal drug delivery systems: conventional liposomes, which are formed by a lipid bilayer that can be cationic, anionic, or neutral which main disadvantage is that they present rapid elimination in the bloodstream, limiting their therapeutic efficacy. The second one, the sterically stabilized liposomes, generally are modified with hydrophilic polymers like polyethylene glycol (PEG) that improve the stability and increase the time of blood circulation (Ning et al. 2007). Finally, ligand-targeted liposomes are the more recent developed; these are modified to show selectivity over specific ligands (antibodies, peptides, proteins, carbohydrates) and have been studied as an alternative for intensive therapy where the selection of ligand-target depends on infection or cancer class and its location due to the expression of receptors is particular for each one of them (Saraf et al. 2020).

Micelles are systems constituted by amphiphilic units, which in aqueous solution produce a self-assemble core-shell structure, when their critical micellar concentration (CMC) is exceeded, allowing hydrophobic drug encapsulation (Kwon and

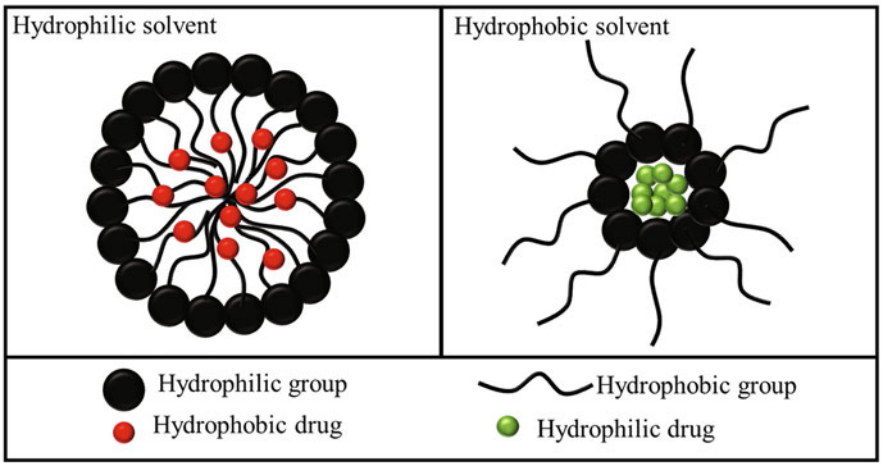

Fig. 8 Schematic structure of micelles in a hydrophilic and hydrophobic solvent

Okano 1996). Figure 8 shows the structure of micelles in hydrophilic and hydrophobic solvents, micelles can organize depending on the environment. These systems have a longer lifetime in the bloodstream and more load capacity than liposomes, however, the facility to penetrate membranes and biocompatibility are lower, and only can load hydrophobic drugs. The self-assembly process is thermodynamic and reversible. It is the product of an entropy increase by the liberation of the water that was around hydrophobic blocks; as a result, micelles are very stable systems over their CMC although dissociate below this (Gong et al. 2020).

Recently, it has grown studies about the use of micelles to improve the efficacy of some drugs since they have a local carrier behavior (Guo et al. 2020). Sonawane et al. designed polymeric micelles for vancomycin load, used an amphiphilic block copolymer, which contains a hydrazone bond cleavable by pH (Sonawane et al. 2017). Polymeric micelles were achieved with a CMC of 6 μg mL^{-1} and reached an entrapment efficiency of 39.61% with a 3.6% load. Showing an improved release of the pH-dependent drug and antibiotic activity against strains of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (Sonawane et al. 2020).

6.2 Stimuli Sensitive Polymers

Stimuli sensitive polymers or smart polymers can produce reversible changes in their conformation when be exposed to small variations in their environment. These variations may be physical such as temperature, light, magnetism, and electricity, or chemical such as pH, ionic strength, and presence of bioactive chemical species (antigens, enzymes, etc.) (Qiu and Park 2001). Smart polymers have been widely used for the development of local drug delivery systems since these may respond to

the environment in the target site (Alvarez-Lorenzo et al. 2016). Localized drug delivery systems for infections have the advantage that infection sites show a chemical environment that differs significantly from finding in the organism, characterized by a lower pH (<7.1) and overexpression of enzymes and toxins (Simmen et al. 1994).

According to their physical form, stimuli sensitive polymers can be classified in: free linear chains in solution, covalently cross-linked gels, and grafted chains (Kumar et al. 2007; Bajpai et al. 2016). The first are polymer chains that collapse after a stimulus is applied, which produces precipitation of polymer in solution forming a different phase. Many of these materials change at physiological conditions, minimizing invasive injectable systems for implants or scaffold, and they are widely used in bioseparation processes. Covalently cross-linked gels are microscopic or macroscopic networks that show a change in their separation when be subjected to a stimulus. They are the most investigated for their high storage capacity, which mainly depends on the porosity of the material. They can be synthesized with different pore sizes, generate interconnected pore systems or multi-sensitive interpenetrated networks (Maleki et al. 2016; Zhu 2019). Often, they are used for flow control, biological sensors, and drug delivery systems (Liechty et al. 2010). For example, Boppana et al. fabricated a pH-sensitive interpenetrated network of polyacrylamide-g-locust bean gum (PAAm-g-LBG) that allows intestinal targeted delivery of ketoprofen, in vitro studies, showed a release around 90% in phosphate buffer of pH 7.4 in comparison with 10.6% in pH 1.2 buffer, this system could reduce side effects of ketoprofen (Boppana et al. 2019). Finally, grafted chains allow the production of intelligent surfaces. In this case, the chains collapse on the surface, providing it with hydrophilic or hydrophobic characteristics depending on the conditions of the environment. The change produced will depend on the percentage of modification and the size of the grafted layer (Rubio et al. 2017).

6.2.1 Thermosensitive Polymers

Thermosensitive materials are polymers that are characterized by having a critical solution temperature (T_c), to which occurs a change from a hydrophilic to a hydrophobic state or vice versa. There is a conformational transition from the open coil to globule (Gandhi et al. 2015; Teotia et al. 2015). To present this property polymer structure requires having an amphiphilic composition with a balance in the proportion of hydrophilic and hydrophobic molecules. Hydrophilic part interacts with the solvent through intermolecular forces (hydrogen bridges, dipole-dipole, and ion-dipole interactions) allowing open coil structure, while hydrophobic allows the auto-association of the chains for the formation of globules during the transition (Le et al. 2018; Zarrintaj et al. 2019). Two cases of sensitivity occur lower critical solution temperature polymers and upper critical solution temperature polymers.

Lower critical solution temperature (LCST) polymers show hydrophilicity at temperatures below T_c, and hydrophobicity above it (Clark and Lipson 2012); this change in the properties of the material occurs for its transition of open coil form to

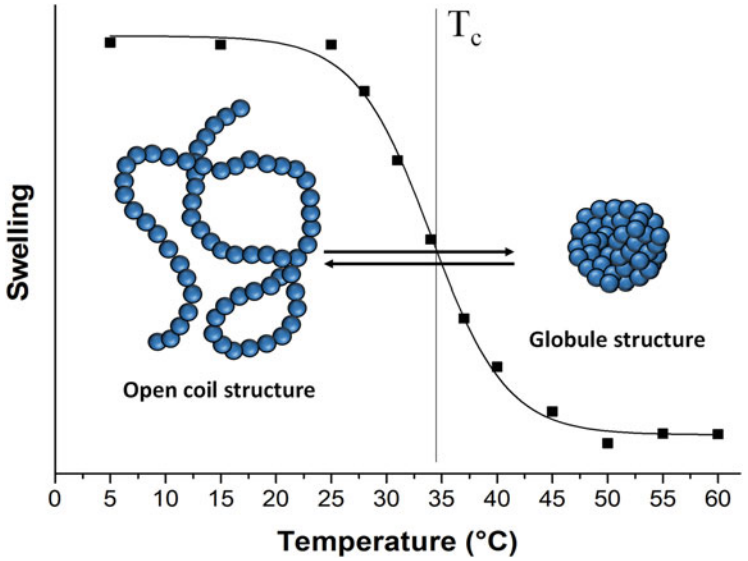

Fig. 9 Critical temperature of a LCST polymer

globular shape, as a result of an increase in the entropy of the system that exceeds enthalpy contribution of the water-polymer intermolecular interactions and leading stabilization to the system by intramolecular hydrophobic forces (Kamath et al. 2013). Figure 9 shows the model behavior of these materials. T_c only depends on the concentration or molecular weight under limit conditions (very diluted or very concentrated), under standard conditions it is related to the hydrophobic/hydrophilic balance in the polymer structure and can be modified by forming copolymers; the binding of hydrophilic monomers increases T_c while the binding to hydrophobic monomers decreases it (Gandhi et al. 2015). These materials are widely used in biomedical applications since their T_c is close to body temperature. Examples of polymers with LCST are poly(*N*-isopropylacrylamide) (PNIPAAm) (Do Nascimento Marques et al. 2015) and poly(*N*-vinylcaprolactam) (PNVCL) (Yang et al. 2020).

Higher critical solution temperature (UCST) polymers are insoluble at temperatures below T_c, but solubility increases at exceeded it. Owing to the forces that maintain the polymer-solvent interactions are broken, as a result, the transition from globular structure to open coil is observed (Seuring and Agarwal 2012). These materials are uncommon in biomedical applications since their T_c is normally at temperatures greater than 50 °C (Clark and Lipson 2012; Blackman et al. 2019). However, currently works look for the formation of copolymers that allow increasing the application range. Poly(methacrylic acid) (Illescas and Burillo 2009) and zwitterionic polymers (Yang et al. 2010) are examples of polymers with this behavior.

For antimicrobial local drug delivery, these systems have been used in implants where the corporal temperature is used as stimuli or as a coating of carriers capable of producing hyperthermia or together with laser irradiation-assisted photothermal therapy (Muñoz-Muñoz et al. 2015; Amoli-Diva et al. 2017). For example, Ramstad et al. synthesized photothermal response polymersomes using a diblock polymer of PNIPAAm and poly(lactic-co-glycolic acid), and gold nanoparticles. In which the gold nanoparticles embedded in the membrane of the system respond to infrared radiation generating highly localized hot spots that result in a rapid change of the amphiphilicity of PNIPAM, which produces holes in the membrane, triggering the release of the drug on the site of interest (Amstad et al. 2012).

6.2.2 pH-Sensitive Polymers

pH-sensitive polymers consist of chains with ionizable groups (cationic or anionic), which have charges depending on the conditions of the medium. Anionic polymers generally have acid groups in their structure, which undergo partial dissociation in aqueous solution. The grade of dissociation depends on the pH of the medium, acid strength, bond polarity, molecule size, and conjugate base stability. The dissociation process occurs because, under determinate conditions of the medium, the ion form is more stable by solvation forces (Rizwan et al. 2017). On the other hand, cationic polymers have structures with amines, which protonate at pH below their pKa. This process of protonation/deprotonation occurs as a result of pH variations and produces chains with equal charges that repel, triggering an increment in the swelling to reduce stress. So cationic polymers such as chitosan (Noel et al. 2008) and polyethyleneimine (Li et al. 2020) show a greater swelling at acidic pH (lower than their pKa). While anionic polymers such as carboxymethyl chitosan and poly (acrylic acid) (Pertici et al. 2019) swell at basic pH (higher than their pKa). This swelling change is very sharp, in narrow ranges of 0.2–0.3 pH units (Gupta and Damodharan 2019).

For antimicrobial treatments, pH sensitivity is one of the best tools, since infections might induce an acidic microenvironment (low pH) as a result of their metabolic activities and immune response, which allows a specific and local response of the material (Simmen et al. 1994). Taking this into account many studies have been performed (Cheng et al. 2015; Cao et al. 2019). Polymeric micelles of poly(ethylene glycol) (PEG) and poly(β-amino ester) were synthesized to be used as carriers of triclosan, a potent antibacterial, and fungicidal agent, for the treatment of staphylococcal biofilms. Poly(β-amino ester) is a pH-sensitive polymer, which undergoes protonation at low pH, close to that of infectious foci while remaining neutral at physiological pH. It was observed that the micelles achieved a penetration of the biofilm, accumulating inside due to electrostatic interactions and allowing the localized release of the drug by diffusion. Besides, the system maintains stability in plasma conditions and increasing the effectiveness of the treatment (Liu et al. 2016). Similarly, polymeric nanoparticles of 2-(dimethylamino) ethyl methacrylate (DMAEMA), butyl methacrylate (BMA), and 2-propylacrylic acid (PAA) showed

positive results for the treatment of cariogenic biofilms, from the pH-controlled release of farnesol, a hydrophobic antibacterial drug. This system reduced both the number and severity of carious lesions in comparison with free drugs. In addition, formulation directs the release and protects the drug (Horev et al. 2015).

6.2.3 Magnetic Sensitive Materials

Magnetic sensitive materials are ferromagnetic or ferrimagnetic materials that respond at an external magnetic field. For drug delivery systems exist two ways to use these materials magnetic hyperthermia and magnetic deformation of gels. In both cases, the formulation can be guided at a target site with a magnetic field (Gutfleisch 2001; Liu et al. 2019).

When ferromagnetic or ferrimagnetic materials are subjected to magnetization and demagnetization processes, in the presence of an alternating field, show heating by energy dissipation, this process is called magnetic hyperthermia (Obaidat et al. 2015). The loss of energy can be given for two phenomena: hysteresis and parasitic currents. Energy losses by hysteresis are the result of the difference between the energy transferred to the field during magnetization and the energy returned in demagnetization, and energy losses by parasitic currents are induced by variations in the magnetic flux and can be reduced with an increase in the resistivity of the material. Magnetic hyperthermia can be used as a local treatment for some types of cancer (Mallory et al. 2016), magnetic nanoparticles are put inside the tumor and exposed at the alternating magnetic field, which increases tumor temperature and can shrink them (Kumar and Mohammad 2011). However, the use of magnetic hyperthermia to stimuli a thermosensitive system is more common. In these systems, magnetic particles are placed in thermosensitive material (polymer, liposome, micelle) and when hyperthermia occurs, the release system is activated (Chen et al. 2019, 2020), Figure 10 shows a schema of this phenomena.

In general, localized hyperthermia treatment in combination with encapsulated drugs can result in higher accumulation of the drug in the target site (Kong et al. 2000; Farr et al. 2018). For example, chitosan microbeads crosslinked with polyethylene glycol dimethacrylate and embedded with magnetic iron oxide

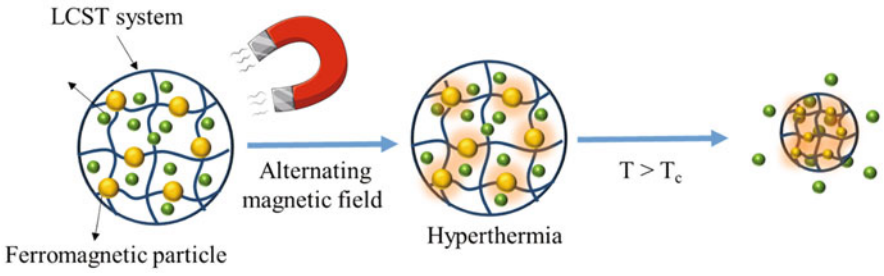

Fig. 10 Schema of a thermosensitive system stimulate by magnetic hyperthermia

nanoparticles were used for controlling vancomycin delivery and studying the influence of magnetic stimulation over this. The system showed greater release when subjected to an external magnetic field generating hyperthermia that destabilizes the polymer and allows greater diffusion of the drug (Mohapatra et al. 2018). Sirivisoot and Harrison also used iron oxide nanoparticles to generate hyperthermia, in this case, nanoparticles were embedded in polycaprolactone microspheres to increase the release of ciprofloxacin, showing improvements in *Staphylococcus aureus* inhibition (Sirivisoot and Harrison 2015).

Another way of using magnetism in sensitive stimulus systems is with magnetic gels, in which nanometric-sized magnetic particles are dispersed in a highly elastic polymer matrix. These systems are characterized in that the magnetic particles couple the shape of the elastomer to the external magnetic fields, since the forces acting on the particles are transmitted directly to the polymer chains, resulting in a deformation that occurs instantaneously and disappears sharply when apply or delete external fields (Zrinyi 2014).

6.2.4 Ionic Force Sensitive Polymers

Ionic strength sensitivity is a characteristic of polymers with ionizable groups in their chains, which also generate pH sensitivity. The ionic strength in a solution is a measure of the concentration of ions present. Ionizable groups at a certain pH dissociate forming ions that increase the ionic strength of the solution (Rasool et al. 2010). In the sensitive stimulus systems, whether cationic or anionic, an increase in swelling is observed by having ionized groups, since equal charges are generated that repel forming a larger interstitial space. By exposing systems to ion-rich environments, they can interact with chain ions by stabilizing them and decreasing swelling (Cabane et al. 2012). Another type of ionic strength sensitive system is zwitterionic polymers that have both anionic and cationic characteristics. These zwitterionic materials exhibit an agglomeration behavior because of attractive interactions between species with opposite charges, which can be decreased by ion presence. So, the polymer can be insoluble in deionized water but soluble in the presence of a critical concentration of electrolytes (Laschewsky 2014; He et al. 2016). Pimenta et al. studied the modification of intraocular lenses with zwitterionic polymers as an alternative for prolonged local administration of moxifloxacin for the prevention of post-operative acute endophthalmitis. Finding effective results against *Staphylococcus aureus* and *Staphylococcus epidermidis* until 12 days after the start, for poly acid 2-acrylamide-2-methylpropane sulfonic modified lenses by plasma-assisted graft, without being cytotoxic (Pimenta et al. 2017).

6.2.5 Chemical Sensitive Polymers

Chemical sensitivity is a phenomenon in which a receptor recognizes and identifies a chemical species through a set of structurally well-defined molecular interactions

(Singh and Nath 2013; Jin et al. 2019). Bacterial infections exhibit overexpression of specific enzymes, including β-galactosidases, alkaline phosphatases, nitroreductases, proteinases, lipases, phospholipases, and hyaluronidases, which are determinants for the survival of infections (Su et al. 2019). This characteristic allows the localization of infectious focus, so they are used to trigger chemical sensitive drug carriers.

There are few studies about these systems but recent reports show them in a good choice (Pornpattananangkul et al. 2011; Xiong et al. 2012; Li et al. 2014). For example, a recent study shows a photosensitive metal-organic framework (MOF) system loaded with Ag ions and coated with hyaluronic acid (HA) as an antimicrobial alternative. The MOF was synthesized with 5,10,15,20-tetrakis (4-methoxycarbonylphenyl) porphyrin (TCPP) as ligands and Zr_6 groups as metal nodes, due to its high porosity, this structure allowed the load of an antimicrobial agent (Ag). Finally, the coating of HA gives high biocompatibility to the system, and in the presence of bacteria with high secretion of hyaluronidase, it is degraded and allows the release of Ag^+ ions that inactivate them in a more efficient and focused way (Zhang et al. 2019). Following the same path, Li et al. synthesized polymeric vesicles sensitive to β-lactamase and G amidase (important enzymes overproduced by different pathogens) from amphiphilic copolymers, consisting of a hydrophilic PEG block and a hydrophobic block, which contains a degradable backbone by the target enzyme, to be tested as carriers of various antibiotics, through an erosion controlled release (Li et al. 2016).

7 Targeted Drug Delivery System

As mentioned throughout the chapter, both localized delivery systems with the method of administration will depend on the target organ. To improve the treatment of infections in organs that are difficult to access by the systemic route, different alternatives have been studied, below are presented some specific delivery systems for treatments in the lungs, brain, and eyes.

7.1 Lung-Specific Antibiotic Delivery

Antibiotic administrated by inhalation allows a localized control increasing the bioavailability in the respiratory tract. This method has been used since the 1940s for the treatment of chronic infections with the use of aerosol formulations. Currently, some antibiotics are accepted by the FDA for use by this route, among which are amphotericin (liposomal form), colistin (solution and dry powder), and tobramycin (solution and dry powder) (Quon et al. 2014).

Additionally, inhalation treatments have been developed, for example, with levofloxacin for advanced cystic fibrosis, and liposomal amikacin for the treatment

of pulmonary disease of the *Mycobacterium avium* complex (Geller et al. 2011). These inhaled systems are under continuous improvement, for example, Reiter, et al. have studied the use of allicin, a natural antibiotic with a low bioavailability when is administrated via oral, for the treatment of lung infections, through an in vitro pulmonary platform, which allowed to accurately model the exposure to medications, they found that the model has the potential to determine the dosage regimes for bacteria that have different resistance to individual antibiotics, which would help in the development of better treatments (Reiter et al. 2020).

On the other hand, Falciani et al. manufactured a nanosystem consisting of the SET-M33 peptide captured in dextran nanoparticles, this peptide is a synthetic antimicrobial-resistant to degradation in biological fluids, the system proved to be effective against *Pseudomonas aeruginosa* with in vivo experiments with a mouse model of pneumonia, the system also showed a longer pulmonary residence time than the aerosolized peptide (Falciani et al. 2020).

7.2 Brain-Specific Antimicrobial Delivery

Infections of the brain are mainly from bacterial origin but also from viruses or fungi vectors of high risk, which treatment is especially tough. Many antimicrobials may target the brain tissue with a different degree of effectiveness, the main classes of anti-infectives with a certain degree of activity into the central nervous system are β-lactams, aminoglycosides, fluoroquinolones, macrolides, tetracyclines, oxazolidinones, metronidazole, rifamycins, sulfonamides, glycopeptides, peptides, antiretrovirals, antifungals, and anti-parasitic drugs (Nau et al. 2010).

One of the most relevant problems related to antimicrobial administration is the need to reach penetration in the nervous central system and keeping the integrity of the blood-brain barrier, which is an indispensable requirement for efficient delivery and to avoid possible side-effects. Intrinsically, some antibiotics may produce severe effects that trigger the development of neuropsychiatric disorders, particularly when administrated at an early age. For example, a study in mice during the perinatal period showed that small doses of penicillin provoke adverse effects of long-term in the progeny, said adverse effects are prolonged anxiety, aggression, and reduced social behavior (Leclercq et al. 2017).

Nevertheless, due to the low permeability of some hydro soluble antibiotics in the blood–brain barrier (Neuwelt et al. 1984), the treatment of infections in the central nervous system requires an administration of drugs locally (Slavc et al. 2018); otherwise, a non-local administration may yield to an ineffective therapy due a low bioavailability (Xie et al. 2015). These issues may be treated using intracerebroventricular devices that allow a direct administration, the use of these devices may help to control the dosage of antimicrobial by slow bolus injection in an isovolumetric delivery. For example, an implanted intracerebroventricular device eases the therapy, making it convenient for the healthcare of patients with chronic treatments (Slavc et al. 2018).

Additional menaces after infection in brain tissue may arise, for example, in neurocysticercosis (NCC) that is originated by a parasite with a heteroxenous life cycle, it causes the most damage in the human brain tissue by the formation of larval cysts, the vector is the pork tapeworm (*Taenia solium*). Being the risk of death is latent, no matter if the cysticidal is administrated in time, because during the posttreatment phase, an inflammatory response may occur. Therefore, the combination of drugs such as anti-inflammatory, anti-tumor necrosis agents, and/or corticosteroids work better throughout the therapy (Mahanty et al. 2017).

Overcoming the concerns associated with drug delivery to the brain may be solved by developing materials, such as lipid nanoparticles, liposomes, dendrimers, poly dendrimers, or polymeric nanoparticles; in which stimuli-responsive properties are exploited (Bors and Erdő 2019). A concrete example is the nanomaterial of PEG/cholesterol micelles of average diameter smaller than 180 nm and loaded with ciprofloxacin, which was specifically designed to penetrate the blood–brain barrier under simulated physiological conditions (pH 7.4 at 37 °C) (Liu et al. 2008).

7.3 Ophthalmic-Specific Antimicrobial Delivery

The eye is an organ which function is vital to perceive the environment, but due to its partial exposure to the outside, it becomes susceptible to form microbial biofilms, this is particularly true during surgery processes. In this section are revised some aspects related to bacterial infections and local antimicrobial therapy in ophthalmic treatments.

Antibiotics are widely used during ophthalmic surgery in both pre-operative and post-operative because the organ is prone to infection as a result of its exposure. A common post-operatory issue associated with the optic organ is endophthalmitis. This inflammatory response to ocular surgery may produce irritation, hyperemia, chemosis, lid edema, and/or blurred vision.

The most severe cases are also complicated with hypopyon or vitritis because of an unfavorable recovery. Exposure to bacteria is the main responsible for these complications, among the more pathogenic there are *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Bacillus sp*., and Coliforms (Starr 1983). Specifically, due to the low penetration of antimicrobials administered via topical, systemically, or by periocular injections, an alternative as the intravitreal injection is indicated to avoid endophthalmitis.

Although intravitreal injection has inherent disadvantages as an invasive maneuver, being the cause of retinal toxicity, the balance ratio, among pros and cons, favors the administration of antimicrobials via intravitreal injection (Baum et al. 1982). Medical studies have proved that the administration of antibiotics during the pre-operative stage reduces significantly the probability of infection (Allen and Mangiaracine 1974). Even with the adverse effects of antibiotics during local administration, therapeutic prophylaxis is highly recommended over a post-

operatory systemic administration. Despite some examples of ophthalmic antibiotics as chloramphenicol, which causing aplastic anemia (Fahmy 1980).

The degree of success for containing bacterial proliferation and complications derived will depend on the correct choice of antibiotic. Local administration of wide-spectrum antibiotics as trimethoprim and polymyxin B (a natural macrolide) may help to treat the most bacterial infections associated. Also, penicillin antibiotics as ampicillin, amoxicillin, cloxacillin, dicloxacillin, and penicillin G may be applied via subconjunctival or topical (Lesar and Fiscella 1985). Nonetheless, it is more extended the use of fluoroquinolones like ciprofloxacin, norfloxacin, and ofloxacin, also these options are available of local administrations and helpful of intraocular infections, these antibiotics act by inhibition of bacterial enzyme DNA gyrase as well as by other intracellular mechanisms.

8 Conclusion

The next generation of antimicrobial materials are double-purpose, the first is to satisfy the function for which they were designed and the second is to achieve a local antimicrobial delivery. Therefore, these systems provide better opportunities to carry and release the antimicrobial in the target organ, either during intensive or prophylactic infections treatment. Besides, they are designed to overcome the inherent limitations of pharmacokinetics and pharmacodynamics of systemic administration. Strategies for achieving antimicrobial materials include modifying the shape and size of metallic or lipid nanoparticles, finding the right balance of solubility between liposoluble and hydrosoluble, and endowing the material with stimuli-responsive features (pH, temperature, magnetic or photo responsiveness). Antimicrobial materials aim to improve pharmacological parameters of selectivity and efficacy, while are minimized side effects. Local delivery systems are especially useful for manufacturing biomedical devices, sanitary materials, anti-biofilms, and antibiotic systems.

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References

Akbarzadeh A et al (2013) Liposome: classification, preparation, and applications. Nanoscale Res Lett 8(102):1–9. https://doi.org/10.1186/1556-276X-8-102

Allen HF, Mangiaracine AB (1974) Bacterial endophthalmitis after cataract extraction. II. Incidence in 36,000 consecutive operations with special reference to preoperative topical antibiotics. Arch Ophthalmol 91(1):3–7. https://doi.org/10.1001/archopht.1974.03900060007002

Alt V, Franke J, Schnettler R (2015) Local delivery of antibiotics in the surgical treatment of bone infections. Tech Orthop 30(4):230–235. https://doi.org/10.1097/BTO.0000000000000153

Alvarez-Lorenzo C et al (2016) Stimuli-responsive polymers for antimicrobial therapy: drug targeting, contact-killing surfaces and competitive release. Expert Opin Drug Deliv 13 (8):1109–1119. https://doi.org/10.1080/17425247.2016.1178719

Amoli-Diva M, Sadighi-Bonabi R, Pourghazi K (2017) Laser-assisted triggered-drug release from silver nanoparticles-grafted dual-responsive polymer. Mater Sci Eng 76:536–542. https://doi.org/10.1016/j.msec.2017.03.089

Amstad E, Kim S-H, Weitz DA (2012) Photo- and thermoresponsive polymersomes for triggered release. Angew Chem Int Ed 51(50):12499–12503. https://doi.org/10.1002/anie.201206531

Anand A et al (2020) Development of antibiotic loaded mesoporous bioactive glass and its drug release kinetics. Ceram Int 46(4):5477–5483. https://doi.org/10.1016/j.ceramint.2019.10.264

Bajpai AK et al (2016) Smart biomaterial devices: polymers in biomedical sciences, vol 1. CRC Press, Boca Raton

Baum U, Peyman GA, Barza M (1982) Intravitreal administration of antibiotic in the treatment of bacterial endophthalmitis. III. Consensus. Surv Ophthalmol 26(4):204–206. https://doi.org/10.1016/0039-6257(82)90080-7

Berlanga M, Guerrero R (2016) Living together in biofilms: the microbial cell factory and its biotechnological implications. Microb Cell Factories 15(165):1–11. https://doi.org/10.1186/s12934-016-0569-5

Birrer GA et al (2001) Parenteral dosage forms. In: Ahuja S, Scypinski S (eds) Handbook of modern pharmaceutical analysis. Academic, Cambridge, pp 269–305. https://doi.org/10.1016/S0149-6395(01)80009-X

Blackman LD et al (2019) An introduction to zwitterionic polymer behavior and applications in solution and at surfaces. Chem Soc Rev 48(3):757–770. https://doi.org/10.1039/c8cs00508g

Boppana R et al (2019) Novel pH-sensitive interpenetrated network polyspheres of polyacrylamide-g-locust bean gum and sodium alginate for intestinal targeting of ketoprofen: In vitro and in vivo evaluation. Colloids Surf B: Biointerfaces 180:362–370. https://doi.org/10.1016/j.colsurfb.2019.04.060

Bors L, Erdő F (2019) Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. Sci Pharm 87(1):6–33. https://doi.org/10.3390/scipharm87010006

Brown RM, Semler MW (2019) Fluid management in sepsis. J Intensive Care Med 34(5):364–373. https://doi.org/10.1177/0885066618784861

Bruschi ML (2015) Main mechanisms to control the drug release. In: Bruschi ML (ed) Strategies to modify the drug release from pharmaceutical systems. Woodhead Publishing, Oxford, pp 37–62. https://doi.org/10.1016/B978-0-08-100092-2.00004-7

Bush K, Bradford PA (2016) β-lactams and β-lactamase inhibitors: an overview. Cold Spring Harb Perspect Med 6(8):1–22. https://doi.org/10.1101/cshperspect.a025247

Cabane E et al (2012) Stimuli-responsive polymers and their applications in nanomedicine. Biointerphases 7(9):1–28. https://doi.org/10.1007/s13758-011-0009-3

Cao J et al (2019) Phosphorylcholine-based polymer encapsulated chitosan nanoparticles enhance the penetration of antimicrobials in a Staphylococcal biofilm. ACS Macro Lett 8(6):651–657. https://doi.org/10.1021/acsmacrolett.9b00142

Chen W, Cheng C-A, Zink JI (2019) Spatial, temporal, and dose control of drug delivery using noninvasive magnetic stimulation. ACS Nano 13(2):1292–1308. https://doi.org/10.1021/acsnano.8b06655

Chen W et al (2020) Magnetic/pH-sensitive double-layer microrobots for drug delivery and sustained release. Appl Mater Today 19(100583):1–9. https://doi.org/10.1016/j.apmt.2020.100583

Cheng T et al (2015) A surface-adaptive nanocarrier to prolong circulation time and enhance cellular uptake. Chem Commun 51(81):14985–14988. https://doi.org/10.1039/C5CC05854F

Clark EA, Lipson JEG (2012) LCST and UCST behavior in polymer solutions and blends. Polymer 53(2):536–545. https://doi.org/10.1016/j.polymer.2011.11.045

Dafale NA et al (2016) Selection of appropriate analytical tools to determine the potency and bioactivity of antibiotics and antibiotic resistance. J Pharm Anal 6(4):207–213. https://doi.org/10.1016/j.jpha.2016.05.006

Daraee H et al (2016) Application of liposomes in medicine and drug delivery. Artif Cells Nanomed Biotechnol 44(1):381–391. https://doi.org/10.3109/21691401.2014.953633

Do Nascimento Marques N, Da Silva Maia AM, De Carvalho Balaban R (2015) Development of dual-sensitive smart polymers by grafting chitosan with poly (N-isopropylacrylamide): an overview. Polimeros 25(3):237–246. https://doi.org/10.1590/0104-1428.1744

Dubald M et al (2018) Ophthalmic drug delivery systems for antibiotherapy—a review. Pharmaceutics 10(1):10–40. https://doi.org/10.3390/pharmaceutics10010010

Fahmy JA (1980) Bacterial flora in relation to cataract extraction. V. Effects of topical antibiotics on the preoperative conjunctival flora. Acta Ophthalmol 58(4):567–575. https://doi.org/10.1111/j.1755-3768.1980.tb08298.x

Falciani C et al (2020) Antimicrobial peptide-loaded nanoparticles as inhalation therapy for pseudomonas aeruginosa infections. Int J Nanomedicine 15:1117–1128. https://doi.org/10.2147/IJN.S218966

Farr N et al (2018) Hyperthermia-enhanced targeted drug delivery using magnetic resonance-guided focussed ultrasound: a pre-clinical study in a genetic model of pancreatic cancer. Int J Hyperth 34(3):284–291. https://doi.org/10.1080/02656736.2017.1336675

Francois I et al (2006) Azoles: mode of antifungal action and resistance development. Effect of miconazole on endogenous reactive oxygen species production in Candida albicans. Anti-Infect Agents Med Chem 5(1):3–13. https://doi.org/10.2174/187152106774755554

Freeman CD, Klutman NE, Lamp KC (1997) Metronidazole. A therapeutic review and update. Drugs 54(5):679–708. https://doi.org/10.2165/00003495-199754050-00003

Gandhi A et al (2015) Studies on thermoresponsive polymers: phase behaviour, drug delivery and biomedical applications. Asian J Pharm Sci 10(2):99–107. https://doi.org/10.1016/j.ajps.2014.08.010

Geller DE et al (2011) Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa. Am J Respir Crit Care Med 183(11):1510–1516. https://doi.org/10.1164/rccm.201008-1293OC

Gibson GG, Skett P (1996) Pathways of drug metabolism. In: Gibson GG, Skett P (eds) Introduction to drug metabolism. Springer, Boston, pp 1–34. https://doi.org/10.1007/978-1-4899-6844-9_1

Gong F et al (2020) Drug-interactive mPEG-b-PLA-Phe(Boc) micelles enhance the tolerance and anti-tumor efficacy of docetaxel. Drug Deliv 27(1):238–247. https://doi.org/10.1080/10717544.2020.1718245

Gordetsky J et al (2018) Second opinion expert pathology review in bladder cancer: implications for patient care. Int J Surg Pathol 26(1):12–17. https://doi.org/10.1177/1066896917730903

Guo L-Y et al (2020) Evaluation of hypocrellin A-loaded lipase sensitive polymer micelles for intervening methicillin-resistant Staphylococcus aureus antibiotic-resistant bacterial infection. Mater Sci Eng 106:1–12. https://doi.org/10.1016/j.msec.2019.110230

Gupta NP, Damodharan N (2019) pH - responsive polymers and its application in drug delivery system and pharmaceutical field. Res J Pharm Technol 12(2):944–958. https://doi.org/10.5958/0974-360X.2019.00159.8

Gutfleisch O (2001) Basic principles of hard magnetic materials. In: Buschow KHJ et al (eds) Encyclopedia of materials: science and technology, 2nd edn. Elsevier, Oxford, pp 3719–3722. https://doi.org/10.1016/B0-08-043152-6/00663-X

Harper KD et al (2018) Administration of intravenous antibiotics in patients with open fractures is dependent on emergency room triaging. PLoS ONE 13(8):1–10. https://doi.org/10.1371/journal.pone.0202013

Hassanein MM (2019) Sulfonamides: far from obsolete. Int J Contemp Pediatr 6(6):2740–2745. https://doi.org/10.18203/2349-3291.ijcp20194768

He M et al (2016) Zwitterionic materials for antifouling membrane surface construction. Acta Biomater 40:142–152. https://doi.org/10.1016/j.actbio.2016.03.038
Hooper DC (1999) Mode of action of fluoroquinolones. Drugs 58(Supplement 2):6–10. https://doi.org/10.2165/00003495-199958002-00002
Horev B et al (2015) pH-activated nanoparticles for controlled topical delivery of farnesol to disrupt oral biofilm virulence. ACS Nano 9(3):2390–2404. https://doi.org/10.1021/nn507170s
Horton J (2000) Albendazole: a review of anthelmintic efficacy and safety in humans. Parasitology 121(S1):S113–S132. https://doi.org/10.1017/S0031182000007290
Illescas J, Burillo G (2009) pH- and temperature-responsive behavior of comb-type graft hydrogels of poly(acrylic acid) synthesized using gamma radiation. Macromol Mater Eng 294 (6–7):414–421. https://doi.org/10.1002/mame.200900006
Jin X et al (2019) Supramolecular nanoscale drug-delivery system with ordered structure. Natl Sci Rev 6(6):1128–1137. https://doi.org/10.1093/nsr/nwz018
Kamath G et al (2013) Thermodynamic considerations for solubility and conformational transitions of poly-N-isopropyl-acrylamide. Phys Chem Chem Phys 15(30):12667–12673. https://doi.org/10.1039/c3cp44076a
Kok-Yong S, Lawrence L (2015) Drug distribution and drug elimination. In: Ahmed TA (ed) Basic pharmacokinetic concepts and some clinical applications. InTech, London. https://doi.org/10.5772/59929
Kong G et al (2000) Efficacy of liposomes and hyperthermia in a human tumor xenograft model: importance of triggered drug release. Cancer Res 60(24):6950–6957
Kotra LP, Haddad J, Mobashery S (2000) Aminoglycosides: perspectives on mechanisms of action and resistance and strategies to counter resistance. Antimicrob Agents Chemother 44 (12):3249–3256. https://doi.org/10.1128/AAC.44.12.3249-3256.2000
Kumar CSSR, Mohammad F (2011) Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Adv Drug Deliv Rev 63(9):789–808. https://doi.org/10.1016/j.addr.2011.03.008
Kumar A et al (2007) Smart polymers: physical forms and bioengineering applications. Prog Polym Sci 32(10):1205–1237. https://doi.org/10.1016/j.progpolymsci.2007.05.003
Kunisawa J et al (2005) Fusogenic liposome delivers encapsulated nanoparticles for cytosolic controlled gene release. J Control Release 105(3):344–353. https://doi.org/10.1016/j.jconrel.2005.03.020
Kwon GS, Okano T (1996) Polymeric micelles as new drug carriers. Adv Drug Deliv Rev 21 (2):107–116. https://doi.org/10.1016/S0169-409X(96)00401-2
Laschewsky A (2014) Structures and synthesis of zwitterionic polymers. Polymers 6:1544–1601. https://doi.org/10.3390/polym6051544
Le PN, Huynh CK, Tran NQ (2018) Advances in thermosensitive polymer-grafted platforms for biomedical applications. Mater Sci Eng 92:1016–1030. https://doi.org/10.1016/j.msec.2018.02.006
Leclercq S et al (2017) Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. Nat Commun 8(1):1–12. https://doi.org/10.1038/ncomms15062
Leppert W et al (2018) Transdermal and topical drug administration in the treatment of pain. Molecules 23(3):681–696. https://doi.org/10.3390/molecules23030681
Lesar TS, Fiscella RG (1985) Antimicrobial drug delivery to the eye. Drug Intell Clin Pharm 19 (9):642–654. https://doi.org/10.1177/106002808501900905
Levison ME, Levison JH (2009) Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin N Am 23(4):791–815. https://doi.org/10.1016/j.idc.2009.06.008
Li L et al (2014) Core–shell supramolecular gelatin nanoparticles for adaptive and “on-demand” antibiotic delivery. ACS Nano 8(5):4975–4983. https://doi.org/10.1021/nn501040h
Li Y et al (2016) Enzyme-responsive polymeric vesicles for bacterial-strain-selective delivery of antimicrobial agents. Angew Chem Int Ed 55(5):1760–1764. https://doi.org/10.1002/anie.201509401

Li W, Ju B, Zhang S (2020) Novel amphiphilic cellulose nanocrystals for pH-responsive pickering emulsions. Carbohydr Polym 229(115401):1–10. https://doi.org/10.1016/j.carbpol.2019.115401

Liechty WB et al (2010) Polymers for drug delivery systems. Annu Rev Chem Biomol Eng 1:149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847

Liu L et al (2008) Polymeric micelles anchored with TAT for delivery of antibiotics across the blood-brain barrier. Biopolymers 90(5):617–623. https://doi.org/10.1002/bip.20998

Liu Y et al (2016) Surface-adaptive, antimicrobially loaded, micellar nanocarriers with enhanced penetration and killing efficiency in Staphylococcal biofilms. ACS Nano 10(4):4779–4789. https://doi.org/10.1021/acsnano.6b01370

Liu JF et al (2019) Use of magnetic fields and nanoparticles to trigger drug release and improve tumor targeting. Nanomed Nanobiotechnol 11(e1571):1–18. https://doi.org/10.1002/wnan.1571

Lopez-Berestein G et al (1985) Liposomal amphotericin B for the treatment of systemic fungal infections in patients with cancer: a preliminary study. J Infect Dis 151(4):704–710. https://doi.org/10.1093/infdis/151.4.704

Lu W et al (2008) The use of solid lipid nanoparticles to target a lipophilic molecule to the liver after intravenous administration to mice. Int J Biol Macromol 43(3):320–324. https://doi.org/10.1016/j.ijbiomac.2008.06.006

Mahanty S et al (2017) TNF-α blockade suppresses pericystic inflammation following anthelmintic treatment in porcine neurocysticercosis. PLOS Negl Trop Dis 11(11):e0006059. https://doi.org/10.1371/journal.pntd.0006059

Maleki H et al (2016) Synthesis and biomedical applications of aerogels: possibilities and challenges. Adv Colloid Interf Sci 236:1–27. https://doi.org/10.1016/j.cis.2016.05.011

Mallory M et al (2016) Therapeutic hyperthermia: the old, the new, and the upcoming. Crit Rev Oncol 97:56–64. https://doi.org/10.1016/j.critrevonc.2015.08.003

Mast N et al (2013) Antifungal azoles: structural insights into undesired tight binding to cholesterol-metabolizing CYP46A1. Mol Pharmacol 84(1):86–94. https://doi.org/10.1124/mol.113.085902

Milkovich G, Piazza CJ (1991) Considerations in comparing intravenous and intramuscular antibiotics. Chemotherapy 37(2):1–13. https://doi.org/10.1159/000238912

Mohapatra A et al (2018) Magnetic stimulus responsive vancomycin drug delivery system based on chitosan microbeads embedded with magnetic nanoparticles. J Biomed Mater Res Pt B 106 (6):2169–2176. https://doi.org/10.1002/jbm.b.34015

Mosges R, Eichel A, Nematian-Samani B (2011) Treatment of acute otitis externa with ciprofloxacin otic 0.2% antibiotic ear solution. Ther Clin Risk Manag 7:325–336. https://doi.org/10.2147/TCRM.S6769

Muñoz-Muñoz F et al (2015) Gamma ray radiation in the design of smart systems for controlled drug release and tissue engineering. In: De Sousa HC, Braga MEM, Sosnik A (eds) Biomateriais aplicados ao desenvolvimento de sistemas terapêuticos avançados. University of Coimbra, Coimbra, pp 485–519. https://doi.org/10.14195/978-989-26-0881-5_12

Nau R, Sorgel F, Eiffert H (2010) Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 23 (4):858–883. https://doi.org/10.1128/CMR.00007-10

Neuwelt EA et al (1984) Cerebrovascular permeability and delivery of gentamicin to normal brain and experimental brain abscess in rats. J Neurosurg 61(3):430–439. https://doi.org/10.3171/jns.1984.61.3.0430

Ning Y-M et al (2007) Liposomal doxorubicin in combination with bortezomib for relapsed or refractory multiple myeloma. Oncology 21(12):1503–1516

Noel SP et al (2008) Chitosan films: a potential local drug delivery system for antibiotics. Clin Orthop Relat Res 466(6):1377–1382. https://doi.org/10.1007/s11999-008-0228-1

