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Review

# A review on various maleic anhydride antimicrobial polymers

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ABSTRACT

The basic requirement of human beings is better health but the serious health effects and numerous infections caused by rapid growth of harmful pathogens resulting in a large number of deaths and is a significant challenge to modern science. Microbes infecting humans can be stopped in two ways: disinfectants and antimicrobial agents. There is considerable interest from both academics and industry in antimicrobial polymers due to their favorable properties. Maleic anhydride incredibly bears diverse commercial applications due to its versatile chemical structure. Maleic anhydride is an electron-acceptor monomer where the property comes from reactive double bonds and also reactive anhydride groups. This review presents the development of antimicrobial polymers involving maleic anhydride in the macromolecular structure. This article also addresses the applications of antimicrobial polymers with maleic anhydride in numerous sectors.

## 1. Introduction

In spite of outstanding advances in medicine, science and public health in the present century, the war against microbial infections has intensified (Michael, 1996). The presence of microbes are everywhere in the environment and they affect the surroundings in which they grow. Sometimes the presence of micro-organisms is essential like in the growth factors of insects and animals. In fact, microbes are used in fermenting food products (like yeast used in the preparation of beer, wine, bread, etc.), in addition to this microbes are also used in the treatment of preventing microbial infections in which they are used in the form of antibiotics and vaccines. Despite these benefits, some microbes, are the cause of infections in animals and plants the spoilage of food and textiles. Bacteria and fungi are the major microbial agents for the cause of microbial infections. Microbial infections cause one-quarter of deaths worldwide, especially in undeveloped countries (Jalageri et al., 2019a, 2019b).

In addition, the microbial infections in developed countries are also escalating because of antibiotic-resistant microbes. Antimicrobial resistance (AMR) scares the effective prevention and treatment of ever-growing infections caused by bacteria, parasites, viruses and fungi. For example, Gram-positive *Staphylococcus aureus* which has become a global epidemic that is responsible for the main surgical site infections (Jain et al., 2014; Chitanu et al., 1997; WHO, 2014). Data analysis from Centers for Disease Control and Prevention (CDC), U. S., reports at least people in million are infected and thousands die annually due to antibiotic-resistant bacteria (Neill, 2014; Mayr et al., 2017; Xue et al., 2015; Huang et al., 2016). The control of AMR to be considered as a priority for national governments and health systems was dictated by the World Health Organization (WHO). Therefore, new prevention and control strategies are urgently required. Microbial infections are the major issues in hospital furniture, dental equipment, food storage and packaging, water purification systems (Jain et al., 2014). Some of the existing biocides and antibiotics are replaced by antimicrobial polymers with an increasing interest due to their advantages over the low molecular weight agents like they not easily susceptible to resistance, reduction in environmental contamination and toxicity etc. (Xue et al., 2015; Siedenbiedel and Tiller, 2012; Lecomte et al., 2011).

Desired physicochemical and biological properties are attained by the structural modifications of polymers leading to antimicrobial property (Jain et al., 2014). In addition, antimicrobial polymers possess non-volatility, chemical stability and long-term activity (Xue et al., 2015)(Majumdar et al., 2009). Antimicrobials such as chitosan, halamines and compounds with quaternary nitrogen groups, have either an inherent capacity to display antimicrobial activity or can be a polymer backbone, incorporated with small biocides and antibiotics (Jain et al., 2014). Antimicrobial polymers have been known since 1965 when Cornell and Dunraruma described polymers and copolymers prepared

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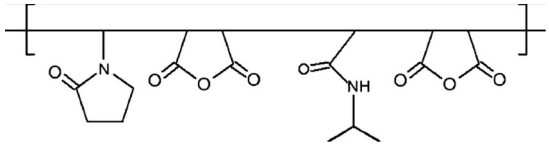
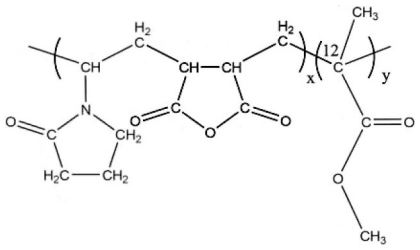
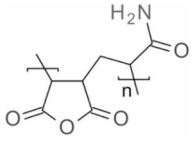
**Table 1**
List of authors synthesized copolymers/terpolymers and tested their antimicrobial activity on various pathogenic microorganisms.

