Natural Antimicrobial Materials

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

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.

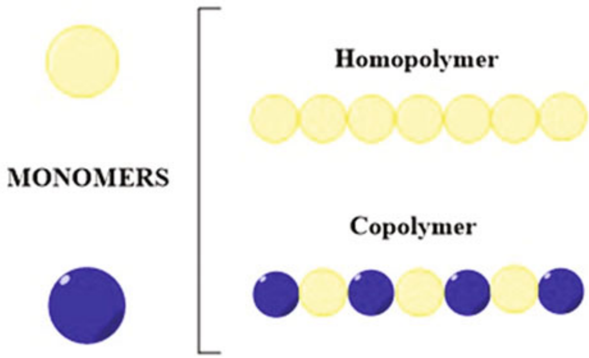


Fig. 1 Formation of homopolymers and copolymer from different monomers

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).

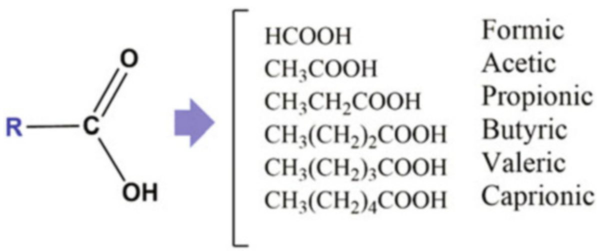
As is known, the microbial activity varies according to the bacterial structure. On the one hand, Gram-positive, such like *S. aureus*, can have a loose cell membrane, unlike Gram-negative, as *E. Coli*, which are characterized by the presence of a membrane external to the cell wall, which serves as 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)



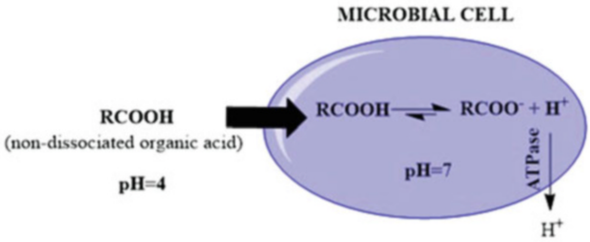


Fig. 3 Antimicrobial activity mechanism from organic acids

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

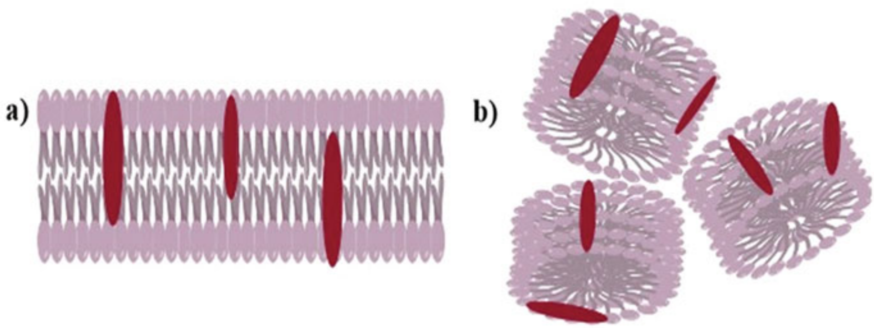


Fig. 4 Mechanism to explain the antimicrobial activity. (**a**) Perpendicular interference through the lipidic membrane. (**b**) "Carpet effect" permeabilization of the membrane surface

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

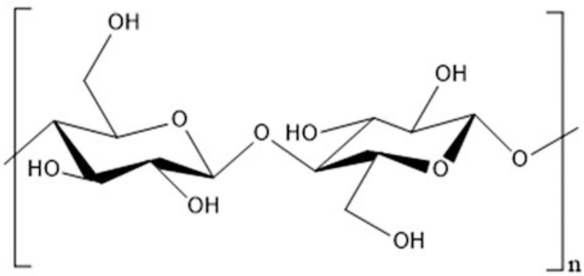
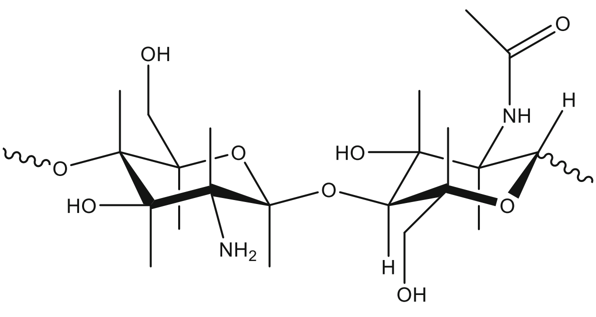


Fig. 6 Chemical structure of chitosan



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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