Obaidat I, Issa B, Haik Y (2015) Magnetic properties of magnetic nanoparticles for efficient hyperthermia. Nanomaterials 5:63–89. https://doi.org/10.3390/nano5010063

Olusanya TOB et al (2018) Liposomal drug delivery systems and anticancer drugs. Molecules 23 (907):1–27. https://doi.org/10.3390/molecules23040907

Osmani R et al (2014) In-situ forming parenteral drug delivery: a new-fangled loom in therapeutics. Am J Pharm Health Res 2:20–47

Paderni C et al (2012) Oral local drug delivery and new perspectives in oral drug formulation. Oral Surg Oral Med Oral Pathol Oral Radiol 114(3):e25–e34. https://doi.org/10.1016/j.oooo.2012.02.016

Patel R, Patel K (2010) Advances in novel parentral drug delivery systems. Asian J Pharm 4 (3):193–199. https://doi.org/10.4103/0973-8398.72117

Pertici V et al (2019) Degradable and injectable hydrogel for drug delivery in soft tissues. Biomacromolecules 20(1):149–163. https://doi.org/10.1021/acs.biomac.8b01242

Pimenta AFR et al (2017) Controlled release of moxifloxacin from intraocular lenses modified by Ar plasma-assisted grafting with AMPS or SBMA: an in vitro study. Colloids Surf B: Biointerfaces 156:95–103. https://doi.org/10.1016/j.colsurfb.2017.04.060

Pornpattananangkul D et al (2011) Bacterial toxin-triggered drug release from gold nanoparticle-stabilized liposomes for the treatment of bacterial infection. J Am Chem Soc 133 (11):4132–4139. https://doi.org/10.1021/ja111110e

Prasad R, Pandey R, Varma A, Barman I (2017) Polymer based nanoparticles for drug delivery systems and cancer therapeutics. In: Kharkwal H, Janaswamy S (eds) Natural polymers for drug delivery. CAB International, Wallingford, pp 53–70

Prasad R, Siddhardha B, Dyavaiah M (2020) Nanostructures for antimicrobial and antibiofilm applications. Springer International Publishing, Cham. ISBN 978-3-030-40336-2. https://www.springer.com/gp/book/9783030403362

Qiu Y, Park K (2001) Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 53 (3):321–339. https://doi.org/10.1016/S0169-409X(01)00203-4

Quon BS, Goss CH, Ramsey BW (2014) Inhaled antibiotics for lower airway infections. Ann Am Thorac Soc 11(3):425–434. https://doi.org/10.1513/AnnalsATS.201311-395FR

Rasool N et al (2010) Synthesis and characterization of novel pH-, ionic strength and temperature-sensitive hydrogel for insulin delivery. Polymer 51(8):1687–1693. https://doi.org/10.1016/j.polymer.2010.02.013

Reiter J et al (2020) Investigation of the deposition behaviour and antibacterial effectivity of allicin aerosols and vapour using a lung model. Exp Ther Med 19(2):1541–1549. https://doi.org/10.3892/etm.2019.8387

Rezk AI et al (2019) Drug release and kinetic models of anticancer drug (BTZ) from a pH-responsive alginate polydopamine hydrogel: towards cancer chemotherapy. Int J Biol Macromol 141:388–400. https://doi.org/10.1016/j.ijbiomac.2019.09.013

Rizwan M et al (2017) pH sensitive hydrogels in drug delivery: brief history, properties, swelling, and release mechanism, material selection and applications. Polymers 9(137):1–37. https://doi.org/10.3390/polym9040137

Rubio N et al (2017) Grafting from versus grafting to approaches for the functionalization of fraphene nanoplatelets with poly(methyl methacrylate). Macromolecules 50(18):7070–7079. https://doi.org/10.1021/acs.macromol.7b01047

Saraf S et al (2020) Advances in liposomal drug delivery to cancer: an overview. J Drug Deliv Sci Technol 56(101549):1–14. https://doi.org/10.1016/j.jddst.2020.101549

Schwach-Abdellaoui K et al (2002) Controlled delivery of metoclopramide using an injectable semi-solid poly(ortho ester) for veterinary application. Int J Pharm 248(1):31–37. https://doi.org/10.1016/S0378-5173(02)00314-9

Sercombe L et al (2015) Advances and challenges of liposome assisted drug delivery. Front Pharmacol 6(286):1–13. https://doi.org/10.3389/fphar.2015.00286

Seuring J, Agarwal S (2012) Polymers with upper critical solution temperature in aqueous solution. Macromol Rapid Commun 33(22):1898–1920. https://doi.org/10.1002/marc.201200433

Siepmann J, Siegel RA, Rathbone MJ (2012) Fundamentals and applications of controlled release drug delivery. In: Siepmann J, Siegel RA, Rathbone MJ (eds) Fundamentals and applications of controlled release drug delivery. Springer, New York, pp 127–152. https://doi.org/10.1007/978-1-4614-0881-9

Simmen H-P et al (1994) Analysis of pH, pO2 and pCO2 in drainage fluid allows for rapid detection of infectious complications during the follow-up period after abdominal surgery. Infection 22 (6):386–389. https://doi.org/10.1007/BF01715494

Singh PK, Nath S (2013) Molecular recognition controlled delivery of a small molecule from a nanocarrier to natural DNA. J Phys Chem B 117(36):10370–10375. https://doi.org/10.1021/jp402902k

Sirivisoot S, Harrison BS (2015) Magnetically stimulated ciprofloxacin release from polymeric microspheres entrapping iron oxide nanoparticles. Int J Nanomedicine 10:4447–4458. https://doi.org/10.2147/IJN.S82830

Sköld O (2000) Sulfonamide resistance: mechanisms and trends. Drug Resist Updat 3(3):155–160. https://doi.org/10.1054/drup.2000.0146

Slavc I et al (2018) Best practices for the use of intracerebroventricular drug delivery devices. Mol Genet Metab 124(3):184–188. https://doi.org/10.1016/j.ymgme.2018.05.003

Sonawane SJ, Kalhapure RS, Govender T (2017) Hydrazone linkages in pH responsive drug delivery systems. Eur J Pharm Sci 99:45–65. https://doi.org/10.1016/j.ejps.2016.12.011

Sonawane SJ et al (2020) AB2-type amphiphilic block copolymer containing a pH-cleavable hydrazone linkage for targeted antibiotic delivery. Int J Pharm 575(118948):1–11. https://doi.org/10.1016/j.ijpharm.2019.118948

Spížek J, Řezanka T (2017) Lincosamides: chemical structure, biosynthesis, mechanism of action, resistance, and applications. Biochem Pharmacol 133:20–28. https://doi.org/10.1016/j.bcp.2016.12.001

Starr MB (1983) Prophylactic antibiotics for ophthalmic surgery. Surv Ophthalmol 27(6):353–373. https://doi.org/10.1016/0039-6257(83)90193-5

Su L et al (2019) Recent advances and future prospects on adaptive biomaterials for antimicrobial applications. Macromol Biosci 19(1900289):1–11. https://doi.org/10.1002/mabi.201900289

Teotia AK, Sami H, Kumar A (2015) Thermo-responsive polymers: structure and design of smart materials. In: Zhang ZBT-S (ed) Switchable and responsive surfaces and materials for biomedical applications. Woodhead Publishing, Oxford, pp 3–43. https://doi.org/10.1016/B978-0-85709-713-2.00001-8

Thornton Spann C, Taylor SC, Weinberg JM (2004) Topical antimicrobial agents in dermatology. Dis Mon 50(7):407–421. https://doi.org/10.1016/j.disamonth.2004.05.011

Weiss M (1984) Definition of pharmacokinetic parameters: influence of the sampling site. J Pharmacokinet Biopharm 12(2):167–175. https://doi.org/10.1007/BF01059276

White RE (2000) High-throughput screening in drug metabolism and pharmacokinetic support of drug discovery. Annu Rev Pharmacol Toxicol 40(1):133–157. https://doi.org/10.1146/annurev.pharmtox.40.1.133

Wilson CG (2013) Oral drug delivery. In: Ratner BD et al (eds) Biomaterials science, 3rd edn. Academic, Cambridge, pp 1083–1087. https://doi.org/10.1016/B978-0-08-087780-8.00102-9

Xie H et al (2015) Pharmacokinetics and bioavailability of a therapeutic enzyme (idursulfase) in cynomolgus monkeys after intrathecal and intravenous administration. PLoS ONE 10(4): e0122453. https://doi.org/10.1371/journal.pone.0122453

Xiong M-H et al (2012) Bacteria-responsive multifunctional nanogel for targeted antibiotic delivery. Adv Mater 24(46):6175–6180. https://doi.org/10.1002/adma.201202847

Yang WW, Pierstorff E (2012) Reservoir-based polymer drug delivery systems. J Lab Automat 17 (1):50–58. https://doi.org/10.1177/2211068211428189

Yang YF et al (2010) Surface hydrophilization of microporous polypropylene membrane by grafting zwitterionic polymer for anti-biofouling. J Membr Sci 362(1–2):255–264. https://doi.org/10.1016/j.memsci.2010.06.048

Yang X et al (2020) Cellulose-based polymeric emulsifier stabilized poly(N-vinylcaprolactam) hydrogel with temperature and pH responsiveness. Int J Biol Macromol 143:190–199. https://doi.org/10.1016/j.ijbiomac.2019.12.019

Zarrintaj P et al (2019) Thermo-sensitive polymers in medicine: a review. Eur Polym J 117:402–423. https://doi.org/10.1016/j.eurpolymj.2019.05.024

Zhanel GG et al (2007) Comparative review of the carbapenems. Drugs 67(7):1027–1052. https://doi.org/10.2165/00003495-200767070-00006

Zhang L et al (2013) Antibiotic administration routes significantly influence the levels of antibiotic resistance in gut microbiota. Antimicrob Agents Chemother 57(8):3659–3666. https://doi.org/10.1128/AAC.00670-13

Zhang Y et al (2019) Silver-infused porphyrinic metal–organic framework: surface-adaptive, on-demand nanoplatform for synergistic bacteria killing and wound disinfection. Adv Funct Mater 29(11):1–9. https://doi.org/10.1002/adfm.201808594

Zhu F (2019) Starch based aerogels: production, properties and applications. Trends Food Sci Technol 89:1–10. https://doi.org/10.1016/j.tifs.2019.05.001

Zrinyi M (2014) Magnetically responsive polymer gels and elastomers: properties, synthesis and applications. In: Smart polymers and their applications. Elsevier, London, pp 134–165. https://doi.org/10.1533/9780857097026.1.134

Antimicrobial Membranes for Water Treatment

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Abstract Biofouling is an ongoing problem that decreases the efficiency of membranes used in wastewater treatment. Fortunately, numerous efforts have been dedicated to improving the antibacterial performance. Providing an effective antibacterial membrane includes methods as grafting, coating, and blending. These methods in most cases involve the addition of antibacterial agents. The modification of membranes aims to prevent bacterial accumulation by bacteriostatic or bactericidal mechanisms. This chapter describes several studies to obtain modified antibacterial membranes, which were developed mainly for water treatment. Particular attention was paid to polymeric membrane modifications by introducing antibacterial agents through different methods to provide antimicrobial activity.

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1 Introduction

Water is vital for human beings and this is essential for many domestic activities, industries, and agronomy, among others. In the last century, global water demand increased at least sevenfold, and this continues increasing with the world´s demography and economy. Nevertheless, water resources are not sufficient to cover the constant and increasing demand, thus becoming a serious social and global problem that causes millions of deaths annually. Unfortunately, major sewage effluent has been identified to discharge notorious anthropogenic pollutants to the aquatic system. Therefore, new water treatments must develop to supply the world's constant water demand, thus protecting the freshwater resources.

Membranes are a competitive, fast, and easy alternative for water treatment (Juang et al. 2007). Membranes present more advantages compared with other water treatment technologies, a membrane is a selective porous material that acts as a filtration medium that allows the selective passage of molecules, ions, or other small particles.

Nowadays, membranes are widely used to eliminate contaminants from water and wastewater. However, despite their enormous success, they have some serious limitations caused by the fouling, which is the result of different factors such as, colloids, chemical compounds, and microorganisms. These factors require special attention because their removal can result in expensive membrane cleaning and replacement. Although extensive research has been conducted, significant challenges still remain in successfully mitigating membrane fouling. Therefore, this chapter will focus on the manufacture of membranes with antimicrobial features.

2 Types of Membranes

Pressure driven membrane processes are classified into different types as reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), and microfiltration (MF). These membrane systems are constantly applied in water and wastewater treatment, biotechnology, food industry, and medicine due to compact size, ease of maintenance, excellent separation efficiency, high yields of purified water. Membranes are mainly polymeric, ceramic, or hybrids depending on the material used to manufacture them.

- *Microfiltration (MF)*: MF is responsible for removing particles with sizes greater than 0.08–2 μm and operates with a range of 7–100 kPa. MF is used to eliminate residual particles, bacteria, and as a previous step to other treatments such as RO.

- *Ultrafiltration (UF)*: UF is capable of removing not only particles larger than 0.005–2 μm in size and operates in a range of 70–700 kPa, but also removing high molecular weight compounds, such as proteins, endotoxins, and carbohydrates, as well as removes virus.
- *Nanofiltration (NF)*: NF is also known to reject particles smaller than 0.002 μm, and this is also used to remove selectively dissolved compounds from wastewater.
- *Reverse osmosis (RO)*: RO is used in many processes to remove dissolved components from water that may remain after advanced treatments. RO removes ions, but requires high pressures between 850 and 7000 kPa to produce ion-free water.

2.1 Ceramic Membranes

Ceramic membranes are basically made of different inorganic materials such as alumina, zirconia, silica, and titanium. These kinds of membranes are recognized for their several advantages compared to polymeric membranes, and these include: (1) a relatively narrow pore distribution with higher porosity, which improves flow and separation properties, (2) better mechanical stability that allows higher pressures in washing processes, (3) greater chemical stability that increases the useful life of the membrane (Moulin et al. 1991; Tsuru 2001; Ciora and Liu 2003; Van Der Bruggen et al. 2003; Oh et al. 2007), and fouling mitigation due to increased hydrophilicity (Van Der Bruggen et al. 2003).

The ceramic membranes are more prone to rupture compared to polymeric membranes (Lerch et al. 2005; Meyn et al. 2008; Shiraishi et al. 2009), but nevertheless, they generally operate at a higher flow compared to polymeric membranes, and backwashing and cleaning procedures are very different than polymeric membranes. On the other hand, polymeric membranes are more versatile for application and modification; therefore, they are more commonly used for specific purposes for example to remove ions, viruses, bacteria, and proteins, among others.

2.2 Polymeric Membranes

Polymeric membranes are the most studied in water treatment due to their versatility compared to other membrane types. Polymeric materials offer the possibility to create and develop membranes targeting specific purposes with high antibacterial efficiency in a one-step process excluding pretreatments or post-treatments. Different membrane morphologies, pore sizes, and properties can be tailored in a membrane by controlling the conditions of the manufacturing process. Usual polymeric membrane manufacturing approaches include phase inversion or phase separation, electrospinning, cross-linking, sintering melt-spinning, cold-stretching, and track

etching among others, offering each method unique advantages and limitations associated with the pore formation process (Tan and Rodrigue 2019a, b).

The polymer used to manufacture the membrane can modify the hydrophilicity of this, which is a very important characteristic since it can determine the membrane´s fouling degree (Park et al. 2005). Similarly, the hydrophilicity of ceramic membranes depends on the manufacturing materials that can cover a broad range like polymeric membranes (Baroña et al. 2007; Zhang et al. 2009; Dobrak et al. 2010). Furthermore, the degree of fouling of polymeric membranes can be controlled by changing the chemical properties of the surface of the latter; in addition to this, other studies also reported that polymeric membranes are more susceptible to adhering to polysaccharides than inorganic membranes.

3 Polymeric Membranes Manufacturing

Continuous research has developed several methods for manufacturing polymeric membranes, among them, the phase inversion method stands out. Although, there are other methods that include electrospinning, track etching, cross-linking, sol-gel, and many more that are continuously emerging as membranes are being endowed with specific properties and characteristics methods.

3.1 Phase Inversion Method

The most versatile manufacturing method to produce porous and non-porous membranes is through phase inversion also known as phase separation (Fig. 1). It consists of a demixing process in which a homogeneous polymer solution passes into a solid-state in a controlled manner (Lalia et al. 2013). There are four approaches that are for this method described as follows:

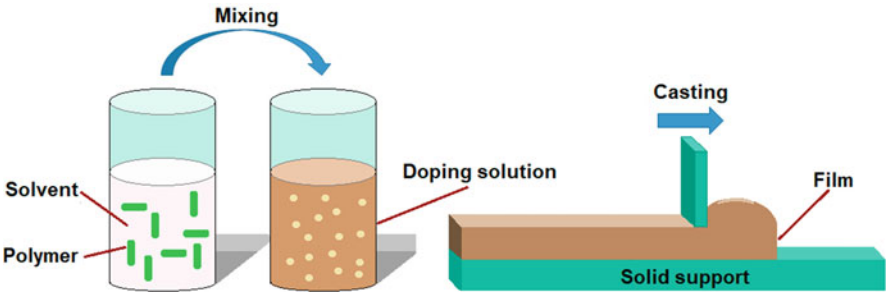

Fig. 1 General scheme of phase inversion method

- *Nonsolvent immersion precipitation (NIPS)* is an approach in which a homogeneous polymer solution is cast on a support, then immersed in a coagulation solution that typically uses water as the solvent. In the coagulation solution, an exchange of solvents takes place that gives form to the membrane (Lalia et al. 2013).
- *Thermally induced phase separation (TIPS)* involves cooling a molten polymer solution to allow phase separation. After inducing separation of the mixture, the solvent was removed by extraction, evaporation, or lyophilization, thereby forming a porous membrane (Tan and Rodrigue 2019a, b).
- *Evaporation-induced phase separation (EIPS)* is a process where a polymer is dissolved in a solvent or in a mixture of a volatile nonsolvent, and cast on a porous support, followed by solvent evaporation in an inert atmosphere, leading to the formation or demixing/precipitation (Lalia et al. 2013).
- *Vapor-induced phase separation (VIPS)* is a process where a polymer solution is vaporized. The vapor phase contains a nonsolvent (usually humid air) that slowly diffuses through the porous membrane before immersion in a coagulation bath, allowing, this way, membranes with unique morphologies (Abitha and Thomas 2018).

3.2 Electrospinning Method

Electrospinning is the second most used membrane fabrication method and this consists of generating highly porous nanofibrous membranes from a variety of polymer (Asad et al. 2020). Electrospinning involves an electrohydrodynamic process in which a liquid droplet is electrified to generate a jet, followed by stretching and elongation to generate nanofibers which are then deposited on a grounded target (Fig. 2) (Feltz et al. 2017; Xue et al. 2019). Electrospinning leads to nonwoven membranes with relatively uniform pore size distribution with high interconnectivity of pores and significantly higher porosity, typically around 80% (Tijing et al. 2017).

3.3 Track-Etching Method

The track-etching process consists of the irradiation of a polymer membrane with high energy heavy ions to produce a linearly damaged track across the irradiated polymer membrane to form nanopores (Fig. 3) (Ramos-Ballesteros et al. 2019). The track-etching method offers precise control of the pore density (from 1 to 10^{10} pores cm^{-2}) and size (from nm to μm) distribution on the membrane (Wang et al. 2018a, b).

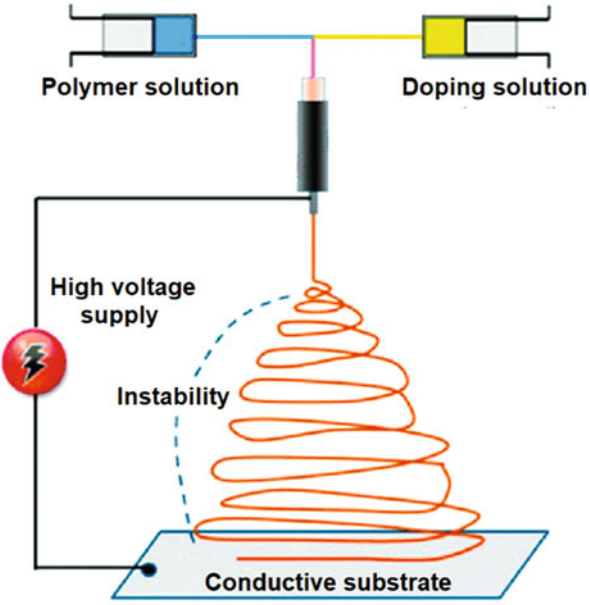

Fig. 2 General scheme of electrospinning method

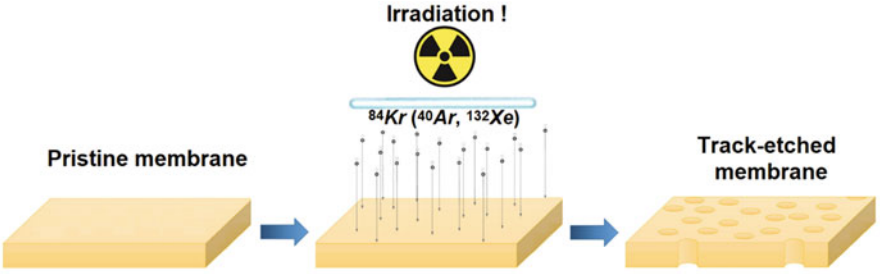

Fig. 3 General scheme of track-etching method

3.4 Cross-Linking Method

Cross-linking consists in the formation of covalent bonds between different polymer chains. Among other applications, cross-linking allows the manufacture of positively charged membranes (Lin et al. 2019). Cross-linking may be achieved via chemical, physical, or biological methods. Chemical cross-linking methods include free-radical polymerization, chemical reaction, high energy ionizing radiation (UV, gamma, or X-ray) (Flores-Rojas et al. 2018). Physical cross-linking may be reached by interactions other than covalent bonding, such as hydrogen bonding, hydrophobic interaction, ionic bonding, and coordinating bonding. A relatively new method is the biological cross-linking method which is achieved using enzymes (Mane et al. 2016).

3.5 Sol-Gel Method

Sol-gel is a method widely used for the manufacture of ceramic or hybrid polymeric-ceramic membranes. In general, this method comprises different approaches, where they all involve the formation of colloidal particles suspended in a liquid medium, colloidal particles can be inorganic, polymeric, or a mixture of both, and even it is possible to use a monomer to generate the hybrid colloidal particle by polymerization methods. When the colloidal particles sediment, they are heat-treated to obtain porous materials (Fig. 4) (Comite 2017).

3.6 Interfacial Polymerization Method

Interfacial polymerization is a technique used in developing ultrathin functional layers. Therefore, this technique is widely used in the manufacture of RO and NF membranes (Tul Muntha et al. 2017). Interfacial polymerization proceeds at the interface of two immiscible phases through a polycondensation or radical reaction between two highly reactive monomers (Fig. 5). Optionally, it is possible to provide the polymerization initiator or catalyst to one of the phases, resulting in a localized reaction and the formation of a polymer (Raaijmakers and Benes 2016; Song et al. 2017).

3.7 Thin Film Composite Method

Thin film composite (TFC) membranes are generally prepared via interfacial polymerization by forming a thin selective layer on the surface of the membrane. These selective layers improve significantly the selectivity and productivity of the

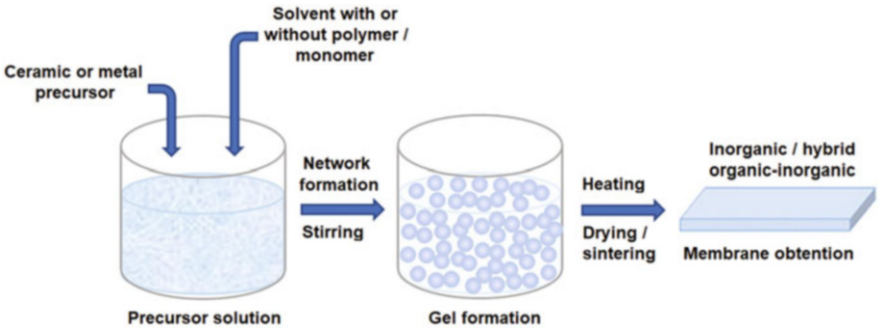

Fig. 4 General scheme of sol-gel method

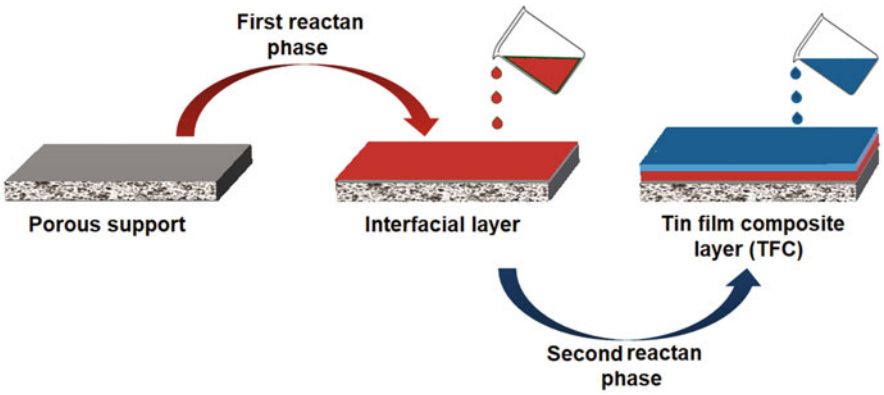

Fig. 5 General scheme of interfacial polymerization

membrane compared to typical asymmetric membranes (Ismail et al. 2015), thus providing, TFC membranes most efficient for example in the desalination processes.

3.8 Molecular Imprinting Method

Molecular printing is considered a technique that allows the construction of selective recognition sites through the use of a template that includes atoms, ions, molecules, complexes or a molecular, ionic or macromolecular assembly, as well as microorganisms (Chen et al. 2016). Molecularly printed materials are prepared using functional monomers that interact with the template and are after polymerized to form a printed matrix. Then, the template is removed from the matrix, leaving a specific recognition site (Rane et al. 2015).

4 Antimicrobial Polymeric Membranes

Several studies have focused on producing novel membranes through the surface and bulk modification with the capacity to decrease microbial attachment and antimicrobial activity. Proper modification can prevent biofilm formation and therefore reduce chemical cleaning cycles or biocide treatments. The antimicrobial and anti-adhesive properties provide the best solution to control membrane biofouling (Liu et al. 2010). Therefore, one strategy for biofouling control is based on the choosing of membrane materials that possess antibacterial affinity or can be easily cleaned. A different approach is to endow membranes with bacteriostatic or bactericidal properties through modification methods that can effectively inhibit the

growth of microorganisms (Hilal et al. 2003). The most effective strategy to modify membranes includes approaches such as blending, grafting, coating, loading, doping, or incorporating inorganic, antimicrobial additives or nanoparticles (NPs). These methods offer a solution to prevent membrane biofouling and improve water flow performance.

4.1 Blending

Blending is a robust method to change the physicochemical behavior of membranes (Kim and Lee 1998). These membranes are formed by a polymer matrix, which is mixed with organic or inorganic compounds (Goh et al. 2016), this method offers the possibility to obtain organic-inorganic hybrid membranes, improving their unique properties such as selectivity, permeability, mechanical strength, and thermal and chemical stability (Souza and Quadri 2013). Some of the problems associated with the blending method are the poor miscibility of raw materials and the stability that they can be present in the manufacturing process.

In this context, research is further presented, describing how antimicrobial membranes have been developed, using bactericidal agents such as fillers NPs, polymers, and carbon nanostructures, among others. The most reported method in literature for blending has been phase inversion. This method allows the stabilization of the blended components during the cast ensuring a better functionality.

4.1.1 Organic Fillers

Organic additives have been widely combined with several polymers in order to obtain antimicrobial membranes. Organic additives can provide antimicrobial activity through the formation of rich in oxygen compounds, quaternary ammonium and zwitterionic moieties, and natural polymers with antimicrobial activity such as chitosan.

Adding antibacterial agents to the polymer in the phase inversion process is the easiest way to obtain antibacterial membranes, for instance, antibacterial UF membranes were prepared by this method adding cethyltrimethylammonium bromide (CTAB) to a polymeric matrix of polysulfone (PSU) and polyethersulfone (PES). CTAB is a strong bactericidal compound and the membranes prepared with a non-critical and critical micelle concentration (CMC) exhibited antibacterial activity on both gram-negative and gram-positive bacteria. Membranes prepared with a CMC detected almost 100% recovery after bacterial filtration, along with leaching experiments detected that 96% of CTAB remained in the membrane (Cihanoğlu and Altinkaya 2020).

Likewise, Kakihana et al. (2017) fabricated an antibacterial polyvinylidene fluoride (PVDF) membrane by a simple modification. For these PVDF membranes, it was added a copolymer of methyl methacrylate (MMA) and dimethylamino-2-ethyl methacrylate (DMAEMA) that was quaternized with iodomethane. The cationic copolymer added to PVDF membrane provides antibacterial activity against *Escherichia coli*, high adhesion resistance. In the same context, sulfonated polyethersulfone/polyrhodanine (SPES/PRh) membranes were synthesized with antibacterial activity via nonsolvent phase inversion method (NIPS). The membrane showed an improved flux, antibacterial, and antibiofouling properties. Antibacterial activity tests reached a 100% bacterial mortality for some membranes and inhibition zones up to 9 mm (Rostam et al. 2018).

RO membranes reported by Waheed et al. (2014) were synthesized with a mixer of cellulose acetate/polyethylene glycol-chitosan polymers. Membrane characteristics were improved by the incorporation of chitosan. All modified membranes exhibited remarkable antibacterial properties compared to the control membrane which showed bacterial growth. The biocidal effect was completely attributed to chitosan which has natural antimicrobial properties.

Padil et al. (2015) functionalized PVA electrospun nanofiber membranes blended with deacetylated gum Kondagogu, and dodecenylsuccinic anhydride. Here, an oxygen plasma treatment was used to crosslink the electrospun nanofiber membranes. The modified membranes presented better stability and hydrophilic properties, which was observed by a diminution in the water contact angle. Antibacterial testing, indicted that the unmodified membrane had no antibacterial potential, whereas inhibition zones around the plasma modified membranes were 8.0 mm for *Escherichia coli,* 7.0 mm for *Pseudomonas aeruginosa,* and 9.0 mm for *Staphylococcus aureus*.

Several carbon nanostructures have been employed to efficiently functionalize membranes with antimicrobial activity. In this regard, Zhang et al. (2019) fabricated antibacterial PSU mixed matrix membranes by UF and incorporating graphene-guanidyl by the NIPS method. Membranes exhibited high permeability, a prominent antifouling property, and antimicrobial activity against *S. aureus* and *E. coli* caused by graphene oxide (GO) action, with the bacterial cytoplasmic membrane, and with the phosphate and guanidyl groups of the bacterial wall, thus inactivating the bacteria. Similar membranes were developed with antifouling and antibacterial properties from sulfonated PES-PSU membranes and GO via a phase inversion method. The obtained membranes showed an 816.9 L h^{-1} m^{-2} water flux and more than 99.2% of BSA rejection under a pressure of 0.1 MPa. Furthermore, the modified membranes also performed a 94.2% of fouling recovery, and 90.0% of antibacterial activity against *E. coli* (Hu et al. 2019).

In another study, PES-carbon nanotubes for UF membranes were manufactured through the NIPS method. The functionalized membranes exhibited about 100% of antibacterial activity after 3 h applying 1.5 V cm^{-1} of direct electric current (Wang et al. 2018a, b). Using the same approach self-cleaning membranes were obtained by Sun et al. (2018). These membranes exhibited high antifouling properties and they

were able to reduce the fouling caused by organic matter in water. *N*-halamine epoxide and siloxane grafted onto multiwalled carbon nanotubes (N-Si-MWNTs) and PVDF were used by Huang et al. (2017) to fabricate hybrid, self-cleaning, antibacterial membranes by a phase separation approach. The functionalized membranes were tested for 3 days to observe their fouling-cleaning behavior, reaching a recovery ratio of over 96.5%. The antibacterial evaluation indicated bacterial death of 98.0% for *S. aureus* and 95.6% for *E. coli*.

4.1.2 Inorganic Fillers

Inorganic fillers include nano-metals such as Ag, TiO_2, Cu, ZnO, Al_2O_3, silica, ZrO_2, and $LiClO_4$ among others (Lin et al. 2002; Borkow and Gabbay 2005; Khayet et al. 2005; Yan et al. 2005; Dror-Ehre et al. 2009). Fillers are integrated into membranes to confer them with antibacterial abilities (Chen et al. 2013); the antimicrobial power of these NPs resides in characteristics such as their surface-area-to-volume-ratio and toxicity against a wide range of microorganisms. Interestingly, they are capable to deactivate bacterial cells by different mechanisms, including cytolysis, disruption of the cell membrane permeability, phosphorus and sulfur cell wall interactions, and metabolic inhibitions, among others (Jin et al. 2015).

For instance, Zodrow et al. (2009) studied the antibacterial effect of PSU membranes embedded with Ag NPs. The modified membranes demonstrated an excellent antimicrobial effect for the virus bacteriophage MS2, *E. coli*, and *Pseudomonas mendocina*. Further reports in the literature suggested (Morones et al. 2005) that the antibacterial effects of functionalized membranes were mainly caused by released Ag^+ able to damage bacterial cells, causing their inactivity. Furthermore, the functionalization of the membranes improved their antimicrobial activity and endowed them with anti-adhesive properties, thus, preventing the formation of biofilms. In a different study (Basri et al. 2011), PES membrane was modified by adding Ag NPs as an antibacterial agent, the results indicated that Ag NPs significantly enhanced the membrane performance, increasing the antibacterial activity and also improving the membrane hydrophilicity as the Ag NPs load was increased. Therefore, hybrid pressure driven membranes prepared with Ag NPs were able to mitigate biofouling and exhibited high antimicrobial activity (Zodrow et al. 2009). TiO_2 NPs have been applied to develop either ceramic or based hybrid membranes. TiO_2 NPs have been used along with an ultraviolet source to degrade contaminants before they reach the membrane surface and therefore preventing biofouling on the membrane surface (Zhang et al. 2008).

Nanolayered double hydroxide compounds (NLDH) own a hydrophilic character and these are extensively used as nanofillers in membranes. Ghalamchi et al. (2019b) integrated PES and Ag phosphate NLDH in microfiltration mixed-matrix membranes. Pure water flux for the modified membrane with 0.5 wt.%, nanocomposite content was 269.5 L m^{-2} h, whereas the pristine PES membrane performed 229.2 L m^{-2} h. Antibiofouling results for this membrane showed 62.3% of flux recovery ratio while for the PES membrane flux recovery ratio was 50.9%. In

addition, it was observed by an ICPOES method that a release of the nanocomposite was less than 5% after 2 months. The bacterial inhibition of the membranes toward *Bacillus anthracis*, *E. coli*, and *S. aureus* showed that the PES membranes containing Ag_3PO_4 and Ag_3PO_4-NLDH exhibited a vast inhibition halo in contrast to the unmodified membrane and the membrane that had no silver content.

ZnO and CuO particles have bactericidal properties against antibiotic resistant bacteria (Malwal and Gopinath 2017). Combining both types of particles enables materials with high antimicrobial potential for water. In this context, He et al. (2019) synthesized eggshell membranes incorporating ZnO and CuO NPs using a biotemplate. The antibacterial evaluation of modified membranes showed inhibition halos of 27.5 mm for *E. coli* and 20.3 mm for *S. aureus*. In the same context, Manaf et al. (2019) reported the fabrication of poly(acrylonitrile-co-butadiene-co-styrene) membranes embedded with ZnO NPs. The membrane was electrospun and then immersed in a ZnO NPs dispersion. The modified membranes were able to separate oil from an oil-water mix, but they performed better filtrating mineral oil than vegetable oil. The antibacterial evaluation showed that ZnO NPs were able to inhibit an 18 mm halo for *E. coli* and 22 mm for *S. aureus*, while the modified membrane showed an inhibition diameter zone of 10 and 11 mm, respectively (Manaf et al. 2019).

4.2 Grafting

Grafting has become an excellent method to modify a great variety of material thus imparting a variety of functional groups not only to polymeric membranes, but also to ceramic membranes. Grafting is a surface modification method, where the antimicrobial organic compounds can be integrated through polymer grafting conferring antimicrobial potential to the membrane. There are several techniques to induce the graft onto backbone chains, thus offering the possibility to produce antifouling membrane surfaces. Grafting can be performed, even at polymer matrix formation resulting in a bulk modification of the membrane. Among various approaches for surface modification, for instance, coating methods, modification by grafting presents extra advantages such as a more stable grafted polymer layer, controlled grafting, and the possibility of grafting.

There are several grafting approaches, in general they can be classified as follows:

- *Chemical graft* consists in generating free radicals and ionic species in the presence of one or more monomers to initiate graft polymerization. The free radical can be generated by a chemical initiator, or by means of oxidation-reduction reactions mixing the matrix polymer with monomers and inducing peroxidation of Ce^{4+} or Fe^{2+} (Flores-Rojas and Bucio 2016; Flores-Rojas et al. 2017).
- *Graft polymerization induced by gamma irradiation* is a more efficient method compared to chemical grafting mainly in that initiators are not required to induce the graft polymerization, eliminating their removal at later stages, although

sometimes it is completely impossible to remove initiators from the final material (Flores-Rojas and Bucio 2016).

- *Plasma induced or plasma treatment graft* is an approach used to introduce functional groups into the membrane to increase wettability, surface hydrophilicity, and to modify chemical and physical surface properties, while bulk properties remain the same (De Velasco-Maldonado et al. 2018). This technique can be done in a direct or indirect manner. The direct way exposes the membrane to plasma in the presence of a gas (i.e., oxygen, inert, fluorine, and nitrogen based) to introduce surface chemical groups. Similarly, in the indirect treatment, plasma generates active sites at the membrane surface inducing graft polymerization. In both, the characteristics of resulting material may depend on different factors including time, type of gas, pressure, energy input, and the composition of the substrate (Al-Jumaili et al. 2019).
- *Graft polymerization induced by UV* is a method that uses an argon gas flow ultraviolet (UV) lamp. The membrane is irradiated submersed in a monomeric solution. Irradiation generates free-radicals inducing graft polymerization between the membrane surface and the monomers. Alternatively, the polymeric membrane may be functionalized only by exposition to UV radiation. Photo induced grafting can produce desired and localized interface active species (Lee et al. 2018).
- *Atom Transfer Radical Polymerization (ATRP)* systems are conformed of an inorganic catalyst on which the atom transfer and the polymerization rate depends. In ATRP, the polymer structure and molecular weight are dynamically controlled, the polymer chains initially are short and grow through all process. The reaction rate may stop by reverse deactivation of reactive radicals (Eskandari et al. 2019; Messina et al. 2020).

Occasionally, polymers may be grafted onto antimicrobial membranes along with quaternary phosphonium or ammonium salts (Tashiro 2001), polyethylene oxide (Desai et al. 1992), and polymers containing chemical groups that allow the immobilization of antimicrobial drugs. However, quaternary ammonium salts are mostly used to enhance hydrophilic and antibacterial membrane properties.

Ma et al. (2017) prepared polystyrene membranes incorporated with trimethyl quaternary ammonium salt grafted lignin. Lignin was grafted with glycidyl quaternary ammonium salts by an etherification reaction. Antibacterial activity evaluation showed an inhibition halo of 10.4 ± 0.06 mm for functionalized membrane while the unfunctionalized membrane had no inhibition ability. In the same context, an antibacterial poly(vinyl chloride) membrane was manufactured by immersing the membrane in a trimethylamine solution. The monomer was grafted onto the membrane by substituting the chlorine atoms in the poly(vinyl chloride). Then, the obtained aminated membrane was immersed in a HCl solution, thus forming an ammonium salt quaternized surface. The surface charge of the functionalized membranes became positive, thus improving the membrane performance. Moreover, an antibacterial test showed that the unfunctionalized membrane had no antibacterial

property, whereas for the modified membranes the antibacterial rate was enhanced as the grafting percentage increased reaching up to 74.2% (Wu et al. 2018).

In this context, Liu et al. (2020) developed a separation membrane through a simple interface grafted polymerization induced by gamma irradiation to enhance the antichlorine and antifouling ability. A PSU membrane was layered with polyamide via interfacial polymerization, and then grafted with diallyl dimethyl ammonium chloride. The unmodified membrane performed a 97.35% of salt rejection, from a 2000 ppm of NaCl feed, while the grafted membranes rejected from 98.61% up to a 99.52%. It was also observed that the modified membranes had better antifouling abilities, and a maximum of 99.9% bacterial inhibition was observed when exposed to *S. aureus* for 24 h. In another investigation PVDF membranes were grafted with 4-vinyl pyridine by gamma irradiation and then immersed in a n-butylchloride-n-heptane solution to promote a quaternization process. It was observed that while the irradiation dose augmented there was a higher grafting percentage up to the point where it was steady. The modified quaternized membranes exhibited a bacterial contact-killing mechanism to *Escherichia coli* decreasing the bacterial concentration gradually (Gu and Jia 2013).

Modification of membrane surfaces can involve more than one process as it was demonstrated in the manufacture of antibacterial polyurethane membranes, prepared by argon plasma exposition, then grafted with 4-vinylpyridine by UV irradiation, and lastly immersed in a hexyl bromide solution to be quaternized. The antibacterial activity evaluation of the quaternized membranes proved up to 99.9% contact antibacterial rate for *E. coli* and 99.999% for *S. aureus* in 4 h.

Grafting modifications of membrane surfaces with electrostatic mechanisms may prevent protein fouling. Since most bacteria and proteins are inhibited, a negatively charged membrane surface may stop the formation of bio and organic fouling. A surface-functionalized membrane with positive and negative charged groups has high hydrophilicity and better antifouling properties. The bipolar betaines are polymers that have exceptional properties and endow the membranes with a high protein antifouling capacity (Liu et al. 2010).

Furthermore, zwitterions are electrically neutral molecules with simultaneous positive and negative charges. Due to their electrical nature, zwitterionic materials induce electrostatic repulsions that may translate in less protein surface adsorption by a formation of a hydration shell (Zhang et al. 2006). Besides, zwitterions are superhydrophilic and biocompatible materials that endow membrane surfaces with such characteristics (Ye et al. 2002).

Shi et al. prepared PES membranes with antifouling properties, using the grafting method which provided cationic tertiary amine groups and anionic sulfonic groups to the polymer matrix of PES, followed by the cast of the membrane through a phase inversion in a process wet using water or an aqueous solution of sodium chloride solution as a coagulation bath. The evaluations indicated that the membranes had superior protein antifouling properties and excellent ultrafiltration performance (Shi et al. 2008). Similarly, PVDF membranes were modified through the grafting of sulfobetaine methacrylate polymer (SBMA) (Fig. 6). The PVDF membranes were activated by ozone creating peroxide clusters that allowed radical grafting and

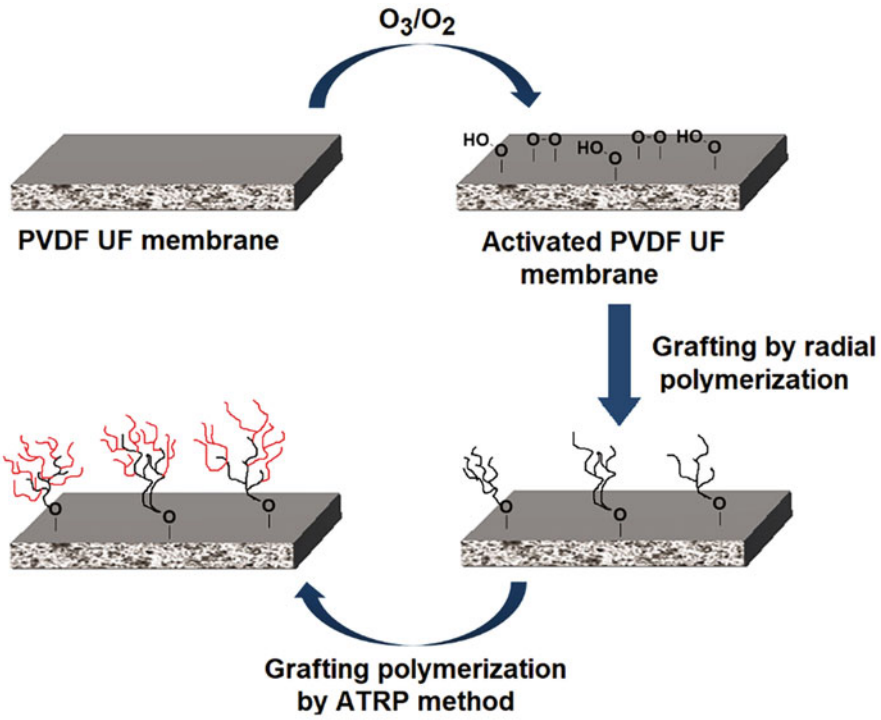

Fig. 6 Scheme of PVDF-g-SBMA membranes synthesized via ATRP polymerization

subsequently ATRP polymerization of SBMA. The characterization showed that SBMA was grafted not only on the membrane surface but also on the membrane pores. Bovine serum albumin (BSA) and γ-globulin attachment were evaluated; the results showed that some in the modified membranes had excellent antifouling properties (Chiang et al. 2009).