| Copolymers/terpolymers | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Muzaffer Talu et al. |  | *S. aureus,* *S. enteridis,* *S. faecalis,* *E. coli,* *K. pneumoniae,* and *P.aeruginosa* | (Talu et al., 2010b) |
| Ajithkumar et al. |  | *E. coli* and *S. aureus* | (Ajithkumar et al., 2018b) |
| Akshatha et al. |  | *E. coli, S. aureus, M. smegmatis and C. albicans* | (Nagaraja et al., 2019a) |

from 2-methacryloxytropononeS that kill bacteria. In the 1970s, several groups synthesized various polymeric structures (Siedenbiedel and Tiller, 2012; Alexandra et al., 2014) that showed antimicrobial action, e.g., polymerized salicylic acid (Vogl et al.) and polymers with quaternary ammonium groups (Panarin et al.) (Siedenbiedel and Tiller, 2012; Alexandra et al., 2014).

This Review focuses on major classes of maleic anhydride antimicrobial polymers because of their wide applications in areas such as water-soluble polymers used in the food industry, disinfectants, and medical devices. Non-woven textile protective clothing, antimicrobial bandages and filters, nano fibre mats for wound dressing, biomedical applications and biological water treatment. In recent years an increased interest has been observed in maleic anhydride polymers because of their copolymerization with a variety of monomers forming charge transfer complexes (CTC). MA copolymers generally have predominantly alternating structure depending on the co-monomer used which participates in CTC in chain propagation. A new class of maleic anhydride copolymers can be obtained by modification with the anhydride group with amino and hydroxyl groups by ring opening reaction, resulting in the formation of ester or amide with carboxylic acid structures. The hydrophilicity can be enhanced effectively by hydrolyzing highly polar anhydride into carboxyl groups (Karakuş et al., 2015; Ignatova et al., 2010). Copolymers synthesized with maleic anhydride and vinyl monomers such as styrene, methyl methacrylate, vinyl acetate, isopropyl acrylamide, methyl vinyl ether, vinyl chloride, N-vinyl pyrrolidone, have been used in biological activities such as tumor inhibitors (Karakuş et al., 2015; Popescu et al., 2011; Spridon et al., 1997).

The classification of maleic anhydride antimicrobial polymers can be done by the reaction of anhydride groups with amines forming polyamides and polymaleimides and the reaction of alcohols with anhydride forming polyhemiesters/polymaleates. Furthermore, quaternary ammonium compounds are also prepared by the reaction of polymaleats, polymaleimides, polyhemiesters/polymaleates with different alkyl chains and a few investigators have worked on the synthesis of maleic anhydride nanoparticles with antimicrobial activity. In this review, maleic anhydride antimicrobial polymers will be discussed including copolymers/terpolymers, polyamides, polymaleimides, polyhemiesters and polymers with quaternary ammonium compounds.

## 2. Copolymers/terpolymers

Most of the water-soluble macromolecules synthesized by acrylic and vinyl derivatives are used in drug delivery carriers (Talu et al., 2010b), protein hybrids and advanced applications in biotechnology (Inada et al., 1995; Lee et al., 1996; Hubbell, 1999). Properties such as hydrophilic/hydrophobic balances, solubility and polarity can be controlled by the copolymerization reaction where macromolecules can be prepared with specific chemical structures (Gallardo et al., 1999). A new water-soluble terpolymer was prepared using maleic anhydride N-vinyl-2-pyrrolidone and N-isopropyl acrylamide with radical initiated polymerization in 2010 by Muzaffer Talu et al. The article describes the effect of content of carboxyl and amide monomer linkage on the degree of crystallinity and thermal behaviour of terpolymers. The antimicrobial activities of terpolymers were tested against pathogenic Gram-positive and Gram-negative bacteria: *S. aureus, S. enteridis, S. faecalis, E. coli, K. pneumoniae,* and *P. aeruginosa.* The antimicrobial activity of the terpolymers increased as the reaction time increased (Talu et al., 2010b).