Also, SBMA was grafted onto polypropylene (PP) membranes modified with 2-hydroxyethyl methacrylate (HEMA). In the first step, pristine PP membranes were exposed to UV rays to graft the monomer HEMA, and then in the second step, SBMA was grafted by ATRP. The membranes (PP-g-HEMA)-g-SBMA showed good performance as protein filtration systems (Zhao et al. 2010a).

PP membranes grafted with zwitterionic brushes as [2-(methacryloyloxy)ethyl] trimethylammonium chloride and 3- sulfopropyl methacrylate potassium salt is a good way to obtain antifouling surfaces. Assays with BSA and lysozyme demonstrated that membranes containing zwitterionic chains were more resistant to biofouling (Ostuni et al. 2001; Zhao et al. 2010a, b).

Obtaining antibiofouling surfaces by grafting zwitterionic polymer allows the incorporation of nanostructures. In this regard, one study reported grafting a zwitterion polyampholite hydrogel onto a PES membrane by UV photoinitiation,

incorporating graphene oxide (GO) nanoblades into the swollen zwitterion by vacuum filtration. The modified membranes showed a mitigated fouling due to a lower propensity to absorb proteins. Contact-killing antibacterial test revealed that membranes with no GO had no toxicity toward *E. coli*, whereas a decline of nearly 80% of the *E. coli* colonies was observed whenever GO nanosheets were present (Zhang et al. 2018). A different approach to inhibit protein fouling and biofouling is to form high hydrophilic surfaces. Poly(ethylene glycol) (PEG) is an excellent candidate for this task and this is widely used to improve the hydrophilicity due to biocompatibility, along with nonspecific protein adsorption provided by the high steric hydration of the PEG. Unfortunately, PEG is a polymer that presents several issues such as the vulnerability to oxidative degradation and chain cleavage caused by aqueous systems and metal ions (Ostuni et al. 2001), loss of its protein antifouling capacity at temperatures above 35 °C (Susanto and Ulbricht 2007) as well as a change in the structure of the membrane and integrity associated with the high hydrophilicity of the graft (Chen et al. 1992).

4.3 Coating

Coating is an approach to modify a preformed membrane, such modification allows to endow the membrane surface with unique characteristics including hydrophilicity, surface texture, and charge. This surface modification can be done by the incorporation of particles or functionalizing agents onto the membrane surface by adsorption or absorption mechanisms. These agents may be coated on the membrane surface via vapor, a solution, a suspension, or a mixture. In some cases, they are crosslinked, overcoated, or treated so they will not leach and may last on the surface. Deposition can endow the membrane with desirable properties without changing the composition or weakening the strength of the matrix material (You et al. 2018, 2019). However, many coatings despite being treated may not have permanent physical and chemical resistance, therefore delamination of the coating material may occur during a chemical cleaning.

In this context, Wai et al. (2020) coated PES and polyvinylpyrrolidone (PVP), (PES/PVP) membranes with polydopamine (PDA) and Ag to improve their hydrophilicity and bactericidal properties. The antibacterial activity proved that the PES membrane was able to eliminate 96.4% *E. coli*, while modified membranes of&spi2;PES-PVP 99.33%, PDA/PES-PVP 99.85%, and Ag/PDA/PES-PVP 100%, respectively.

Immersing a membrane in a solution containing a functionalizing agent is the simplest membrane deposition technique. For instance, sodium hypochlorite is the most frequently used broad-spectrum antibacterial agent with a rapid bactericidal action (Fukuzaki 2006). In the same context, a membrane fabricated from cardo poly (aryl ether ketone) was functionalized by the deposition of sodium hypochlorite. The functionalized membrane showed antimicrobial ability eliminating 94.2% of *E. coli*

and 100% of *Bacillus subtilis*, respectively, when being in contact for 30 min, and about 100% of *E. coli* when in contact for 2 h (Hsueh et al. 2017).

Similarly, Lin et al. (2019) improved the surface of a polytetrafluoroethylene MF membrane by enhancing its fouling and bacterial inhibition properties by deposition of laccase-gallic acid and chitosan, followed by cross-linking with 3-triethoxysilylpropylamine. The study reported better hydrophilic and antibacterial properties for the functionalized membrane. The bacterial tests showed an inhibition zone around the modified membranes. In a different study, a multilayer coating was integrated onto a polyimide membrane, the coating was made by immersing in a tannic acid-metal salt, followed by dipping in a poly(dimethylsiloxane) metal solution (Al^{3+}, Cu^{2+}, and Ti^{4+}). The separation efficiency of membranes was about 99% and 5 ppm of oil in water was reported for twenty separation cycles. Antibacterial activity was assayed against *B. subtilis* and *E. coli*, and reported as inhibition zones around the membranes, attributed to the bactericidal properties of the metallic and phenolic components (Ma et al. 2020). Vacuum filtration deposition is an approach used to disperse particles along a membrane surface. In this perspective, a PDA coated membrane was functionalized by adding TiO_2 on its surface by vacuum filtration followed by the integration with antibacterial Ag NPs. The modified membrane became more hydrophilic due to TiO_2 and the water permeability was notably enhanced (40.6 L m^{-2} h^{-1} bar^{-1}) showing high dye removal. The modified membrane antibacterial activity exhibited 99.7% of inhibition growth (Lin et al. 2019).

Sui et al. (2012) modified membranes of PVDF through coating with 3,4-dihydroxyphenylalanine, followed by the ATRP grafting of 2-hydroxyethyl methacrylate (HEMA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA). The evaluation showed that PHEMA grafting provided to the membranes a higher water flux, thus being less prone to the protein attachment. While the antimicrobial activity was obtained by the quaternization of PVDF-g-DMAEMA, PVDF-g-DMAEMA-b-PHEMA membranes and evaluated against *S. aureus* exhibiting excellent antibacterial properties.

4.3.1 Modification of Membranes with Nanomaterials

To provide surface membranes with specific or precisely defined functions and antibacterial properties, many studies have turn to membrane modification by incorporating nanomaterials on its structure. The NPs used to develop antimicrobial membranes can be of different nature and they are classified into metallic NPs, ceramic NPs, polymeric NPs, and lipid-based NPs, among others (Khan et al. 2019). Membrane coating with NPs sometimes requires membrane surface preparation following either one of two techniques. One consists of generating functional groups capable of binding NPs and improving the NPs coat and durability. Functional groups include amines, carboxylates, thiols, or any other electron-donating chemical group. In the other technique, electron-donating groups are incorporated in the

polymer dope before membrane casting or chemical treatment is applied to the polymer dope to generate electron-donating groups.

In this context, by proper incorporation of antimicrobial nanomaterials, microorganisms are incapable to develop and form a surface biofilm, being this considered a permanent type of biofouling (Rahaman et al. 2014). The most investigated NPs are of Ag, it is reported in the literature as an exceptional biocidal due to its unique physicochemical features. Ag NPs are usually applied as a main water disinfectant agent because of its antibacterial, antifungal, and antiviral power (Zhang et al. 2016). Therefore, extensive research covering the antibacterial activity and the ability of these nanomaterials to mitigate biofouling is currently conducted. Moreover, research has found that certain types of polymeric NPs can provide novel alternatives to achieve antimicrobial surfaces.

For example, Yin et al. (2013) developed antimicrobial RO membranes by coating their surface with Ag NPs and cross-linking them, providing electron-donating thiol groups to promote bonding between the Ag NPs and the membrane surface (Fig. 7). The modified membranes water flux went from 67.1 L m^{-2} h^{-1} for the pristine membrane to 90.6 L m^{-2} h^{-1} for the surface modified membrane while the amount of salt removed was very close for both membranes. Flow tests revealed that there was a slight loss NPs from the membrane surface. Additionally, the antimicrobial tests with Ag NPs loaded showed better inhibition against *E. coli*.

In a different work, polyvinyl chloride ultrafiltration electrospun membranes were functionalized by incorporating Ag NPs. Results of antibacterial tests revealed that the pristine membrane was not able to inhibit bacteria, conversely, the functionalized membranes were able to inhibit bacterial growth and the inhibiting areas surrounding the membranes increased as the Ag NPs concentration increased in the surface (Behboudi et al. 2018).

Nanopolymers such as polyrhodanine have been reported as antimicrobial and antiviral agents since they may inhibit bacterial RNA synthesis (Aktij et al. 2017). Soleymani Lashkenrai et al. (2019) fabricated an antibacterial polyamide membrane, embedding polyrhodanine nanoparticles by a direct filtration method. Antibacterial tests showed that the modified membranes had an excellent biocidal potential toward

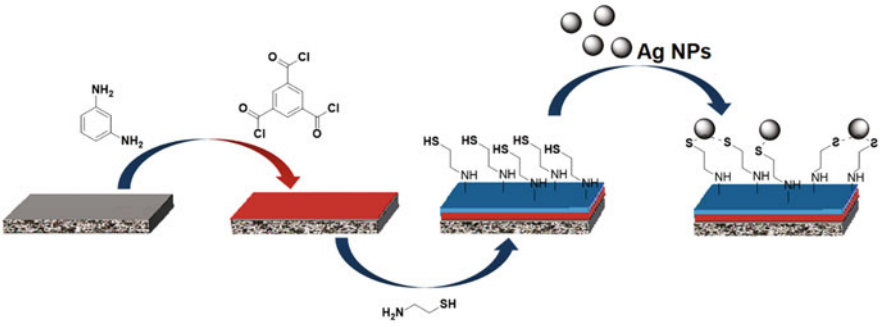

Fig. 7 Process of Ag NPs incorporation onto a TFC membrane

E*scherichia coli* and S*taphylococcus aureus* strains. A 24-h colony formation assay showed that bacteria inhibition was higher for nanopolymer composite membrane than for the unmodified one, making evident that the polyrhodanine NPs on the membrane surface induced bacterial death. Additionally, the membrane modified with 0.5% of NPs exhibited the best antifouling performance while the one with 0.75% performed the maximum salt removal.

A composite membrane is made up of one or more discontinuous phases embedded in a continuous phase (matrix). Therefore, a nanocomposite membrane is made up of a matrix material and one or more nanofillers which improve the matrix properties (Rallini and Kenny 2017). In this regard, Shukla et al. (2019) prepared an antibacterial nanocomposite membrane by incorporating carbon nanotubes onto a polyphenylsulfone membrane surface. The obtained membranes presented bacterial inhibition, enhanced antifouling ability, chemical and physical stability, and improved hydrophilic properties. Therefore, the modified membrane showed an effective salt rejection from aqueous solutions in contrast to the unmodified membrane. The bacteriostatic rate for the functionalized membrane was 80.43% toward *E. coli* and 86.02% for *S. aureus*.

Multiwalled carbon nanotubes (MWNTs) may form water-transport channels to improve the permeability of membranes, while blocking hydrated salt ions (Hu et al. 2019). Antibacterial hybrid PES membranes were prepared incorporating MWNTs previously modified with Ag NPs. The ultrafiltration functionalized membranes were evaluated using *E. coli* and *S. aureus*; results showed an improved antibacterial ability toward both strains. Membranes with a 10 wt% of Ag showed a higher bacterial inhibition compared to that of 20 wt% Ag content; inhibition zones were 19.7 mm for *E. coli* and 15.2 mm for *S. aureus* (Al Aani et al. 2017).

Zeolites are aluminosilicate minerals that possess high polarity and the ability to separate heavy toxic metals, chemical pesticides, among other compounds. In addition, they have a very high ability to absorb water and other polar materials, even if the concentration of these in the environment is very low (Kianfar 2019). Zeolites are usually modified with other materials for specific functions. For instance, zeolites were modified with silver compounds and then integrated onto the surface of a PVDF membrane through an electrospinning process by a tri-orifice spinneret. The antibacterial activity was evaluated by a bactericidal analysis; results showed that the viable bacteria remaining in a phosphate-buffered saline solution was 3.5%, indicating that 96.5% of *E. coli* bacteria were dead (Shi et al. 2014).

Other NPs used to provide antimicrobial activity are Fe NPs, Cu NPs, and TiO_2 NPs, among others, which have provided an option to Ag NPs since these have a less toxicity to human beings. For example, zero-valent iron NPs are widely utilized to degrade environmental contaminants. The antibacterial mechanism through Fe^0 NPs oxidation produces reactive-oxygen species which are highly toxic to microbial cells. These species damage the bacterial cell wall by oxidative stress, destroying the cell and causing bacterial death (Hsueh et al. 2017). Biocide Fe^0 NPs were grafted on a thin film membrane surface by two approaches. The first approach dipped the membrane into a Fe^0 NPs solution and curated. The second approach involved the deposition of a $FeCl_3$ solution on the membrane, and after dried,

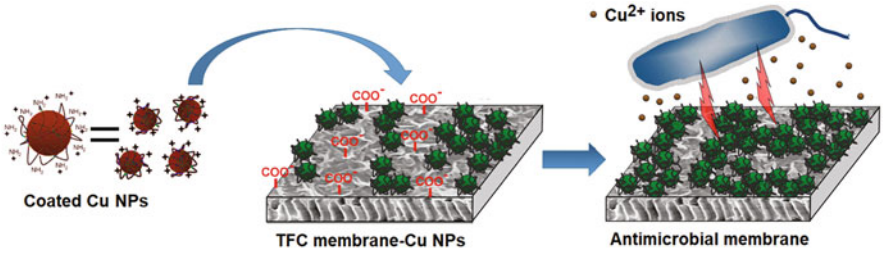

Fig. 8 Schematic method of immobilization of Cu NPs charged positively onto TFC membrane

immersion in a $NaBH_4$ solution to form Fe^0 on the surface. The unmodified membrane permeated 12.93 L m^{-2} h^{-1} of a NaCl solution whereas the membranes permeated 13.9 and 13.6 L m^{-2} h^{-1}, respectively. Likewise, flux recovery from river water using modified membranes was 89% and 71.29% using TFC membrane. Antibacterial evaluation with river or seawater natural bacteria showed an appropriate non-adhesion behavior on the Fe^0 NPs modified membrane (Khajouei et al. 2017).

In another study, Ben-Sasson et al. (2014) employed a simple dip-coating technique to functionalize a TFC surface membrane with a copper suspension coated with polyethylenimine (PEI). The positively charged PEI created an intense electrostatic pull to the TFC layer with a negative charge (Fig. 8). The biocidal activity was tested against *E. coli, S. aureus*, and *Pseudomonas aeruginosa*. The functionalized membranes with Cu NPs exhibited a significative 96% bacterial decrease after 1 h in contrast to the unmodified membrane.

The potential bactericidal property of TiO_2 NPs was examined by depositing them onto a TFC polyamide membranes. The modified membrane antibacterial ability was evaluated through exposition to different microbial suspensions under UV irradiation (Kim et al. 2003). The results indicated a considerable decrease of *E. coli* growth on the modified membrane in presence of UV light, while the pristine membrane showed a high bacterial growth.

5 Applications

5.1 Water Treatment and Purification

Water contamination is a worldwide issue that poses environmental and human health hazards. Contaminants in water are from different types, they can be natural or synthetic including physical, chemical, and biological. Water treatment and water purification are the most researched environmental issues. Treating water requires a series of process or steps and the application of different approaches that can be physical and/or chemical and may include filtration, centrifugation, sedimentation,

precipitation, coagulation, gravity and flocculation, microorganism degradation, oxidation, electrolysis, crystallization, distillation, photocatalysis, chelation, and adsorption among others (Bolisetty et al. 2019). Membrane systems are among the most reliable and widely used technologies to eliminate contaminants from water due to their high efficiency at low cost. At present, a considerable amount of research has been done regarding the design of novel, antibacterial, cost-effective, versatile, with tailored properties membranes for water purification. For instance, a mixed-matrix PES-chitosan-ZnO nanocomposite membrane was investigated to disinfect water by Munnawar et al. (2017). First, it was observed that increasing the content of the chitosan-ZnO nanocomposite on the membrane improved characteristics as a uniform pore size, adequate texture, and hydrophilic behavior. A biofouling test showed a decrease in bacterial colony counts for each membrane, thus membranes with 15% w/w NPs concentration were able to diminish fouling caused by both bacteria and fungi. The maximum water flux reported was 4135.8 J, for the membrane with 15% NPs content, owing to the hydrophilic and porosity improvement. The antibacterial activity was assessed on the membrane with most content of NPs (15% w/w) through bacterial colony count. The bacterial count in the control membrane was 3.17×10^9 cfu mL^{-1} for *Bacillus cereus* and 3.5×10^9 cfu mL^{-1} for *S. aureus*, while the modified membrane showed a decreased to 0.36×10^9 and 0.40×10^9 cfu mL^{-1}, respectively. The bacterial count in the control was 3.2×10^9 for *E. coli* and 3.7×10^9 cfu mL^{-1} for *Salmonella typhi*, whereas for the modified membrane decreased to 0.48×10^9 and 0.61×10^9 cfu mL^{-1}, respectively. Additionally, significant 85.6% of colony count decline was observed for the modified membrane. In another investigation, Haider et al. (2016) modified PES with an amine (APES) and Ag NPs to treat water by regulated releasing of Ag^+. The study revealed an enhanced antibiofouling property by the addition of Ag NPs on the membranes. Regarding the controlled release of Ag^+, it was observed that the AgNPs-APES (0.1 wt.%) membrane released silver ions at an approximate rate of 5.1 μg L^{-1} h^{-1} while the AgNPs-APES (0.2 wt.%) release rate was approximately 7.5 μg L^{-1} h^{-1} over a period of 12 days. The no aminated AgNPs-PES membrane showed Ag leaching rate at 35 μg L^{-1} h^{-1} for 5 days. Overall, an evaluation indicated that Ag^+ release from the membranes was about 70% for 12 days. The antibacterial evaluation of the pristine PES membrane did not dislay antibacterial properties against *E. coli*, as expected, while the AgNPs-PES membrane displayed a minimal inhibition halo, but the aminated membranes (AgNPs-APES) exhibited the highest antibacterial activity displaying noticeable inhibition rings.

Alternatively, the photocatalytic disinfection activity induced by TiO_2 NPs has been widely investigated for water treatment. In this instance, Song et al. (2017) prepared flexible photocatalytic membranes with Ag, TiO_2, and ZnO NPs for water filtration. The functionalized membrane showed a high antibiotic photocatalytic degradation potential and higher antibacterial activity compared to the membranes embedded with TiO_2 and ZnO-TiO_2. In addition, it was found that membranes were photocatalytically stable and reusable. The functionalized membranes performed 91.6% photodegradation of tetracycline hydrochloride after one-hour exposure and almost a 100% inhibition of *Escherichia coli*.

5.2 Antibiotics Separation and Fermentation Broth Concentration

Antibiotics are antimicrobial drugs that hinder bacterial growth or cause bacterial death. They are commonly organic compounds industrially obtained by natural fermentation or synthetically. The natural fermentation production process is usually preferred over synthetic and semisynthetic processes due to the intricate composition of most antibiotics. Erythromycin (ERY) is an antibiotic metabolized by the actinomycete bacteria *Saccharopolyspora erythraea*. During fermentation some byproducts for example ERY B, C, D, E, and F, and some intermediate products, such as azithromycin and clarithromycin. Therefore, purification and separation of ERY are complex and high-cost processes (Shoushtari et al. 2020). Within context, the presence of antibiotics in water bodies poses an environmental and health treat (Danner et al. 2019). Therefore, the EPA included ERY in the Contaminant Candidate List. Antibiotic removal may be done through fine tune NF membranes in an efficient way. In this respect, Weng et al. (2016) fabricated antibacterial zwitterionic PSU-polyamide NF membranes with zwitterionic *N*-aminoethyl piperazine propane sulfonate to remove ERY as a model to further investigate removal of antibiotics from industrial and environmental water. Performance of zwitterionic membrane showed 8.4 L m^{-1} h^{-1} bar^{-1} of water permeability and 96.5% of ERY retention. ERY concentration in the recirculation reached 350.7 mg L^{-1} after 7.25 h of uninterrupted filtration. Likewise, the zwitterionic membranes performed steadily for 168 h of filtration and showed good antibacterial adhesion against *E. coli*. In a similar work by Qi et al. (2019) was modified a PES membrane incorporating Ag NPs to concentrate a fermentation broth. The flux of the modified membrane was better than the flux of the unmodified membrane. A fouling evaluation disclosed that bacteria was effectively inactivated at the membrane surface and could be efficiently removed during the backwash cleaning process. Additionally, leaching of Ag NPs down in a low rate thus having no effect over the fermentative bacteria.

5.3 Arsenite and Arsenate Removal from Drinking Water

Arsenic is a metalloid that has been detected in different environmental sites due to its mobility. Mobility of arsenic may depend on the oxidation number, mineral source, and the transportation pathway. Arsenic may be found in four oxidation states: As^{3+} which is the most common, As^{5+} which is more stable, As^{0}, and As^{3+}. Arsenite and arsenate are the predominant forms found in water. Moreover, arsenic is a very toxic substance to all living organisms and it has been categorized as carcinogenic to humans by the World Health Organization (Nicomel et al. 2015; Bhakta and Ali 2020). Arsenic contamination of drinking water is a global concern that can be resolved by removing this contaminant in an efficient and environmental way by the application of membrane technology. Roy et al. (2016) designed an

imprinted membrane functionalized with a cysteine-TiO_2-ZnS nanomonomer to remove As^{3+} and As^{5+} in water. The functionalized membranes removed As^{3+} and $As^{5+}$and showed an improved water flux. Antibacterial efficiency for the modified membrane was 96% for *E. coli* and 90% for *S. aureus*. The antibacterial activity may be attributed to the electrostatic interaction of ZnS NPs and the bacterial cell wall. Regeneration and reuse of the imprinted membrane was possible without losing its properties. In addition, filtration of water from Jharkhand and West Bengal in India resulted in 95% of arsenic removal.

5.4 Membrane Bioreactor Technology

Membrane bioreactors are a hybrid technology that integrates an activated sludge process characterized by a suspended growth of biomass with micro or ultrafiltration membrane technology (Deowan et al. 2019). The technology of membrane bioreactors is effective to treat industrial and municipal wastewater. Nonetheless fouling is the most important disadvantage of membrane bioreactors which diminishes the membrane performance and increases substantially maintenance and operating costs (Iorhemen et al. 2016). From this perspective, fouling mitigation strategies are being researched. Ghalamchi et al. (2019a) prepared mixed-matrixed PES membranes modified with Ag_3PO_4-NH_2-g-C_3N_4 NPs to address biofouling and high flux for a membrane bioreactor. Hydrophilicity of the modified membrane increased due to the introduction of the NPs. As well, water permeability, antifouling properties, and retention efficiency improved as the NPs content augmented in the range of 0.1 to 0.5 wt%. Nevertheless, concentrations such as 1.0 wt% caused extreme membrane hydration to the point to get perforated. The antibacterial properties of the composite membranes prevented bacterial adhesion and increased their antibiofouling ability

5.5 Groundwater Defluoridation and Disinfection

Fluoride is an anionic form of fluorine; its presence in groundwater occurs naturally due to geological formation (Kumar Swarnakar et al. 2007). At the present time, groundwater is the only water supply for over two hundred million people worldwide. Intake of toxic levels of fluoride causes fluorosis, a condition that affects pathologically teeth and bones (Vijayeeswarri et al. 2019). The World Health Organization established a daily fluoride maximum permissible level of 1.5 mg L^{-1} considering 2 L of water intake per day (Kimambo et al. 2019). Since fluorosis is irreversible the most appropriate solution to prevent it is by reducing fluoride intake by way of water. Removal of fluoride from groundwater has been attempted by NF and inverse osmosis removal. Nevertheless, high energy requirements may limit the operation costs of membrane treatments. To circumvent those limitations, mixed-matrix membranes are favorable for fluoride filtration. For instance, PSU membranes

were impregnated using carbonized bone meal to defluoridate and disinfect groundwater. The modified membrane with 15 wt% carbonized bone meal decreased its permeability to 2.8×10^{-11} m Pa^{-1} s^{-1}, compared to 5×10^{-10} m Pa^{-1} s^{-1} for the unmodified membrane, resulting in decrease of molecular weight from 85 to 23 kDa due to the membrane becoming dense by addition of carbonized bone meal. However, the hydrophilic character and the surface texture of the mixed-matrix membranes were enhanced enabling fluoride adsorption to a maximum of 5 mg g^{-1} through the membrane with 15 wt% of carbonized bone meal content. Filtration experiments recirculating real groundwater during 18 h showed that the bacterial concentration in the permeate was 0 cfu mL^{-1} (Chatterjee et al. 2020).

5.6 Desalination

More than 50% of total population in the world suffers lack of fresh water at least one month per year (Garrick et al. 2020). Fresh water shortage emphasizes the importance to find sustainable solutions to satisfy the increasing water demand. Desalination methods remove salts and minerals from saline water (brackish/seawater) delivering potable water. Among different desalination technologies, membrane systems are the most applied technology (Rajakumar et al. 2018; Al-Najar et al. 2020). At present, RO is the leading technology for brackish and seawater desalination. Above 50% of desalination plants worldwide are RO membrane based due to its capacity to remove monovalent and divalent ions (Lee et al. 2020). Xu et al. (2020) fabricated multifunctional thin film covalent organic nanosheets (CONs) membranes for efficient RO desalination. The separation improved when the CONs load was 50 μg cm^{-2}, water permeability increased to 2.2 L m^{-2} h^{-1} bar^{-1}, and NaCl rejection to 97.7% compared to the pristine membrane, water permeability 0.7 L m^{-2} h^{-1} bar^{-1}, and 96.3% of NaCl rejection, respectively. Due to the CONs the modified membranes yielded an outstanding chlorine resistance of 18000 ppm. The antimicrobial activity of the modified membranes was evaluated through a fluorescence microscope-lamination technique using *E. coli* and *S. aureus*. Results showed that incorporation of CONs endowed the membranes with up to 99.8% of antibacterial efficiency.

5.7 Dye Removal and Textile Wastewater Treatment

Textile industry is characterized for consuming the largest amount of water and polluting water bodies. In general, the textile industry wastewater is characterized for excessive content of chemical and biochemical oxygen demand (COD), high color, no neutral pH, suspended solids, metallic components, temperature, and salts, while the main component of textile wastewater are dyes. Textile dyes substantially endanger the quality of bodies of water by increasing the chemical and biochemical

oxygen demand, by hindering and inhibiting organisms' activity, by entering and altering the food chain, also they are toxic, mutagenic, and carcinogenic (Lellis et al. 2019; Yaseen and Scholz 2019). Membrane technologies offer a distinctive separation process involving electrostatic and intermolecular interactions; in this respect NF membranes in the range of 200–1000 Da are very effective in removing dyes from water (Wang et al. 2017). In view of this Gao et al. (2020) prepared composite NF membranes with antibacterial activity by a layer by layer electrostatic approach to recover dye in the industrial field. Three NF polyethylenimine-metal ion membranes (Ag^{+}, Cu^{2+}, and Fe^{3+}) exhibited permeabilities of 121 L m^{-2} h^{-1} MPa^{-1}, 71 L m^{-2} h^{-1} MPa^{-1}, and 73 L m^{-2} h^{-1} MPa^{-1}, respectively. Rejection of fuchsine acid was 96.5%, 94.5%, and 91.6% respectively, and rejection of $MgSO_4$ was 31.5%, 27.5%, and 23.7%, correspondingly. The membrane antifouling ability was determined by flux recovery ratios. The flux recovery ratio for the modified membranes were 76.4%, 83.2%, and 91.5%, respectively. In addition, the modified membranes showed high hydrophilicity with contact angles of 59 °, 39 °, and 35 °, respectively. The antibacterial activity results showed 99.61%, 97.63%, and 95.26% of *E. coli* bacterial death, respectively, and 99.95%, 92.01%, and 90.02% against *S. aureus*, respectively.

In another investigation was developed an antibacterial membrane to remove dyes and coliforms from water. The membrane was prepared with polyurethane and GO by the electrospinning method. Membranes were intended to remove rhodamine B and methylene blue dyes. The study reported an adsorption capacity for the modified membrane of 109.88 mg g^{-1} of methylene blue and 77.15 mg g^{-1} of rhodamine B. Besides, the membrane with 10% GO exhibited a 17706 L m^{-2} h^{-1} water flux. The membrane also exhibited 99.99% separation efficiency, proving good oil-in-water emulsions antifouling property. The antifouling property was determined through a Hermia model showing that the 10% GO modified membrane inhibited more than 90% of *E. coli* and *S. aureus* bacterial growth (Sundaran et al. 2019).

5.8 Wastewater Treatment

Wastewater from industrial, commercial, domestic, and agricultural activities, generates contaminants as organic residues, heavy metals, and of biological risk. All these contaminants endanger the environment and human health, and it is important to adapt methods to effectively remove them according to their intrinsic characteristics (Herrera-Melian 2019). Even when current membrane technologies remove contaminants from wastewater, new membranes tries to eliminate specific contaminants in water. In this context Zhao et al. (2017) fabricated PVDF membranes embedded with GO and CuO NPs to treat wastewater. The PVDF membrane modified presented high antifouling properties. It was observed that the dispersion of nanoparticles influenced the final morphology, structure, and hydrophilic properties of the modified membrane, additionally the flux recovery ratio was improved

compared to the pristine membrane. The modified membrane containing 5 wt% Cu_xO performed the best flux recovery ratio (92.09%). Fouling resistance improved with the introduction of Cu_xO and GO; the results were 87.04% (Cu_xO/GO = 1), 86.38% (Cu_xO/GO = 3), and 91.36% (Cu_xO/GO = 5). The modified membranes exhibited antibacterial ability against *E. coli*, showing that a higher concentration of Cu_xO increased the inhibition zone from 1.7 mm (Cu_xO/GO = 1) and 2.03 mm (Cu_xO/GO = 3) to 2.53 mm (Cu_xO/GO = 5), hence demonstrating that copper was providing the antibiofouling activity.

A similar study developed polyacrylonitrile electrospun nanofiber membranes integrated with Ag and AgBr NPs. Removal of particulate contaminants was performed by filtration of an aqueous dispersion of red 1 (R1). The size distribution of the R1 suspension measure was in the size range of 90–400 nm. The functionalized membrane overall performance was evaluated using an aqueous solution containing salicylic acid, *E. coli*, and R1 obtaining a clear water permeate without presence of Ag^+ or Ag NPs. The antibacterial activity results showed 30%, 91%, and 100% of bacterial death after contact for 1, 30, and 60 min, respectively (Qayum et al. 2019).

5.9 Oil-Water Separation

Oil wastewater is a high impact environmental issue as a result of the frequent chemical leakage and oil spill. Oil-water emulsions are extremely difficult to treat because of the small size of emulsified oil droplets and its complex composition which may contain other pollutants such as particles, surfactants, and organic matter (Kang et al. 2020; Shao et al. 2020). Oil and organic contaminants may reduce the amount of dissolved oxygen, affecting considerably the aquatic life form and destroying water sources. Overall, oily water may cause severe damage to the environment. Some methods for oil-water separation include oil flotation, foam separation, oil coagulation, biological treatments, and membrane technology (Kang et al. 2020). Membrane systems are low cost and effective for separation of oil-water effluents including immiscible liquids, and all types of emulsions. Permeable membranes with special wettability and specific surface roughness are able to separate effectively oil-water mixtures (Lin and Hong 2019). In this context, Ma et al. (2020) fabricated hydrophobic polyimide membranes integrating a tannic acid-metal complex on the surface. Results showed that the modified membrane presented a high hydrophobic character, the water contact angle measure was 153.64° ± 1.6°, and the oil contact angle was close to 0°. Superhydrophobicity was proved by membrane low water adhesion and achieving good oil-water separation. The membrane performed water flux up to 6935 L m^{-2} h^{-1} and more than 99% separation efficiency; the final content of oil was less than 5 ppm at the end of 20 cycles. The self-cleaning capability of the membrane was determined by covering the membrane surface with MnO_2 powder, it was observed that the water droplets moved easily from the surface taking away the powder. Additionally, the membrane

showed more than 90% of UV-shielding efficiency at 320 nm radiation wavelength, attributed to the UV-absorbing capability of tannic acid. The antibacterial activity against *E. coli* and *Bacillus subtilis* of untreated polyimide membrane was null, while the modified membranes inhibited bacterial growth efficiently.

5.10 Produced Water Treatment

Produced water (PW) is generated during petroleum-based fuel extraction, petroleum-based energy production, and some industrial operations (Nasiri et al. 2017). During oil and gas extraction procedures a vast amount of freshwater is pumped into the reservoir to maintain the undersoil pressure, reemerging along with hydrocarbons (Ricceri et al. 2019). PW can contain components from the reservoir and the chemical substances applied in several stages such as drilling and extraction (Nasiri et al. 2017). The chemical and mineral composition of PW is unsteady and depends on the site, geological factors, and operating conditions. Ion content may include chlorides, sulfides, sulfates, carbonates, and predominantly alkaline metals. Additionally, PW contains radioactive elements usually in the form of Ra-226 and Ra-228. The total dissolved solids content in PW is in the range from 10,000 mg L^{-1} to 260,000 mgL^{-1}. PW total organic carbon concentration is usually under 1000 mg L^{-1} but sometimes may reach up to 6000 mg L^{-1}. PW may also contain acid producing bacteria, sulfate, thiosulfate, and sulfur-reducing bacteria (Coonrod et al. 2020).

Treated PW can be used for industrial and agricultural activities. PW treatment involves a number of removal stages, each one targeting specific contaminants (pretreatment, main treatment, and final polishing treatment), and hybrid processes combining chemical, physical, and biological techniques (Al-Ghouti et al. 2019). PW treatment disadvantages such as high-cost technology, use of toxic substances, and secondary contamination have prompted the development of membrane systems for PW treatment. Nevertheless, up-to-date the main drawback of a membrane technology for PW treatment is membrane fouling and scaling (Nasiri et al. 2017). In this regard, zwitterionic forward osmosis membranes for PW treatment were obtained by a PSU-polyamide membrane modification via interfacial polymerization integrating zwitterions. The modified membrane hydrophilicity improved with the addition of zwitterions, reducing the contact angles from approximately 80° on the polyamide layer to approximately 15° on the functionalized membrane. Zwitterions endowed the modified membrane surface with antibacterial. The antibacterial properties were evaluated by a confocal microscopic image and *E. coli* on the membrane surface. The unmodified membrane showed 4810 cell mm^{-2} bacterial adhesion while the modified membrane presented 352 cell mm^{-2} (Chiao et al. 2019).

5.11 Pesticide Removal from Water

Pesticides use is meant to reduce crop losses and increase crop production (Nie et al. 2020). The consumption and exposition of pesticide polluted water poses adverse environmental and health risks. For instance, organochlorine pesticides may hinder animal growth and disturb their nerve system. These compounds may progressively bioaccumulate in different trophic level species via the food chain (Nie et al. 2020). Currently, there are several methods to remove pesticide from water such as combined photo-Fenton and biological oxidation, photocatalytic degradation, advanced oxidation processes, aerobic degradation, ozonation, NF membranes, coagulation, fluid extraction, solid-phase extraction, and adsorption (Tarannum and Khan 2020).

NF and RO technologies have been widely applied and accepted as means of remediation of contaminated water by trace organic contaminants including pesticides (Nikbakht Fini et al. 2020). In this regard, Mehta et al. (2019) modified PSU membranes by integrating a poly(piperazine-amide) interfacial layer and Cu^{2+}. The unmodified membrane was label as M1. Membranes were prepared using two different sequences. The first sequence M2 consisted on dipping the PSU membrane in piperazine, then in a Cu(II) acetate solution, and lastly into a trimesoyl chloride solution. The other sequence M3 involved dipping the PSU membrane in Cu(II) acetate solution, next in the piperazine solution, and later in the trimesoyl chloride solution. Filtration tests indicated that the modified membranes exhibited different removal efficiency for salts, disaccharides, and hexaconazole. The ion selective separation of SO_4^{-2} and Cl^- for the M2 was 3.92, whereas for M3 was 2.27. The modified membranes showed a separation performance of saccharide molecules in the molecular mass range of 180–520. M2 showed low removal ability and a higher flux compared to the M3 which removed approximately 90%. Hexaconazole maximum removal was given by M3 followed by M1 and lastly by M2 which exhibited the highest flux. Antibacterial activity against *E. coli* and *B. subtilis* evidenced that the presence of Cu NPs developed a better antibacterial property. Since M2 contained more Cu compared to M3, and M1, it showed an attachment count of *E. coli* was 30% and 33.7% *B. subtilis* in contrast to M1.

6 Conclusion

At the present time, antimicrobial membranes for water treatment are emerging as a global frontline technology for water purification; they are cost-effective and simple technologies that are widely used to clean wastewater. Different types of membranes have been developed from different perspectives, where the antimicrobial activity is important, and biofouling mitigation, which is a complex mechanism that affects water quality, is required.

The membrane inherent properties, the species present in water, and the operating conditions influence the formation of biofouling that appears by microbial adhesion forming a film on the membrane surface. In this sense, a great diversity of membranes has been developed to provide new alternatives to eliminate pathogenic bacteria from water and reduce biofouling, thus increasing the useful life of the membranes. These alternatives have combined different approaches that include the use of NPs, antimicrobial polymer, and compounds, among others. Offering alternative solutions to this problem that is constantly growing and affects the world population.

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References

Abitha VK, Thomas S (2018) Fabrication methods: polymer membranes for liquid transport, transport properties of polymeric membranes. Elsevier, London. https://doi.org/10.1016/B978-0-12-809884-4.00003-3

Aktij SA, Rahimpour A, Figoli A (2017) Low content nano-polyrhodanine modified polysulfone membranes with superior properties and their performance for wastewater treatment. Environ Sci 4(10):2043–2054. https://doi.org/10.1039/c7en00584a

Al Aani S, Gomez V, Wright CJ, Hilal N (2017) Fabrication of antibacterial mixed matrix nanocomposite membranes using hybrid nanostructure of silver coated multi-walled carbon nanotubes. Chem Eng J 326:721–736. https://doi.org/10.1016/j.cej.2017.06.029

Al-Ghouti MA, Al-Kaabi MA, Ashfaq MY, Da'na DA (2019) Produced water characteristics, treatment and reuse: a review. J Water Process Eng 28:222–239. https://doi.org/10.1016/j.jwpe.2019.02.001

Al-Jumaili A, Alancherry S, Grant D, Kumar A, Bazaka K, Jacob MV (2019) Plasma treatment of polymeric membranes, non-thermal plasma technology for polymeric materials. Elsevier, London. https://doi.org/10.1016/b978-0-12-813152-7.00008-1

Al-Najar B, Peters CD, Albuflasa H, Hankins NP (2020) Pressure and osmotically driven membrane processes: a review of the benefits and production of nano-enhanced membranes for desalination. Desalination 479:114323. https://doi.org/10.1016/j.desal.2020.114323

Asad A, Sameoto D, Sadrzadeh M (2020) Overview of membrane technology. In: Nanocomposite membranes for water and gas separation. Elsevier, London. https://doi.org/10.1016/b978-0-12-816710-6.00001-8

Baroña GNB, Cha BJ, Jung B (2007) Negatively charged poly(vinylidene fluoride) microfiltration membranes by sulfonation. J Membr Sci 290(1–2):46–54. https://doi.org/10.1016/j.memsci.2006.12.013

Basri H, Ismail AF, Aziz M (2011) Polyethersulfone (PES)-silver composite UF membrane: Effect of silver loading and PVP molecular weight on membrane morphology and antibacterial activity. Desalination 273(1):72–80. https://doi.org/10.1016/j.desal.2010.11.010

Behboudi A, Jafarzadeh Y, Yegani R (2018) Enhancement of antifouling and antibacterial properties of PVC hollow fiber ultrafiltration membranes using pristine and modified silver nanoparticles. J Environ Chem Eng 6(2):1764–1773. https://doi.org/10.1016/j.jece.2018.02.031

Ben-Sasson M, Zodrow KR, Genggeng Q, Kang Y, Giannelis EP, Elimelech M (2014) Surface functionalization of thin-film composite membranes with copper nanoparticles for antimicrobial surface properties. Environ Sci Technol 48(1):384–393. https://doi.org/10.1021/es404232s

Bhakta JN, Ali M (2020) Arsenic water resources contamination: challenges and solutions. Springer, New York, pp 207–230. https://doi.org/10.1007/978-3-030-21258-2

Bolisetty S, Peydayesh M, Mezzenga R (2019) Sustainable technologies for water purification from heavy metals: review and analysis. Chem Soc Rev 48(2):463–487. https://doi.org/10.1039/c8cs00493e

Borkow G, Gabbay J (2005) Copper as a biocidal tool. Curr Med Chem 12(18):2163–2175. https://doi.org/10.2174/0929867054637617

Chatterjee S, Mukherjee M, De S (2020) Groundwater defluoridation and disinfection using carbonized bone meal impregnated polysulfone mixed matrix hollow-fiber membranes. J Water Process Eng 33:101002. https://doi.org/10.1016/j.jwpe.2019.101002

Chen V, Fane AG, Fell CJD (1992) The use of anionic surfactants for reducing fouling of ultrafiltration membranes: their effects and optimization. J Membr Sci 67(2–3):249–261. https://doi.org/10.1016/0376-7388(92)80028-I

Chen Y, Zhang Y, Zhang H, Liu J, Song C (2013) Biofouling control of halloysite nanotubes-decorated polyethersulfone ultrafiltration membrane modified with chitosan-silver nanoparticles. Chem Eng J 228:12–20. https://doi.org/10.1016/j.cej.2013.05.015

Chen L, Wang X, Lu W, Wu X, Li J (2016) Molecular imprinting: perspectives and applications. Chem Soc Rev 45(8):2137–2211. https://doi.org/10.1039/c6cs00061d

Chiang YC, Chang Y, Higuchi A, Chen WY, Ruaan RC (2009) Sulfobetaine-grafted poly(vinylidene fluoride) ultrafiltration membranes exhibit excellent antifouling property. J Membr Sci 339(1–2):151–159. https://doi.org/10.1016/j.memsci.2009.04.044

Chiao YH, Chen ST, Patra T, Hsu CH, Sengupta A, Hung WS, Huang SH, Qian X, Wickramasinghe R, Chang Y, Lee KR, Lai JY (2019) Zwitterionic forward osmosis membrane modified by fast second interfacial polymerization with enhanced antifouling and antimicrobial properties for produced water pretreatment. Desalination 469:114090. https://doi.org/10.1016/j.desal.2019.114090

Cihanoğlu A, Altinkaya SA (2020) A facile route to the preparation of antibacterial polysulfone-sulfonated polyethersulfone ultrafiltration membranes using a cationic surfactant cetyltrimethylammonium bromide. J Membr Sci 594:117438. https://doi.org/10.1016/j.memsci.2019.117438

Ciora RJ, Liu PKT (2003) Ceramic membranes for environmental related applications. Fluid 15 (1):51–60

Comite A (2017) Preparation of silica membranes by sol-gel method. In: Current trends and future developments on (bio-) membranes: silica membranes: preparation, modelling, application, and commercialization. Elsevier, London. https://doi.org/10.1016/B978-0-444-63866-3.00001-7

Coonrod CL, Ben Yin Y, Hanna T, Atkinson AJ, Alvarez PJJ, Tekavec TN, Reynolds MA, Wong MS (2020) Fit-for-purpose treatment goals for produced waters in shale oil and gas fields. Water Res 173:115467. https://doi.org/10.1016/j.watres.2020.115467

Danner MC, Robertson A, Behrends V, Reiss J (2019) Antibiotic pollution in surface fresh waters: occurrence and effects. Sci Total Environ 664:793–804. https://doi.org/10.1016/j.scitotenv.2019.01.406

De Velasco-Maldonado PS, Hernández-Montoya V, Montes-Morán MA, Vázquez NAR, Pérez-Cruz MA (2018) Surface modification of a natural zeolite by treatment with cold oxygen plasma: characterization and application in water treatment. Appl Surf Sci 434:1193–1199. https://doi.org/10.1016/j.apsusc.2017.11.023

Deowan SA, Korejba W, Hoinkis J, Figoli A, Drioli E, Islam R, Jamal L (2019) Design and testing of a pilot-scale submerged membrane bioreactor (MBR) for textile wastewater treatment. Appl Water Sci 9(3):1–7. https://doi.org/10.1007/s13201-019-0934-8

Desai NP, Hossainy SFA, Hubbell JA (1992) Surface-immobilized polyethylene oxide for bacterial repellence. Biomaterials 13(7):417–420. https://doi.org/10.1016/0142-9612(92)90160-P

Dobrak A, Verrecht B, Van den Dungen H, Buekenhoudt A, Vankelecom IFJ, Van der Bruggen B (2010) Solvent flux behavior and rejection characteristics of hydrophilic and hydrophobic mesoporous and microporous TiO2 and ZrO2 membranes. J Membr Sci 346(2):344–352. https://doi.org/10.1016/j.memsci.2009.09.059

Dror-Ehre A, Mamane H, Belenkova T, Markovich G, Adin A (2009) Silver nanoparticle-E. coli colloidal interaction in water and effect on E. coli survival. J Colloid Interface Sci 339 (2):521–526. https://doi.org/10.1016/j.jcis.2009.07.052

Eskandari P, Abousalman-Rezvani Z, Roghani-Mamaqani H, Salami-Kalajahi M, Mardani H (2019) Polymer grafting on graphene layers by controlled radical polymerization. Adv Colloid Interf Sci 273:102021. https://doi.org/10.1016/j.cis.2019.102021

Feltz KP, Kalaf EAG, Chen C, Martin RS, Sell SA (2017) A review of electrospinning manipulation techniques to direct fiber deposition and maximize pore size. Electrospinning 1(1):46–61. https://doi.org/10.1515/esp-2017-0002

Flores-Rojas GG, Bucio E (2016) Radiation-grafting of ethylene glycol dimethacrylate (EGDMA) and glycidyl methacrylate (GMA) onto silicone rubber. Radiat Phys Chem 127:21–26. https://doi.org/10.1016/j.radphyschem.2016.05.015

Flores-Rojas GG, López-Saucedo F, Bucio E, Isoshima T (2017) Covalent immobilization of lysozyme in silicone rubber modified by easy chemical grafting. MRS Commun 7 (4):904–912. https://doi.org/10.1557/mrc.2017.115

Flores-Rojas GG, López-Saucedo F, Bucio E (2018) Gamma-irradiation applied in the synthesis of metallic and organic nanoparticles: a short review. Radiat Phys Chem. https://doi.org/10.1016/j.radphyschem.2018.08.011

Fukuzaki S (2006) Mechanisms of actions of sodium hypochlorite in cleaning and disinfection processes. Biocontrol Sci 11(4):147–157. https://doi.org/10.4265/bio.11.147

Gao Z, Liu S, Wang Z, Yu S (2020) Composite NF membranes with anti-bacterial activity prepared by electrostatic self-assembly for dye recycle. J Taiwan Inst Chem Eng 106:34–50. https://doi.org/10.1016/j.jtice.2019.10.020

Garrick D, Iseman T, Gilson G, Brozovic N, O'Donnell E, Matthews N, Miralles-Wilhelm F, Wight C, Young W (2020) Scalable solutions to freshwater scarcity: Advancing theories of change to incentivise sustainable water use. Water Secur 9:100055. https://doi.org/10.1016/j.wasec.2019.100055

Ghalamchi L, Aber S, Vatanpour V, Kian M (2019a) A novel antibacterial mixed matrixed PES membrane fabricated from embedding aminated Ag3PO4/g-C3N4 nanocomposite for use in the membrane bioreactor. J Ind Eng Chem 70:412–426. https://doi.org/10.1016/j.jiec.2018.11.004

Ghalamchi L, Aber S, Vatanpour V, Kian M (2019b) Development of an antibacterial and visible photocatalytic nanocomposite microfiltration membrane incorporated by Ag3PO4/CuZnAl NLDH. Sep Purif Technol 226(January):218–231. https://doi.org/10.1016/j.seppur.2019.05.104

Goh PS, Matsuura T, Ismail AF, Hilal N (2016) Recent trends in membranes and membrane processes for desalination. Desalination 391:43–60. https://doi.org/10.1016/j.desal.2015.12.016

Gu Q, Jia Z (2013) Preparation of quaternized poly(vinylidene fluoride) membranes by γ-ray irradiation induced graft polymerization and their antibacterial property. React Funct Polym 73(8):1114–1121. https://doi.org/10.1016/j.reactfunctpolym.2013.04.009

Haider MS, Shao GN, Imran SM, Park SS, Abbas N, Tahir MS, Hussain M, Bae W, Kim HT (2016) Aminated polyethersulfone-silver nanoparticles (AgNPs-APES) composite membranes with controlled silver ion release for antibacterial and water treatment applications. Mater Sci Eng C 62:732–745. https://doi.org/10.1016/j.msec.2016.02.025

He X, Yang DP, Zhang X, Liu M, Kang Z, Lin C, Jia N, Luque R (2019) Waste eggshell membrane-templated CuO-ZnO nanocomposites with enhanced adsorption, catalysis and antibacterial properties for water purification. Chem Eng J 369:621–633. https://doi.org/10.1016/j.cej.2019.03.047

Herrera-Melian JA (2019) Sustainable wastewater treatment systems (2018–2019). Sustainability 12:1–5. https://doi.org/10.3390/su12051940

Hilal N, Al-Khatib L, Atkin BP, Kochkodan V, Potapchenko N (2003) Photochemical modification of membrane surfaces for (bio)fouling reduction: a nano-scale study using AFM. Desalination 158(1–3):65–72. https://doi.org/10.1016/S0011-9164(03)00434-X

Hsueh YH, Tsai PH, Lin KS, Ke WJ, Chiang CL (2017) Antimicrobial effects of zero-valent iron nanoparticles on gram-positive Bacillus strains and gram-negative Escherichia coli strains. J Nanobiotechnol 15(1):1–12. https://doi.org/10.1186/s12951-017-0314-1

Hu M, Cui Z, Li J, Zhang L, Mo Y, Dlamini DS, Wang H, He B, Li J, Matsuyama H (2019) Ultra-low graphene oxide loading for water permeability, antifouling and antibacterial improvement of polyethersulfone/sulfonated polysulfone ultrafiltration membranes. J Colloid Interface Sci 552:319–331. https://doi.org/10.1016/j.jcis.2019.05.065

Huang YW, Wang ZM, Yan X, Chen J, Guo YJ, Lang WZ (2017) Versatile polyvinylidene fluoride hybrid ultrafiltration membranes with superior antifouling, antibacterial and self-cleaning properties for water treatment. J Colloid Interface Sci 505:38–48. https://doi.org/10.1016/j.jcis.2017.05.076

Iorhemen OT, Hamza RA, Tay JH (2016) Membrane bioreactor (Mbr) technology for wastewater treatment and reclamation: membrane fouling. Membranes 6(2):13–16. https://doi.org/10.3390/membranes6020033

Ismail AF, Padaki M, Hilal N, Matsuura T, Lau WJ (2015) Thin film composite membrane - recent development and future potential. Desalination 356:140–148. https://doi.org/10.1016/j.desal.2014.10.042

Jin JC, Xu ZQ, Dong P, Lai L, Lan JY, Jiang FL, Liu Y (2015) One-step synthesis of silver nanoparticles using carbon dots as reducing and stabilizing agents and their antibacterial mechanisms. Carbon 94:129–141. https://doi.org/10.1016/j.carbon.2015.05.084

Juang LC, Tseng DH, Lin HY (2007) Membrane processes for water reuse from the effluent of industrial park wastewater treatment plant: a study on flux and fouling of membrane. Desalination 202(1–3):302–309. https://doi.org/10.1016/j.desal.2005.12.068

Kakihana Y, Cheng L, Fang LF, Wang SY, Jeon S, Saeki D, Rajabzadeh S, Matsuyama H (2017) Preparation of positively charged PVDF membranes with improved antibacterial activity by blending modification: effect of change in membrane surface material properties. Colloids Surf A Physicochem Eng Asp 533(August):133–139. https://doi.org/10.1016/j.colsurfa.2017.08.039

Kang H, Zhang X, Li L, Zhao B, Ma F, Zhang J (2020) Polydopamine and poly(dimethylsiloxane) modified superhydrophobic fiberglass membranes for efficient water-in-oil emulsions separation. J Colloid Interface Sci 559:178–185. https://doi.org/10.1016/j.jcis.2019.10.016

Khajouei M, Jahanshahi M, Peyravi M, Hoseinpour H, Shokuhi Rad A (2017) Anti-bacterial assay of doped membrane by zero valent Fe nanoparticle via in-situ and ex-situ aspect. Chem Eng Res Des 117:287–300. https://doi.org/10.1016/j.cherd.2016.10.042

Khan I, Saeed K, Khan I (2019) Nanoparticles: properties, applications and toxicities. Arab J Chem 12(7):908–931. https://doi.org/10.1016/j.arabjc.2017.05.011

Khayet M, Villaluenga JPG, Valentin JL, López-Manchado MA, Mengual JI, Seoane B (2005) Filled poly(2,6-dimethyl-1,4-phenylene oxide) dense membranes by silica and silane modified silica nanoparticles: Characterization and application in pervaporation. Polymer 46 (23):9881–9891. https://doi.org/10.1016/j.polymer.2005.07.081

Kianfar E (2019) Nanozeolites: synthesized, properties, applications. J Sol-Gel Sci Technol 91 (2):415–429. https://doi.org/10.1007/s10971-019-05012-4

Kim JH, Lee KH (1998) Effect of PEG additive on membrane formation by phase inversion. J Membr Sci 138(2):153–163. https://doi.org/10.1016/S0376-7388(97)00224-X

Kim SH, Kwak SY, Sohn BH, Park TH (2003) Design of TiO2 nanoparticle self-assembled aromatic polyamide thin-film-composite (TFC) membrane as an approach to solve biofouling problem. J Membr Sci 211(1):157–165. https://doi.org/10.1016/S0376-7388(02)00418-0

Kimambo V, Bhattacharya P, Mtalo F, Mtamba J, Ahmad A (2019) Fluoride occurrence in groundwater systems at global scale and status of defluoridation – state of the art. Groundwater for. Sustain Dev 9:100223. https://doi.org/10.1016/j.gsd.2019.100223

Kumar Swarnakar A, Choubey D, Sar DK, Scholar ME (2007) Defluoridation of water by various technique-a review development of phase-I campus including building for IIM Raipur at Naya Raipur carrying out of water test for construction & drinking purpose. View project analysis for total nitrogen and total phospho. Int J Innovat Res Sci Eng Technol 3297:13174–13178. https://doi.org/10.15680/IJIRSET.2016.0507192

Lalia BS, Kochkodan V, Hashaikeh R, Hilal N (2013) A review on membrane fabrication: structure, properties and performance relationship. Desalination 326:77–95. https://doi.org/10.1016/j.desal.2013.06.016

Lee XJ, Show PL, Katsuda T, Chen WH, Chang JS (2018) Surface grafting techniques on the improvement of membrane bioreactor: state-of-the-art advances. Bioresour Technol 269:489–502. https://doi.org/10.1016/j.biortech.2018.08.090

Lee WJ, Ng ZC, Hubadillah SK, Goh PS, Lau WJ, Othman MHD, Ismail AF, Hilal N (2020) Fouling mitigation in forward osmosis and membrane distillation for desalination. Desalination 480(February):114338. https://doi.org/10.1016/j.desal.2020.114338

Lellis B, Fávaro-Polonio CZ, Pamphile JA, Polonio JC (2019) Effects of textile dyes on health and the environment and bioremediation potential of living organisms. Biotechnol Res Innovat 3 (2):275–290. https://doi.org/10.1016/j.biori.2019.09.001

Lerch A, Panglisch S, Buchta P, Tomita Y, Yonekawa H, Hattori K, Gimbel R (2005) Direct river water treatment using coagulation/ceramic membrane microfiltration. Desalination 179:41–50. https://doi.org/10.1016/j.desal.2004.11.054

Lin X, Hong J (2019) Recent advances in robust superwettable membranes for oil–water separation. Adv Mater Interfaces 6(12):1–23. https://doi.org/10.1002/admi.201900126

Lin DJ, Chang CL, Huang FM, Cheng LP (2002) Effect of salt additive on the formation of microporous poly(vinylidene fluoride) membranes by phase inversion from LiC1o4/water/DMF/PVDF system. Polymer 44(2):413–422. https://doi.org/10.1016/S0032-3861(02)00731-0

Lin CE, Fang LF, Du SY, Yao ZK, Zhu BK (2019) A novel positively charged nanofiltration membrane formed via simultaneous cross-linking/quaternization of poly(m-phenylene isophthalamide)/polyethyleneimine blend membrane. Sep Purif Technol 212(November 2018):101–109. https://doi.org/10.1016/j.seppur.2018.11.026

Liu PS, Chen Q, Wu SS, Shen J, Lin SC (2010) Surface modification of cellulose membranes with zwitterionic polymers for resistance to protein adsorption and platelet adhesion. J Membr Sci 350(1–2):387–394. https://doi.org/10.1016/j.memsci.2010.01.015

Liu C, Guo Y, Wei X, Wang C, Qu M, Schubert DW, Zhang C (2020) An outstanding antichlorine and antibacterial membrane with quaternary ammonium salts of alkenes via in situ polymerization for textile wastewater treatment. Chem Eng J 384:123306. https://doi.org/10.1016/j.cej.2019.123306

Ma Y, Dai J, Wu L, Fang G, Guo Z (2017) Enhanced anti-ultraviolet, anti-fouling and anti-bacterial polyelectrolyte membrane of polystyrene grafted with trimethyl quaternary ammonium salt modified lignin. Polymer 114:113–121. https://doi.org/10.1016/j.polymer.2017.02.083

Ma W, Ding Y, Zhang M, Gao S, Li Y, Huang C, Fu G (2020) Nature-inspired chemistry toward hierarchical superhydrophobic, antibacterial and biocompatible nanofibrous membranes for effective UV-shielding, self-cleaning and oil-water separation. J Hazard Mater 384:121476. https://doi.org/10.1016/j.jhazmat.2019.121476

Malwal D, Gopinath P (2017) Efficient adsorption and antibacterial properties of electrospun CuO-ZnO composite nanofibers for water remediation. J Hazard Mater 321:611–621. https://doi.org/10.1016/j.jhazmat.2016.09.050

Manaf O, Anjana K, Prasanth R, Reshmi CR, Juraij K, Rajesh P, Chingakham C, Sajith V, Sujith A (2019) ZnO decorated anti-bacterial electrospun ABS nanocomposite membrane for oil-water separation. Mater Lett 256:126626. https://doi.org/10.1016/j.matlet.2019.126626

Mane S, Ponrathnam S, Chavan N (2016) Effect of chemical crosslinking on properties of polymer microbeads: a review. Can Chem Trans 3(4):473–485. https://doi.org/10.13179/canchemtrans.2015.03.04.0245

Mehta R, Brahmbhatt H, Bhojani G, Mukherjee M, Bhattacharya A (2019) Poly(piperizinamide) with copper ion composite membranes: application for mitigation of Hexaconazole from water and combat microbial contamination. J Hazard Mater 376(March):102–111. https://doi.org/10.1016/j.jhazmat.2019.05.026

Messina MS, Messina KMM, Bhattacharya A, Montgomery HR, Maynard HD (2020) Preparation of biomolecule-polymer conjugates by grafting-from using ATRP, RAFT, or ROMP. Prog Polym Sci 100:101186. https://doi.org/10.1016/j.progpolymsci.2019.101186

Meyn T, Bahn A, Leiknes TO (2008) Significance of flocculation for NOM removal by coagulation-ceramic membrane microfiltration. Water Sci Technol 8(6):691–700. https://doi.org/10.2166/ws.2008.148

Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, Yacaman MJ (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16(10):2346–2353. https://doi.org/10.1088/0957-4484/16/10/059

Moulin C, Bourbigot MM, Tazi-Pain A, Bourdon F (1991) Design and performance of membrane filtration installations: capacity and product quality for drinking water applications. Environ Technol 12(10):841–858. https://doi.org/10.1080/09593339109385079

Munnawar I, Iqbal SS, Anwar MN, Batool M, Tariq S, Faitma N, Khan AL, Khan AU, Nazar U, Jamil T, Ahmad NM (2017) Synergistic effect of chitosan-zinc oxide hybrid nanoparticles on antibiofouling and water disinfection of mixed matrix polyethersulfone nanocomposite membranes. Carbohydr Polym 175:661–670. https://doi.org/10.1016/j.carbpol.2017.08.036

Nasiri M, Jafari I, Parniankhoy B (2017) Oil and gas produced water management: a review of treatment technologies, challenges, and opportunities. Chem Eng Commun 204(8):990–1005. https://doi.org/10.1080/00986445.2017.1330747

Nicomel NR, Leus K, Folens K, Van Der Voort P, Du Laing G (2015) Technologies for arsenic removal from water: current status and future perspectives. Int J Environ Res Public Health 13 (1):1–24. https://doi.org/10.3390/ijerph13010062

Nie J, Sun Y, Zhou Y, Kumar M, Usman M, Li J, Shao J, Wang L, Tsang DCW (2020) Bioremediation of water containing pesticides by microalgae: mechanisms, methods, and prospects for future research. Sci Total Environ 707:136080. https://doi.org/10.1016/j.scitotenv.2019.136080

Nikbakht Fini M, Madsen HT, Sørensen JL, Muff J (2020) Moving from lab to pilot scale in forward osmosis for pesticides rejection using aquaporin membranes. Sep Purif Technol 240:116616. https://doi.org/10.1016/j.seppur.2020.116616

Oh HK, Takizawa S, Ohgaki S, Katayama H, Oguma K, Yu MJ (2007) Removal of organics and viruses using hybrid ceramic MF system without draining PAC. Desalination 202 (1–3):191–198. https://doi.org/10.1016/j.desal.2005.12.054

Ostuni E, Chapman RG, Holmlin RE, Takayama S, Whitesides GM (2001) A survey of structure-property relationships of surfaces that resist the adsorption of protein. Langmuir 17 (18):5605–5620. https://doi.org/10.1021/la010384m

Padil VVT, Nguyen NHA, Rozek Z, Ševců A, Černík M (2015) Synthesis, fabrication and antibacterial properties of a plasma modified electrospun membrane consisting of gum Kondagogu, dodecenyl succinic anhydride and poly (vinyl alcohol). Surf Coat Technol 271:32–38. https://doi.org/10.1016/j.surfcoat.2015.01.035

Park N, Kwon B, Kim IS, Cho J (2005) Biofouling potential of various NF membranes with respect to bacteria and their soluble microbial products (SMP): characterizations, flux decline, and transport parameters. J Membr Sci 258(1–2):43–54. https://doi.org/10.1016/j.memsci.2005.02.025

Qayum A, Wei J, Li Q, Chen D, Jiao X, Xia Y (2019) Efficient decontamination of multi-component wastewater by hydrophilic electrospun PAN/AgBr/Ag fibrous membrane. Chem Eng J 361(December 2018):1255–1263. https://doi.org/10.1016/j.cej.2018.12.161

Qi L, Hu Y, Chai Q, Wang Q (2019) Enhanced filtration performance and anti-biofouling properties of antibacterial polyethersulfone membrane for fermentation broth concentration. J Ind Eng Chem 72:346–353. https://doi.org/10.1016/j.jiec.2018.12.036

Raaijmakers MJT, Benes NE (2016) Current trends in interfacial polymerization chemistry. Prog Polym Sci 63:86–142. https://doi.org/10.1016/j.progpolymsci.2016.06.004

Rahaman MS, Thérien-Aubin H, Ben-Sasson M, Ober CK, Nielsen M, Elimelech M (2014) Control of biofouling on reverse osmosis polyamide membranes modified with biocidal nanoparticles and antifouling polymer brushes. J Mater Chem B 2(12):1724–1732. https://doi.org/10.1039/c3tb21681k

Rajakumar G, Thiruvengadam M, Mydhili G, Gomathi T, Chung I-M (2018) Green approach for synthesis of zinc oxide nanoparticles from Andrographis paniculata leaf extract and evaluation of their antioxidant, anti-diabetic, and anti-inflammatory activities. Bioprocess Biosyst Eng 41 (1):21–30. https://doi.org/10.1007/s00449-017-1840-9

Rallini M, Kenny JM (2017) Nanofillers in polymers. In: Modification of polymer properties. Elsevier, London. https://doi.org/10.1016/B978-0-323-44353-1.00003-8

Ramos-Ballesteros A, Pino-Ramos VH, López-Saucedo F, Flores-Rojas GG, Bucio E (2019) γ-rays and ions irradiation. In: Surface modification of polymers. Springer, Cham, pp 185–209. https://doi.org/10.1002/9783527819249.ch7

Rane J, Adhikar P, Bakal RL (2015) Molecular imprinting: an emerging technology. Asian J Pharm Technol Innovat 3(11):2015

Ricceri F, Giagnorio M, Farinelli G, Blandini G, Minella M, Vione D, Tiraferri A (2019) Desalination of produced water by membrane distillation: effect of the feed components and of a pre-treatment by fenton oxidation. Sci Rep 9(1):1–12. https://doi.org/10.1038/s41598-019-51167-z

Rostam AB, Peyravi M, Ghorbani M, Jahanshahi M (2018) Antibacterial surface modified of novel nanocomposite sulfonated polyethersulfone/polyrhodanine membrane. Appl Surf Sci 427:17–28. https://doi.org/10.1016/j.apsusc.2017.08.025

Roy E, Patra S, Madhuri R, Sharma PK (2016) A single solution for arsenite and arsenate removal from drinking water using cysteine@ZnS:TiO2 nanoparticle modified molecularly imprinted biofouling-resistant filtration membrane. Chem Eng J 304:259–270. https://doi.org/10.1016/j.cej.2016.06.064

Shao S, Liu Y, Shi D, Qing W, Fu W, Li J, Fang Z, Chen Y (2020) Control of organic and surfactant fouling using dynamic membranes in the separation of oil-in-water emulsions. J Colloid Interface Sci 560:787–794. https://doi.org/10.1016/j.jcis.2019.11.013

Shi Q, Su Y, Zhao W, Li C, Hu Y, Jiang Z, Zhu S (2008) Zwitterionic polyethersulfone ultrafiltration membrane with superior antifouling property. J Membr Sci 319(1–2):271–278. https://doi.org/10.1016/j.memsci.2008.03.047

Shi H, Liu F, Xue L, Lu H, Zhou Q (2014) Enhancing antibacterial performances of PVDF hollow fibers by embedding Ag-loaded zeolites on the membrane outer layer via co-extruding technique. Compos Sci Technol 96:1–6. https://doi.org/10.1016/j.compscitech.2014.03.005

Shiraishi K, Koseki H, Tsurumoto T, Baba K, Naito M, Nakayama K, Shindo H (2009) Antibacterial metal implant with a TiO2-conferred photocatalytic bactericidal effect against Staphylococcus aureus. Surf Interface Anal 41(1):17–22. https://doi.org/10.1002/sia.2965

Shoushtari BA, Pazuki G, Shahrouzi JR, Shahriari S, Hadidi N (2020) Separation of erythromycin using aqueous two-phase system based on acetonitrile and carbohydrates. Fluid Phase Equilib 505:112360. https://doi.org/10.1016/j.fluid.2019.112360

Shukla AK, Alam J, Ansari MA, Alhoshan M, Alam M, Kaushik A (2019) Selective ion removal and antibacterial activity of silver-doped multi-walled carbon nanotube/polyphenylsulfone nanocomposite membranes. Mater Chem Phys 233(May):102–112. https://doi.org/10.1016/j.matchemphys.2019.05.054

Soleymani Lashkenrai A, Najafi M, Peyravi M, Jahanshahi M, Mosavian MTH, Amiri A, Shahavi MH (2019) Direct filtration procedure to attain antibacterial TFC membrane: a facile developing route of membrane surface properties and fouling resistance. Chem Eng Res Des 149:158–168. https://doi.org/10.1016/j.cherd.2019.07.003

Song Y, Fan JB, Wang S (2017) Recent progress in interfacial polymerization. Mater Chem Front 1 (6):1028–1040. https://doi.org/10.1039/c6qm00325g

Souza VC, Quadri MGN (2013) Organic-inorganic hybrid membranes in separation processes: a 10-year review. Braz J Chem Eng 30(4):683–700. https://doi.org/10.1590/S0104-66322013000400001

Sui Y, Gao X, Wang Z, Gao C (2012) Antifouling and antibacterial improvement of surface-functionalized poly(vinylidene fluoride) membrane prepared via dihydroxyphenylalanine-initiated atom transfer radical graft polymerizations. J Membrane Sci 394–395:107–119. https://doi.org/10.1016/j.memsci.2011.12.038

Sun M, Zucker I, Davenport DM, Zhou X, Qu J, Elimelech M (2018) Reactive, self-cleaning ultrafiltration membrane functionalized with iron oxychloride nanocatalysts. Environ Sci Technol 52(15):8674–8683. https://doi.org/10.1021/acs.est.8b01916

Sundaran SP, Reshmi CR, Sagitha P, Manaf O, Sujith A (2019) Multifunctional graphene oxide loaded nanofibrous membrane for removal of dyes and coliform from water. J Environ Manag 240(March):494–503. https://doi.org/10.1016/j.jenvman.2019.03.105

Susanto H, Ulbricht M (2007) Photografted thin polymer hydrogel layers on PES ultrafiltration membranes: characterization, stability, and influence on separation performance. Langmuir 23 (14):7818–7830. https://doi.org/10.1021/la700579x

Tan XM, Rodrigue D (2019a) A review on porous polymeric membrane preparation. Part I: production techniques with polysulfone and poly (vinylidene fluoride). Polymers 11(8):1310. https://doi.org/10.3390/polym11081310

Tan XM, Rodrigue D (2019b) A review on porous polymeric membrane preparation. Part II: production techniques with polyethylene, polydimethylsiloxane, polypropylene, polyimide, and polytetrafluoroethylene. Polymers 11(8):1310. https://doi.org/10.3390/polym11081310

Tarannum N, Khan R (2020) Cost-effective green materials for the removal of pesticides from aqueous medium. In: Green materials for wastewater treatment. Springer, Cham. https://doi.org/10.1007/978-3-030-17724-9_5

Tashiro T (2001) Antibacterial and bacterium adsorbing macromolecules. Macromol Mater Eng 286(2):63–87. https://doi.org/10.1002/1439-2054(20010201)286:2<63::AID-MAME63>3.0.CO;2-H

Tijing LD, Woo YC, Yao M, Ren J, Shon HK (2017) Electrospinning for membrane fabrication: strategies and applications. Comprehens Membr Sci Eng 1:16. https://doi.org/10.1016/b978-0-12-409547-2.12262-0

Tsuru T (2001) Inorganic porous membranes for liquid phase separation. Separat Purif Methods. https://doi.org/10.1081/SPM-100108159

Tul Muntha S, Kausar A, Siddiq M (2017) Advances in polymeric nanofiltration membrane: a review. Polymer 56(8):841–856. https://doi.org/10.1080/03602559.2016.1233562

Van Der Bruggen B, Vandecasteele C, Van Gestel T, Doyen W, Leysen R (2003) A review of pressure-driven membrane processes in wastewater treatment and drinking water production. Environ Prog 22(1):46–56. https://doi.org/10.1002/ep.670220116

Vijayeeswarri J, Geethapriyai M, Ramamurthy V (2019) Community level defluoridation of groundwater with limestone derived adsorbent. Process Saf Environ Prot 127:9–15. https://doi.org/10.1016/j.psep.2019.04.029

Waheed S, Ahmad A, Khan SM, Gul S e, Jamil T, Islam A, Hussain T (2014) Synthesis, characterization, permeation and antibacterial properties of cellulose acetate/polyethylene glycol membranes modified with chitosan. Desalination 351:59–69. https://doi.org/10.1016/j.desal.2014.07.019

Wai KP, Koo CH, Pang YL, Chong WC, Lau WJ (2020) In situ immobilization of silver on polydopamine-coated composite membrane for enhanced antibacterial properties. J Water Process Eng 33:100989. https://doi.org/10.1016/j.jwpe.2019.100989

Wang J, Qin L, Lin J, Zhu J, Zhang Y, Liu J, Van der Bruggen B (2017) Enzymatic construction of antibacterial ultrathin membranes for dyes removal. Chem Eng J 323:56–63. https://doi.org/10.1016/j.cej.2017.04.089

Wang Z, Wu A, Ciacchi LC, Wei G (2018a) Recent advances in nanoporous membranes for water purification. Nanomaterials 8(2):65. https://doi.org/10.3390/nano8020065

Wang W, Zhu L, Shan B, Xie C, Liu C, Cui F, Li G (2018b) Preparation and characterization of SLS-CNT/PES ultrafiltration membrane with antifouling and antibacterial properties. J Membr Sci 548(November 2017):459–469. https://doi.org/10.1016/j.memsci.2017.11.046

Weng XD, Ji YL, Ma R, Zhao FY, An QF, Gao CJ (2016) Superhydrophilic and antibacterial zwitterionic polyamide nanofiltration membranes for antibiotics separation. J Membr Sci 510:122–130. https://doi.org/10.1016/j.memsci.2016.02.070

Wu C, Wang Z, Liu S, Xie Z, Chen H, Lu X (2018) Simultaneous permeability, selectivity and antibacterial property improvement of PVC ultrafiltration membranes via in-situ quaternization. J Membr Sci 548:50–58. https://doi.org/10.1016/j.memsci.2017.11.008

Xu L, Shan B, Gao C, Xu J (2020) Multifunctional thin-film nanocomposite membranes comprising covalent organic nanosheets with high crystallinity for efficient reverse osmosis desalination. J Membr Sci 593:117398. https://doi.org/10.1016/j.memsci.2019.117398

Xue J, Wu T, Dai Y, Xia Y (2019) Electrospinning and electrospun nanofibers: methods, materials, and applications. Chem Rev 119(8):5298–5415. https://doi.org/10.1021/acs.chemrev.8b00593

Yan L, Li YS, Xiang CB (2005) Preparation of poly(vinylidene fluoride)(pvdf) ultrafiltration membrane modified by nano-sized alumina (Al2O3) and its antifouling research. Polymer 46 (18):7701–7706. https://doi.org/10.1016/j.polymer.2005.05.155

Yaseen DA, Scholz M (2019) Textile dye wastewater characteristics and constituents of synthetic effluents: a critical review. Int J Environ Sci Technol. https://doi.org/10.1007/s13762-018-2130-z

Ye SH, Watanabe J, Iwasaki Y, Ishihara K (2002) Novel cellulose acetate membrane blended with phospholipid polymer for hemocompatible filtration system. J Membr Sci 210(2):411–421. https://doi.org/10.1016/S0376-7388(02)00421-0

Yin J, Yang Y, Hu Z, Deng B (2013) Attachment of silver nanoparticles (AgNPs) onto thin-film composite (TFC) membranes through covalent bonding to reduce membrane biofouling. J Membr Sci 441:73–82. https://doi.org/10.1016/j.memsci.2013.03.060

You YW, Xiao CF, Huang QL, Huang Y, Wang C, Liu HL (2018) Study on poly (tetrafluoroethylene-: Co-hexafluoropropylene) hollow fiber membranes with surface modification by a chemical vapor deposition method. RSC Adv 8(1):102–110. https://doi.org/10.1039/c7ra09822g

You M, Li W, Pan Y, Fei P, Wang H, Zhang W, Zhi L, Meng J (2019) Preparation and characterization of antibacterial polyamine-based cyclophosphazene nanofiltration membranes. J Membr Sci 592:117371. https://doi.org/10.1016/j.memsci.2019.117371

Zhang Z, Chen S, Chang Y, Jiang S (2006) Surface grafted sulfobetaine polymers via atom transfer radical polymerization as superlow fouling coatings. J Phys Chem 110(22):10799–10804. https://doi.org/10.1021/jp057266i

Zhang X, Du AJ, Lee P, Sun DD, Leckie JO (2008) TiO2 nanowire membrane for concurrent filtration and photocatalytic oxidation of humic acid in water. J Membr Sci 313(1–2):44–51. https://doi.org/10.1016/j.memsci.2007.12.045

Zhang Q, Fan Y, Xu N (2009) Effect of the surface properties on filtration performance of Al2O3-TiO2 composite membrane. Sep Purif Technol 66(2):306–312. https://doi.org/10.1016/j.seppur.2008.12.010

Zhang XF, Liu ZG, Shen W, Gurunathan S (2016) Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci 17(9):1534. https://doi.org/10.3390/ijms17091534

Zhang W, Cheng W, Ziemann E, Be'er A, Lu X, Elimelech M, Bernstein R (2018) Functionalization of ultrafiltration membrane with polyampholyte hydrogel and graphene oxide to achieve dual antifouling and antibacterial properties. J Membr Sci 565:293–302. https://doi.org/10.1016/j.memsci.2018.08.017

Zhang G, Zhou M, Xu Z, Jiang C, Shen C, Meng Q (2019) Guanidyl-functionalized graphene/polysulfone mixed matrix ultrafiltration membrane with superior permselective, antifouling and antibacterial properties for water treatment. J Colloid Interface Sci 540:295–305. https://doi.org/10.1016/j.jcis.2019.01.050

Zhao YH, Wee KH, Bai R (2010a) Highly hydrophilic and low-protein-fouling polypropylene membrane prepared by surface modification with sulfobetaine-based zwitterionic polymer through a combined surface polymerization method. J Membr Sci 362(1–2):326–333. https://doi.org/10.1016/j.memsci.2010.06.037

Zhao YH, Zhu XY, Wee KH, Bai R (2010b) Achieving highly effective non-biofouling performance for polypropylene membranes modified by UV-induced surface graft polymerization of two oppositely charged monomers. J Phys Chem B 114(7):2422–2429. https://doi.org/10.1021/jp908194g

Zhao C, Lv J, Xu X, Zhang G, Yang Y, Yang F (2017) Highly antifouling and antibacterial performance of poly (vinylidene fluoride) ultrafiltration membranes blending with copper oxide and graphene oxide nanofillers for effective wastewater treatment. J Colloid Interface Sci 505:341–351. https://doi.org/10.1016/j.jcis.2017.05.074

Zodrow KR, Alvarez PJJ, Brown GR (2009) Polysulfone ultrafiltration membranes impregnated with master of science. Environ Eng 1911:61826

Antimicrobial Fillers for Dental Restorative Materials

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Abstract Primary cause of restoration failure in dentistry is mainly due to bacterial adhesion, proliferation, colonization and formation of biofilm onto the surface of restorative materials, the so-called secondary caries. Meanwhile, biofilms also affect the longevity of the materials. Chronic denture wearers suffer from denture stomatitis due to the inability of denture base resins to prevent the colonization of fungi *Candida albicans*. Nowadays, novel strategies incorporate nanofillers such as inorganic metal ion nanoparticles and organic nanoparticles into the restorative materials to formulate improved dental materials. Nanomaterials offer a new strategy for averting and remedying dental infections. Hence it is necessary to incorporate antimicrobial nanofillers in dental restorative materials to accomplish improved antimicrobial property.

Keywords Nanomaterials · Antimicrobial fillers · Dental restorative materials · Secondary caries · Denture stomatitis

1 Introduction

Oral cavity relentlessly come across surplus of microorganisms and most of them are normal commensals. Under favourable environment, these microorganisms multiply and cause various infections and diseases. Plaque is the foremost cause of periodontitis, caries, peri-implantitis that results in failure of dental restoration (Fernandes

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et al. 2018). The combat between surgeons and bacteria is an extended war, due to the formation of biofilm. Biofilms are multicellular communities of microorganisms (bacteria, fungi and protists) that contribute to adhesion, proliferation and persistent colonization in living and non-living surfaces (Lear and Lewis 2012). The biofilm producers display unique phenotype with increased resistance to potent antimicrobials and host defence mechanism. Moreover, they form a slimy extracellular polymeric matrix (EPS) consisting of polysaccharides, proteins, lipids and DNA (Hall-Stoodley et al. 2004). They exist in a subclinical state, and upon appropriate favourable condition, they spread and cause severe infections.

2 Dental Caries

Dental caries is one of the most common, prevalent, dynamic oral disease of multifactorial origin that affects people of all age groups (Mahfouz and Esaid 2014). Primary caries occurs at the margin of the restoration due to incomplete removal of the carious lesion (Lai and Li 2012). Acid production and biofilm formation by cariogenic bacteria violate the equilibrium between demineralization and remineralization of the tooth surface. Drop in pH leads to loss in calcium and phosphate and makes the penetration deeper. The oral biofilm formation begins with the adherence of salivary pellicle (free of bacteria) on the tooth and restorative cement surface, where the acquired salivary pellicle acts as a receptor to which the adherence of microbacterium occurs (Lendenmann et al. 2000). Consequently, bacterial multiplication occurs and progresses through passive transportation of bacteria into the pellicle (Marsh 2004). Thus, results in an irreversible adhesion. Moreover, *Streptococcus mutans*, the primary inhabitant of oral cavity is capable of degrading restorative cements due to the significant esterase activity (Bourbia et al. 2013). Microleakage at the restoration-tooth interface allows microcavities, contamination and residual stresses (Venhoven et al. 1993).

Lack of interfacial integrity for a longer period would indeed predisposes to secondary caries beneath the filling material (Sakaguchi 2005) and results in restoration failure (fracture or dislodgement). Meanwhile, it is a potential cause of hypersensitivity, pulp inflammation and necrosis (Larsen and Munksgaard 1991). More specifically, matrix metalloproteinases (MMPs) present in saliva and cysteine cathepsins expressed by dentin-pulp complexes act synergistically and degrade the hybrid layer thus aid in caries progress (Nascimento et al. 2011). It has been realized that severe bacterial contamination would definitely result in treatment failure (Turner et al. 1975).

Risk factors and amenable causes for caries

- Consistency and flow rate of saliva
- Patients hygiene
- Diets rich in carbohydrates
- Mechanical and surface property of the restorative materials

- Physical and chemical property (pH and buffering capacity) of the restorative materials
- Biological property (antibacterial/antibiofilm) of the restorative materials
- Location and the extent of the caries lesion

3 Antimicrobial Agents

An Antimicrobial agent is defined as a substance or an agent that causes interference with the harmful effects of the bacteria. It inhibits the growth, mitogenesis of the microorganisms and destroys it, thus preventing microbial colony formation. On the other hand, the term bioactive is described as the biological effect of any substance that induces cell growth, proliferation and tissue formation. Meanwhile, it implies the antibacterial effect of a biomaterial to prevent infection. Dr. Larry Hench was the first to coin the term "bioactive material" (Jasmine et al. 2020).

4 Restorative Materials in Dentistry

Restorative materials used in dentistry should possess good aesthetics, superior mechanical properties and should also have excellent antimicrobial properties, thereby increasing the longevity of the restorative materials. Nowadays, innovation of new restorative materials with microbicidal activity is the current trend and a possible mean to effectively prevent and inhibit pathogenic microbial colonization on the tooth surface (Zoergiebel and Ilie 2013). Similarly, these materials should release lethal dose of antibacterial agent in a controlled manner. Some of the dental restorative materials that have incorporated various antibiotics shown to have short-term effects. Moreover, few of them encourage bacterial resistance at sub-lethal concentration and counteractively favour biofilm formation. Organic antibacterials possess greater resistance. Hence, development of metal-based antimicrobials (inorganic) have acquired significant popularity. These attractive alternates have redox properties, unique binding with minimum bacterial resistance. Despite their benefits, toxicity against human tissues should be taken into consideration and hence their therapeutic value have to be focused primarily. Metal ions with optimum properties and biocompatibility could be a better choice.

Recent studies have focused on novel strategies that incorporate nanoparticles, especially metal ions into the restorative materials with altered surface chemistry (Nguyen and Hiorth 2015). Nanomaterials offer a new strategy for averting and remedying dental infections (Magalhães et al. 2016). Nanomaterial is defined as a material which has particle size ranging from 1 nm to 100 nm in an unbound state or as an aggregate/agglomerate that has an internal or surface structure with one or more dimensions and has a specific surface of about more than 60 m^2/cm^3. Meanwhile, they possess unusual physical, biological and chemical properties that differ

with different materials. Nanoparticles (NPs) exhibit increased surface area, and disperse evenly without aggregates. Incorporation of nano and microparticles into the dental materials can significantly reduce or block the microbial colonization thus improve the oral health. An important proposed strategy to be focused is the incorporation of remineralizing and antibacterial agents to reduce plaque adherence and to repair the demineralized dentin.

5 Classification of Nanoparticles

Classification of Nanoparticles

Based on the origin
- Organic (Natural/Artificial) (Onaizi et al 2011., Perinelli et al 2018)
- Inorganic. (Whitesides 2003)

Based on the structural configuration (Hall et al. 2007)

Carbon-based Metal NP Dendrimers Composites

Based on the dimension (Zhang et al. 2008)
- Zero dimensional/ Nanoparticles
- One dimensional/Nanorods
- Two dimensional/films

5.1 Organic Nanomaterials

Organic materials are unique in structural and electronic characters. Carbon nanotubes, lipids and polymers are some of the organic types that have multifaceted applications (Hatton et al. 2008). Polymers may be of natural and synthetic origin. Natural antimicrobial fillers are Antimicrobial peptides (AMP) (Onaizi and Leong 2011) and Antimicrobial enzymes (AME) (Thallinger et al. 2013). Biopolymers are biodegradable, biocompatible and nontoxic. Sources of biopolymers are chitin, chitosan, cellulose, starch and pectin (Perinelli et al. 2018).

5.2 *Inorganic Nanomaterials*

Inorganic metal oxide NPs such as titanium oxide, zinc oxide, copper oxide, magnesium oxide and silver oxide have the ability to withstand adverse processing conditions (Whitesides 2003). Moreover, due to their tunable optical and physical properties, these NPs have attained greater attention (Makhluf et al. 2005). Restorative materials that do contain metal oxides of Ag, Hg, Cu, Ni, Zn and fluoride have a well-documented antimicrobial property (Wang et al. 2016). Acidic pH enhances the growth of aciduric and acidogenic bacteria in abundance. Hence these nanoparticles should also have cariostatic property to counteract the acidic pH caused by cariogenic bacteria to retard secondary caries. Apart from antibacterial activity, ZnO NPs has the potential of tissue regeneration.

5.2.1 Silver NPs

Silver (Ag) ions are biocompatible, less toxic, and the sustained release of ions provide a long-term antimicrobial effect (Slenters et al. 2008). With the advent of nanotechnology, AgNPs have a wide range of antimicrobial activity against bacteria and fungi species with a low bacterial resistance (Morones et al. 2005; Aziz et al. 2016; Prasad 2014, 2016, 2017). Smaller the filler size, greater the surface area, hence a high antibacterial effect is seen even with minimum quantity of incorporated filler. Thus, nanoparticles allow a greater interaction with the environmental surroundings and enhance bacterial elimination (Seil and Webster 2012). The filler shape plays important role in the production of ROS and also induces destruction of the bacteria (Pal et al. 2007). Compared to spherical shape, rods and wires exhibit more active facets. This facilitates easy penetration into the cell wall of the bacteria (Yang et al. 2009). Thus, it influences the internalization mechanism of the material. Advantages of nanoparticles are higher antibacterial activity with less influence on mechanical properties. Limitations are discoloration and agglomeration of the AgNPs (Melo et al. 2013). Development of resistant strains occurs against AgNPs due to gene mutations (Graves Jr et al. 2015). Further, they crosses the blood–brain barrier and gets accumulated in the brain (Padovani et al. 2015). AgNPs, phthalocyanine and graphite oxide composites have proven to have lasting antimicrobial activity (Gerasymchuk et al. 2016) and a promising way to prevent bacterial resistance (Karasenkov et al. 2015).