The terpolymers with different composition of N-vinyl pyrrolidone-maleic anhydride-methyl methacrylate were synthesized by Ajithkumar et al. (2018a), studied their monomer-monomer interactions by calculating the reactivity ratio. Polymers with methylmethacrylate are biocompatible and exhibit many biological activities. As the content of methylmethacrylate in the terpolymer increases, increase in the glass transition was noticed. The terpolymers exhibited antibacterial activity against *E. coli and S. epidermidis* (Karakus et al., 2013; Ajithkumar et al., 2018b; Kumar et al., 2008; Ajithkumar et al., 2017). Akshatha et al. in 2019 synthesized maleic anhydride-acrylamide copolymer with different initiator (AIBN) concentration and fabrication of ultrathin coatings on various substrates. The copolymer and ultrathin coatings exhibited superior antimicrobial activity against *E. coli, S. aureus, M. smegmatis* and *C. albicans* (Nagaraja et al., 2019a). The list of maleic anhydride copolymers with antimicrobial activity synthesized so far are listed in Table 1.

## 3. Polymaleimdies/amides

Antimicrobial agents can be incorporated in linear or crosslinked carrier polymers via covalent bonds. Antimicrobial agent bound polymers to exhibit antimicrobial activities by slowly releasing active agents

through hydrolysis. Linear polymers release the active agents faster than the crosslinked polymers because the duration period required for water penetration into the labile bonds and hydrolysis is normally shorter for linear polymers. Due to biocompatibility, multifunctionality, polyamides, vinyl polymers, methacrylate polymers are been widely used as drug carriers (Patel et al., 2007). Patel et al. in 1998 studied the release behaviour of acriflavine(Acr) bounded to poly (styrene-*co*-maleic anhydride) and poly (methyl methacrylate-*co*-maleic anhydride).

The antimicrobial effect of Acr bounded to poly (styrene-co-maleic anhydride) exhibited an increasing inhibition with increase in time against *B. subtilis,* suggesting slow release of Acr from poly (styrene-co-maleic anhydride), Acr bounded to poly (methyl methacrylate-co-maleic anhydride) were tested against *B. subtilis, S. aureus* and *E.coli*, the polymer required 8–16 h to exhibit activity, whereas free drug exhibited complete inhibition by 4 h (Patel et al., 1998; Patel et al., 1997). In 2007, they continued to study on the release of drug at controlled rates by bounding amoxicillin to poly (butyl methacrylate-*co*-maleic anhydride). The specific goal was to develop an improved oral dosage form for amoxicillin. The synthesized polymer showed a positive response against *S. aureus* and *B. subtilis* and *E. coli* (Patel et al., 2007).

In the development of prodrugs, the pharmacological active polymers serve as a carrier for low molecular weight drugs (Patel et al., 1999; Konsulov et al., 2008; Alexandra et al., 2014; Cowie, 2013). Prodrugs are a special type of a drug with controlled release rate, accomplished by the breaking of chemical bonds (Ajithkumar et al., 2017). Jignesh et al. in 1999 developed a polymer-prodrug, by reacting ampicillin with poly (styrene-*co*-maleic anhydride) through an amide bond. The antimicrobial activity was tested against *Escherichia coli, Bacillus Subtilis and Staphylococcus aureus* (Patel et al., 1999).

Jeong et al. in 2001 made a study on a bioactive agent with reactive groups i.e. 4-amino benzoic acid and amino phenol which is covalently bonded to poly(styrene-*alt*-maleic anhydride) through a ring opening reaction. The model compound was chosen to react with poly (styrene-*alt*-maleic anhydride) as they are known to exhibit antimicrobial activity. The antibacterial activity of 4-aminobenzoic acid against certain microorganisms was greater than that of commonly used acidulants such as formic, propionic, lactic, acetic and citric acids (Jeong et al., 2002; Jeong et al., 2001). The active agents released from polymers may be hazardous to the environment, and protection may be limited in time. In this type of polymer, the bioactive moieties are fixed to the polymers in a permanent way. However, the active agents are attached to the polymer backbones via hydrolysable bonds can also be industrially used as long as the released biocide agents are not very toxic and the protection time required is not too long.