5.2.2 Zinc Oxide NPs

ZnO NPs possess a variety of shapes like nanorods, nanospheres, microspheres and microrod. These shapes or morphologies act differently against Gram-positive and Gram-negative bacterial pathogens, thus which confirms their broad-spectrum activity (Rago et al. 2014; Raghupathi et al. 2011). Size, colour and quantity of the fillers may affect the physical and mechanical properties (Sakaguchi et al. 2006). Taken

these into consideration, characters such as temperature, precursor types, pH, solvents should be given importance and methods to control over it (Sirelkhatim et al. 2015). This gives restorative materials a good clinical longevity and an acceptable outcome. The important antimicrobial mechanism suggested is the production of ROS (peroxide) that favours inhibition of bacterial growth (Ranjita 2017; Zhang et al. 2007; Bhuyan et al. 2015). Comparison between micro and nanorods revealed that nanorods have superior antibacterial effect against *Staphylococcus aureus* and *Bacillus subtilis* (Rago et al. 2014). Study results of Kasraei et al. also correlated with that of Rago et al., i.e. ZnO nanoparticles inhibited *Streptococcus mutans* and *Lactobacillus* significantly. Even with the lower concentration (10% (w/w)) of ZnO, the reduction of biofilm formation is up to 80% (Sevinç et al. 2010) without affecting the mechanical properties (compressive and tensile strength) (Rastelli et al. 2012). On the other hand, it also provides a better dispersion of the filler into the composite resin (Chen et al. 2017a). Microspheres of ZnO at 5 μg/ml of concentration inhibited *S. aureus*, *S. typhimurium* and *K. pneumonia,* whereas *E. coli* at 155 μg/ml (Wahab et al. 2012).

5.2.3 Copper and Nickel Oxide NPs

Copper and nickel NPs possess broad-spectrum of antibacterial activity against a wide range of pathogenic bacteria. And also, a good alternate and inexpensive than Ag and gold NPs (Chatterjee et al. 2012; Pang et al. 2009). Hallow oxide formation through oxidation of Cu and Ni nanoparticles surface also exhibits strong antibacterial property (Ren et al. 2009; Borkow et al. 2010). Copper oxide NPs also possess antibacterial activity against Gram-positive and Gram-negative bacteria. The primary mechanisms ascribed are adsorption of metal ions and reduction reaction at the bacterial cell wall and degradation of the cytoplasm (Raffi et al. 2010; Yadav et al. 2017). Moreover, the antibacterial efficacy is based on both the concentration of NPs and the initial bacterial concentration. Being bactericidal/bacteriostatic, Cu and Ni NPs can be used in preparation of bone cements, coating for devices, sterilization, irrigation of the root canal system and in various other probable applications in the field of dentistry (Argueta-Figueroa et al. 2014). Novel nanocomposites prepared using bioglass coated with Cu NPs have significant antibacterial property with improved angiogenesis (Li et al. 2016a). However, incorporated Ti-Cu NPs as immobilized antibacterial agent in dental materials provide a long-term antimicrobicidal activity. Moreover, they have effective antibacterial and antibiofilm activity against *Porphyromonas gingivalis* and *S. mutans* (Li et al. 2016b). Optimum Cu content (5%) is indicated to maintain excellent mechanical property and a better antimicrobial property that aids in greater reduction of biofilm formation (Liu et al. 2018). By means of contact sterilization, the dissolved Cu ions tend to damage the bacteria (Cao et al. 2011). Further, they adversely affect the gene expression of extracellular polymeric substance on the MRSA (Methicillin resistant *Staphylococcus aureus*) biofilm producing bacteria. Thus, it leads to minimal adherence of the bacteria by down-regulating the production of polysaccharide intercellular adhesion and

clumping factor A that disable the formation of biofilm colonies (Liu et al. 2018). Meanwhile, due to its antibacterial activity and excellent anticorrosive nature Ti-Cu alloy has the potential to be a novel dental implant material.

5.2.4 Titanium Oxide NPs

Titanium and its alloys are the choice of material to be used commonly in the field of dental implants. In fact, they are biocompatible with good mechanical properties. Cell adhesive proteins that adhere on the surface of Ti implant surface proved to be the site for binding of osteoblast precursors that favours bone ingrowth and stabilization. Inappropriate intervention of these sequences by bacterial colonization results in peri-implantitis. Further apart, this has to be prevented before the integration process. Incorporation of metal NPs (Cu, Ag) into the dental implant materials permit a better control over the biofilm formation, since they acquire less resistance (Rosenbaum et al. 2017). The most commonly encountered strains are *Staphylococcus aureus* (16%), *Escherichia coli* (26%) and *Pseudomonas aeruginosa* (9%) (Von Eiff et al. 2006). Cu NPs derived TiO_2 surface when exposed in a stimulated plasma solution revealed high biocide potential against biofilm producing bacterial pathogens especially *S. aureus* and *E. coli* (Rosenbaum et al. 2017).

5.2.5 Chitosan

Chitosan is an organic bioactive compound derived naturally from chitin, an extract of seafood shells, crabs, lobsters and shrimps (Yan and Chen 2015). Being biocompatible, biodegradable and less toxic, it has shown promising results in tissue regeneration. Carboxymethylated chitosan is a derivative of chitosan exhibits extensive antimicrobial property. The major mechanism involved is, the chelation of ions, that removes the trace metals and essential nutrients that are essential for bacterial survival (Shin et al. 2005). Powdered form of this material have been used in drug delivery technology, implants and in scaffolds (Alhajj et al. 2019). In addition, BisGMA and TEGDMA monomers used for crosslinking chitosan have toxicity against pulp cells (Goldberg 2008). Furthermore, its use in composites, glass ionomer cement, denture based resins and in dental adhesives is an emerging new method. The major disadvantage is it reduces the mechanical strength of the restorative material (Takagi et al. 2003). Electrospray and electrospinning methods are used to produce microspheres and nanofibres, respectively (Chen et al. 2018). The electrospinning method incorporates calcium phosphate with chitosan microspheres and generates dibasic calcium phosphate anhydrous, a novel material with antimicrobial property. Even at the lowest concentration chitosan (0.5%) possesses antimicrobial property (Raafat and Sahl 2009). It is well established that composite loaded with chitosan exhibits strong antimicrobial potential across the restorative material without compromising its biocompatibility (Tanaka et al. 2020). The major disadvantage of chitosan is reduction in the mechanical strength of the restorative

material. In addition, BisGMA and TEGDMA monomers used for crosslinking of chitosan possess toxicity against dental pulp cells.

The three main methods that render effective antibacterial activity to the dental restorative materials are

1. Release killing method.
2. Contact killing method.
3. Multirelease functional method (Cloutier et al. 2015)

Release Killing method

Local delivery of preloaded antimicrobial agents into the environment is the main mechanism of action. Examples are antibiotics and silver compounds

Advantages

1. No systemic toxicity
2. Minimal drug resistance
3. Release of high doses of antimicrobial agents over time
4. Broad spectrum antimicrobial activity (Campoccia et al. 2013).

Drawbacks

1. Inherent depletion of the reservoir source.
2. Short acting.

Contact Killing method

To evade the reservoir exhaustion of the antimicrobial agents and incorporation of antibacterial fillers into the polymers that exert their antimicrobial property through contact killing mechanism is an attractive alternate (Jia et al. 2017). Polycations, antimicrobial peptides (AMPs) (Onaizi and Leong 2011), antimicrobial enzymes (AMEs), proteolytic enzymes, polysaccharide degrading enzymes, oxidative enzymes (Thallinger et al. 2013) and chitosan are typical examples (Munoz Bonilla and Marta Fernández 2012). Also incorporation of quaternary ammonium compounds (QACs) into dental composites such as dental adhesives, glass ionomer cements (GIC), resin modified GIC, pulp capping agents, root canal sealers and acrylic resins provide a long lasting bactericide-immobilized restorative materials (Imazato 2003).

Advantages

1. Nontoxic and non-irritant
2. Long-term antibacterial property

Drawbacks

1. Bacteriostatic
2. Surface biofouling

Multirelease functional method (Responsive and Synergistic Antimicrobial Properties)

Photothermal materials based on near infrared irradiation convert light energy to thermal energy have gained increased attention owing to their distinct antimicrobial mechanism (Gharatape et al. 2016; Wang et al. 2016). Examples are gold based nanomaterials (GNPs), reduced graphene oxide (rGO) and polypyrrole nanoparticles. They cause physical destruction and penetrate the living tissues with sufficient intensity by generating local heat, thus evading resistance strains (Liang et al. 2014; Yang et al. 2009). GNPs are biocompatible and exert its antimicrobial property via surface plasmon resonance (Gharatape et al. 2016). Moreover, antimicrobial property could be further improved by surface conjugation with specific antibodies (Millenbaugh et al. 2015). The innovation of smart antibacterial surfaces is based on the "kill and release" approach that have the ability to destroy the material associated bacteria as well as eradicate dead bacteria and debris especially multidrug resistance bacteria, thus uphold long-term antimicrobial property (Qu et al. 2019). Photo therapy basically of two types—antibacterial photothermal therapy (APTT) and antibacterial photodynamic therapy (APDT). A combination of biocidal agents and phototherapy have improved antimicrobial property due to synergistic effects. Examples are gold nanorod and kanamycin against *E. coli* (Hu et al. 2013), rGO and vancomycin against multidrug resistance *E. coli* (Yang et al. 2009)

6 Mechanism of APDT action

APDT has been paid great attention in recent years owing to its potential antimicrobial activity against various oral pathogens and biofilms (Al-Shammery et al. 2019). The primary mechanism implicates interaction between photosensitizer and low energy laser that produce reactive oxygen species in the existence of oxygen (Hu et al. 2018). These agents do surface modification through different mechanisms such as disinfection, photocatalysis, photothermal lysis and photodynamic killing, thereby eliminating multidrug resistance bacteria. Based on the types of photosensitizing agents, they can be delivered through intravenous injection, topical application and oral ingestion (Konopka and Goslinski 2007).

Advantages

1. Improbable development of antimicrobial resistance
2. Prompt suppression of the contributing microbes due to oxidative changes in bacterial cell membrane (Hu et al. 2018).
3. Biopolymers and NPs hauling photosensitizers have the advantage of (1) Improved antibacterial efficiency. (2) Enhanced biocompatibility and biodegradability. (3) Reduced accumulation of photosensitizers (Zhang et al. 2016)

Drawbacks

1. Photosensitivity due to the presence of accumulated photosensitizing agents for a few days (Takasaki et al. 2009).

Materials with antimicrobial property supplemented with remineralizing and protein repellent properties come under this category. Moreover, they respond to the microenvironmental cues of the microbial infections (Wei et al. 2019). Examples are silver nanoparticles (AgNPs), amorphous calcium phosphate (NACPs), a combination of NACPs and QAM.

7 Mechanism of Action of NPs

Nanoparticles exert their antibacterial effect through interaction with the peptidoglycan of the bacterial cell wall and thereby increasing the membrane permeability (Qiu et al. 2016). In addition, NPs bind to mesosomes and impede bacterial respiration. They also inhibit DNA replication via interaction with sulphydryl groups and block signal transduction (Giannousi et al. 2014; Pal et al. 2007). The surface of NPs interacts with the transport proteins and inhibits transportation across the semipermeable membrane (Moghimi and Szebeni 2003). Further, NPs generate reactive oxygen species, dysregulate metal ion homeostasis and ATP production that are essential for cell growth and survival. This in turn causes distortion of cell membrane (Nel et al. 2006; Aziz et al. 2014, 2015). NPs mediate amino acid oxidation and produce protein bound carbonyls which results in deactivation of various enzymes (Lynch and Dawson 2008). The positively charged NPs bind to the negatively charged bacterial cell membrane and exert their antibacterial activity (Cao et al. 2018; Prasad and Swamy 2013; Swamy and Prasad 2012). Moreover, the size of nanoparticles allows them easy penetration through the bacterial membrane (Melo et al. 2013).

8 Factors Influencing the Antibacterial Property of NPs

A minimum concentration of nanofillers provide a greater release of ions without affecting the mechanical properties of the cements (Xu et al. 2011). Moreover, the components that adsorbed over the NPs, their composition and structure have a direct influence over the antibacterial activity (Olenin and Lisichkin 2011). Indeed, thick layer impedes antimicrobial activity and vice versa. Studies revealed that incorporation of NPs into polymers or coated onto biomaterials seems to have superior antimicrobial properties (Saafan et al. 2018). Moreover, it is advantageous in drug resistance microbes (Fernandes et al. 2018). Some researchers found that NPs of lower concentration do not exhibit cytotoxic effects and established a dose dependent activity. In fact, the concentration, type, form, size and distribution of the NPs influence the duration and potency of antibacterial effect.

9 Antimicrobial Fillers in Pulp Capping Agents

Pulp exposure is common as a sequalae of caries progression or due to trauma and during cavity or crown preparation (Stanley 1989). Therefore, to preserve the vitality, functional and biological activities of the exposed pulp temporarily and permanently, pulp capping procedure is being done (Haskell et al. 1978). The most commonly used pulp capping agents are calcium hydroxide (CaOH) and mineral trioxide aggregate (MTA) (Camilleri and Pitt Ford 2006). CaOH possesses high antibacterial activity through the release of hydroxyl ions in an aqueous environment (Siqueira 2001). These ions cause denaturation of proteins and damage the microorganisms cytoplasmic membrane. In addition, the alkaline pH (12.5) of the material also enhances the antibacterial effect. MTA is composed of 15–25% of silicon dioxide and 50–75% of CaOH. However, it has been shown that MTA forms silicate hydrate gel on hydration. Hence, both MTA and CaOH have similar mechanism of action (Roberts et al. 2008). Moreover, MTA discharges antimicrobial action even in anaerobic state (Reston and de Souza Costa 2009). Similarly, calcium silicate-based material otherwise called biodentine has been used for indirect pulp capping (IPT). The provisional use of biodentine seems to be beneficial in uncooperative paediatric patients in whom complete removal of caries lesion is not possible. In addition it can be used as IPT agent under dental composites and also in minimal invasive treatment. It has been investigated that biodentine has the potential to inhibit *S. mutans*, *S. gordonii* and *S. sorbinus*. The study by Deveci et al. revealed that Biodentine, Chlorhexidine (CHX) and cetrimide combination proved to have much bacterial inhibition zone of *Lactobacillus* and *S. mutans* (Deveci et al. 2019).

10 Antimicrobial Fillers in Root Canal Sealers

Root canal treatment is the chemomechanical debridement and shaping of the root canal and effective elimination of the microorganisms from them. Antibiotics, steroids and calcium hydroxide are commonly used intracanal medicaments. Despite their benefits, they may produce resistant strains and even host sensitization. Therefore, a better alternative might be nanosized metal ions such as nanomonosodium titanate and gold titanates that are much effective (Eiampongpaiboon et al. 2015). When these particles are exposed to water or while mixed up with calcium hydroxide, they occlude the dentinal tubules as well as the bacteria significantly, even at micromolar concentration (Drury et al. 2018). Due to increase in surface area to volume ratio, the ion exchange property is also more efficient (Beyth et al. 2014). Studies have proved that gold nanoparticles have the antibacterial potency against both gram-positive and gram-negative bacteria such as *Staphylococcus aureus*, *Lactobacillus casei*, *Escherichia coli* and *Pseudomonas aeruginosa* (Morim 2016).

11 Antimicrobial Fillers in Glass Ionomer Cement (GIC)

In 1969 Wilson and Kent introduced glass ionomer cement (GIC). They are frequently used material for luting, lining, fissure sealants, and also in temporary, permanent and atraumatic restorations. Composition of the conventional GIC powder is alumina, silica and calcium fluoride. In addition, Ba and Sr salts are added to impart radiopacity to the cement. The liquid of GIC contains polycarboxylic acid, tricarboxylic acid, maleic, itaconic acid and tartaric acid (Phillips and Anusavice 2013; Baig and Fleming 2015). Incorporation of tartaric acid improves the handling property and thus sufficient working time. The setting reaction of GIC is basically an acid base reaction. Among all the restorative materials, GIC is well known for their practical benefits that includes fluoride release and recharge, chemical bonding, low coefficient of thermal expansion and pleasing aesthetic quality. The inclusion of silicates and fluorides prevent caries progression. Furthermore, chelation between carboxyl group of acid polymer with the hydroxyapatite of enamel, dentin and bone enables a better chemical bond between them. The fact is that, it releases appropriate amount of fluoride that inhibit the metabolism of carcinogenic organisms, thus favouring remineralization (Wiegand et al. 2007).

Moreover, the fluoride release is continuous throughout the materials life time. The linear expansion coefficient of GIC is comparable with that of the tooth. The major drawbacks of GIC are significantly reduced wear resistance, brittleness (Papacchini et al. 2005), synergism and imbibition. Resulting in dimensional changes, decrease surface wear resistance and interfacial gaps that restrict its application in the area of high occlusal load. Years of extensive research have attained considerable changes in the composition that significantly modified the mechanical and handling properties of GIC. These include resin modified GIC, fibre reinforced and bioactive GIC that incorporates of zirconia, zinc, strontium oxide, silica particles, N-vinylpyrrolidone and amino acids (Gu et al. 2005; Zoergiebel and Ilie 2013; Boyd and Towler 2005). Nowadays studies have shifted focus on the incorporation of various nanoparticles to obtain efficient bioactivity (Yli-Urpo et al. 2005). Zinc, silica, ceramics, ytterbium fluoride, titanium oxide, bioactive glass, titanium dioxide, montmorillonite clay, aluminosilicate glass, hydroxyapatite and fluoroapatite, phosphopeptide-amorphous calcium phosphate are some of the particles that are added to obtain desirable strength (Poorzandpoush et al. 2017). In general, metallic oxides such as SrO and $BaSO_4$ have been found to result in desirable mechanical properties (Moheet et al. 2019).

GIC possess chemical bonding and strong adhesion that allows them to bond on both enamel and dentin. Thus, it would be a better opportune material for posterior restoration. When increased crosslinking and polysalt bridge formation are perceived in the set cement, they improve the mechanical properties of the set cement (Oliva et al. 1996). Reinforcement of GIC with hollow and solid discontinuous glass fiber fillers increase the fracture toughness, compressive strength and flexural strength. GICs containing nanohydroxyl apatite (nHA) and fluoroapatite (FA) have improved bonding to the dentin with good mechanical properties (Moshaverinia

et al. 2008). Casein phosphopeptide-amorphous calcium phosphate incorporation at 3% concentration inhibited demineralization and encouraged remineralization by enhancing calcium and phosphate release (Al Zraikat et al. 2011). Addition of 5% niobium pentoxide (Nb_2O_5) revealed bioactivity and biocompatibility (Garcia et al. 2016). Hydroxyapatite-alumina/zirconia nanocomposite (HANBG) when added to BAG improves antibacterial activity, bioactivity and also mechanical properties (Thampi et al. 2014). Inclusion of fluoroaluminosilicate glass provoked an acid base reaction with polyacrylic acid and yielded pre-reacted glass ionomer (S-PRG) filler (Ikemura et al. 2003). In turn, capable of releasing fluoride with recharge functions (Han et al. 2002). Fluoride released from the dental materials when interact with apatite of the tooth surfaces forms fluoroapatite (Feagin and Thiradilok 1979)

Addition of titanium oxide nanoparticles (TiO_2) increase the adhesiveness. TiO_2 nanotubes (TiO_2 nt) have increased surface to volume ratio. Hence, even at minimum concentration (3–5%), TiO_2 nt is stable, nontoxic, and increases the fluoride release thus have antimicrobial effects. Moreover, a better particle distribution protects the matrix effectually and increases the microhardness. Hence, an overall improvement in mechanical property of GIC to resist abrasion is essential. At a concentration of 10%, niobium pentoxide affects the interaction between powder and polyacrylic acid and negatively influence the chemical bonding of GIC to the tooth (Garcia et al. 2016). GIC appended with chlorhexidine diacetate and digluconate have bactericidal action against Streptococcus mutans and Lactobacillus acidophilus (Türkün et al. 2008).

12 Antimicrobial Fillers in Dental Composite Resins

Dental composite resins are considered to be the suitable material for tooth cavity restoration due to improved aesthetics and physical properties. The first formulated earlier composites experienced low abrasion resistance, colour instability and inadequate mechanical strength (De Gee et al. 1990). Due to extensive research, the current dental composites with good mechanical properties and excellent colour match have emerged. It is the versatile material of choice with optimal aesthetic property in all classes of direct restorative treatment (Lynch et al. 2014). Also, the wear rate is equal to that of enamel. Most of the current composites material composition is basically silane coated glass/ceramic particles dispersed in methacrylate resin that include bifunctional monomers (Chen 2010). Hardening of the material occurs through free radical polymerization, activated by visible light or initiated chemically (Stansbury 2000). It attributes to 49% of all restorations.

However, clinical studies have revealed that 74% of the failed composite restorations are due to secondary caries (SC) (Xie et al. 2011; Wiegand et al. 2007). This could be due to its surface property, release of unreacted monomers and absence of antibacterial property that accumulates more plaque and forms thick biofilm (Zhang et al. 2008). Most commonly used monomers in the conventional composites are 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropoxy)phenyl]propane (BisGMA) and

triethylene glycol dimethacrylate (TEGDMA). However, Bisphenol A (BPA) is used as a raw material for the synthesis of the monomer of the dental composites. After the placement of BPA based composites, trace amount of BPA was found on saliva and urine. Hence, substitution of BisGMA monomer with tris(4-hydroxyphenyl)methane triglycidyl methacrylate (TTM) is a novel approach. The advantages of TTM over BisGMA are comparable mechanical, biological properties and also the ability to photopolymerize with visible light.

Classification of Composites

Based on the filler size and the properties,

- Macrofill (10–50 μm) conventional composites-monodisperse
- Midifill (1–5 μm)
- Minifill (0.4 μm)
- Microfill (0.01–0.1 μm) homogeneous/heterogenous
- Hybrids (0.01–5 μm) polydisperse
- Microhybrid (0.01–1 μm) polydisperse
- Nanofill (0.01–0.04 μm) monodisperse
- Nanohybrid (0.01–1 μm) polydisperse

Fixing orthodontic brackets is the primary step in orthodontics and is achieved through bonding agents (Eliades 2002). In spite of their advantages like ease of application and excellent aesthetics, composite resins and dental adhesives as such are unable to hamper bacterial adhesion and demineralization. Moreover, drawbacks such as bond failure, plaque accumulation, white spots and demineralization around the brackets are unfortunately unavoidable (Allaker 2010). In earlier days, antimicrobials such as chlorhexidine, fluorides were used as effective means to prevent these drawbacks. The current trend is application of nanotechnology into the dental restorative materials to improve their properties (Leung et al. 2005; Sodagar et al. 2013). Metal nanoparticles such as Ag, Zno, Tio_2, Cuo, zirconia and magnesium oxides and hydroxyapatite have gained greater popularity among inorganic fillers. Moreover their physical, optical properties and the concentration can be tailored according to the needs. The carbon nanotubes, lipids and polymers are some of the organic NPs with the unique structural characters. Chitosan are either incorporated into the polymers or coated onto the biomaterials (Magalhães et al. 2016), due to the demonstrated broad spectrum antimicrobial properties (Saafan et al. 2018). A combination of chitosan and ZnO NPs less than 5% (Sodagar et al. 2013) of incorporation into dental composites have an potency to enhance antibacterial activity with superior mechanical properties (Mirhashemi et al. 2013). Application of TiO_2 into composite resins confers antibacterial properties. TiO_2 NPs at 1% concentration prominently inhibited *S. mutans* (Poosti et al. 2013), whereas more than 5% of TiO_2 NPs inhibited *S. mutans* and *S. sanguinis* but not on biofilm producing *L. acidophilus* (Sodagar et al. 2017).

Various methods have been used to modify the composite resins that prevent bacterial proliferation. Incorporation of low molecular weight organic or inorganic moieties including antibiotics, fluoride, iodine, zinc, QAM, chlorhexidine and silver based nanomaterials may have limitations toward antimicrobial property and

mechanical property (Beyth et al. 2006). Due to the release of soluble agents, they are cytotoxic to the human tissues (Cocco et al. 2015). Inclusion of nanoparticles into dental materials have the benefit of antimicrobial property as well as remineralization of dental hard tissues (Angel Villegas et al. 2019). The composition, particle size, filler loading and the surface treatment of the antimicrobial fillers should permit release of ions even in an aqueous environment. Release of ions such as calcium, phosphate and fluoride ions have the benefits of reducing postoperative dentin hypersensitivity that enhance precipitation of hydroxyapatite crystals, better bonding of the material with tooth surface and durability (Tarle and Par 2018). However the mechanical properties such as polymerization shrinkage, shrinkage stress, elastic modulus, degradation, degree of conversion and biocompatibility should not be compromised.

Diverse research has been accomplished so far, to develop antimicrobial fillers of various types to provide the composite materials with enhanced antibacterial activity. Numerous studies have been employed on composites with added organic materials such as quaternary ammonium polyethylenimine nanoparticles, benzalkonium chloride, chlorhexidine, acrylic acid, triclosan and chitosan aminohexadecyl methacrylate. Also with additives like, quaternary ammonium dimethacrylate (QADM), 12-methacryloyloxydodecylpyridinium bromide (MDPB), dimethylaminohexadecyl methacrylate (DMAHDM), dimethyl-hexadecyl-methacryloxyethyl-ammonium iodide (DHMAI), and dimethylaminohexadecyl methacrylate that gave varying degree of success. In addition, inorganic fillers (mesoporous silica with chlorhexidine, zinc oxide and silver ions) can also be mixed with monomers. They get entrapped into polymers after polymerization and exert their antimicrobial property (Ohashi et al. 2004). Antibacterial activity of A-glass-CyCl-Ag is due to interaction of sulfadiazine with DNA and silver ion binding leads to deactivation of protein as well as expiration of the bacteria

Fluoridated glass, inorganic fluoride compounds and pre-reacted glass ionomer fillers (S-PRG) are the forms of fluoride that are incorporated with resin composites. Dental composites with S-PRG is termed as giomer. Giomer releases small amount of fluoride, and it exhibits superior optical properties and strength than conventional GIC (Garoushi et al. 2017). Moreover, inclusion of CaF_2 nanoparticles reduced mineral loss from the tooth margins. When strontium replaces Ca, it enhances the radiopacity and improves the antibacterial activity. Addition of 10–20% of monocalcium phosphate monohydrate (MCPM), tricalcium phosphate or tristrontium phosphate, help relief of residual stress by encouraging water induced expansion (Park and Ferracane 2014). This compensates the polymerization shrinkage of the composites (Aljabo et al. 2015). Nanoparticle amorphous calcium phosphate (NACP-size of 116 nm) decreased the demineralization depth of the enamel and increased the remineralization of adjacent tooth surface (Tezvergil-Mutluay et al. 2017). Also it reduced the penetration depth of the bacteria (Khvostenko et al. 2016). The ability of nanoassemblies to inhibit high bacterial load through bacterial membrane fusing, clumping and disintegration that causes significant bacterial death (Schnaider et al. 2019).

13 Bioactive Glass (BAG)

The bioactive glass was invented by Hench in 1969 (Hench et al. 2004). It is a soluble form of glass. The composition of BAG consists of SiO_2, CaO,Na_2O and P_2O_5 in a variable concentration (Jones 2013) and can act as source of fluoride, calcium, strontium ions, and also control their release (Shahid et al. 2014). Therefore, by altering specific ingredient in a small proportion according to the particular need, it is possible to tailor BAG (Kaur et al. 2014). The BAG is capable to form apatite layer through precipitation of HA spontaneously (Jones 2013), and makes it a potential source of remineralizing ions (calcium and phosphate). BAG when exposed to water, exchanges sodium and calcium ions with the hydrogen ion of water and forms Si–OH groups (silica rich layer). During the rise in local pH, the hydroxyl ions attack Si–O–Si bonds and form $Si(OH)_4$. Then condensation of Si–OH groups occur and attract more calcium and phosphates ions (Hench 2006). Further, crystallization occurs in the form of amorphous calcium phosphate (ACP) to hydroxyl appatite (HA). It has been reported that the ability of BAG to form silicon-rich layer could serve as a template for HA precipitation. For this to happen, appropriate adjustment in hydrophilicity should be taken place (Spanovic et al. 2017). BAG increases the local pH initially and inhibits the matrix metalloprotinase activity that aids in precipitation of HA (Profeta 2014). Furthermore, it inhibits collagen degradation, upsurges the hardness of demineralized dentin. Henceforth, BAG has the ability to increase the longevity and stability of the hybrid layer by defending it from hydrolytic degradation (Tezvergil-Mutluay et al. 2017). The antimicrobial effect of BAG is mainly by the change in the local pH, in addition, direct contact toxicity also contributes to the improved effect (Chatzistavrou et al. 2014). Inclusion of 10% Al_3 to BAG improved the compressive strength without causing any adverse effect (De Caluwé et al. 2017). Incorporation of fluoride containing bioactive glass (BAG) reduces the susceptibility to SC. Monocalcium, dicalcium and tricalcium phosphates, hydroxyapatite and amorphous calcium phosphate are some of the fillers added to dental composites. Among these fillers, ACP is a direct precursor of HA (Dorozhkin 2010). When exposed to water, ACP dissolves and releases phosphates and calcium ions that subsequently transformed into HA ions (Eanes and Meyer 1977). The ACP/HA conversion is autocatalytic and forms a nuclei that progress the crystallization process (Boskey and Posner 1973). Hence, HA aids in remineralization (Skrtic et al. 2000). Pure form of ACP is unstable, thereby readily converts into HA within few hours (Pan et al. 2010).

14 Quaternary Ammonium Compounds

The development of quaternary ammonium methacrylate (QAM), and their incorporation into dental resins has promoted antimicrobial activities (Weng et al. 2018). Studies revealed that hydrophobic positively charged long polymeric alkyl chain of

QAM has the ability to penetrate the negatively charged cell membrane of the microorganisms (Skrtic et al. 2000). This enables cell membrane disruption, cytoplasmic leakage and finally death of microorganisms. Antibacterial mechanism of positively charged ammonium groups is mainly due to contact killing, and is governed by factors like chain length, number of nitrogen atoms and the nature of compound that attaches to this group. 5–10 wt% of QAMs can be used for composite resin (Liang et al. 2014). Specifically, long cationic polymers promote an increase in hydrophobicity of QAM. Hence, hydrophobicity property of QAM is directly proportional to the alkyl chain length of QAM (Tiller et al. 2001). Addition of chlorhexidine diacetate (1%) and 5% of dimethylamino-hexadecyl methacrylate (DMAHDM), a derivative of quaternary ammonium salts to self-cured resins showed significant antimicrobial action against *S. mutans* and *C. albicans* exhibits synergistic effect. These agents reduce the biofilm development without influencing the mechanical and physical properties (Campos et al. 2020).

A novel composite that consists of nanoparticles of amorphous calcium phosphate (NACP) and DMAHDM exhibited remineralizing and antimicrobial capabilities (Zhang et al. 2016). This is mainly due to the increase in CL of DMAHDM from 3 to 16 that significantly reduced the colony forming unit of microorganism and decrease the biofilm formation up to tenfold. Hence it is promising material for tooth cavity restoration. Incorporation of calcium phosphate nanoparticles along with quaternary ammonium dimethacrylate (QADM) and silver nanoparticles (Ag NP) into composites stimulated regenerative capacity and antibacterial activity (Cheng et al. 2012a).

15 Methods to Improve Mechanical Property

Zirconia particles block HA nucleation site and have the benefits of retardation of ACP conversion with improved mechanical properties (Skrtic et al. 2002). Thus it provides a long-lasting bioactive effect. Further, ACP composites when reinforced with 10% of inert glass fillers, there is an increase in mechanical properties (Marovic et al. 2014) as well as reduction in polymerization shrinkage. Thus incorporation of more inert fillers is significantly important to reduce filler/composite ratio. Also, addition of nano ACP particles is an alternative approach to increase the mechanical property with low cohesive strength that enables adequate ions release due to high surface area (Xu et al. 2011). A combination of nanoparticle amorphous calcium phosphate (NACP) and AgNP contributes to the antimicrobial property and remineralization capacity to composite material (Cheng et al. 2012b). Addition of zinc oxide particles ensures a better opacity and good antimicrobial property to the material. The primary effect of ZnO on bacteria is inhibition of the enzymes involved (Maas et al. 2017). It exhibits antibacterial activity only on the bacteria contacting it and also makes the resin weaker. To overcome this, AgNP can be mixed up along with QAMs (Zhang et al. 2013).

16 Chlorhexidine

Chlorhexidine (CHX) is a broad spectrum potent antimicrobial agent. Hence, believed as a gold standard for antibacterial application (Amin et al. 2009). Studies have shown that a gradual release into the environment leads to toxic effects to the tissues and affects the mechanical properties of the materials. Moreover, CHX is highly soluble and has poor substantivity (Bonesvoll and Gjermo 1978). It usually provides short-term antimicrobial effect and declines after a time period (Imazato 2003). The concept of Imazato et al. is "immobilized bactericide action" that means the antimicrobial monomers are not released in the environment as such, but contact inhibition takes place when the bacteria comes in direct contact with the material. Until then, it is stabilized in a carrier material (Imazato 2003). Hence, any antimicrobial agent when incorporated into a biomaterial have a finite duration of release. Thus, it has a long-lasting antibacterial effect without compromising the mechanical properties. GIC appended with chlorhexidine diacetate and digluconate have bactericidal action against *Streptococcus mutans and Lactobacillus acidophilus* (Türkün et al. 2008). Compared to these, CHX hexametaphosphate showed reduced solubility and a sustained release (Wood et al. 2015).

The DMAHDM monomer, one of the derivatives of quaternary ammonium salt along with chlorhexidine have a synergistic antimicrobial effect against *Streptococcus mutans and Candida albicans* without influencing the flexural strength, surface roughness and colour stability of the composite. Previous studies also demonstrated a synergistic effect of chlorhexidine when incorporated with other potent antifungal agents in dental materials. Recharge capacity of GIC with CHX has been recently investigated. The GIC has the ability to uptake CHX from its environment and release them in higher concentration via reversible process (Bellis et al. 2018). Matrix metalloproteinases (MMPs) present in saliva and cysteine cathepsins expressed by dentin-pulp complexes act synergistically, degrade hybrid layer and aide in caries progress (Nascimento 2011). CHX and green tea polyphenolepigallocatechin-3-gallate (EGCG) are potent inhibitors of MMP (Pallan et al. 2012). They reduced the rate of collagen degradation by preventing over activation of MMPs (Hashimoto et al. 2003). Further, these agents have the capability of inhibiting glucosyltranferases action, acid tolerance and acid production, hence the growth of cariogenic bacteria suppressed (Xu et al. 2011).

17 Antimicrobial Fillers in Dental Implants

Dental implant is a standard, recommended treatment protocol to replace, repair the lost or missing tooth structure. Peri-implant disease (PID) is the inflammation of the soft tissue around the implant, mainly due to plaque accumulation and biofilm formation (Renvert et al. 2018). PID can be of two types, peri-implant mucositis (PIM) and peri-implantitis (PI) (Berglundh et al. 2018). A high prevalence of

anaerobic gram-negative organisms is associated with PIM, in addition to *S. aureus*, *S. mutans*, *E. coli*, *P. gingivalis* and *C. albicans* and can eventually progress into PI. Meanwhile, with appropriate treatment PIDs can be reversed, if not may lead to gradual bone loss and bacterial associated implant failure (Rosen et al. 2013). Hence, clinical management of PIDs is still challenging. Defensins and cathelicidins are the naturally occurring antimicrobial peptides (AMPs) that are present both in salivary and gingival secretions (Chen et al. 2017a). Further, AMPs are the key mediator in regulating microbial homeostasis normally and they establish the first line defence mechanism particularly in the gingival and periodontal disease progress (Khurshid et al. 2018). They are highly degradable by bacterial and host cell proteases.

Hence, incorporation of AMPs into engineered bioadhesive hydrogels not only protect AMPs from degradation but also deliver controlled antimicrobial activity over a period of time. Light curable gelatin methacryloyl hydrogel incorporated with AMPs gives gelatin methacryloyl antimicrobial peptide bioadhesives. Antimicrobial hydrogel bioadhesives revealed high antibacterial activity against *P. gingivalis* and are cytocompatible (Sani et al. 2019). Moreover, they create a favourable environment for the growth of migratory progenitor cells that stimulate bone regeneration. Hence, they can be used to treat PIDs. AMP coated dental implants protect against PIDs.

Titanium dioxide (TiO_2) NPs exhibits pronounced optical property, bioactivity, chemical stability and antibacterial activity. TiO_2 is most promising to have photocatalytic effect, hence when exposed to UV-A light generates electrons and holes at the valence band (Foster et al. 2011). The electrons from the valence band get excited and produce superoxide ion, whereas the holes form hydroxyl radicals (Mohammed et al. 2018). Further, production of reactive oxygen species attack the bacterial cell membrane and leads to cytoplasmic leakage (Gogniat et al. 2006). The direct contact toxic effect of TiO_2 is mainly due to photocatalytic disinfections that eventually leads to lipid peroxidation (Maness et al. 1999), protein alteration (Goulhen-Chollet et al. 2009) and DNA damage (Gogniat and Dukan 2007). TiO_2 binds to *E. coli*, causes cell disruption and lysis (Gumy et al. 2006; Carré et al. 2014). TiO_2 also possesses improved osteoinductive and osteointegration property (Li et al. 2015). The rutile TiO_2 nanorod arrays expressed potent photocatalytic antifungal and antibacterial activity against *C. albicans*, *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* (Jia et al. 2017). Moreover, implant surface modified with TiO_2 coating promoted adhesion and proliferation of periodontal ligament stem cells (PDLSCs) (Li et al. 2017) and also osteogenic differentiation of mesenchymal stem cells (MSCs) (Qiu et al. 2016). Anatase microspheres which is of $Ti(SO_4)$ origin, impregnated with AgNPs improved the antibacterial activity of the implant surface against *S. aureus* and *E. coli* (Weng et al. 2018). The Ag/TiO_2 combination exhibited excellent antibacterial effect due to the Schottky barrier effect and also possesses cytocompatibility with Newborn mouse calvaria-derived preosteoblastic cells (MC3T3-E1).

18 Denture Base Resins

Tooth loss or edentulism is seen in all races and across all nations of the world. An US study places the rate of edentulism of American elderly of age 65 years or more to be 19% (Dye et al. 2015), whereas 15% of UK people of the same age are edentulous (Peltzer et al. 2014). For completely edentulous people, complete dentures are still most commonly used treatment of choice. Partial dentures with acylic base plate are still used in several developing countries for partial edentulism.

Poly methyl methacrylate (PMMA) resin is the most commonly used denture base acrylic material for both types of edentulism for more than 70 years since its introduction. However, PMMA suffers from inherent drawbacks like high surface roughness, porosity and bad thermal conductor (Nandal et al. 2013). Unfortunately, these disadvantages plus its high hydrophobicity in aqueous environment do not prevent the overgrowth of a fungus *C. albicans* in chronic denture wearers. Though *C. albicans* is normally present in oral cavity as indigenous microbial flora (Cannon and Chaffin 1999), its overgrowth contributes to the clinical condition called Denture Stomatitis (DS).

19 Denture Stomatitis

DS refers to inflammatory condition of palatal mucosa corresponding to the place where the denture base remains in contact with the tissue (Dorocka-Bobkowska et al. 2010). DS is especially prevalent in elderly people with systemic diseases leading to immunocompromised status along with poor denture hygiene and xerostomia (Uzunoglu et al. 2014). *C. albicans* is not the primary pathogen as the recent reports show that DS can also be caused by other fungal species like *C. glabrata*, *C. dubliniensis*, *C. parapsilosis*, *C. krusei* and *C. tropicalis* (de Oliveira Mima et al. 2011). This has a special clinical relevance in today's time as most of the above mentioned species are resistant to common antifungal drugs (Redding et al. 2003). Bacteria like *S. mutans* and *Lactobacillus* species are also implicated in DS (Webb et al. 1998). So, prevention of such problems assumes greater importance than treatment. Keeping this in mind, a PMMA denture base with antimicrobial properties that can prevent the occurrence of DS is definitely preferable.

20 Antimicrobial Fillers in Denture Base Resins

It was found out that coating the PMMA resin with glow-discharge plasma (Zamperini et al. 2013), Mannan (Sato et al. 2013) or reactive oxygen species (ROS)-based disinfectant (Odagiri et al. 2012) could inhibit *C. albicans* but the coatings did not sustain longer in the aqueous oral environment. Thus, an external

application of antimicrobial coating is of less clinical value. Incorporating the antimicrobial material as a filler into the PMMA resin is the logical next step in the research process.

The organic NPs have been primarily used to prevent the formation of secondary caries. Quaternary ammonium molecules can be combined with methacrylate monomer using silane bonds to produce quaternary ammonium methacrylate (QAMs). QAMs undergo polymerization with bisGMA (bisphenol A-glycidyl methacrylate) to produce resin polymer which is clinically useful (Gong et al. 2012). They are primarily not successfully used with PMMA denture base resin due to their inability to withstand high temperature and pressure generally required for curing the resin (Chen et al. 2017a). Though chitosan, yet another organic NPs is most abundantly available naturally, its clinical use is limited (Song and Ge 2019).

Incorporation of inorganic NPs, typically Silver (AgNPs) into the PMMA resin has stimulated a lot of research primarily due to their ability to withstand extreme environments (Arunachalam et al. 2015). Besides, they are not toxic to human tissues and equal importance is the fact that these metal fillers can be incorporated either into the powder or the liquid component of resin (Chladek et al. 2016) giving the flexibility of its usage. Their versatility lies in the fact that they can be manufactured in large-scale using variety of methods (Thomas et al. 2018). In fact, the most documented research focuses on using AgNPs into PMMA resin to produce antibacterial and antifungal denture base resin material that can be adopted clinically (Kassaee et al. 2008; Jabłońska-Stencel et al. 2018; Thomas et al. 2018; Chladek et al. 2019a, b; Jo et al. 2017; Chen et al. 2017b).

AgNPs possess broad spectrum of action covering the bacteria, fungi and viruses. The active silver ions released in the aqueous environment interact with proteins present in bacteria and cause cell lysis. In order to achieve this action, they are supplied in a variety of nanoforms and shapes like spheres, pores, capsules, tubes, shells, dendrimers or quantum dots (Şuhani et al. 2018). Kurt et al. (2017) studied the effect of adding AgNPs to PMMA denture base material in increasing concentrations and concluded that as the concentration of AgNPs increased, the antifungal activity also increased. The material was not cytotoxic to L929 mouse fibroblast cell line (Kurt et al. 2017).

In order to assess the long-lasting antimicrobial effect of AgNPs, the particles were incorporated in silver-sulfadiazine (AgSD) to form AgSD-loaded mesoporous silica nanoparticles (AgMSNs) which can release silver ions very slowly and for a prolonged duration in the aqueous medium. Besides acting as a carrier, sulfadiazine has anti-adhesive effect which is beneficial for preventing candida adhesion to oral mucosa. Jeong-Ki Jo et al. (2017) combined AgMSNs with PMMA to form a "rechargeable" resin. They found that flexural strength, hardness and anti-adhesive effects increased for up to a month (Jo et al. 2017)

Though AgNPs looks like an ideal antimicrobial filler to PMMA, it has some disadvantages. Mainly, due to its plasmon resonance effect, it imparts a dark brown colour to the final material. Obviously, it is aesthetically unacceptable in the oral cavity (Chladek et al. 2019b; Jabłońska-Stencel et al. 2018). In order to circumvent this clinical problem, AgNPs is used as silver sodium hydrogen zirconium phosphate

(SSHZP) which is white in colour and clinically acceptable. According to Jabłońska-Stencel et al. (2018), SSHZP filler concentration between 2 and 10 weight percentage (wt%) gave the best antimicrobial effect without compromising other essential mechanical properties (Jabłońska-Stencel et al. 2018).

Zirconium oxide nanoparticles (nano-ZrO_2) also have received a lot of attention for their ease of manufacturing and their efficiency (Gowri et al. 2014). Nano-ZrO_2 in various concentrations of 0% wt, 2.5% wt, 5% wt and 7.5% wt was polymerized with PMMA by Gad et al. (2017a) in their research work. The highest reduction in *C. albicans* was observed with 7.5% wt of nano-ZrO_2 (Gad et al. 2017b).

Ultrafine dispersed diamonds or detonation nanodiamonds (ND) have some eye-catching properties of high strength, chemical stability, thermal conductivity and good biocompatibility for use in biomedical applications (Mochalin et al. 2012). Mangal et al. (2019) compared ND performance with PMMA vs standard ZrO_2 with PMMA and discovered that 0.1–0.5 wt.% ND significantly improved the flexural strength, elastic modulus and surface hardness of resin and provided considerable resistance to *C. albicans* and reduction in salivary biofilm formation (Mangal et al. 2019). The same result was corroborated by Fouda et al. (2019).

Whiskers are a type of filamentary crystal, the tip of which is less than 1 nm with semi-conductive property and ability to release ROS. Silver-supported zirconium phosphate (Novaron) and Tetrapod-like zinc oxide whiskers (T-ZnOw) exhibited higher flexural strength and surface hardness and increased antibacterial activity (Chen et al. 2017a).

Glass fibres represent the architype fibre to reinforce denture base polymers due to its well known improvements in flexural strength and fatigue resistance. They were found to increase candida resistance also (Moreno-Maldonado et al. 2012; Gad et al. 2017b)

21 Antimicrobial Fillers for Other Applications

AgNPs was combined with vanadate nanowires to form silver vanadate decorated with AgNPs (β-$AgVO_3$). Ferreira et al. (2020) used silver vanadate as a filler in dental porcelain material and evaluated the mechanical and anti-microbiological properties. All the different strengths of silver vanadate increased the antimicrobial efficacy without changing hardness property (Ferreira et al. 2020).

Portland cement is a calcium silicate-based cement can be impregnated with AgNPs to form Portland cement nanocomposites. AgNPs give antimicrobial property to a bone graft and increased its bio-mechanical properties. This was confirmed by Nam (2017).

Dendrimer or Cascade polymer or Arborole is a type of nanoparticle consisting of lyophilic layer inside and lyophobic shell outside, act as drug carrier. It can be used to create different sizes and shapes of hydroxyapatite crystal to be used as a filler for dental materials (Bapat et al. 2019).

22 Conclusion

Incorporating an antimicrobial filler in restorative dental materials seems no more an option but a prerequisite for an ideal replacement material. The research for an ideal filler material which is not only antimicrobial but also augments the mechanical properties of the material is promising in some areas.

References

Al-Shammery D, Michelogiannakis D, Ahmed ZU et al (2019) Scope of antimicrobial photodynamic therapy in orthodontics and related research: a review. Photodiagn Photodyn Ther 25:456–459

Al Zraikat H, Palamara JE, Messer HH, Burrow MF, Reynolds EC (2011) The incorporation of casein phosphopeptide-amorphous calcium phosphate into a glass ionomer cement. Dent Mater 27:235–243

Alhajj N, Zakaria Z, Naharudin I, Ahsan F, Li W, Wong TW (2019) Critical physicochemical attributes of chitosan nanoparticles admixed lactose-PEG 3000 microparticles in pulmonary inhalation. Asian J Pharm Sci 15:374–384

Aljabo A, Xia W, Liaqat S, Khan MA, Knowles JC, Ashley P, Young AM (2015) Conversion, shrinkage, water sorption, flexural strength and modulus of re-mineralizing dental composites. Dent Mater 31:1279–1289

Allaker RP (2010) The use of nanoparticles to control oral biofilm formation. J Dent Res 89:1175–1186

Amin WM, Al-Ali MH, Salim NA, Al-Tarawneh SK (2009) A new form of intraoral delivery of antifungal drugs for the treatment of denture-induced oral candidosis. Eur J Dent 3:257–266

Argueta-Figueroa L, Morales-Luckie RA, Scougall-Vilchis RJ, Olea-Mejía OF (2014) Synthesis, characterization and antibacterial activity of copper, nickel and bimetallic Cu–Ni nanoparticles for potential use in dental materials. Prog Nat Sci Mater Int 24:321–328

Arunachalam A, Dhanapandian S, Manoharan C, Sivakumar G (2015) Physical properties of Zn doped TiO2 thin films with spray pyrolysis technique and its effects in antibacterial activity. Spectrochim Acta A Mol Biomol Spectrosc 138:105–112

Aziz N, Fatma T, Varma A, Prasad R (2014) Biogenic synthesis of silver nanoparticles using *Scenedesmus abundans* and evaluation of their antibacterial activity. J Nanopart, Article ID: 689419. https://doi.org/10.1155/2014/689419

Aziz N, Faraz M, Pandey R, Sakir M, Fatma T, Varma A, Barman I, Prasad R (2015) Facile algae-derived route to biogenic silver nanoparticles: synthesis, antibacterial and photocatalytic properties. Langmuir 31:11605–11612. https://doi.org/10.1021/acs.langmuir.5b03081

Aziz N, Pandey R, Barman I, Prasad R (2016) Leveraging the attributes of *Mucor hiemalis*-derived silver nanoparticles for a synergistic broad-spectrum antimicrobial platform. Front Microbiol 7:1984. https://doi.org/10.3389/fmicb.2016.01984

Baig MS, Fleming GJP (2015) Conventional glass-ionomer materials: a review of the developments in glass powder, polyacid liquid and the strategies of reinforcement. J Dent 43:897–912

Bapat RA, Dharmadhikari S, Chaubal TV, Amin MCIM, Bapat P, Gorain B, Choudhury H, Vincent C, Kesharwani P (2019) The potential of dendrimer in delivery of therapeutics for dentistry. Heliyon 5:e02544

Bellis CA, Addison O, Nobbs AH, Duckworth PF, Holder JA, Barbour ME (2018) Glass ionomer cements with milled, dry chlorhexidine hexametaphosphate filler particles to provide long-term antimicrobial properties with recharge capacity. Dent Mater 34:1717–1726

Berglundh T, Armitage G, Araujo MG, Avila-Ortiz G, Blanco J, Camargo PM, Chen S, Cochran D, Derks J, Figuero E (2018) Peri-implant diseases and conditions: consensus report of workgroup 4 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Periodontol 89:S313–SS18

Beyth N, Yudovin-Farber I, Bahir R, Domb AJ, Weiss EI (2006) Antibacterial activity of dental composites containing quaternary ammonium polyethylenimine nanoparticles against Streptococcus mutans. Biomaterials 27:3995–4002

Beyth N, Farah S, Domb AJ, Weiss EI (2014) Antibacterial dental resin composites. React Funct Polym 75:81–88

Bhuyan T, Mishra K, Khanuja M, Prasad R, Varma A (2015) Biosynthesis of zinc oxide nanoparticles from *Azadirachta indica* for antibacterial and photocatalytic applications. Mater Sci Semicond Process 32:55–61

Bonesvoll P, Gjermo P (1978) A comparison between chlorhexidine and some quaternary ammonium compounds with regard to retention, salivary concentration and plaque-inhibiting effect in the human mouth after mouth rinses. Arch Oral Biol 23:289–294

Borkow G, Zhou SS, Page T, Gabbay J (2010) A novel anti-influenza copper oxide containing respiratory face mask. PLoS One 5:e11295

Boskey AL, Posner AS (1973) Conversion of amorphous calcium phosphate to microcrystalline hydroxyapatite. A pH-dependent, solution-mediated, solid-solid conversion. J Phys Chem 77:2313–2317

Bourbia M, Ma D, Cvitkovitch DG, Santerre JP, Finer Y (2013) Cariogenic bacteria degrade dental resin composites and adhesives. J Dent Res 92:989–994

Boyd D, Towler MR (2005) The processing, mechanical properties and bioactivity of zinc based glass ionomer cements. J Mater Sci Mater Med 16:843–850

Camilleri J, Pitt Ford TR (2006) Mineral trioxide aggregate: a review of the constituents and biological properties of the material. Int Endod J 39:747–754

Campoccia D, Montanaro L, Arciola CR (2013) A review of the biomaterials technologies for infection-resistant surfaces. Biomaterials 34:8533–8554

Campos K d PL, Viana GM, Cabral LM, Portela MB, Junior RH, Cavalcante LM, Lourenço EJV, de Moraes Telles D (2020) Self-cured resin modified by quaternary ammonium methacrylates and chlorhexidine: cytotoxicity, antimicrobial, physical, and mechanical properties. Dent Mater 36:68–75

Cannon RD, Chaffin WL (1999) Oral colonization by Candida albicans. Crit Rev Oral Biol Med 10:359–383

Cao H, Liu X, Meng F, Chu PK (2011) Biological actions of silver nanoparticles embedded in titanium controlled by micro-galvanic effects. Biomaterials 32:693–705

Cao W, Yu Z, Wang X, Li Q, Xiao Y, Li P, Wang L, Ye Z, Xing X (2018) Novel resin-based dental material with anti-biofilm activity and improved mechanical property by incorporating hydrophilic cationic copolymer functionalized nanodiamond. J Mater Sci Mater Med 29:162

Carré G, Hamon E, Ennahar S, Estner M, Lett M-C, Horvatovich P, Gies J-P, Keller V, Keller N, Andre P (2014) TiO2 photocatalysis damages lipids and proteins in Escherichia coli. Appl Environ Microbiol 80:2573–2581

Chatterjee AK, Sarkar RK, Chattopadhyay AP, Aich P, Chakraborty R, Basu T (2012) A simple robust method for synthesis of metallic copper nanoparticles of high antibacterial potency against E. coli. Nanotechnology 23:085103

Chatzistavrou X, Christopher Fenno J, Faulk D, Badylak S, Kasuga T, Boccaccini AR, Papagerakis P (2014) Fabrication and characterization of bioactive and antibacterial composites for dental applications. Acta Biomater 10:3723–3732

Chen M-H (2010) Update on dental nanocomposites. J Dent Res 89:549–560

Chen J, Zhu Y, Song Y, Lin W, Zhan J, He J, Zheng J, Zhong C, Shi X, Liu S (2017a) Preparation of an antimicrobial surface by direct assembly of antimicrobial peptide with its surface binding activity. J Mater Chem B 5:2407–2415

Chen R, Han Z, Huang Z, Karki J, Wang C, Zhu B, Zhang X (2017b) Antibacterial activity, cytotoxicity and mechanical behavior of nano-enhanced denture base resin with different kinds of inorganic antibacterial agents. Dent Mater J 36:693–699

Chen Y, Xueyan M, Wang F (2018) Preparation and drug release of PVA composite nanofibers loaded chitosan microsphere. Polym Sci Ser A 60:311–321

Cheng L, Weir MD, Xu HHK, Antonucci JM, Kraigsley AM, Lin NJ, Lin-Gibson S, Zhou X (2012a) Antibacterial amorphous calcium phosphate nanocomposites with a quaternary ammonium dimethacrylate and silver nanoparticles. Dent Mater 28:561–572

Cheng L, Weir MD, Xu HHK, Kraigsley AM, Lin NJ, Lin-Gibson S, Zhou X (2012b) Antibacterial and physical properties of calcium–phosphate and calcium–fluoride nanocomposites with chlorhexidine. Dent Mater 28:573–583

Chladek G, Basa K, Mertas A, Pakieła W, Żmudzki J, Bobela E, Król W (2016) Effect of storage in distilled water for three months on the antimicrobial properties of poly (methyl methacrylate) denture base material doped with inorganic filler. Materials 9:328

Chladek G, Pakiela K, Pakiela W, Zmudzki J, Adamiak M, Krawczyk C (2019a) Effect of antibacterial silver-releasing filler on the physicochemical properties of poly(methyl methacrylate) denture base material. Materials 12:41–46

Chladek G, Pakieła K, Pakieła W, Żmudzki J, Adamiak M, Krawczyk C (2019b) Effect of antibacterial silver-releasing filler on the physicochemical properties of poly (methyl methacrylate) denture base material. Materials 12:4146

Cloutier M, Mantovani D, Rosei F (2015) Antibacterial coatings: challenges, perspectives, and opportunities. Trends Biotechnol 33:637–652

Cocco AR, de Oliveira da Rosa WL, da Silva AF, Lund RG, Piva E (2015) A systematic review about antibacterial monomers used in dental adhesive systems: Current status and further prospects. Dent Mater 31:1345–1362

De Caluwé T, Vercruysse CWJ, Ladik I, Convents R, Heidi D, Martens LC, Verbeeck RMH (2017) Addition of bioactive glass to glass ionomer cements: effect on the physico-chemical properties and biocompatibility. Dent Mater 33:e186–e203

De Gee AJ, Pallav P, Werner A, Davidson CL (1990) Annealing as a mechanism of increasing wear resistance of composites. Dent Mater 6:266–270

de Oliveira Mima EG, Pavarina AC, Silva MM, Ribeiro DG, Vergani CE, Kurachi C, Bagnato VS (2011) Denture stomatitis treated with photodynamic therapy: five cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 112:602–608

Deveci C, Tuzuner T, Cinar C, Odabas ME, Buruk CK (2019) Short-term antibacterial activity and compressive strength of biodentine containing chlorhexidine/cetirimide mixtures. Niger J Clin Pract 22:227

Dorocka-Bobkowska B, Zozulinska-Ziolkiewicz D, Wierusz-Wysocka B, Hedzelek W, Szumala-Kakol A, Budtz-Jörgensen E (2010) Candida-associated denture stomatitis in type 2 diabetes mellitus. Diabetes Res Clin Pract 90:81–86

Dorozhkin SV (2010) Amorphous calcium (ortho) phosphates. Acta Biomater 6:4457–4475

Drury JL, Chen YW, Plancich BJ, Taylor-Pashow KM, Hobbs DT, Wataha JC (2018) Release of calcium ions from particulate monosodium titanates for dental mineralization applications. Am J Dent 31:42B–48B

Dye B, Thornton-Evans G, Li X, Iafolla T (2015) Dental caries and tooth loss in adults in the United States, 2011-2012. NCHS Data Brief 2015:197

Eanes ED, Meyer JL (1977) The maturation of crystalline calcium phosphates in aqueous suspensions at physiologic pH. Calcif Tissue Res 23:259–269

Eiampongpaiboon T, Chung WO, Bryers JD, Chung K-H, Chan DCN (2015) Antibacterial activity of gold-titanates on Gram-positive cariogenic bacteria. Acta Biomater Odontol Scand 1:51–58

Eliades WAB (2002) Orthodontic material: scientific and clinical aspect. Thieme Medical Publishers, New York

Feagin F, Thiradilok S (1979) Effects of magnesium and fluoride on ion exchange and acid resistance of enamel. J Oral Pathol Med 8:23–27

Fernandes GL, Delbem ACB, Do Amaral JG, Gorup LF, Fernandes RA, de Souza Neto FN, Souza JAS, Monteiro DR, Hunt AMA, Camargo ER (2018) Nanosynthesis of silver-calcium glycerophosphate: promising association against oral pathogens. Antibiotics 7:52

Ferreira I, Vidal CL, Botelho AL, Ferreira PS, da Costa Valente ML, Schiavon MA, Alves OL, Reis ACD (2020) Effect of nanomaterial incorporation on the mechanical and microbiological properties of dental porcelain. J Prosthet Dent 123:529

Foster HA, Ditta IB, Varghese S, Steele A (2011) Photocatalytic disinfection using titanium dioxide: spectrum and mechanism of antimicrobial activity. Appl Microbiol Biotechnol 90:1847–1868

Fouda SM, Gad MM, Ellakany P, Al-Thobity AM, Al-Harbi FA, Virtanen JI, Raustia A (2019) The effect of nanodiamonds on candida albicans adhesion and surface characteristics of PMMA denture base material-an in vitro study. J Appl Oral Sci 2019:27

Gad MM, Al-Thobity AM, Shahin SY, Alsaqer BT, Ali AA (2017a) Inhibitory effect of zirconium oxide nanoparticles on Candida albicans adhesion to repaired polymethyl methacrylate denture bases and interim removable prostheses: a new approach for denture stomatitis prevention. Int J Nanomedicine 12:5409

Gad MM, Fouda SM, Al-Harbi FA, Näpänkangas R, Raustia A (2017b) PMMA denture base material enhancement: a review of fiber, filler, and nanofiller addition. Int J Nanomedicine 12:3801

Garcia IM, Leitune VCB, Balbinot GDS, Samuel SMW, Collares FM (2016) Influence of niobium pentoxide addition on the properties of glass ionomer cements. Acta Biomater Odontol Scand 2:138–143

Garoushi S, Vallittu P, Lassila L (2017) Hollow glass fibers in reinforcing glass ionomer cements. Dent Mater 33:e86–e93

Gerasymchuk Y, Lukowiak A, Wedzynska A, Kedziora A, Bugla-Ploskonska G, Piatek D, Bachanek T, Chernii V, Tomachynski L, Strek W (2016) New photosensitive nanometric graphite oxide composites as antimicrobial material with prolonged action. J Inorg Biochem 159:142–148

Gharatape A, Davaran S, Salehi R, Hamishehkar H (2016) Engineered gold nanoparticles for photothermal cancer therapy and bacteria killing. RSC Adv 6:111482–111516

Giannousi K, Lafazanis K, Arvanitidis J, Pantazaki A, Dendrinou-Samara C (2014) Hydrothermal synthesis of copper based nanoparticles: antimicrobial screening and interaction with DNA. J Inorg Biochem 133:24–32

Gogniat G, Dukan S (2007) TiO2 photocatalysis causes DNA damage via Fenton reaction-generated hydroxyl radicals during the recovery period. Appl Environ Microbiol 73:7740–7743

Gogniat G, Thyssen M, Denis M, Pulgarin C, Dukan S (2006) The bactericidal effect of TiO2 photocatalysis involves adsorption onto catalyst and the loss of membrane integrity. FEMS Microbiol Lett 258:18–24

Goldberg M (2008) In vitro and in vivo studies on the toxicity of dental resin components: a review. Clin Oral Investig 12:1–8

Gong SQ, Niu LN, Kemp LK, Yiu CK, Ryou H, Qi YP, Blizzard JD, Nikonov S, Brackett MG, Messer RL, Wu CD, Mao J, Bryan Brister L, Rueggeberg FA, Arola DD, Pashley DH, Tay FR (2012) Quaternary ammonium silane-functionalized, methacrylate resin composition with antimicrobial activities and self-repair potential. Acta Biomater 8:3270–3282

Goulhen-Chollet F, Josset S, Keller N, Keller V, Lett M-C (2009) Monitoring the bactericidal effect of UV-A photocatalysis: a first approach through 1D and 2D protein electrophoresis. Catal Today 147:169–172

Gowri S, Rajiv Gandhi R, Sundrarajan M (2014) Structural, optical, antibacterial and antifungal properties of zirconia nanoparticles by biobased protocol. J Mater Sci Technol 30:782–790

Graves JL Jr, Tajkarimi M, Cunningham Q, Campbell A, Nonga H, Harrison SH, Barrick JE (2015) Rapid evolution of silver nanoparticle resistance in Escherichia coli. Front Genet 6:42

Gu YW, Yap AUJ, Cheang P, Khor KA (2005) Zirconia–glass ionomer cement—a potential substitute for Miracle Mix. Scr Mater 52:113–116

Gumy D, Morais C, Bowen P, Pulgarin C, Giraldo S, Hajdu R, Kiwi J (2006) Catalytic activity of commercial of TiO2 powders for the abatement of the bacteria (E. coli) under solar simulated light: influence of the isoelectric point. Appl Catal B Environ 63:76–84

Hall-Stoodley L, William Costerton J, Stoodley P (2004) Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol 2:95–108

Han L, Mu LI, Kazuaki N, Neamat AB, Akira O, Naoko H, Masaaki I (2002) Effect of fluoride mouth rinse on fluoride releasing and recharging from aesthetic dental materials. Dent Mater J 21:285–295

Hashimoto M, Ohno H, Sano H, Kaga M, Oguchi H (2003) In vitro degradation of resin–dentin bonds analyzed by microtensile bond test, scanning and transmission electron microscopy. Biomaterials 24:3795–3803

Haskell EW, Stanley HR, Chellemi J, Stringfellow H (1978) Direct pulp capping treatment: a long-term follow-up. J Am Dent Assoc 97:607–612

Hatton RA, Miller AJ, Silva SRP (2008) Carbon nanotubes: a multi-functional material for organic optoelectronics. J Mater Chem 18:1183–1192

Hench LL (2006) The story of Bioglass. J Mater Sci Mater Med 17:967–978

Hench LL, Xynos ID, Polak JM (2004) Bioactive glasses for in situ tissue regeneration. J Biomater Sci 15:543–562

Hu X, Yuyun Z, Zhijian H, Aditya S, Shuai H, Tao W, Wenqi L et al (2013) Gold nanorods core/AgPt alloy nanodots shell: a novel potent antibacterial nanostructure. Nano Res 6:822–835

Hu X, Huang YY, Wang Y, Wang X, Hamblin MR (2018) Antimicrobial photodynamic therapy to control clinically relevant biofilm infections. Front Microbiol 9:1299

Ikemura K, Tay FR, Kouro Y, Endo T, Masahiro Y, Miyai K, Pashley DH (2003) Optimizing filler content in an adhesive system containing pre-reacted glass-ionomer fillers. Dent Mater 19:137–146

Imazato S (2003) Antibacterial properties of resin composites and dentin bonding systems. Dent Mater 19:449–457

Jabłońska-Stencel E, Pakieła W, Mertas A, Bobela E, Kasperski J, Chladek G (2018) Effect of silver-emitting filler on antimicrobial and mechanical properties of soft denture lining material. Materials 11:318

Jasmine S, Thangavelu A, Krishnamoorthy R et al (2020) Platelet concentrates as biomaterials in tissue engineering: a review. Regen Eng Transl Med. https://doi.org/10.1007/s40883-020-00165-z

Jia L, Qiu J, Lingqian D, Li Z, Liu H, Ge S (2017) TiO2 nanorod arrays as a photocatalytic coating enhanced antifungal and antibacterial efficiency of Ti substrates. Nanomedicine 12:761–776

Jo J-K, El-Fiqi A, Lee J-H, Kim D-A, Kim H-W, Lee H-H (2017) Rechargeable microbial anti-adhesive polymethyl methacrylate incorporating silver sulfadiazine-loaded mesoporous silica nanocarriers. Dent Mater 33:e361–ee72

Jones JR (2013) Review of bioactive glass: from Hench to hybrids. Acta Biomater 9:4457–4486

Karasenkov Y, Frolov G, Pogorelsky I, Latuta N, Gusev A, Kuznetsov D, Leont'ev V (2015) Colloidal metal oxide nanoparticle systems: the new promising way to prevent antibiotic resistance during treatment of local infectious processes. IOP Conf Ser 98:012038

Kassaee MZ, Akhavan A, Sheikh N, Sodagar A (2008) Antibacterial effects of a new dental acrylic resin containing silver nanoparticles. J Appl Polym Sci 110:1699–1703

Kaur G, Pandey OP, Singh K, Homa D, Scott B, Pickrell G (2014) A review of bioactive glasses: their structure, properties, fabrication and apatite formation. J Biomed Mater Res A 102:254–274

Khurshid Z, Zafar MS, Naseem M, Khan RS, Najeeb S (2018) Human oral defensins antimicrobial peptides: a future promising antimicrobial drug. Curr Pharm Des 24:1130–1137

Khvostenko D, Hilton TJ, Ferracane JL, Mitchell JC, Kruzic JJ (2016) Bioactive glass fillers reduce bacterial penetration into marginal gaps for composite restorations. Dent Mater 32:73–81

Konopka K, Goslinski T (2007) Photodynamic therapy in dentistry. J Dent Res 86:694–707

Kurt A, Erkose-Genc G, Uzun M, Emrence Z, Ustek D, Isik-Ozkol G (2017) The antifungal activity and cytotoxicity of silver containing denture base material. Niger J Clin Pract 20:290–295
Lai G, Li M (2012) Secondary caries. In: Contemporary approach to dental caries. InTech, London
Larsen IB, Munksgaard EG (1991) Effect of human saliva on surface degradation of composite resins. Eur J Oral Sci 99:254–261
Lear G, Lewis GD (2012) Microbial biofilms: current research and applications. Horizon Scientific Press, Poole
Lendenmann U, Grogan J, Oppenheim FG (2000) Saliva and dental pellicle-a review. Adv Dent Res 14:22–28
Leung D, Spratt DA, Pratten J, Gulabivala K, Mordan NJ, Young AM (2005) Chlorhexidine-releasing methacrylate dental composite materials. Biomaterials 26:7145–7153
Li Y, Li F, Zhang C, Gao B, Tan P, Mi B, Zhang Y, Cheng H, Liao H, Huo K (2015) The dimension of titania nanotubes influences implant success for osteoclastogenesis and osteogenesis patients. J Nanosci Nanotechnol 15:4136–4142
Li J, Dong Z, Lv F, Yu Q, Ma H, Yin J, Yi Z, Liu M, Chang J, Chengtie W (2016a) Preparation of copper-containing bioactive glass/eggshell membrane nanocomposites for improving angiogenesis, antibacterial activity and wound healing. Acta Biomater 36:254–266
Li M, Zheng M, Zhu Y, Xia H, Yao M, Chu X, Wang X, Yang K, Yang M, Yu Z (2016b) Toward a molecular understanding of the antibacterial mechanism of copper-bearing titanium alloys against Staphylococcus aureus. Adv Healthc Mater 5:557–566
Li Z, Qiu J, Ling Qian D, Lu J, Liu H, Ge S (2017) TiO2 nanorod arrays modified Ti substrates promote the adhesion, proliferation and osteogenic differentiation of human periodontal ligament stem cells. Mater Sci Eng 76:684–691
Liang X, Söderling E, Liu F, He J, Lassila LVJ, Vallittu PK (2014) Optimizing the concentration of quaternary ammonium dimethacrylate monomer in bis-GMA/TEGDMA dental resin system for antibacterial activity and mechanical properties. J Mater Sci Mater Med 25:1387–1393
Liu R, Tang Y, Zeng L, Zhao Y, Zheng M, Sun Z, Xiang L, Ren L, Yang K (2018) In vitro and in vivo studies of anti-bacterial copper-bearing titanium alloy for dental application. Dent Mater 34:1112–1126
Lynch I, Dawson KA (2008) Protein-nanoparticle interactions. Nano Today 3:40–47
Lynch CD, Opdam NJ, Hickel R, Brunton PA, Gurgan S, Kakaboura A, Shearer AC, Vanherle G, Wilson NHF (2014) Guidance on posterior resin composites: academy of operative dentistry-European section. J Dent 42:377–383
Maas MS, Alania Y, Natale LC, Rodrigues MC, Watts DC, Braga RR (2017) Trends in restorative composites research: what is in the future? Braz Oral Res 31:e55
Magalhães A-P-R, Francine-Couto LM, Alves C-RD-R-S, Estrela A, Estrela C, Carrião M-S, Bakuzis A-F, Lopes L-G (2016) Silver nanoparticles in resin luting cements: antibacterial and physiochemical properties. J Clin Exp Dent 8:e415
Mahfouz M, Esaid AA (2014) Dental caries prevalence among 12–15 year old Palestinian children. Int Sch Res Notices 2014:785404
Makhluf S, Dror R, Nitzan Y, Abramovich Y, Jelinek R, Gedanken A (2005) Microwave-assisted synthesis of nanocrystalline MgO and its use as a bacteriocide. Adv Funct Mater 15:1708–1715
Maness P-C, Smolinski S, Blake DM, Huang Z, Wolfrum EJ, Jacoby WA (1999) Bactericidal activity of photocatalytic TiO2 reaction: toward an understanding of its killing mechanism. Appl Environ Microbiol 65:4094–4098
Mangal U, Kim J-Y, Seo J-Y, Kwon J-S, Choi S-H (2019) Novel poly (methyl methacrylate) containing nanodiamond to improve the mechanical properties and fungal resistance. Materials 12:3438
Marovic D, Tarle Z, Hiller K-A, Müller R, Rosentritt M, Skrtic D, Schmalz G (2014) Reinforcement of experimental composite materials based on amorphous calcium phosphate with inert fillers. Dent Mater 30:1052–1060
Marsh PD (2004) Dental plaque as a microbial biofilm. Caries Res 38:204–211

Melo MAS, Weir MD, Rodrigues LKA, Xu HHK (2013) Novel calcium phosphate nanocomposite with caries-inhibition in a human in situ model. Dent Mater 29:231–240
Millenbaugh NJ, Baskin JB, DeSilva MN, Elliott WR, Glickman RD (2015) Photothermal killing of Staphylococcus aureus using antibody-targeted gold nanoparticles. Int J Nanomed 10:1953–1960
Mirhashemi AH, Bahador A, Kassaee MZ, Daryakenari G, Ahmad-Akhoundi MS, Sodagar A (2013) Antimicrobial effect of nano-zinc oxide and nano-chitosan particles in dental composite used in orthodontics. J Med Bacteriol 2:1–10
Mochalin VN, Shenderova O, Ho D, Gogotsi Y (2012) The properties and applications of nanodiamonds. Nat Nanotechnol 7:11
Moghimi SM, Szebeni J (2003) Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization and protein-binding properties. Prog Lipid Res 42:463–478
Mohammed FH, Niazy MA, El-Sharkawy DA (2018) The antibacterial activity of titanium dioxide nanoparticles incorporated into resin composite restoration (in vivo study). Al-Azhar Dent J Girls 5:173–180
Moheet IA, Luddin N, Rahman IA, Kannan TP, Ghani NRNA, Masudi SM (2019) Modifications of glass ionomer cement powder by addition of recently fabricated nano-fillers and their effect on the properties: a review. Eur J Dent 13(3):470–477
Moreno-Maldonado V, Acosta-Torres LS, Barceló-Santana FH, Vanegas-Lancón RD, Plata-Rodríguez ME, Castano VM (2012) Fiber-reinforced nanopigmented poly (methyl methacrylate) as improved denture base. J Appl Polym Sci 126:289–296
Morim S (2016) Antibacterial efficacy of gold-titanate nanoparticles as an intracanal medicament. MSD Thesis. University of Washington
Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, Yacaman MJ (2005) The bactericidal effect of silver nanoparticles. Nanotechnology 16:2346
Moshaverinia A, Ansari S, Moshaverinia M, Roohpour N, Darr JA, Rehman I (2008) Effects of incorporation of hydroxyapatite and fluoroapatite nanobioceramics into conventional glass ionomer cements (GIC). Acta Biomater 4:432–440
Munoz Bonilla A, Marta Fernández G (2012) Polymeric materials with antimicrobial activity. Prog Polym Sci 37:281–339
Nam KY (2017) Characterization and antimicrobial efficacy of Portland cement impregnated with silver nanoparticles. J Adv Prosthodont 9:217–223
Nandal S, Ghalaut P, Shekhawat H, Gulati MS (2013) New era in denture base resins: a review. Dent J Adv Stud 1:136–143
Nascimento FD, Minciotti CL, Geraldeli S, Carrilho MR, Pashley DH, Tay FR, Nader HB, Salo T, Tjäderhane L, Tersariol ILS (2011) Cysteine cathepsins in human carious dentin. J Dent Res 90:506–511
Nel A, Xia T, Mädler L, Li N (2006) Toxic potential of materials at the nanolevel. Science 311:622–627
Nguyen S, Hiorth M (2015) Advanced drug delivery systems for local treatment of the oral cavity. Ther Deliv 6:595–608
Odagiri K, Sawada T, Hori N, Seimiya K, Otsuji T, Hamada N, Kimoto K (2012) Evaluation of denture base resin after disinfection method using reactive oxygen species (ROS). Dent Mater J 31:443–448
Ohashi S, Saku S, Yamamoto K (2004) Antibacterial activity of silver inorganic agent YDA filler. J Oral Rehabil 31:364–367
Olenin AY, Lisichkin GV (2011) Metal nanoparticles in condensed media: preparation and the bulk and surface structural dynamics. Russ Chem Rev 80:605
Oliva A, Ragione FD, Salerno A, Riccio V, Gianpaolo T, Cozzolino A, Salvatore D'A, Pontoni G, Zappia V (1996) Biocompatibility studies on glass ionomer cements by primary cultures of human osteoblasts. Biomaterials 17:1351–1356
Onaizi SA, Leong SS (2011) Tethering antimicrobial peptides: current status and potential challenges. Biotechnol Adv 29:67–74

Padovani GC, Feitosa VP, Sauro S, Tay FR, Durán G, Paula AJ, Durán N (2015) Advances in dental materials through nanotechnology: facts, perspectives and toxicological aspects. Trends Biotechnol 33:621–636

Pal S, Tak YK, Song JM (2007) Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the gram-negative bacterium Escherichia coli. Appl Environ Microbiol 73:1712–1720

Pallan S, Araujo MVF, Cilli R, Prakki A (2012) Mechanical properties and characteristics of developmental copolymers incorporating catechin or chlorhexidine. Dent Mater 28:687–694

Pan H, Liu XY, Tang R, Hong Yao X (2010) Mystery of the transformation from amorphous calcium phosphate to hydroxyapatite. Chem Commun 46:7415–7417

Pang H, Lu Q, Li Y, Gao F (2009) Facile synthesis of nickel oxide nanotubes and their antibacterial, electrochemical and magnetic properties. Chem Commun 2009:7542–7544

Papacchini F, Goracci C, Sadek FT, Monticelli F, Garcia-Godoy F, Ferrari M (2005) Microtensile bond strength to ground enamel by glass-ionomers, resin-modified glass-ionomers, and resin composites used as pit and fissure sealants. J Dent 33:459–467

Park JW, Ferracane JL (2014) Water aging reverses residual stresses in hydrophilic dental composites. J Dent Res 93:195–200

Peltzer K, Hewlett S, Yawson AE, Moynihan P, Preet R, Wu F, Guo G, Arokiasamy P, Snodgrass JJ, Chatterji S, Engelstad ME, Kowal P (2014) Prevalence of loss of all teeth (edentulism) and associated factors in older adults in China, Ghana, India, Mexico, Russia and South Africa. Int J Environ Res Public Health 11:11308–11324

Perinelli DR, Fagioli L, Campana R et al (2018) Chitosan-based nanosystems and their exploited antimicrobial activity. Eur J Pharm Sci 117:8–20

Phillips RW, Anusavice KJ (2013) Phillips' science of dental materials. Elsevier, London

Poorzandpoush K, Omrani L-R, Jafarnia SH, Golkar P, Atai M (2017) Effect of addition of Nano hydroxyapatite particles on wear of resin modified glass ionomer by tooth brushing simulation. J Clin Exp Dent 9:e372

Poosti M, Ramazanzadeh BA, Zebarjad M, Javadzadeh P, Naderinasab M, Shakeri MT (2013) Shear bond strength and antibacterial effects of orthodontic composite containing TiO2 nanoparticles. Eur J Orthod 35:676–679

Prasad R (2014) Synthesis of silver nanoparticles in photosynthetic plants. J Nanopart, Article ID: 963961. https://doi.org/10.1155/2014/963961

Prasad R (2016) Advances and applications through fungal nanobiotechnology. Springer International Publishing, Cham. ISBN 978-3-319-42989-2

Prasad R (2017) Fungal nanotechnology: applications in agriculture, industry, and medicine. Springer Nature Singapore Pte Ltd., Singapore. ISBN 978-3-319-68423-9

Prasad R, Swamy VS (2013) Antibacterial activity of silver nanoparticles synthesized by bark extract of *Syzygium cumini*. J Nanopart. https://doi.org/10.1155/2013/431218

Profeta AC (2014) Dentine bonding agents comprising calcium-silicates to support proactive dental care: origins, development and future. Dent Mater J 33:443–452

Qiu J, Li J, Wang S, Ma B, Zhang S, Guo W, Zhang X, Tang W, Sang Y, Liu H (2016) TiO2 nanorod array constructed nanotopography for regulation of mesenchymal stem cells fate and the realization of location-committed stem cell differentiation. Small 12:1770–1778

Qu J, Huang Y, Lv X (2019) Crisis of antimicrobial resistance in China: now and the future. Front Microbiol 10:2240

Raafat D, Sahl H-G (2009) Chitosan and its antimicrobial potential–a critical literature survey. Microb Biotechnol 2:186–201

Raffi M, Mehrwan S, Bhatti TM, Akhter JI, Hameed A, Yawar W, Masood Ul Hasan M (2010) Investigations into the antibacterial behavior of copper nanoparticles against Escherichia coli. Ann Microbiol 60:75–80

Raghupathi KR, Koodali RT, Manna AC (2011) Size-dependent bacterial growth inhibition and mechanism of antibacterial activity of zinc oxide nanoparticles. Langmuir 27:4020–4028

Rago I, Chandraiahgari CR, Bracciale MP, De Bellis G, Zanni E, Guidi MC, Sali D, Broggi A, Palleschi C, Sarto MS (2014) Zinc oxide microrods and nanorods: different antibacterial activity and their mode of action against Gram-positive bacteria. RSC Adv 4:56031–56040

Ranjita RM (2017) Metal nanoparticles in pharma, 1st edn. Springer, Berlin

Rastelli ANS, Jacomassi DP, Faloni APS, Queiroz TP, Rojas SS, Bernardi MINÊB, Bagnato VS, Hernandes AÔC (2012) The filler content of the dental composite resins and their influence on different properties. Microsc Res Tech 75:758–765

Redding SW, Kirkpatrick WR, Saville S, Coco BJ, White W, Fothergill A, Rinaldi M, Eng T, Patterson TF, Lopez-Ribot J (2003) Multiple patterns of resistance to fluconazole in Candida glabrata isolates from a patient with oropharyngeal candidiasis receiving head and neck radiation. J Clin Microbiol 41:619–622

Ren G, Hu D, Cheng EWC (2009) Int J Antimicrob Agents 33:587–590

Renvert S, Rutger Persson G, Pirih FQ, Camargo PM (2018) Peri-implant health, peri-implant mucositis, and peri-implantitis: case definitions and diagnostic considerations. J Clin Periodontol 45:S278–SS85

Reston EG, de Souza Costa CA (2009) Scanning electron microscopy evaluation of the hard tissue barrier after pulp capping with calcium hydroxide, mineral trioxide aggregate (MTA) or ProRoot MTA. Aust Endod J 35:78–84

Roberts HW, Toth JM, Berzins DW, Charlton DG (2008) Mineral trioxide aggregate material use in endodontic treatment: a review of the literature. Dent Mater 24:149–164

Rosen P, Clem D, Cochran DL, Froum S, McAllister B, Renvert S, Wang HL (2013) Peri-implant mucositis and peri-implantitis: a current understanding of their diagnoses and clinical implications. J Periodontol 84:436–443

Rosenbaum J, Versace DL, Abbad-Andallousi S, Pires R, Azevedo C, Cénédese P, Dubot P (2017) Antibacterial properties of nanostructured Cu–TiO 2 surfaces for dental implants. Biomater Sci 5:455–462

Saafan A, Zaazou MH, Sallam MK, Mosallam O, El Danaf HA (2018) Assessment of photodynamic therapy and nanoparticles effects on caries models. Open Access Macedon J Med Sci 6:1289

Sakaguchi R (2005) Review of the current status and challenges for dental posterior restorative composites: clinical, chemistry, and physical behavior considerations. Summary of discussion from the Portland Composites Symposium (POCOS) June 17-19, 2004, Oregon Health & Science University, Portland, Oregon. Dent Mater 21:3–6

Sakaguchi RL, Powers JM, Craig S (2006) Restorative dental materials. Mosby, St. Louis

Sani ES, Lara RP, Aldawood Z, Bassir SH, Nguyen D, Kantarci A, Intini G, Annabi N (2019) An antimicrobial dental light curable bioadhesive hydrogel for treatment of peri-implant diseases. Matter 1:926–944

Sato M, Ohshima T, Maeda N, Ohkubo C (2013) Inhibitory effect of coated mannan against the adhesion of Candida biofilms to denture base resin. Dent Mater J 32:355–360

Schnaider L, Ghosh M, Bychenko D, Grigoriants I, Ya'ari S, Antsel TS, Matalon S, Sarig R, Brosh T, Pilo R (2019) Enhanced nanoassembly-incorporated antibacterial composite materials. ACS Appl Mater Interfaces 11:21334–21342

Seil JT, Webster TJ (2012) Antimicrobial applications of nanotechnology: methods and literature. Int J Nanomedicine 7:2767

Sevinç A, Berdan A, Hanley L (2010) Antibacterial activity of dental composites containing zinc oxide nanoparticles. J Biomed Mater Res B Appl Biomater 94:22–31

Shahid S, Hassan U, Billington RW, Hill RG, Anderson P (2014) Glass ionomer cements: effect of strontium substitution on esthetics, radiopacity and fluoride release. Dent Mater 30:308–313

Shin S-Y, Park H-N, Kim K-H, Lee M-H, Choi YS, Park Y-J, Lee Y-M, Young K, Rhyu I-C, Han S-B (2005) Biological evaluation of chitosan nanofiber membrane for guided bone regeneration. J Periodontol 76:1778–1784

Siqueira JF (2001) Strategies to treat infected root canals. CDA 29:825–838

Sirelkhatim A, Mahmud S, Seeni A, Kaus NHM, Ann LC, Bakhori SKM, Hasan H, Mohamad D (2015) Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. Nano-Micro Lett 7:219–242

Skrtic D, Antonucci JM, Eanes ED, Eichmiller FC, Schumacher GE (2000) Physicochemical evaluation of bioactive polymeric composites based on hybrid amorphous calcium phosphates. J Biomed Mater Res 53:381–391

Skrtic D, Antonucci JM, Eanes ED, Brunworth RT (2002) Silica-and zirconia-hybridized amorphous calcium phosphate: Effect on transformation to hydroxyapatite. J Biomed Mater Res 59:597–604

Slenters TV, Hauser-Gerspach I, Daniels AU, Fromm KM (2008) Silver coordination compounds as light-stable, nano-structured and anti-bacterial coatings for dental implant and restorative materials. J Mater Chem 18:5359–5362

Sodagar A, Bahador A, Khalil S, Shahroudi AS, Kassaee MZ (2013) The effect of TiO2 and SiO2 nanoparticles on flexural strength of poly (methyl methacrylate) acrylic resins. J Prosthodont Res 57:15–19

Sodagar A, Akhoundi MSA, Bahador A, Jalali YF, Behzadi Z, Elhaminejad F, Mirhashemi AH (2017) Effect of TiO2 nanoparticles incorporation on antibacterial properties and shear bond strength of dental composite used in Orthodontics. Dent Press J Orthodont 22:67–74

Song W, Ge S (2019) Application of antimicrobial nanoparticles in dentistry. Molecules 24:1033

Spanovic N, Par M, Marovic D, Sever EK, Gamulin O, Tarle Z (2017) Development of experimental bioactive composites with reduced water sorption. In: 3rd international congress of the school of dental medicine. University of Zagreb, Zagreb

Stanley HR (1989) Pulp capping: conserving the dental pulp—can it be done? Is it worth it? Oral Surg Oral Med Oral Pathol 68:628–639

Stansbury JW (2000) Curing dental resins and composites by photopolymerization. J Esthet Restor Dent 12:300–308

Şuhani MF, Băciuț G, Băciuț M, Şuhani R, Bran S (2018) Current perspectives regarding the application and incorporation of silver nanoparticles into dental biomaterials. Clujul Med 91:274

Swamy VS, Prasad R (2012) Green synthesis of silver nanoparticles from the leaf extract of *Santalum album* and its antimicrobial activity. J Optoelectron Biomed Mater 4(3):53–59

Takagi S, Chow LC, Hirayama S, Eichmiller FC (2003) Properties of elastomeric calcium phosphate cement–chitosan composites. Dent Mater 19:797–804

Takasaki AA, Aoki A, Mizutani K, Schwarz F, Sculean A, Wang CY et al (2009) Application of antimicrobial photodynamic therapy in periodontal and peri-implant diseases. Periodontol 51:109–140

Tanaka CB, Lopes DP, Kikuchi LNT, Moreira MS, Catalani LH, Braga RR, Kruzic JJ, Gonçalves F (2020) Development of novel dental restorative composites with dibasic calcium phosphate loaded chitosan fillers. Dent Mater 36:551–559