Norfloxacin, an antibacterial agent, a derivative of quinolone carboxylic acid containing fluorine and piperazine ring at the sixth and seventh position and active against *Pseudomonas aeruginosa* and enteric pathogens (Kim et al., 2005). The two norfloxacin containing polymers were prepared, where it was grafted onto polypropylene-*graft*-maleic anhydride and poly(styrene-*co*-maleic anhydride) by Mal-Nam Kim et al. in 2004 and their activity was compared with neat norfloxacin. Release of the drug can be controlled due to the immobilization of norfloxacin in a polymer matrix (Kim et al., 2005). The antimicrobial activity was tested against both gram-positive and gram-negative bacteria (Kim et al., 2005; Sauvet et al., 2000).

In the field of biomedical, performances like antimicrobial action, biocompatibility, reactivity with biomolecules, etc., depends on the surface property of polymer materials (Michl et al., 2015; Ackart et al., 1975; Xing et al., 2005; Vendra et al., 2011). The surface modification can be achieved by grafting polymeric material on to the surface through various methods like chemical reagents (Xing et al., 2005), UV and plasma irradiation, electronic beam and gamma-ray. In 2005 Chang et al. worked on the surface modification through grafting vinylpyrrolidone/maleic anhydride monomers under UV irradiation. The property enhancement like hydrophilicity and antimicrobial activity were tested for the modified surface.

The fields like biology and medical sciences are focused on using well-defined amphiphilic polymers (Ilker et al., 2008). A novel class of amphiphilic homopolymers was synthesized by FiratIlker et al. in 2007 using norbornene derivatives. Derivatives of norbornene contain 2-mono or 2, 3-difunctionalization are known to be excellent monomers for ring-opening metathesis polymerization (ROMP). The amphiphilic polymers were synthesized by monomer with dual functionalities, which polymerized leading norbornene derivative polymers with functionalities at seventh position. The amphiphilic property is tuned by providing regular space between hydrophobic and hydrophilic groups (Thölmann et al., 2003; Liu et al., 2006).