Tarle Z, Par M (2018) Bioactive dental composite materials. Med Sci 45:83–100

Tezvergil-Mutluay A, Seseogullari-Dirihan R, Feitosa VP, Cama G, Brauer DS, Sauro S (2017) Effects of composites containing bioactive glasses on demineralized dentin. J Dent Res 96:999–1005

Thallinger B, Prasetyo EN, Nyanhongo GS, Guebitz GM (2013) Antimicrobial enzymes: an emerging strategy to fight microbes and microbial biofilms. Biotechnol J 8:97–109

Thampi VVA, Prabhu M, Kavitha K, Manivasakan P, Prabu P, Rajendran V, Shankar S, Kulandaivelu P (2014) Hydroxyapatite, alumina/zirconia, and nanobioactive glass cement for tooth-restoring applications. Ceram Int 40:14355–14365

Thomas R, Snigdha S, Bhavitha KB, Babu S, Ajith A, Radhakrishnan EK (2018) Biofabricated silver nanoparticles incorporated polymethyl methacrylate as a dental adhesive material with antibacterial and antibiofilm activity against Streptococcus mutans. Biotech 8:404

Tiller JC, Liao C-J, Lewis K, Klibanov AM (2001) Designing surfaces that kill bacteria on contact. Proc Natl Acad Sci 98:5981–5985

Türkün LSE, Türkün M, Rul FE, Ates M, Brugger S (2008) Long-term antibacterial effects and physical properties of a chlorhexidine-containing glass ionomer cement. J Esthet Restor Dent 20:29–44

Turner JE, Moore DW, Shaw BS (1975) Prevalence and antibiotic susceptibility of organisms isolated from acute soft-tissue abscesses secondary to dental caries. Oral Surg Oral Med Oral Pathol 39:848–857

Uzunoglu E, Bicer AZY, Dolapci I, Dogan A (2014) Biofilm-forming ability and adherence to poly-(methyl-methacrylate) acrylic resin materials of oral Candida albicans strains isolated from HIV positive subjects. J Adv Prosthodont 6:30–34

Venhoven BAM, De Gee AJ, Davidson CL (1993) Polymerization contraction and conversion of light-curing BisGMA-based methacrylate resins. Biomaterials 14:871–875

Villegas A, Natalia MJSC, Ajá MS, Rocca DM, Becerra MC, Molina GF, Palma SD (2019) Novel antibacterial resin-based filling material containing nanoparticles for the potential one-step treatment of caries. J Healthc Eng 2019:8

Von Eiff C, Arciola CR, Lucio M, Becker K, Campoccia D (2006) Emerging Staphylococcus species as new pathogens in implant infections. Int J Artif Organs 29:360–367

Wahab R, Mishra A, Soon-Il Y, Hwang IH, Mussarat J, Al-Khedhairy AA, Kim Y-S, Shin H-S (2012) Fabrication, growth mechanism and antibacterial activity of ZnO micro-spheres prepared via solution process. Biomass Bioenergy 39:227–236

Wang D, Lin Z, Wang T, Yao Z, Qin M, Zheng S, Wei L (2016) Where does the toxicity of metal oxide nanoparticles come from: the nanoparticles, the ions, or a combination of both? J Hazard Mater 308:328–334

Webb BC, Thomas CJ, Willcox MDP, Harty DWS, Knox KW (1998) Candida-associated denture stomatitis. Aetiology and management: a review: Part 1. Factors influencing distribution of candida species in the oral cavity. Aust Dent J 43:45–50

Wei G, Sun F, Liu F, Cao L, Yang J, Chen Y (2019) Antimicrobial resistance surveillance and prediction of gram-negative bacteria based on antimicrobial consumption in a hospital setting: a 15-year retrospective study. Medicine (Baltimore) 98:e17157

Weng S, Xu Z, Liu G, Guan Y, Wu F, Luo Y (2018) Synthesis, characterization, antibacterial activity in dark and in vitro cytocompatibility of Ag-incorporated TiO 2 microspheres with high specific surface area. J Mater Sci 29:50

Whitesides GM (2003) The 'right' size in nanobiotechnology. Nat Biotechnol 21:1161–1165

Wiegand A, Buchalla W, Attin T (2007) Review on fluoride-releasing restorative materials—fluoride release and uptake characteristics, antibacterial activity and influence on caries formation. Dent Mater 23:343–362

Wood NJ, Jenkinson HF, Davis SA, Mann S, O'Sullivan DJ, Barbour ME (2015) Chlorhexidine hexametaphosphate nanoparticles as a novel antimicrobial coating for dental implants. J Mater Sci Mater Med 26:201

Xie D, Weng Y, Guo X, Zhao J, Gregory RL, Zheng C (2011) Preparation and evaluation of a novel glass-ionomer cement with antibacterial functions. Dent Mater 27:487–496

Xu HHK, Moreau JL, Sun L, Chow LC (2011) Nanocomposite containing amorphous calcium phosphate nanoparticles for caries inhibition. Dent Mater 27:762–769

Yadav L, Tripathi RM, Prasad R, Pudake RN, Mittal J (2017) Antibacterial activity of Cu nanoparticles against *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Nano Biomed Eng 9(1):9–14. https://doi.org/10.5101/nbe.v9i1.p9-14

Yan N, Chen X (2015) Sustainability: don't waste seafood waste. Nature 524:155–157

Yang H, Liu C, Yang D, Zhang H, Xi Z (2009) Comparative study of cytotoxicity, oxidative stress and genotoxicity induced by four typical nanomaterials: the role of particle size, shape and composition. J Appl Toxicol 29:69–78

Yli-Urpo H, Lassila LVJ, Närhi T, Vallittu PK (2005) Compressive strength and surface characterization of glass ionomer cements modified by particles of bioactive glass. Dent Mater 21:201–209

Zamperini CA, de Lima Carneiro H, Rangel EC, Cruz NC, Vergani CE, Machado AL (2013) In vitro adhesion of Candida glabrata to denture base acrylic resin modified by glow-discharge plasma treatment. Mycoses 56:134–144

Zhang L, Jiang Y, Ding Y, Povey M, York D (2007) Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). J Nanopart Res 9:479–489

Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC (2008) Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Therap 83:761–769

Zhang K, Li F, Imazato S, Cheng L, Liu H, Arola DD, Bai Y, Xu HHK (2013) Dual antibacterial agents of nano-silver and 12-methacryloyloxydodecylpyridinium bromide in dental adhesive to inhibit caries. J Biomed Mater Res Pt B 101:929–938

Zhang K, Cheng L, Weir MD, Bai Y-X, Xu HHK (2016) Effects of quaternary ammonium chain length on the antibacterial and remineralizing effects of a calcium phosphate nanocomposite. Int J Oral Sci 8:45–53

Zoergiebel J, Ilie N (2013) Evaluation of a conventional glass ionomer cement with new zinc formulation: effect of coating, aging and storage agents. Clin Oral Investig 17:619–626

Molecular Imprinting Technology: A New Approach for Antibacterial Materials

E. Kweinor Tetteh, S. Rathilal, M. Amankwa Opoku, I. D. Amoah, and M. N. Chollom

Abstract This chapter presents Molecular Imprinting Technology (MIT) as a biomimetic technique suitable as binding sites for synthetic receptor molecules and functional monomers owing to their definite interest of selectivity, sensitivity, recognition, and applications. MIT has been used extensively for the detection of pharmaceutical compounds like antibiotics which have become a global challenge due to their occurrence in the environment. Also, their detection and recognition in various industrial sample matrices are time-consuming, laborious, expensive, and very intricate. Additionally, MIT has shown great potential in producing antibacterial coatings, which could play a critical role in the fight against antibiotic-resistant bacteria especially in biomedical devices.

In this chapter, recently advanced materials used for biorecognition in terms of their morphological, physiological, and chemical properties together with their preparation techniques, are highlighted. Among the types of MITs, the sol–gel imprinting route based materials derived from polymers, ceramics, and glass which seems very promising are presented here. Additionally, the chapter investigates the strength and limitations of the sol–gel imprinting route to design antibacterial agents or receptors from pharmaceutical compounds, biomaterials, chitosan, nanomaterials, and cell implanting for biomedical applications. It was found to be economically viable with benefits good for both healthcare and environment sustainability. Therefore, MIT development presents economical application for antibacterial detection, recognition, and quantification, due to the high

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selectivity, rapid response, excellent stability, simplicity, and robustness of their materials when integrated with sensor detection technology.

Keywords Antibacterial · Antibiotics · Biosensors · Nanomaterials · Magnetized nanomaterials polymers · Pharmaceuticals · Sol–gel synthesis · Virus (COVID-19)

1 Introduction

Molecular imprinting technology (MIT) is a binding phenomenon for creating ligand selective recognition sites. This involves the binding of a high order structural element or template (ion, atom, molecule, molecular or complex macromolecular or ionic assembly, as well as microorganisms) with a natural molecular species such as receptors (e.g. Antibodies, enzymes, nucleic acids, peptides) (Alexander et al. 2006; Lofgreen and Ozin 2014; Whitcombe et al. 2014; Chen et al. 2016). MIT is mostly used as a molecular lock to mimic designs lock to match a molecular key (Chen et al. 2016). For instance, MIT is employed to facilitate recognition sites of biopolymer during natural interaction occurring in a covalent assembly of a bulk phase through a polycondensation or polymerization process, following the removal of the targeted template species (Alexander et al. 2006; Chen et al. 2016). According to Chen et al. (2011), MITs present unique features, including recognition specificity, structure predictability, and application universality. Since its promulgation by Polyakov in 1931, using silica matrices has received great attention as a practical synthetic method in designing durable molecular identification materials (Polyakov 1931).

In recent years, the concept of the MIT has been built upon by various scholars, which have progressively evolved to be economical and effective in providing versatile receptors with a broader interest in designing, preparations, and characterization (Fu et al. 2015). These include chromatographic sorbents, sewage treatment, purification, separation, receptor systems, biosensors, artificial antibodies, drug delivery, polymers, catalysis, and photocatalytic degradation (Castell et al. 2011; Fu et al. 2015; Chen et al. 2016). The versatile application of MIT is attributed to their significant strength, high physical stability, low cost of operating, and upfront preparation (Nicholls et al. 2013; Qiu et al. 2013; Fu et al. 2015; Chen et al. 2016). However, MIT's biological related research information is limited compared to advanced technologies such as nanomaterial synthesis (Chen et al. 2016). Also, some of the imprinting functional monomers are usually neglected to a certain degree with a restriction on their selectivity for specific applications. Meanwhile, antibodies or antigens have been utilized for the quantification and identification of microorganisms and other complex emerging sample matrices. Of public concern, imprinting bioentity materials like a virus, microbes, bacterial and mammalian cells with tolerable toxic side effects for bioanalytical recognition and biomedical applications must be of importance to stimulate MIT development (Fig. 1).

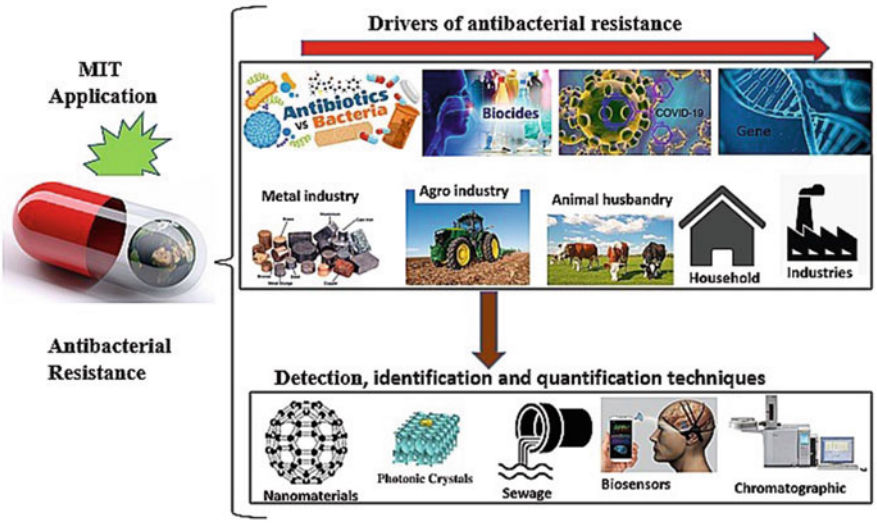

Fig. 1 Schematic account on current emerging antibacterial resistances route and molecular imprinting technology

Since the discovery of antibiotics like Penicillin by Alexander Fleming in 1928, its application has improved healthcare to curb various forms of infections caused by bacteria, viruses, fungi, and parasites (Chollom et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). Of interest, most of these antibiotics are amphipathic (having both hydrophilic and hydrophobic properties), amphoteric, or ionizable organic compounds (Mühlen et al. 2020; Chollom et al. 2019). However, their physiological properties and structural chemistries (size, shape, solubility, and hydrophobicity) can undergo series of phase transformations processes such as biodegradation, dilution, and photolysis (Mühlen et al. 2020; Chollom et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). This usually affects their mobility, persistence, and bioavailability as well as their behaviour in the environment either in a solid or liquid state (Mühlen et al. 2020; Chollom et al. 2020). Despite this, the overuse and misuse of antibiotics in humans, animals, and plants are estimated to rise with an increase in the human population projected to be 9–10 billion by 2050 (Chollom et al. 2020; Zhang et al. 2020). Although there is a remarkable interest in antibiotics (Table 2), some of these biorecognition components like biomarkers of cancer or pathogens used in biomedical applications are becoming infections and resistance, owing to their technical complexity and extraction procedure (Chen et al. 2020; Levy and Marshall 2004; Zhang et al. 2020). For example, the recent coronavirus (COVID-19), antibacterial resistance, and medical implantable device infections are difficult issues to handle (Chen et al. 2020; Levy and Marshall 2004; Zhang et al. 2020) because most of the microbes or bacterial species are no longer susceptible to some of the produced antibiotic compounds (Zhang et al. 2020). In addition to these drawbacks, biomolecules are suggestible, denature easily, and hard-wearing for reuse

(Alexander et al. 2006; Chen et al. 2016). Today, antibacterial resistance is a primary health concern globally, which is caused by a genetic mutation of bacteria in human, animals, and plants or exposure to antibiotic or heavy metal selective pressure in the environment (Levy and Marshall 2004; Zhang et al. 2020). These selective pressures could be from the agricultural, hospitals, pharmaceutical, nanomaterials, sewage, water, and wastewater treatment settings (Fig. 1) (Levy and Marshall 2004; Chollom et al. 2019; Zhang et al. 2020).

Recently, this has prompted many efforts to put forth in designing and synthesizing of artificial materials with antibody-like functions for analytical detection, quantification, and identification of bacteria species as well as monitoring of their growth (Zhang et al. 2020). This has hastened the high demand for MIT based nanomaterials (Sharma and Kandasubramanian 2020; Pandey et al. 2020). Conventionally, some of these include the use of silica nanoparticles, carbon nanotubes homogenized with sensor technology, titanium dioxide (TiO2), zinc oxide, zeolite, silver oxide, liquid crystals, and microfluidics. Whereas TiO_2 nanoparticles have been widely used due to their superior-excellent biological compatibility and photocatalytic properties (Chollom et al. 2020; Tetteh et al. 2020). For instance, composite materials which incorporate silver nanoparticles (AgNPs) have been developed and tried out for antimicrobial purposes (Chen et al. 2009; Castell et al. 2011). Herein, antimicrobial efficiency of Ag–TiO_2 composite as reported can be improved under light irradiation (Chen et al. 2009; Komiyama et al. 2018).

Today, biological imprinting as a kind of nonantibiotic and the antimicrobial agent has received little attention as compared to fluorescent probe techniques and nanomaterial synthesis. Meanwhile, MIT's seems very promising as an alternative to synthesis bioreceptors for biomedical applications (Sharma and Kandasubramanian 2020). Therefore, with a desktop approach, the principles of MIT based on direct and indirect imprinting of materials with antibody-like functions are presented in this chapter. Compared to other recognition systems, techniques relating to the preparation of biorecognition molecule for detection, quantification, and identification of antibiotics and bacteria species are highlighted. Also, the recent development of MIT with nanomaterials, polymer, and other natural based materials to exhibit the antibody like selectivity and binding affinity via size, shape, and functional groups matching is discussed. Furthermore, materials that possess remarkable characteristics for MIT reusability, including easy availability, low cost, and high stability to withstand severe physical and chemical ambience are also reported.

2 History and Types of MIT's

Generally, in the presence of imprinted molecules, MIT which is a part of molecular imprinting polymers (MIPs) is prepared from functional monomers by way of copolymerization and cross-linkers serving as target analytes (Chen et al. 2011).

The historical background of molecule imprinting can be traced as far back as 1931 (Chen et al. 2011). Polyakov (1931) hypothesized the concept as "unusual adsorption properties of silica particles prepared using a novel synthesis procedure". Based on the "adsorption properties" having displayed countless polymers during the experimentation, the concept of MIP has now been adopted by many researchers (Alexander et al. 2006; Fu et al. 2015). Patrikeev (1960) also employed bacteria templates in the 1960s. In the 1970s, Wulff and colleagues went further to develop the techniques being used for polymer imprinting (Wulff et al. 1972; Takagishi and Klotz 1972; Wulff 1995). Fu et al. (2015) further proposed two broad techniques for MIPs, which include covalent and non-covalent imprinting polymerization. Liu et al. (2019) also affirmed the two types of MIPs in their study of using MIP fluorescent sensors in food and environmental analysis. Huang et al. (2015) and Ren and Chen (2015) further built upon the existing technologies and categorize them into five types including non-covalent, semi-covalent, covalent, ionic/electrostatic, and metal centre-coordination.

Further development setbacks reported include incompatibility in aqueous media, irregular material shape, template leakage, and low binding capacity (Fu et al. 2015; Liu et al. 2019). Based on smart preparation technology, Chen et al. (2016) proposed three principal MIT types, which include ingenious technologies, special imprinting strategies, and stimuli-responsive imprinting technologies. Subsequent ingenious imprinting technologies (IITs) involve nanoimprinting (Fig. 2), porous polymer synthesis, microfluidic on-line synthesis, surface imprinting, solid-phase synthesis, click chemistry cycloaddition reaction, and living or controlled radical polymerization (Chen et al. 2011; Pandey et al. 2020). Researchers base the principle of IIT on the template and receptors molecule efficiency to rebind the imprinted sites, which are usually termed as an angiotensin-converting enzyme. A recent claim by Chinese scientists shows that nanoimprinting materials is a possible receptor to absorb and deactivate the COVID-19 virus in humans with an accuracy of 96.5–99.9% (Chen et al. 2020).

The development of nanostructured MIPs (N-MIPs) research interest has significantly improved their characteristics in contrast to bulk MIPs (Fig. 2). Also, surface imprinting, segment imprinting, nanoimprinting, dummy imprinting, multiple-template imprinting strategies are some of the special imprinting strategies that have recently been popularized (Komiyama et al. 2018). For instance, surface imprinting methods are used in the extraction of pentamidine from solid-phase extraction (urine) (Chen et al. 2011), Ethynylestradiol from river water (Bravo et al. 2009), estrone from well water (Xu et al. 2009), Oxytetracycline from tissue (Chen et al. 2009), and Diosgenin from herb (Sun and Qiao 2008). These various outcomes indicated that the suggested surface imprinting would be possibly applicable for clinical screening of other biomarkers. From the above-mentioned types of MITs, the novel stimuli-responsive technology has gained very attractive attention as being superior for imprinting of receptors and is considered and explained in detail.

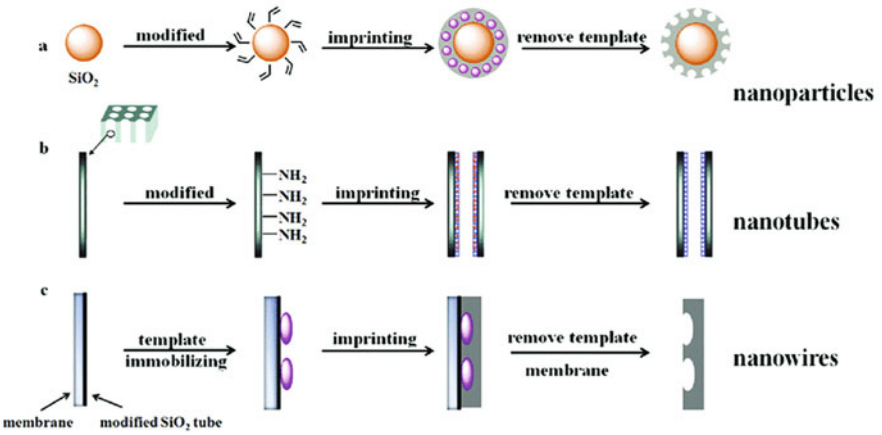

Fig. 2 Schematic portrayal of a nanoimprinting procedure for various types of N-MIPs (**a**) Imprinting on the SiO2 support for the development of centre shell nanoparticles imprinting, (**b**) Imprinting on silica nanotubes for the arrangement of nanotubes imprinting, and (**c**) Imprinting on a conciliatory layer bolster. Source adapted Chen et al. (2016)

2.1 Stimuli-Responsive Imprinting Technologies

Stimuli-responsive MIPs (SR-MIPs) use SR technology for imprinting molecules by mimicking the natural receptors' characteristics to achieve intelligent materials (Chen et al. 2016). Chen et al. (2011) stated that SR-MITs, including magnetic response technology, thermos-responsive technology, photo-responsive technology, pH-responsive technology, and other responsive technologies could occur either through single responses or multiple responses. However, most of these imprinting technologies use nanomaterials like magnetite, silver nitrate, and titanium dioxide as their principal imprinting template (Chen et al. 2016). These technologies have a smart application in fields like bio/chemosensing, biotechnology, separation of science, cell encapsulation, and drug delivery in biochemistry (Ren and Chen 2015; Schirhagl 2014).

Unfortunately, some conventional MIT which have highly cross-linked polymers have relatively rigid structures, thereby, limiting their availability to bind with a targeted molecule (Yan and Row 2006). Such that polymer gels with lightly cross-linked structures can be subjected to a degree of temperature change in response to either reversible swelling or shrinking (Yan and Row 2006; Zhang et al. 2014). This type of imprinting technologies is usually known as "thermo-responsive" and is used as smart materials in cell encapsulation, tissue engineering, and drug delivery in biochemistry (Yan and Row 2006; Wulff 1995). They also have the potency for the design and application of protein-imprinted polymer matrices. For instance, a temperature-responsive polymer like Poly (N-isopropyl acrylamide) (PNIPAAm) is subjected to temperatures of 32.1 °C greater than its lower critical solution

temperature (LCST) during the phase separation stage (Venkatesh et al. 2014; Whitcombe et al. 2014). However, at high LCST, the hydrophilicity/hydrophobicity equilibrium becomes relatively inactive due to the high thermodynamic transition. Also below the LCST, water can be emitted from the interior of the polymer, which can lead to a massive reduction in the volume of the polymer.

2.1.1 Magnetic Responsive Technology

Molecular imprinting together with nanotechnology has improved both selectivity and sensitivity for recognizing diverse analytes, going from little particles to huge proteins and macromolecules (Wang and Zhang 2008; Li et al. 2014a, b; Whitcombe et al. 2014; Liu et al. 2019; Sharma and Kandasubramanian 2020). The imprinted nanostructures present a large surface area, which exposes more of their binding sites in order to trap the targeted analyte (Schirhagl 2014). Hence, integrating magnetite with MIPs has an extraordinary driving potential for some promising applications. These applications include drug delivery, sewage pretreatment, enzyme immobilization, catalysis, and magnetic bioseparation, which are among few to be mentioned (Sharma and Kandasubramanian 2020; Singh 2017). Due to their rapid, more accessible, cheap, high magnetic susceptibility, recoverability, and practical separation ability from a medium, it makes them essential to use (Singh 2017; Chen et al. 2009).

Herein, by magnetic imprinting technology, an artificial antibody-microbial was imprinted with silver materials as known—antibiotic or antimicrobial agents for microbial inactivation. Silver materials have hefty bacterial and inhibitory effects as well as a wide spectrum of antimicrobial activity (Chen et al. 2009; Sharma and Kandasubramanian 2020; Sun and Qiao 2008; Komiyama et al. 2018). However, there are reports of microbes developing resistance to silver, thus considered as silver-resistant (Singh 2017; Zhang et al. 2020; Chen et al. 2016). Singh (2017) reported on ways to reduce the risk of developing silver-resistant strains by imprinting composite materials with silver nanoparticles (AgNPs). A composite of Ag–TiO_2 made by synthesizing AgNPs with TiO_2 for antimicrobial activity showed dramatic efficiency as reported by Sharma and Kandasubramanian (2020), suggested the need to improve the efficiency by light irradiation.

Furthermore, incorporation of magnetic components like Fe_3O_4 nanoparticles into MIPs is in good direction upon application of an external magnetic field for separation of adsorbed analytes without additional centrifugation or filtration process (Li et al. 2014a, b; Zhang et al. 2020; Yan and Row 2006). Some of the standard techniques used in preparing M-MIPs including suspension, grafting, emulsion, and precipitation polymerization, offer better shape and size than bulk polymerization processes (Ren and Chen 2015; Liu et al. 2019). There have also been several reports that to obtain Fe_3O_4–MIP nanoparticles (Fig. 2), a well-regulated protocol MIPs has to be coated on the surface of superparamagnetic (Fe_3O_4) nanoparticles for rapid

Table 1 Diverse imprinting methods and preparation procedures of MIPs

Method	Benefits	Drawbacks
Bulk polymerization	Purity in the produced MIPs; simplicity and rapidity in preparation; no requirement for expensive and sophisticated instrumentation	Low-affinity sites; irregular particles in size and shape; time-consuming for sieving and grinding
Suspension	Spherical particles; one step and simple polymerization process	Poor recognition; big particle size (a few to a few hundred micrometers)
Precipitation polymerization	Uniform; high-quality; one single preparative step	High dilution factor; a substantial amount of template
Emulsion polymerization	Water-soluble polymers; monodispersed polymeric particles; High yield	Low imprinting capacity; suffers from the presence of remnants of surfactants
Sol–gel process	Eco-friendly reaction solvent; ease of fabrication at room temperature	Lack of polymerization; high cost of raw materials
Seed polymerization	Controllable, regularly spherical particles; monodispersity; suitable for HPLC	Laborious process; time-consuming

enrichment and separation (Lofgreen and Ozin 2014; Chen et al. 2009). In Table 1, the sol–gel process comes in handy and is useful for preparing M-MIPs due to its free radicals for polymerization (Lofgreen and Ozin 2014). Therefore, the steps in preparing of Fe_3O_4–MIP nanoparticles are as follows:

1. By synthesizing the Fe_3O_4 magnetic nanoparticles by solvothermal reduction approach or coprecipitation approach.
2. By functionalizing or surface modifying Fe_3O_4 magnetic nanoparticles.
3. By imprinting molecules on Fe_3O_4 magnetic particles in order to prepare M-MIPs via a free radical polymerization or sol–gel process.

2.1.2 Photo-Responsive Technology MIPs (P-MIPs)

Recent interest in producing P-MIPs has resulted in the integration of a photoreactive moiety in a polymeric system. Thus dimerization and isomerization are a product of converted chemical signals from photo-irradiation via photoreactions (Komiyama et al. 2018; Chen et al. 2011; Huang et al. 2015). Due to their photoreactive moieties, photoisomerization is seen to be faster, reversible, and reliable (Fu et al. 2015), for examples include, azobenzene and spiropyran used in functionalizing MIPs (Chen et al. 2009, 2016; Castell et al. 2011). Photo-responsive functional monomers are generally grouped into three categories; (1) the polymerizable group, (2) the recognition group, and (3) the photo-responsive group (Chen et al. 2009, 2011). This acts as a stimulus or kind of "clean energy" in various molecular devices and smart materials, which are due to their adjustable parameters such as intensity, duration, and wavelength (Chen et al. 2016; Castell

et al. 2011). Ideally, P-MIPs are generated by imprinting MIP with uniform nanoparticles, including zinc oxide or titanium dioxide (Chen et al. 2009, 2016; Fu et al. 2015). For instance, Komiyama et al. (2018) were able to synthesize a photo-responsive functional monomer with azobenzene moieties and siloxane polymerizable group via a sol–gel route, which was able to release and selectively bind a template molecule upon irradiation at 440 and 360 nm, respectively.

2.1.3 Other Responsive Imprinting Technologies

1. *Salt ion and biomolecule responsive*: The influence of salt ions on penicillin and propranolol as a targeted template for binding MIPs in water–acetonitrile mixtures has been reported (Mosbach and Ramström 1996; Parry and Humphreys 2009). Following the Hofmeister series with kosmotropic ions, studies show that 3M salt solutions in 100% aqueous solution augment the binding of templates to a substantial increment (Mosbach and Ramström 1996; Parry and Humphreys 2009). This supposed that the hydration of kosmotropic particles diminished the water movement in water-poor media, giving a balancing impact on the MIP-template of water-sensitive reactions (Bravo et al. 2009; Chen et al. 2016).
2. *Multi-stimuli responsive MIPs*: These are receptive to at least two stimuli being emerged. Double responsive polymers essentially incorporate salt/thermo, pH/thermo, photo/thermo, photo/magnetic, thermos/magnetic dual responsive MIPs (DR-MIPs) (Chen et al. 2016, 2011; Lofgreen and Ozin 2014).
3. *PH-responsive technology*: pH-responsive polymers are polymers containing an amino-functional group or a carboxylic acid, sensitive to changes in pH (Chen et al. 2009, 2011; Bravo et al. 2009). Such a polymeric network contains ionizable groups and can accept or donate protons at a specific pH (Chen et al. 2009; Bravo et al. 2009). The pH-responsive MIP hydrogel/nanospheres composite is a covering sensor with implantable glucose. By using a template molecule of dexamethasone-phosphate disodium (DXP) via a process of precipitation polymerization within the pH range tested (6.0–7.4), H-sensitive nanospheres also exhibited a faster DXP discharge rate at a lesser pH value.

2.2 The Components of MIT's

MIPs are prepared (Fig. 3) from functional monomers by way of polymerization and cross-linkers in the presence of the imprinted molecules serving as target analytes (Chen et al. 2011). As mentioned above, imprinting technologies (Table 1) have a distinct template and corresponding functional monomers for a constellation of template–monomer complexes. These are mostly hinged on the non-covalent and covalent interactions between the functional monomer and the template (Ansell et al. 1996; Whitcombe et al. 2014; Chen et al. 2016). Wang and Zhang (2008) assert that since the rate of chain propagation is not subject to control, preparing regular MIPs is

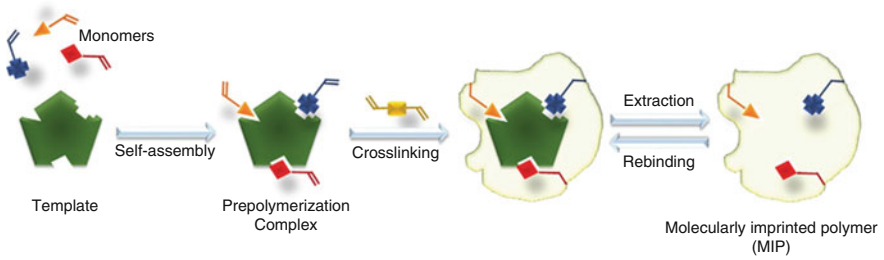

Fig. 3 Schematic portrayal of the process of molecular imprinting (Chen et al. 2011)

not simple in standard radical polymerization. The reason being that polymers generally have an expansive distributive size due to termination, chain transfer, and side reactions. Meanwhile, covalent imprinting, on the other hand, being stoichiometric, warrants functional monomer residues to exist in the imprinted cavities (Ramström and Ansell 1998; Schirhagl 2014). Also, polymerization reactions (Table 1 and Fig. 3) can be affected by some essential elements of MIT. These include the amount and type of monomers, temperature, cross-linker, time of polymerization reaction, and the initiator and the type of solvent (Ramström and Ansell 1998; Chen et al. 2016). To overcome such problems, there is a need for thermodynamic control of the polymer chain growth with a slower reaction rate and negligible chain termination. This will result in a narrow and homogeneous spread of networks of polymers as opposed to the highly cross-linked monomers (Chen et al. 2016; Whitcombe et al. 2014).

2.2.1 Target Template

According to Chen et al. (2011), potential MIPs must have high affinity and specificity compared to biological receptors, such that the template molecule (Figure 3) must meet the following requirements; (1) functional groups that cannot curtail polymerization, (2) functional groups to form complexes with functional monomers, and (3) excellent chemical stability during polymerization. For instance, in ion-imprinting, ligand complexes and metal ions are used due to their ability to pre-polymerize with functional monomers, contribute to high selectivity and adsorption of metals (Singh 2017). For instance, Zhang et al. (2014) conducted an experiment using a sol–gel route for dithizone chelating agent, with 3 aminopropyltriethoxysilane as a functional monomer and dithizone-Hg^{2+} chelate as a template. The result showed that Hg-IIPs had a perfect selectivity toward Hg^{2+} over its natural states and other metal ions. So far, MIPs have been successfully applied for the recognition and detection of a wide scope of nanoscopic natural molecules.

2.2.2 Functional Monomers

Chen et al. (2016) contend that by providing functional groups with the target template, they form a pre-polymerization complex. As a known fact, there are limited functional monomers for molecular imprinting (Table 1), which restricts their selectivity for further application to some extent (Zhang et al. 2014, 2020; Yan and Row 2006). Figure 4 presents the chemical structure of some of the most common photo-responsive functional monomers. In essence, functional monomers must be able to interact with the target template to form antibody–antigen complexes or specific donor–receptor before polymerization. Moreno-Bondi et al. (2008) noted that it is essential to design and amalgamate new functional monomers due to their ability to form a strong bond with templates. Besides, most functional monomers comprise two units, for example, silicon hydroxyl and a vinyl double bond, for recognition and polymerization, as shown in Fig. 4. For instance, a photopolymerizable diacetylene monomer was imprinted with dinuclear zinc cyclen receptors (Zn_2PCDA, compound 36) amidst a template peptide to simultaneously hobble two receptors of a membrane fluid (Zhang et al. 2020; Xu et al. 2009). In essence, this photo-induced polymerization of polydiacetylene formed shapes on the surface of the vesicle with organized varieties of receptor sites.

2.2.3 Cross-Linkers

As shown in Fig. 3, cross-linkers are used to fix functional monomers around template molecules in the process of polymerization (Xu et al. 2015). In the process, forms a highly cross-linked rigid polymer after removing the template. For instance,

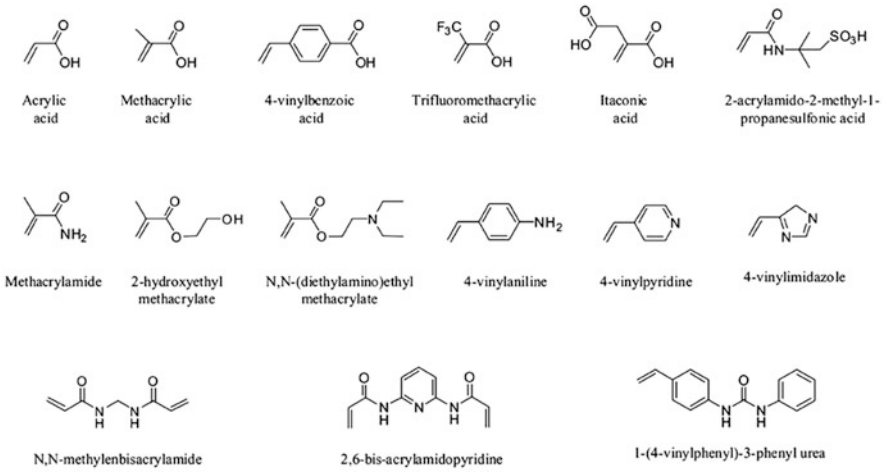

Fig. 4 Chemical structures of photo-responsive functional monomers (adapted from Zhang et al. 2020; Xu et al. 2009; Chen et al. 2016)

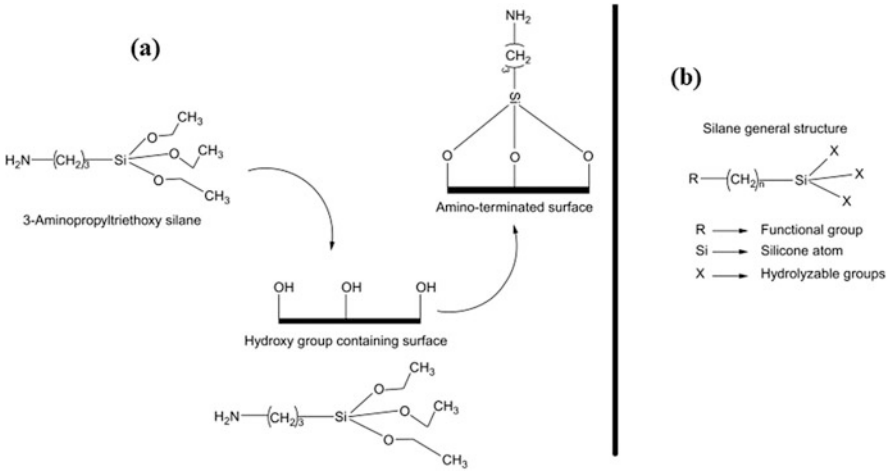

Fig. 5 Cross-linked structure of silicone in (**a**) sol–gel routes and (**b**) free radical polymerization (adapted from Li et al. 2014a, b)

in Chinese medicine, due to the non-toxicity and biodegradability of resin, it is used as a raw material for separating and purifying ingredients of the Chinese herbs (Xu et al. 2015; Li et al. 2014a, b). However, the binding capacity and selectivity of MIPs depend on the amount and type of cross-linker present. Generally, unstable mechanical properties of cross-linkers are due to low cross-linking degrees, whereas an extremely high amount of cross-linker will reduce the number of recognition sites per unit mass of MIPs. According to Li et al. (2014a, b), cross-linkers have three double bonds with excellent rigidity which can participate in polymerization reactions (Fig. 5). Thus the imprinted cavity, even in an organic solvent enhances the degree of cross-linking in a way that is maintained in the template molecule structure. An example of an imprinted cross-linked structure of silicone in sol–gel routes and free radical polymerization is shown in Fig. 5.

2.2.4 Porogens

In the polymerization process, porogens serve as pore-forming agents or dispersion media (Chen et al. 2016). These are solvents that play an important role during MIP synthesis and polymerization; these include N dimethylformamide (DFM), methanol, 2-methoxy ethanol, acetonitrile, toluene, tetrahydrofuran (THF), chloroform, and dichloroethane (Gladis and Rao 2004; Zhang et al. 2020). However, in non-covalent interaction systems, the extremity of porogens can influence the pace of interaction between the functional monomer and the template molecule. Ionic liquids (RTILs) are now used as solvents due to their unique characteristics (Chen et al. 2016). As solvent polarity subsequently affects the adsorption and morphological properties of the polymer, it is, therefore, vital to consider theoretical calculations before MIP selectivity (Yan and Row 2006; Zhang et al. 2020). Since

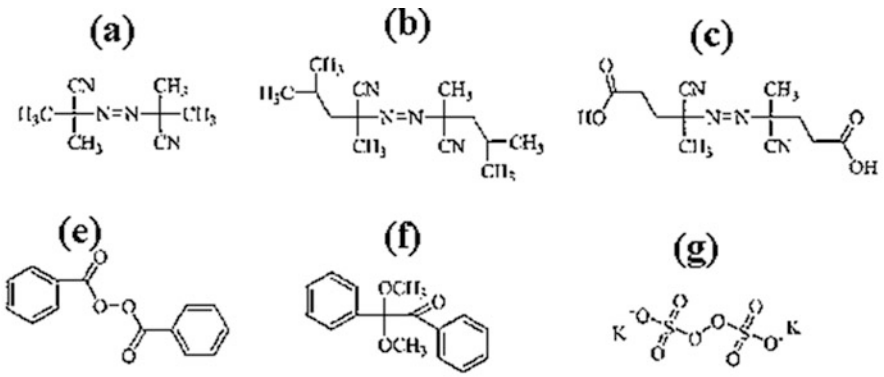

Fig. 6 Chemical structures of known initiators in molecular imprinting. (**a**) Azobisisobutyronitrile (AIBN); (**b**) azobisdimethylvaleronitrile (ADVN); (**c**) 4,40-azo (4-cyanovaleric acid) (ACID); (**d**) benzoyl peroxide (BPO); (**e**) dimethyl acetal of benzyl (BDK); and (**f**) potassium persulfate (KPS) (adapted from Chen et al. 2016)

this will give an insight for monomers and solvent types to be selected. For instance, the effects of acetone, acetonitrile, chloroform, and methanol were studied on monomer–template binding energy by Gladis and Rao (2004), whereby the density functional theory (DFT) was employed to determine their structural, vibrational frequency and selectivity for molecular imprinting.

2.2.5 MIP Initiators

Electropolymerization, free radical polymerization (FRP), or photopolymerization are among the most commonly used initiators for MIPs (Chen et al. 2011, 2016). With a wide range of template structures and functional groups, FRP can be ignited by either thermal or photochemical means during the imprinting process (Yan and Row 2006), wherein Fig. 6, azo-compounds can also be used as initiators apart from peroxy compounds (Chen et al. 2016). Azobisisobutyronitrile (AIBN) is most convenient among them to be utilized at the decomposition temperatures of 50–70 °C (Chen et al. 2016, 2011). Usually, in the polymerization reactions, inert gases, like nitrogen or argon, are used to deoxygenate the dissolved oxygen from polymerization solutions before proliferation.

3 Characterization of MIPs or Biomaterials

The imprinting of monomers to biocompatible and nontoxic materials requires ideal preparation protocols, this is to ascertain the attainability of the desired qualities for industrial production (Yan and Row 2006; Singh 2017; Ren and Chen 2015). The

orientation of monomers is directed based on the template being chemically stable and inert under polymerization (Schirhagl 2014; Ren and Chen 2015). Also, the ratio of functional monomer and template could have an impact on the efficiency of the imprinting polymer. In this instance, some of the preparation mechanisms including the sol–gel processes and the free radical polymerization as mentioned earlier are essential for the production of MIPs (Schirhagl 2014; Singh 2017; Whitcombe et al. 2014).

Ensuring large-scale production, detection, and characterization of MIPs plays a major role including screening of the monomers and obtaining information from template interactions (Chen et al. 2016; Wu and Qiu 2014). Monomer–template interactions, which are the most essential aspect of MIP design, are usually characterized by a UV-Vis and infrared (IR) spectroscopies and nuclear magnetic resonance (NMR) (Chen et al. 2011; Singh 2017). The forms of MIPs can be explored by the transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Furthermore, various fluorescence method and atomic force microscopy (AFM) method have also been employed in characterizing thin-film MIPs (Sun and Qiao 2008; Li et al. 2014a, b). Also, studies on ligand–MIP interactions including the use of X-ray photoelectron spectroscopy (XPS), diffraction, and X-ray absorption fine structures have become very attractive (Sharma and Kandasubramanian 2020; Singh 2017). Also, thermogravimetric analysis (TGA) can be employed when conducting a thermal stability. By nitrogen adsorption experiments via the Brunauer–Emmett–Teller (BET) analysis, the pore sizes and the exact surface areas of the polymers could be measured (Li et al. 2014a, b; Liu et al. 2019). The vibrating sample magnetometer (VSM) is used to measure magnetic properties (Fe_3O_4) during magnetic imprinting technology (Li et al. 2014a, b; Lofgreen and Ozin 2014). Apart from the morphological analysis, MIPs efficacy can also be examined by looking at the molecule's durability, robustness, and endurance for reuse. At equilibrium, the binding capacity (Q_e, mol/g) representing the total of adsorbed template/weight of the polymer could be calculated by using Eq. (1) (Lofgreen and Ozin 2014).

$$Q_e = \frac{(C_i - C_e) \times v}{m} \tag{1}$$

where c_e and C_i (mol/L) are the equilibrium and initial template concentrations, respectively, m (g) is the weight of the polymer and V (L) is the volume of the solution.

4 Application of MIT's

Global interest in polymerization for industrialization has inspired the rapid development and improvement of MITs for diverse applications (Fig. 7). The MIPs, nanoimprinted, and magnetized nanomaterials prepared using the novel sol–gel

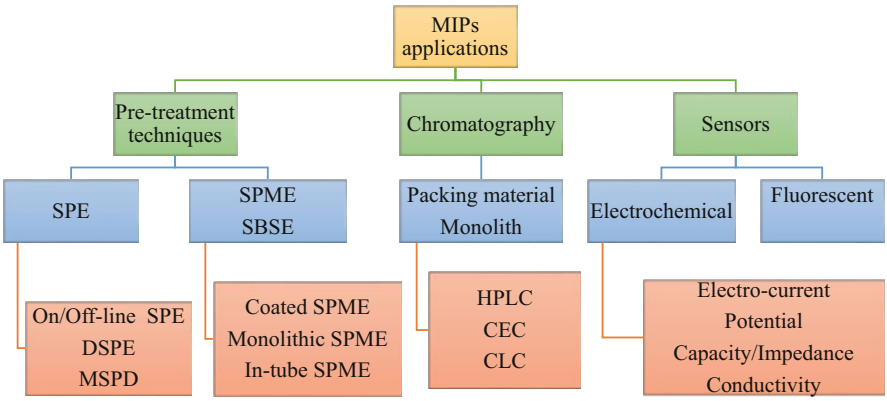

Fig. 7 Structural outline MIPs application in sensors, chromatography, and in pretreatment techniques. Abbreviations: *CLC* capillary liquid chromatography, *CEC* capillary electrochromatography, *HPLC* high-performance liquid chromatography, *SBSE* stir bar sorption extraction, *SPME* solid-phase microextraction, *MSPD* matrix solid-phase dispersion, *DSPE* dispersive SPE, *SPE* solid-phase extraction (Adapted from Chen et al. 2016)

Table 2 Classical types of antibiotics (adapted from Zhang et al. 2020; Wulff 1995; Chollom et al. 2020)

Class	Antibiotics
β-lactams	Penicillin, amoxicillin; ceftiofur
Macrolides and lincosamides	Tylosin; tilmicosin; tulathromycin, lincomycin
Aminoglycosides	Gentamicin; neomycin
Fluoroquinolones	Enrofloxacin, danofloxacin
Tetracyclines	Tetracycline; oxytetracycline, chlortetracycline
Sulphonamides	Sulfamethazine, sulfamethexazole and sulfasalazine
Streptogramins	Virginiamycin
Polypeptides	Bacitracin
Phenicols	Florfenicol
Pleuromutilin	Tiamulin

process (Fig. 2) are known to have an outstanding interface, electrical and optical properties, stability and suitable for chemical/biological sensors (Liu et al. 2019; Chen et al. 2020; Sun and Qiao 2008; Bravo et al. 2009). Subsequently, SIT-MIPs with which makes judicious use of hollow porous polymer synthesis technology for polymerizing precipitation results in high MIPs efficiency, ideal surface properties, uniform size, good morphology, and adsorption capacity (Chollom et al. 2020; Bravo et al. 2009). However, monitoring of pharmaceuticals (Table 2) is essential, because they are made up of different chemical structures and physicochemical properties, which can metabolize into different forms (Chollom et al. 2020; Wu and Qiu 2014; Wulff 1995; Chen et al. 2009). Figure 7 presents MIT techniques for detection and quantification of nanomaterials, pharmaceuticals, and environmental pollutants (Chen et al. 2016).

4.1 Pharmaceuticals (Antibiotics)

Pharmaceutical compounds are drugs that are commonly used to prevent and cure diseases and infections as well as improve health (Chollom et al. 2020; Zhang et al. 2020). They are classified according to the anatomical, therapeutic, and chemical functional groups as in the target anatomical system, therapeutic properties of the drug, or chemical characteristics of the molecule (Chollom et al. 2020; Wulff 1995; Zhang et al. 2020). There are a lot of pharmaceuticals (Table 2) which are widely used including endocrine-disrupting compounds, antibiotics, steroid hormones, antiretroviral drugs, and non-steroidal anti-inflammatory drugs (NSAIDs). These are usually found in the environment via various sources such as households, hospitals, wastewater treatment plants (WWTPs), industrial units, and human excretion as metabolites (Zhang et al. 2020; Xu et al. 2009; Wulff 1995). For instance, NSAIDs like diclofenac, ketoprofen, naproxen, and ibuprofen are rejected from the body of humans with 10, 70, 80, and 100% of unchanged compounds, respectively, which are swept into the WWTPs (Chollom et al. 2020; Wulff 1995; Wu et al. 2019). Most studies have reported that during the treatment of sewage and wastewater, pharmaceuticals and other emerging contaminants are partially removed during the treatment process, this is due to the fact these contaminants are recalcitrant, and therefore still persist even after the treatment process (Chollom et al. 2020; Zhang et al. 2020). Yet still, there is limited data and information on altered pharmaceutical waste streams, which pose a high risk to food security, human health, and the ecosystem sustainability (Zhang et al. 2020; Chen et al. 2016). Hence, integrating MIT (Fig. 7) into robust and effective monitoring and detecting technologies comes in handy for the environmentalist.

4.1.1 Sample Analysis

Comprehensively, assessing emerging environmental contaminants like the pharmaceuticals in a broader range involves the use of high liquid performance chromatography (HPLC) and liquid chromatography (LC). For example, antibiotics in food have been set at a 4–1500 μg/kg for milk and 25–6000 μg/kg for the other foodstuff of animal origin (Parry and Humphreys 2009; Liu et al. 2019; Li et al. 2014a, b). As a known fact, gas chromatography (GC) in the early 1930s was commonly used for the chromatographic separation of diverse compounds (Polyakov 1931; Ramström and Ansell 1998). However, the steps of GC include sample preparation to increase the selectivity and quantification by the analytical unit (Liu et al. 2019; Mühlen et al. 2020; Mosbach and Ramström 1996).

Conventionally, the treatment of pharmaceuticals in wastewater settings using degradation or advanced oxidation processes remains complex (Chollom et al. 2020; Zhang et al. 2020). This has necessitated the development of particular analytical approach for detecting and quantifying pharmaceutical compounds in the environment (Table 3) by applying MIPs as a sorbent in the pre-concentration step of the sample to enhance its sensitivity (Li et al. 2014a, b; Ren and Chen 2015; Liu et al. 2019). Some of the sorbents commonly used during the extraction steps before

Table 3 SPE protocols used in analysing pharmaceuticals (Wulff 1995; Zhang et al. 2020)

Analyte	Amount of sorbent (mg)	Effluent sample loading	Elution	Analytical method and detection limit
Diclofenac	35	1000 mL river water and wastewater	2 mL of methanol	LC-M5/M5
Carbamazepine	200	100 mL wastewater effluent at pH11	5 mL of methanol	LC-UV LOD— 25 μg L^{-1}
Metformin	50	50 mL aqueous samples including wastewater at pH10	1 mL of acetic acid and methanol (1.9)	LC-DAD-ESI/MS LOD— 1.5–3.4 ng L^{-1}
Ketaprofen	14	50 mL wastewater at pH5	1 mL of methanol	LC-UV LOD— 0.23 μg L^{-1}
Indomethacin	200	100 mL river water at pH5	2 mL methanol	LC-UV LOD— 0.03 μg ml^{-1}

filtration include chitosan, biochars, silica, zeolites, graphene, others (Moreno-Bondi et al. 2008; Chen et al. 2009; Li et al. 2014a, b; Wu and Qiu 2014; Xu et al. 2015; Huang et al. 2015). On the other hand, the solid-phase extraction (SPE) technique has proven to be efficient for pre-concentration and extraction of hydrophobic compounds (Chen et al. 2009, 2011; Bravo et al. 2009; Li et al. 2014a, b; Zhang et al. 2020). SPEs have been the drive for the application of MIPs as chromatographic stationary phases. Bravo et al. (2009) reported that this can be executed through slurry packaging of the readied MIPs into the stainless steel chromatographic column. The result is that the MIP attaches the packed material firmly during the application response with a strong retention time (Ren and Chen 2015; Chen et al. 2009).

4.1.2 Preparation of Pharmaceutical Templates

Recalcitrant traces of pharmaceuticals and personal care products are reported to be present in water bodies (Chollom et al. 2020; Ren and Chen 2015). In the environment, their presence poses potential risks with few toxicological pieces of information available to address their negative effects on the ecosystem and human health (Wu and Qiu 2014; Huang et al. 2015). However, most of these pharmaceutical compounds have a molecular structure with a variety of functional groups, which makes them highly selective for the imprinting process (Whitcombe et al. 2014; Wu and Qiu 2014; Wang and Zhang 2008). In the synthetic reaction shown in Fig. 8, the methacrylic acid, ethylene glycol dimethacrylate, and fluconazole are used to represent a template, cross-linker, and functional monomer, respectively, where the functional group's presence makes it easy for the template to undergo molecular

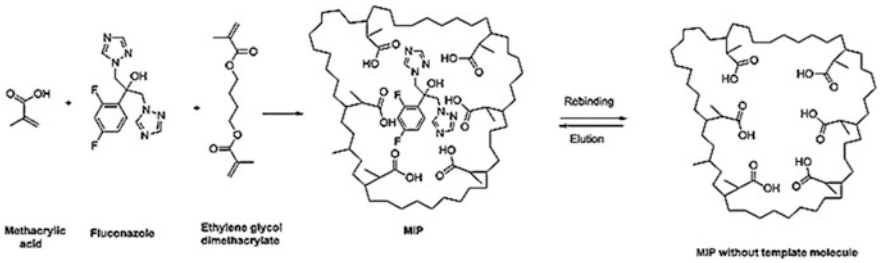

Fig. 8 Scheme of a MIP of fluconazole as a pharmaceutical detection agent (adapted from Wulff et al. 1972)

Table 4 MIPs in hydrolysis reactions for pharmaceutical products

MIP composition	Template	Substrate	Reference
Radical copolymerization of vinyl imidazole with divinylbenzene	*p*-Nitrophenyl phosphate	p-Nitrophenyl acetate	Chen et al. (2016)
Polymerization of N, N-diethyl(4-vinyl phenyl) amidine in the presence of phosphate transition state analog	Cholesteryl 4-nitrophenyl Phosphate	Cholesterol 4-nitrophenyl carbonate	Wulff et al. (1972)
Radical copolymerization of N,N′-diethyl-4-vinylbenzamidine with methyl methacrylate in the presence of the template	(4-carboxybenzyl) triphenylphosphonium bromide Phthalic acid, di(3,5-dimethylphenyl) ester	N-(4Carboxybenzoyl)-i-amino acid (3,5-dimethylphenyl) esters derived from land D-leucine and I- and D-valin	Chen et al. (2016) Chen et al. (2011)
Suspension polymerization of methyl methacrylate in the presence of the template	Diphenyl phosphate	Diphenyl carbonate and diphenyl carbonate	Whitcombe et al. (2014)
Co(coordinated monomers template assemblies of N-methacryloyl-l-serine; N-methacryloyl-l-aspartic acid and N-methacryloyl-histidine with the templates	N-Actyltrosyl-2 amino pyrazinamide and N-nicotinoyltrosyl benzyl ester	N-Acetyl tyrosyl-para nitrophenyl ester and N-benzoyl tyrosyl-para nitrophenyl ester	Xu et al. (2015)
Allyl 1H-imidazole-1-carboxylate	p-Nitrophenyl phosphate	p-Nitrophenyl acetate	Wu and Qiu (2014)

interactions with the hydrogen bonding in the acidic medium (Xu et al. 2015; Wulff 1995; Wulff et al. 1972). This makes it easy for smaller molecules to be able to penetrate the pores. Table 4 also presents pharmaceuticals being used as molecular imprinting templates, where companies like MIP Technologies in Lund (Sweden, Europe), Biotage in Barcelona (Spain, Europe), and Supelco in Bellefonte (PA,

USA) have been able to commercialize MIP sorbents (Wulff et al. 1972; Wulff 1995; Moreno-Bondi et al. 2008; Li et al. 2014a, b).

4.1.3 Chitosan as a Pharmaceutical Template

Chitosan (Fig. 9) is a versatile hydrophilic polysaccharide material which can be derived from chitin, and can be used for antimicrobial activity (Li et al. 2014a, b). The reactive functional groups (amino and hydroxyl groups) present in chitosan can readily be transformed to enlarge its biocompatibility, mechanical and solubility properties (Li et al. 2014a, b; Chen et al. 2009; Liu et al. 2019). These characteristics render chitosan as a right template for MIPs, although the potential exists, chitosan has not been applied for this purpose yet. Subsequently, chitosan and chitin have been investigated as an antimicrobial material in position to a broad spectrum of target organisms such as fungi, yeasts, bacteria, and algae (Moreno-Bondi et al. 2008; Li et al. 2014a, b). Likewise, in the biomedical sector, chitosan films are used as scaffolds for bone and tissue engineering and therapeutic wound dressing (Li et al. 2014a, b). Chitosan, as a biological activity depends extensively on the degree of acetylation (DA) and its molecular weight (MW) (Xu et al. 2015). Even though these parameters independently impact the chitosan antimicrobial activity, the effect of the DA is lesser than the effect of the MW on the antimicrobial activity (Wu and Qiu 2014; Xu et al. 2015). Three mechanisms by which chitosan can be used as an antibacterial agent are being proposed (1) the forming of chelating metals, external barriers and suppressing essential nutrients for the growth of microbial (2) inhibiting protein synthesis and mRNA through the perforation of chitosan microorganism via its nuclei (3) ionic surface interaction resulting in the leakage of the cell wall (Wu and Qiu 2014; Xu et al. 2015; Mühlen et al. 2020). These are likely to be used simultaneously or at different strengths, depending on the targeted product.

4.2 Sol–Gel-Derived Biomaterials

Sol–gel imprinting technology with biochemistry offers a great alternative to produce bioactive surface area for various biomedical applications (Table 1). During

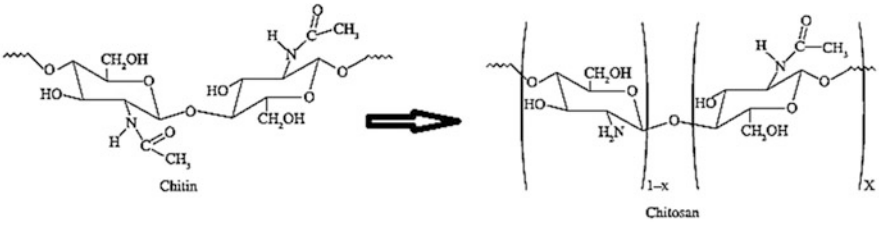

Fig. 9 Schematic scheme of chitosan in MIP (adapted from Xu et al. 2015; Wu and Qiu 2014)

biochemical reactions in constrained matrices, the MIPs enhance the bioactivity for easy controlling, as a result of their high surface area, micro-pores, and residual hydroxyl ions (Sun and Qiao 2008; Chen et al. 2009; Li et al. 2014a, b). In medical device designs, sol–gel imprinting is used to treat the device surfaces by either coating or modifying their characteristics, e.g. biocompatibility, functionality, hydrophobicity, hydrophilicity, and lubricity (Qiu et al. 2013; Mühlen et al. 2020; Nicholls et al. 2013).

Current development in imprinting technology allows for the prevention and treatment of bone infections in the clinical environment, without excluding drug delivery which allows for no extensive bodily reactions during healing responses (Mühlen et al. 2020; Schirhagl 2014). Also, sol–gel films or layers do not only have a high specific surface area as adsorbed drug carriers but also provide biocompatibility with external functional monomers (Xu et al. 2009). However, there remains a significant challenge in the apt use of magnetic nanoparticles in drug delivery vectors, even though no composite material produced can be compared to its magnetic response strength (Takagishi and Klotz 1972; Ren and Chen 2015; Chen et al. 2016). Despite that setback, imprinting magnetic nanoparticles involving inorganic matrices like silica with rich chemistry and useful outer surface makes them an auspicious material to be used as magnetic carriers for imprinting other biomolecules, medical drugs, proteins, and antibodies (Yan and Row 2006; Mühlen et al. 2020). Also, the distribution of pore-size and thickness of the silica nanomaterials are usually controlled by sol–gel dip-coating techniques, which gives an unmediated approach to modify the duration and rate of drug delivery (Nicholls et al. 2013; Lofgreen and Ozin 2014; Mühlen et al. 2020). Furthermore, sol–gel imprinting technology offers numerous merits which include controlling of chemical reactions, precise and ease in fabricating microstructures, and low-temperature processing (Fig. 10).

Other sol–gel applications in MIT include the following;

1. *Mixed-oxide layers*: This involves the tailoring of oxide layers to influence its adsorption ability with elements which are biocompatible like Ta, Zr, Nb, and Ti by using mixed precursors (Li et al. 2014a, b; Moreno-Bondi et al. 2008). The imprinting efficiency usually depends on the surface oxide layer, especially the electronic structure, for example, solid electrolytes for fuel elements, ceramic passive bioimplants, eye and neuro-microsurgery and producing nanocrystalline powders for paediatrics using ZrO_2 (Hanak and Manovic 2018; Fu et al. 2015).
2. *Superparamagnetic nanoparticle*: This involves integrating two useful functional monomers with luminescence and superparamagnetism, alongside an effortlessly conjugated silica surface (Chen et al. 2011; Fu et al. 2015). Silica ends up being a quality material for a defensive lattice by virtue of its stability and biocompatibility and in many biosystems including magnetic resonance imaging (MRI), targeted drug delivery, magnetic separation, as well as in bioanalysis for sensing and detection (Mosbach and Ramström 1996; Moreno-Bondi et al. 2008). Sol–gel methods are used globally in preparing powders made of magnetic iron oxide like Fe_3O_4, γ-Fe_2O_3, and α-Fe_2O_3 of nanometre-size (Moreno-Bondi et al. 2008).

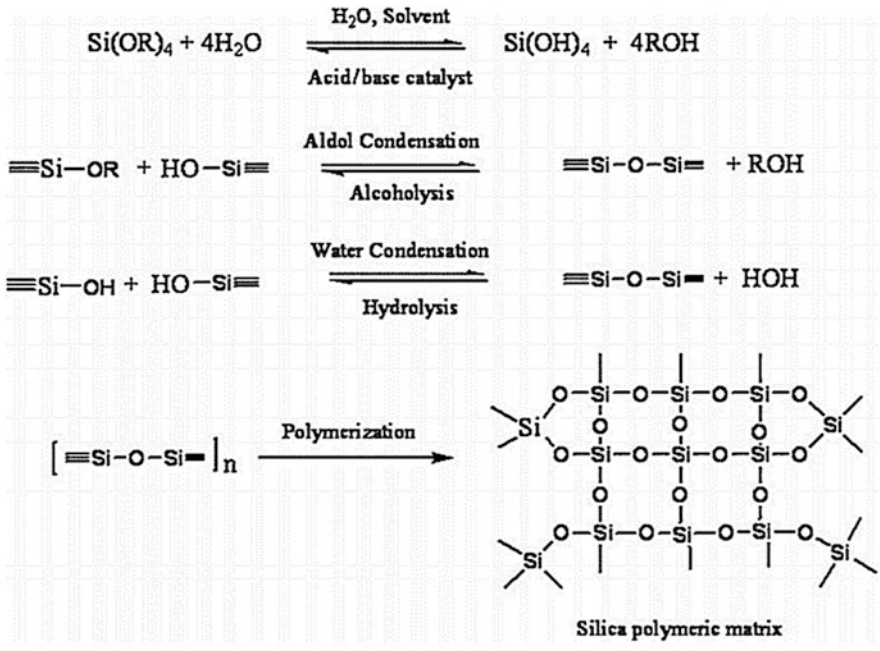

Fig. 10 Chemical reactions of molecularly sol–gel silica (adapted from Lofgreen and Ozin 2014)

These are usually characterized based on their particle size, discrete and superparamagnetic properties for a discrete biomedical application with their chemical reactions in Fig. 10 (Lofgreen and Ozin 2014).

3. *Bioactive hybrids (organic–inorganic):* Living bone is created by the kind of impulsive bond when implanted in a defective bone, makes glass-ceramics and bioactive glasses to be very captivating for numerous biomedical applications (Parry and Humphreys 2009; Tetteh and Rathilal 2019). This is a bond to increase their flexibility by making inorganic–organic hybrid materials by integrating important parts for bioactivity (calcium and Si–O ions) with natural polymers (Lofgreen and Ozin 2014). Also, with plasma spray methods, metal implants (stainless steel alloys and titanium) can be covered with a film of hydroxyapatite to get bioactive materials of high mechanical strength (Fu et al. 2015).
4. *Surface modification with metallic implants*: These are classified as metallic, ceramics, and polymers. The metallic materials have high ductility and strength properties as opposed to ceramics and polymers (Gladis and Rao 2004; Chen et al. 2009, 2016). Likewise, ceramics and polymers are more corrosive as opposed to metallic materials (Chen et al. 2011). This imprinting technology comes in handy, as corrosion can reduce the strength of the implants, which might cause untimely failure and impose harmful effects on its surroundings. In this case, cobalt alloys, titanium alloys, and stainless steels are often utilized for implanted biomaterials (Chen et al. 2016; Fu et al. 2015).

4.3 Antibacterial Coating

The field of antibacterial coating technology (Table 5) as a concept in MIT has entered an energizing phase with innovations constantly evolving (Chen et al. 2016). In the biomedical device industry of the medical community, a strong pull of MIT has gained much popularity in the rapid concern of detecting and recognizing infections (Levy and Marshall 2004; Gladis and Rao 2004; Chen et al. 2020).

Table 5 Application of MIT as antibacterial and antimicrobial agents for characterizations (Levy and Marshall 2004; Gladis and Rao 2004; Chen et al. 2016)

Template	Functional monomer	Imprinting technique	Determination technique
Saccharomyces cerevisiae	*Polyurethane*	Surface printing	QCM
Saccharomyces cerevisiae	*Titanium ethyate*	Surface printing	QCM
Escherichia coli	*Polyurethane*	Surface printing	QCM
Deinococcus radiodurans	*Tetraethoxysilane*	Bulk printing	Fluorescence
Escherichia coli	*Tetraethoxysilane*	Bulk printing	Fluorescence
Bacillus subtilis	*Tetraethoxysilane*	Bulk printing	Fluorescence
Sphaerotilus natans	*Tetraethoxysilane*	Bulk printing	Fluorescence
Pseudomonas aeruginosa	*Pyrrole*	Electro polymerization	Fluorescence
Escherichia coli	*Pyrrole*	Electro polymerization	QCM
Pseudomonas aeruginosa	*Pyrrole*	Electro polymerization	QCM
A. calcoaceticus	*Pyrrole*	Electro polymerization	QCM
S. marcescens	*Pyrrole*	Electro polymerization	QCM
Escherichia coli	*Tetraethoxysilane*	Bulk printing	QCM
Sulfate-reducing bacteria	*Chitosan reduced graphene*	Electro polymerization	EIS
Bacillus subtilis endospore	*Pyrrole*	Electro polymerization	EIS
Escherichia coli	*Silane*	Electro polymerization	Electrochemical sensor
Escherichia coli	*MAH*	Electro polymerization	Captive biosensor
Escherichia coli	*MAH*	Electro polymerization	QCM
Escherichia coli	*MAH*	Electro polymerization	SPR

[a]*CFU* colony-forming unit, *EIS* electrochemical impedance spectroscopy, *QCM* quartz crystal microbalance, *SPR* surface plasmon resonance, *MAH* N-methacryloyl-L-histidine methyl ester

Subsequently, medically implanted devices like central venous and urinary catheters and prosthetic hip implants are risked to bacterial infections with serious complications (Gladis and Rao 2004; Fu et al. 2015; Chen et al. 2016). Classically, these are prone to early removal of implants that might be fatal, very expensive, and stressful to the patient (Levy and Marshall 2004; Chen et al. 2020). Furthermore, immediately after surgery, aggressive bacteria could still be located at the imbedded sites despite preventative measures like sterilization (Chen et al. 2011). For instance, explanted orthopaedic devices which have biofilms on it are formed from species of *Staphylococci,* including *Staphylococcus epidermidis and Staphylococcus aureus* (Wulff 1995; Wu et al. 2019).

The sol–gel dip-coating process has shown to be an effective technique to develop immobilization of an antimicrobial agent using nanoparticles (Huang et al. 2015; Levy and Marshall 2004). Examples of nanoparticles include silver and titanium dioxide, which could be immobilized covalently or electrostatically to films of plasma polymer housing suitable surface functionalities (Gladis and Rao 2004; Komiyama et al. 2018). This becomes very interesting to bind the microbes with the different surfaces of the antimicrobial or antibacterial materials in the matrix (Komiyama et al. 2018). Therefore, imprinting technology comes in handy to control and prevent microbial contamination of medical devices during antibacterial activities.

Recent studies show that silver ions or silver have wide-range antibacterial action as opposed to Gram-negative and Gram-positive bacterial strains, including safe antimicrobial strains (Parry and Humphreys 2009; Pandey et al. 2020). This makes it increasingly hard for microbes to create protection from silver as contrasted with ordinary antimicrobial. Figure 11 presents the multifaceted mechanism of action of silver oxidizes when putting in a physiological medium and discharges silver particles. These ions act by stopping the replication of DNA and bind the cell membrane, enzymes, and proteins, causing interference with the bacterial metabolism (Pandey et al. 2020). This approach takes into account simple control of the silver nanoparticles immobilized on a superficial level and can prompt coatings giving full insurance against bacterial colonization, a favourable combination of mammalian cells and tissue, as well as in the absence of adverse immune responses.

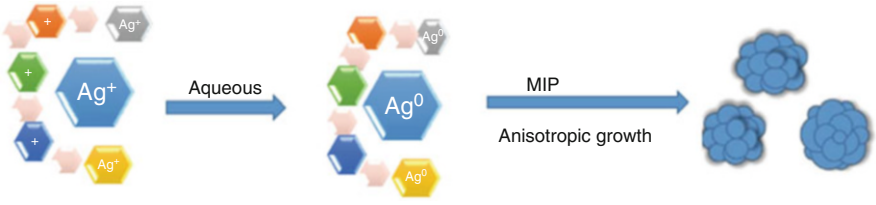

Fig. 11 Dissolving silver nanoparticles in an aqueous condition releases silver ions

4.4 Biomedical Application of MITs

4.4.1 Biomaterial Scaffold

Today imprinting biomaterials have become very useful in developing cell adhesion and proliferation materials in replacing damaged tissue, especially in the wound healing process (Li et al. 2014a, b; Mühlen et al. 2020). For instance, a manufactured extracellular grid and building new bone tissue with cells has been the methodology in the recovery of mineralized tissues contrasted with regular transplantation of bone (Mühlen et al. 2020; Parry and Humphreys 2009). As shown in Fig. 12, scaffold materials based on smart technology are easy to attach, proliferate, and differentiate cells into functional and suitable structures of tissues. Example minerals and proteins like carbonate-apatite, fluorapatite, and hydroxyapatite (HA) [Ca10(PO4)6(OH)2] are mostly considered for cartilage regeneration and engineering bone tissue (Mühlen et al. 2020; Chen et al. 2016). Among these biomaterials, the porosity in HA structures makes them essential for the growth of bones and tissues surrounding a supportive framework by allowing free passage of nutrients (Mühlen et al. 2020; Mosbach and Ramström 1996). HA seems to be a very promising biomaterial, i.e. improving bioactivity. Pandey et al. (2020) reported that by using sol–gel technology in bioactivity and biocompatibility of HA scaffolds, the biomedical application could be improved via its morphology, crystal size, impurity concentration, and controlling composition.

4.4.2 Cell Coating

In the biomedical settings, MIT has become an alternative technique to conventional cell culture developing systems, which incurs cost through the multi-construction steps (Chen et al. 2009). This becomes crucial to develop a distinct pattern of mammalian cell adhesion and monitor their growth (Wulff 1995; Levy and Marshall 2004; Li et al. 2014a, b). In terms of the MIT (Table 5), this involves conjugation of a cell surface to cell-adhesive affinity reagent, which is carried out by using specialized methods like microfluidics, 3D printing, photoablation, and photolithography

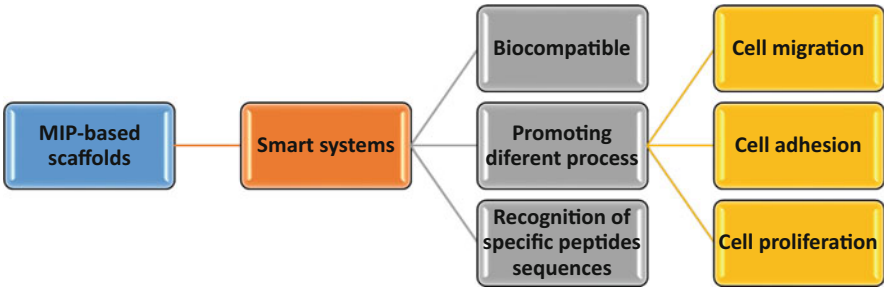

Fig. 12 Schematic of MIT based scaffold applications (Chen et al. 2016)

(Mühlen et al. 2020; Nicholls et al. 2013). A research group of DePorter effectively developed imprinted polyacrylamide hydrogels like MRC-9 (fibroblast-like cells), HEK-293T (epithelial-like cells), and HeLa cells as substrates for mammalian cell growth and adhesion (Wulff et al. 1972; Xu et al. 2015; Wang and Zhang 2008).

4.4.3 Biosensors

In recent years, many biomedical engineers are trying their best possible means to develop implantable glucose sensors, which can give direction on administering an amount of insulin and monitor ambulatory diabetic patients' blood level (Nicholls et al. 2013; Pandey et al. 2020). The biosensors are also employed for clinical diagnostics, drug detection, pollutant monitoring and food analysis (Levy and Marshall 2004; Li et al. 2014a, b; Liu et al. 2019), for example, improvement of MIP for cell recognition in cancer therapy and regenerative medicines (Moreno-Bondi et al. 2008). Therefore, the interest of advancing biological sensors and MIP-based chemical comes in handy. It is very significant to have an ideal interface amid the transducer and the recognition element (Li et al. 2014a, b). Therefore, developing and processing of MIP particles or films for MIP-based sensors becomes essential in biomedical engineering settings. Some of these materials are made up of nanomaterials, electropolymerized thin-film matrices, stimuli-responsive hydrogel, and inorganic materials (Levy and Marshall 2004; Li et al. 2014a, b; Liu et al. 2019). However, high MIP-based throughput exhibit sensors, including multisensory units, have challenging and promising possibilities for simultaneous multi-part analysis (Qiu et al. 2013; Singh 2017; Sun and Qiao 2008). Despite this, imprinting sensors towards enzymes, cells, bacteria, viruses, and gas seem very promising with economic opportunities for explorations (Levy and Marshall 2004; Huang et al. 2015; Hanak and Manovic 2018).

4.5 Social-Economic Interest

MITs have gained attractive attention as a synthetic approach to mimic natural molecular recognition (Mosbach and Ramström 1996; Ansell et al. 1996; Ramström and Ansell 1998). Molecularly imprinted biomaterials reported (Table 5) are physically robust due to their highly desirable selectivity, thermal stability, easy preparation, and low cost. These properties and other derivatives make them very attractive for various industrial applications including pharmaceuticals, breweries, biomedical, health, sewage treatment, and so on (Chen et al. 2011). Wu et al. (2019) also highlighted various forms of MIT applications in nanotechnology.

Currently, world grapples with food and water insecurity (Ghuman and Sharma 2019), health and sanitation crisis (Parry and Humphreys 2009), climate change as well as the destruction of natural resources (Parry 2019). Whereby the United Nations have disseminated 17 sustainable development goals (SDGs) towards the

year 2030, as a way to meet the needs of the world without compromising that of the future generation. Furthermore, to curb this, it is expedient that integrating MITs into the conventional process will be economically viable and possible leeway to improve most systems to sustain the world. For instance, Wu and Qiu (2014) found that the adsorption rate for imprinted polymer in artificial seawater was about 71.57 m^3/s with an adsorption capacity of 2.505 mg/g. This method provides an efficient treatment of water at a low cost as compared to lanthanum nitrate modified chitosan. Many researchers have also used MIPs (imprinted-polymeric organic or inorganic coagulants) in wastewater and water treatment (Venkatesh et al. 2014; Kweinor Tetteh and Rathilal 2020).

Singh (2017) reported on nanoimprinting technology in agricultural and food production, which aided in the crop growth as well as post-harvest preservation. Hanak and Manovic (2018) also demonstrated the application of MIT for carbon dioxide (CO_2) capturing for energy generation. Remarkably, most literature findings on MITs are geared towards higher economic efficiency (Chen et al. 2011), low production cost (Liu et al. 2019; Teixeira et al. 2015), low energy consumption (Hanak and Manovic 2018), equipment improvement, and eco-friendliness (Wu and Qiu 2014), which propels MIT as a promising, smart, and sustainable technology for social-economic growth and development.

5 Conclusion

In this chapter, MIT represents an advanced method for formulating and designing engineered antibacterial and biomaterials valuable for biomedical, nanotechnology, cell adhesion, and environmental applications. Different types of MITs were defined based on structural designs of polymeric materials, by highlighting their applications and definite structural arrays with their corresponding binding sites that allow a specific recognizing of bioreceptor patterns. Among the imprinting technologies, materials derived by the sol–gel route have interesting, stimulating characteristics which have been employed in several hands-on applications, extending from glass materials, ceramics, nanomaterials, medical devices, and biosensors. The expediency of the sol–gel route for formulating super magnetic and bioactive nanomaterials, glasses, hybrids, and coatings for biomedical applications with possibilities of designing more biocompatible or antibacterial agents was further elaborated. Also considering molecularly imprinting polymers (MIPs) hinged on their hydrophobicity and inhomogeneity could be useful to improve the selectivity or sensitivity of devices for different kinds of target molecules. The prospects of MIT are, therefore, foreseen to be a successful venture as commercial MIP sorbents that exist are being utilized. Furthermore, as antibacterial resistance and emerging contaminants like pharmaceuticals are still being recognized in the environment, their future rise can economically be detected by the possible applications of molecularly imprinted materials.

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References

Alexander C, Andersson HS, Andersson LI, Ansell RJ, Kirsch N, Nicholls IA, Whitcombe MJ (2006) Molecular imprinting science and technology: a survey of the literature for the years up to and including 2003. J Mol Recognit 19(2):106–180

Ansell RJ, Kriz D, Mosbach K (1996) Molecularly imprinted polymers for bioanalysis: chromatography, binding assays and biomimetic sensors. Curr Opin Biotechnol 7(1):89–94

Bravo JC, Garcinuño RM, Fernández P, Durand JS (2009) Selective solid-phase extraction of ethynylestradiol from river water by molecularly imprinted polymer microcolumns. Anal Bioanal Chem 393(6-7):1763–1768

Castell OK, Barrow DA, Kamarudin AR, Allender CJ (2011) Current practices for describing the performance of molecularly imprinted polymers can be misleading and may be hampering the development of the field. J Mol Recognit 24(6):1115–1122

Chen L, Liu J, Zeng Q, Wang H, Yu A, Zhang H, Ding L (2009) Preparation of magnetic molecularly imprinted polymer for the separation of tetracycline antibiotics from egg and tissue samples. J Chromatogr A 1216(18):3710–3719

Chen L, Xu S, Li J (2011) Recent advances in molecular imprinting technology: current status, challenges and highlighted applications. Chem Soc Rev 40(5):2922–2942

Chen L, Wang X, Lu W, Wu X, Li J (2016) Molecular imprinting: perspectives and applications. Chem Soc Rev 45(8):2137–2211

Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 395(10226):809–815

Chollom MN, Rathilal S, Swalaha FM, Bakare BF, Tetteh EK (2019) Comparison of response surface methods for the optimization of an upflow anaerobic sludge blanket for the treatment of slaughterhouse wastewater. Environ Eng Res 25(1):114–122

Chollom MN, Rathilal S, Swalaha FM, Bakare BF (2020) Adsorptive removal of veterinary antibiotics from water using an integrated photocatalyst (IPCA). Int J Environ Stud 77:1–19

Fu J, Chen L, Li J, Zhang Z (2015) Current status and challenges of ion imprinting. J Mater Chem A 3(26):13598–13627

Ghuman RS, Sharma R (2019) Emerging water insecurity in India: lessons from an agriculturally advanced state. Cambridge Scholars Publishing, Cambridge

Gladis JM, Rao TP (2004) Effect of porogen type on the synthesis of uranium ion imprinted polymer materials for the preconcentration/separation of traces of uranium. Microchim Acta 146 (3-4):251–258

Hanak DP, Manovic V (2018) Techno-economic feasibility assessment of CO2 capture from coal-fired power plants using molecularly imprinted polymer. Fuel 214:512–520

Huang DL, Wang RZ, Liu YG, Zeng GM, Lai C, Xu P, Huang C (2015) Application of molecularly imprinted polymers in wastewater treatment: a review. Environ Sci Pollut Res 22(2):963–977

Komiyama M, Mori T, Ariga K (2018) Molecular imprinting: materials nanoarchitectonics with molecular information. Bull Chem Soc Jpn 91(7):1075–1111

Kweinor Tetteh E, Rathilal S (2020) Evaluating pre-and post-coagulation configuration of dissolved air flotation using response surface methodology. Processes 8(4):383

Levy SB, Marshall B (2004) Antibacterial resistance worldwide: causes, challenges and responses. Nat Med 10(12):S122–S129

Li X, Li M, Li J, Lei F, Su X, Liu M, Tan X (2014a) Synthesis and characterization of molecularly imprinted polymers with modified rosin as a cross-linker and selective SPE-HPLC detection of basic orange II in foods. Anal Methods 6(16):6397–6406

Li P, Wang T, Lei F, Tang P, Tan X, Liu Z, Shen L (2014b) Rosin-based molecularly imprinted polymers as the stationary phase in high-performance liquid chromatography for selective separation of berberine hydrochloride. Polym Int 63(9):1699–1706

Liu G, Huang X, Li L, Xu X, Zhang Y, Lv J, Xu D (2019) Recent advances and perspectives of molecularly imprinted polymer-based fluorescent sensors in food and environment analysis. Nanomaterials 9(7):1030

Lofgreen JE, Ozin GA (2014) Controlling morphology and porosity to improve performance of molecularly imprinted sol–gel silica. Chem Soc Rev 43(3):911–933

Moreno-Bondi MC, Navarro-Villoslada F, Benito-Peña E, Urraca JL (2008) Molecularly imprinted polymers as selective recognition elements in optical sensing. Curr Anal Chem 4(4):316–340

Mosbach K, Ramström O (1996) The emerging technique of molecular imprinting and its future impact on biotechnology. Biotechnology 14(2):163–170

Mühlen S, Ramming I, Pils MC, Koeppel M, Glaser J, Leong J, Flieger A, Stecher B, Dersch P (2020) Identification of antibiotics that diminish disease in a murine model of enterohemorrhagic Escherichia coli infection. Antimicrob Agents Chemother 64(4):e02159

Nicholls IA, Karlsson BC, Olsson GD, Rosengren AM (2013) Computational strategies for the design and study of molecularly imprinted materials. Ind Eng Chem Res 52(39):13900–13909

Pandey H, Khare P, Singh S, Singh SP (2020) Carbon nanomaterials integrated molecularly imprinted polymers for biological sample analysis: a critical review. Mater Chem Phys 239:121966

Parry ML (2019) Climate change and world agriculture. Routledge, Abingdon

Parry J, Humphreys G (2009) Health amid a financial crisis: a complex diagnosis: the global financial crisis could have profound implications for the health spending plans of national governments. Unless countries have safety nets in place, the poor and vulnerable will be the first to suffer. Bull World Health Organ 87(1):4–6

Patrikeev GA (1960) The molecular mechanism underlying deformaation of polymers. In Doklady academii Nauk. Russian Acad Sci 133(2):405–408

Polyakov MV (1931) Adsorption properties and structure of silica gel. Zhur Fiz Khim 2:799–805

Qiu H, Fan L, Li X, Li L, Sun M, Luo C (2013) A microflow chemiluminescence sensor for indirect determination of dibutyl phthalate by hydrolyzing based on biological recognition materials. J Pharm Biomed Anal 75:123–129

Ramström O, Ansell RJ (1998) Molecular imprinting technology: challenges and prospects for the future. Chirality 10(3):195–209

Ren X, Chen L (2015) Preparation of molecularly imprinted polymer-coated quantum dots to detect nicosulfuron in water samples. Anal Bioanal Chem 407(26):8087–8095

Schirhagl R (2014) Bioapplications for molecularly imprinted polymers. Anal Chem 86 (1):250–261

Sharma G, Kandasubramanian B (2020) Molecularly imprinted polymers for selective recognition and extraction of heavy metal ions and toxic dyes. J Chem Eng Data 65(2):396–418

Singh NA (2017) Nanotechnology innovations, industrial applications, and patents. Environ Chem Lett 15(2):185–191

Sun HW, Qiao FX (2008) Recognition mechanism of water-compatible molecularly imprinted solid-phase extraction and determination of nine quinolones in urine by high-performance liquid chromatography. J Chromatogr A 1212(1-2):1–9

Takagishi T, Klotz IM (1972) Macromolecule-small molecule interactions; introduction of additional binding sites in polyethyleneimine by disulfide cross-linkages. Biopolymers 11 (2):483–491

Teixeira R, Dopico-García S, Andrade PB, Valentão P, López-Vilariño JM, González-Rodríguez V, Silva LR (2015) Volatile phenols depletion in red wine using molecular imprinted polymers. J Food Sci Technol 52(12):7735–7746

Tetteh EK, Rathilal S (2019) Application of organic coagulants in water and wastewater treatment. In: Organic polymers. InTech Open, London

Tetteh EK, Obotey Ezugbe E, Rathilal S, Asante-Sackey D (2020) Removal of COD and SO42− from oil refinery wastewater using a photo-catalytic system—comparing TiO2 and zeolite efficiencies. Water 12(1):214

Venkatesh A, Chopra N, Krupadam RJ (2014) Removal of acutely hazardous pharmaceuticals from water using multi-template imprinted polymer adsorbent. Environ Sci Pollut Res 21 (10):6603–6611

Wang L, Zhang Z (2008) The study of oxidization fluorescence sensor with molecular imprinting polymer and its application for 6-mercaptopurine (6-MP) determination. Talanta 76(4):768–771

Whitcombe MJ, Kirsch N, Nicholls IA (2014) Molecular imprinting science and technology: a survey of the literature for the years 2004–2011. J Mol Recognit 27(6):297–401

Wu H, Qiu J (2014) Adsorption performance for bromine ion using bromide ion–lanthanum nitrate modified chitosan imprinted polymer. Anal Methods 6(6):1890–1896

Wu Z, Li N, Zhang X, Xu Y, Shu T, Liu W, Hu B (2019) Effective recovery of trans-resveratrol from the leaching solution of muscat grape pomace by developing a novel technology of foam fractionation. J Food Eng 241:41–50

Wulff G (1995) Molecular imprinting in cross-linked materials with the aid of molecular templates—a way towards artificial antibodies. Angew Chem Int Ed 34(17):1812–1832

Wulff G, Sarhan AW, Sarhan H (1972) Use of polymers with enzyme-analogous structures for the resolution of racemates. Angew Chem Int Ed 11:341–344

Xu Z, Chen S, Huang W, Fang G, Pingzhu H, Wang S (2009) Study on an on-line molecularly imprinted solid-phase extraction coupled to high-performance liquid chromatography for separation and determination of trace estrone in environment. Anal Bioanal Chem 393 (4):1273–1279

Xu L, Huang YA, Zhu QJ, Ye C (2015) Chitosan in molecularly-imprinted polymers: current and future prospects. Int J Mol Sci 16(8):18328–18347

Yan H, Row KH (2006) Characteristic and synthetic approach of molecularly imprinted polymer. Int J Mol Sci 7(5):155–178

Zhang Z, Li J, Song X, Ma J, Chen L (2014) Hg^{2+} ion-imprinted polymers sorbents based on dithizone–Hg^{2+} chelation for mercury speciation analysis in environmental and biological samples. RSC Adv 4(87):46444–46453

Zhang Y, Ruan H, Guo C, Liao J, Shen J, Gao C (2020) Thin-film nanocomposite reverse osmosis membranes with enhanced antibacterial resistance by incorporating p-aminophenol-modified graphene oxide. Sep Purif Technol 234:116017