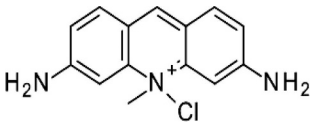
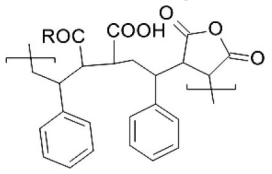
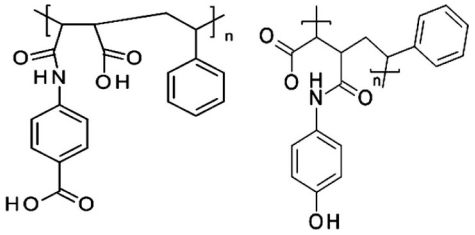
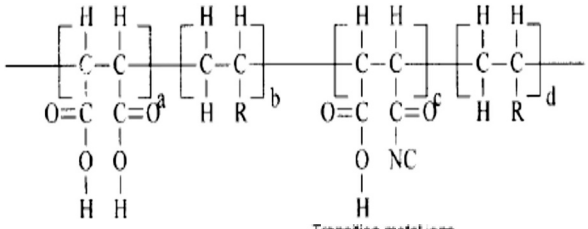
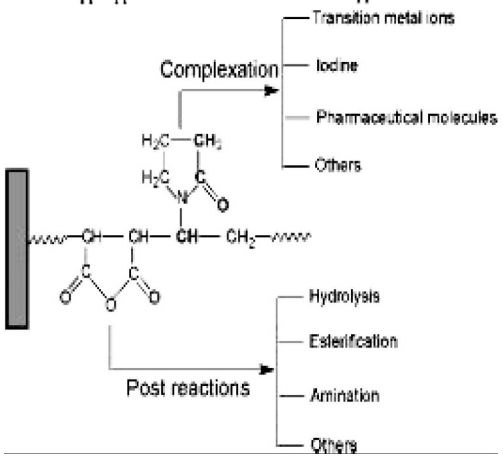
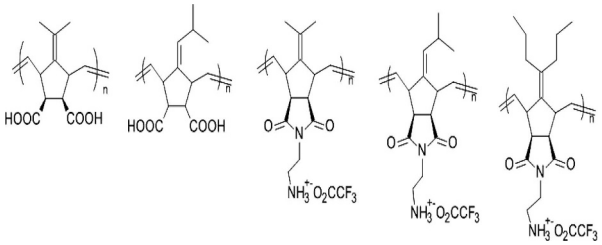
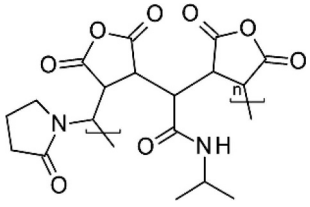
The norborene derived amphiphilic polymers exhibited good antibacterial activity against *B. anthracis, F. tularensis,* and *Y. pestis*, *L. monocytogenes, P. aeruginosa,* and MRSA. The dramatic change in antibacterial activity was noticed as the hydrophobic groups in the polymer were modified. The authors concluded that norborene derived amphiphilic polymers are applicable in homeland defense application and the prevention and treatment of bacterial infections (Ilker et al., 2008). The properties such as solubility, polarity, hydrophilicity and hydrophobicity can be controlled by copolymers with specific chemical structure. A water-soluble terpolymer was prepared by Muzaffar et al. in 2010 using maleic anhydride (MA), N-isopropyl acrylamide (NIPA) and N-vinyl pyrrolidone (NVP). Synthesized water soluble terpolymer displayed activity against three gram positive and gram negative bacteria and can find their use in the food industry, hospitals as disinfectants and as drug component in medicine (Talu et al., 2010a).

Due to the potential applications in various sectors, the great interest has drawn towards the fabrication of antimicrobial non-woven textile (Ignatova et al., 2010). Various approaches are found in the preparation of such materials includes electrospinning, surface coatings on electrospun nano and microfibers, etc.(Ignatova et al., 2012; Jain et al., 2014; Kenawy and Worley, 2007; Kenawy et al., 2007). Microfibers were prepared by Ignatova et al. in 2010 by electrospinning poly (styrene-*alt*-maleic anhydride) and poly (styrene-*co*-maleic anhydride) grafted with jeffamine M-600 on electrospun mats with direct modification by antibacterial agents (CHX and 5NH28Q). The non-woven mats exhibits activity against *S. aureus, E. coli* and fungi *C. albicans* and also prevents the bacterial adhesion of *S. aureus.* Therefore, the non-woven mats are applicable in areas like protective clothing, bandages, medical devices and antimicrobial filters (Ignatova et al., 2010).

Antimicrobial coatings are developed to avoid biofilm formation where it leads bacteria to develop resistance against antibiotics (Zhou et al., 2010). The paper reported by Jin et al. in 2010 explains the use of pathogenic bacteria for their own destruction by releasing toxins to rupture vesicles. The aim of the authors was to prepare a smart wound dressing material which releases antibacterial agent only in the presence of pathogenic bacteria, without responding to harmless bacteria. In this article plasma deposition of maleic anhydride was used for vesicle attachment which is either attached to the surface or floating in aqueous suspension.

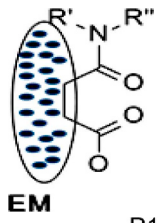
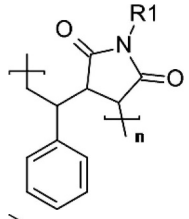
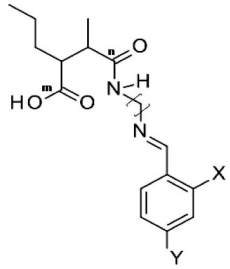
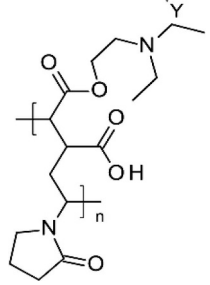
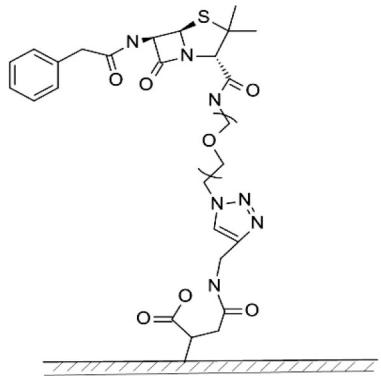
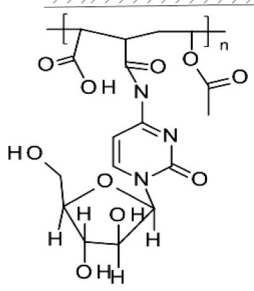
The promising technology in filtration systems is the use of membrane technology due to the uncontrollable attachment of microorganisms on to the surface which results in fouling and biofouling. Membrane surface modification is the effective method of controlling fouling compared to bacteriophages, nutrient control and the use of electric current. A class of furanone compounds is reported to inhibit surface colonization and also possess antimicrobial property against a wide range of bacteria (Kenawy et al., 2007; Kenawy and Worley, 2007). Gule et al. in 2012 fabricated nanofibers, where furanone derivatives 5-(2-(2-aminoethoxy)ethoxy)methyl)-2(5H)-furanone and 4-(2-(2-aminoethoxy)-2,5-dimethyl-3(2H)-furanone were immobilized on poly(styrene-*co*-maleic anhydride) and tested their antimicrobial and cell-adhesion inhibition efficiency against *P. aeruginosa* Xen 5, *E. coli* Xen 14, S. *typhimurium* Xen 26, *S. aureus* Xen 36, and *K. pneumoniae* Xen (Klumperman, 2012).

**Table 2**
List of authors synthesized various polymaliamides/imides and tested their antimicrobial activity on various pathogenic microorganisms.

| Polymaleimdies/ amides | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Patel et al. |  | *B. subtilis* | (Patel et al., 1998) |
| Patel et al. |  | *E. coli, B. subtilis and S. aureus* | (Patel et al., 1999) |
| Jeong et al. |  | *E. coli* and *S. aureus* | (Jeong et al., 2001; Jeong et al., 2002) |
| Mal-Nam Kim et al. |  | *B. cereus, V. fluvialis*and *V. parahaemolyticus* | (Kim et al., 2005) |
| XIng et al. |  | *E. coli, S. aureus* and *C. albicans* | (Xing et al., 2005) |
| Patel et al. | Poly (butyl methacrylate-co-maleic anhydride) grafted with amoxicillin | *S. aureus, B. subtilis* and *E. coli* | (Patel et al., 1999) |
| FiratIlker et al. |  | *B. anthracis, F. tularensis, Y. pestis, L. monocytogenes, P. aeruginosa,* and MRSA | (Ilker et al., 2008) |
| Muzaffer et al. |  | *S. aureus, S. enteridis, S. faecalis, E. coli, K. pneumoniae,* and *P. aeruginosa* | (Talu et al., 2010b) |

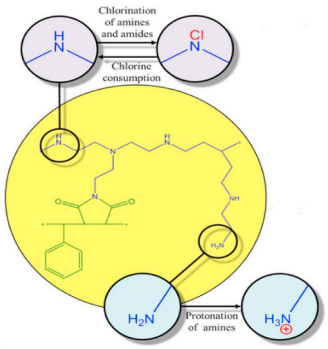
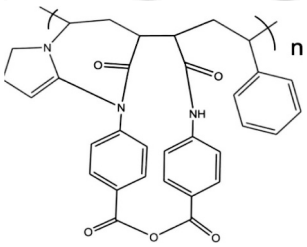
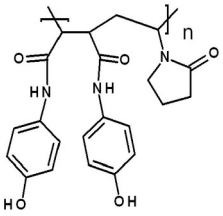
(*continued on next page*)

**Table 2** (*continued*)

| Polymaleimdies/ amides | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Ignatova et al. |  EM | *S. aureus, E. coli* and *C. albicans* | (Ignatova et al., 2010) |
| Gule et al. |  | *K. pneumonia, S. aureus, E. coli, P. aeruginosa,* and *S. tymphimurium* | (Klumperman, 2012) |
| Mohamed et al. |  | *E. coli, P. aeruginosa, S. typhi, S. aureus, A. niger, A. flavus C. albicans* and *C. neoformans* | (El-Newehy et al., 2014) |
| Hemalatha et al. |  | *K. aerogenes E. coli, P. aeruginosa, P. desmolyticum* and *S. aureus* | (Hemalatha et al., 2014) |
| Heather et al. |  | *S. aureus* | (Pearson and Urban, 2014) |
| Karakus et al. |  | Antiproliferative activity | (Karakuş, 2015) |

(*continued on next page*)

**Table 2** (*continued*)

| Polymaleimdies/ amides | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Luis et al. |   | *L. monocytogenes* | (Bastarrachea and Goddard, 2015) |
| Ajithkumar et al. |  | *E. coli* and *S. epidermidis* | (Ajithkumar et al., 2017) |
| Nagaraja et al. |  | *E. coli, S. aurues, M. smegmatis and C. albicans* | (Nagaraja et al., 2019b) |

Phenols release the intracellular constituents of the cell by targeting cell membrane leading to cell lysis, hence they are known as biocidal agents. Phenols are considered as environmental safe antimicrobial agents and also as algaecide, bactericide and fungicide (El-Newehy et al., 2014; Alamri et al., 2012; Jain et al., 2014). In 2014 new antimicrobial polymers were synthesized by immobilization of benzaldehyde derivatives, 4-hydroxybenzaldehyde and 2,4-dihydroxybenzaldehyde onto poly (ethylene-*alt*-maleic anhydride) by Mohamed et al. The prepared polymers were tested for their antimicrobial activity against different types of gram-negative, gram-positive bacteria and also on fungi. The synthesized polymers find applications in biomedical sectors and water treatment. Hemalatha et al. in 2014 worked on the synthesis of a copolymer of NVP and MA. The copolymer was hydrolyzed and reacted with different ratios of N-diethylaminoethanol. The copolymer and its macro complex had activity against gram-positive and negative bacteria and finds applications in the food industry and biomedical sectors (Hemalatha et al., 2014; Vijayasekaran et al., 1996; Ranucci et al., 1995).

In 2014 Heather et al. maleic anhydride was reacted to PE and PP to obtain a surface with –COOH groups followed by their conversion to an acid chloride and further reacted with propargylamine to obtain alkyne functionalized polymeric surfaces to which any azide-containing molecule may be reacted. The surface with poly azides was further reacted with digylcidyl ether PEG having terminal epoxide groups to yield surfaces with ampicillin. The “clicked” AMP on both PE and PP facilitates a major enhancement of the antimicrobial activity against *Staphylococcus aureus* (Pearson and Urban, 2014). Maleic anhydride copolymers synthesized with vinyl monomers like vinyl acetate, styrene and methyl methacrylate are often used as reactive polymers for various biological activities (Karakuş et al., 2015).In 2015 Karakus et al. synthesized a biologically active maleic anhydride-vinyl acetate copolymer (MAVA) and further grafted with cytosine β-D-arabinofuranoside hydrochloride (CF), which is an anticancer agent, commonly known as cytarabine. The aim of the study was (1) to use a copolymer which is non-biodegradable and noncytotoxic as a carrier of biomolecule, CF and (2) to achieve antiproliferative activity on both HeLa and C6 cell lines. The article concluded that the modified polymer deserves further investigation to evaluate its antimicrobial, antifungal and antitumor activity.

The growing desire on personal care products and safe food has given rise to materials with active packaging which reduces the growth rate of microorganisms and increases the shelf life of products and henceforth beneficial to the food industries and consumers. Linear density polyethylene has attracted attention in the field of film production due to their outstanding mechanical properties. In 2015 Wang and his coworkers blended polyhexamethylene guanidine hydrochloride which is of great interest in fabricating sterile surfaces with starch to develop thermoplastic starch with the antimicrobial property. Later, a non-leaching linear density polyethylene antimicrobial film was prepared by compounding antimicrobial thermoplastic starch and linear density polyethylene in the presence of polyethylene-grafted maleic anhydride. The films exhibited high activity with a high content of polyhexamethylene guanidine hydrochloride (around 1.0 wt% within the film)(Wang et al., 2015).

The polycationic and halamine coatings are used to overcome the problems in the development of microbial resistance. Antimicrobial compounds with N-halamines produce continuous antimicrobial activity by recharging themselves with halogens for many cycles. In 2015 Luis et al. developed a coating composed of styrene-maleic anhydride copolymer and polyethylenimine and exhibited its effectiveness in both unchlorinated cationic form and N-halamine after application on to plastic polymer (polyethylene) which are widely used in food

contacting surfaces and tested their activity against *Listeria monocytogenes* a common food pathogen (Bastarrachea and Goddard, 2015). A terpolymer with N-vinyl-2-pyrrolidone, maleic anhydride and styrene were prepared by Ajith et al. in 2016 and further grafted with para-aminobenzoic acid an antimicrobial agent treated for rickettsial infections (typhus and rocky mountain spotted fever) (Ajithkumar et al., 2017). The grafted terpolymer exhibited activity against *E. coli* and *S. epidermidis* (Richards et al., 1995; Richards and Xing, 1992). The hydrophilic efficient antimicrobial thin film was fabricated by Nagaraja et al. in 2019 using maleic anhydride-N-vinyl-pyrrolidone copolymer grafted with antimicrobial aminophenol. The synthesized post-polymerized polymer and fabricated thin film exhibited activity against *E. coli, S. aureus, M. smegmatis* and *C. albicans* (Nagaraja et al., 2019b). Maleic anhydride polymers reacted with various antimicrobial agent bearing amine groups through amination to result in antimicrobial polymers are listed in Table 2.

## 4. Polymaleates/hemiesters

Jeong et al. in their study synthesized an intermediate polymer with chemical modification of poly(styrene-*alt*-maleic anhydride) and tested for their antimicrobial activity in 2001. SMA was made to react with model compounds 4-aminobenzoic acid and 4-hydroxybenzoic. SMA with ABA and HBA showed excellent bacteriocidal activity against *E.coli* and *S. aureus* even though their antifungal activity against *A.niger* was not satisfactory. The glass transition temperature of the polymer was greater than that of SMA because of hydrogen interactions between the polymer chains (Jeong et al., 2002; Jeong et al., 2001).

Surface grafting is one of the pleasing methods for surface modification where the desired graft chains can be incorporated into the polymeric materials. Performances like antimicrobial action, biocompatibility and reactivity with biomolecules depends on surface properties in the biomedical field (Xing et al., 2005). Xing et al. in 2005 made work on surface functionalization of polypropylene film via UV induced photografting of N-vinylpyrrolidone/ maleic anhydride binary monomers. The grafted NVP and MA units enhanced the surface wettability, resulting in a drastic decrease of surface contact angle within short irradiation time and the modified surface exhibited antimicrobial activity (Xing et al., 2005).

Styrene-maleic anhydride copolymer has been studied over a long period since they provide electron accepting property. DMSO is known for its wide usage as a solvent, also acts as an electron donor during complex formation with various agents (Rajput et al., 2009). The styrene-maleic anhydride copolymers modified with DMSO acts as a pH lowering polymer and also exhibit antibacterial activity against *E. coli.* Maleic anhydride containing etheric oxygen (−O−) is highly reactive with pure DMSO and also helps in the creation of styrene-maleic anhydride derivatives with hydroxyl compounds, amines, aliphatic alcohols and aminophenol conjugates by half esterification reaction. The styrene-maleic anhydride copolymer was modified with 4-Hydroxybenzoic acid in 2009 by Ravish and his coworkers (Rajput et al., 2009).

The crosslinking (physical or chemical) of water-soluble polymer produce a three-dimensional network known as hydrogels which can be developed by various synthetic routes. The application of hydrogels is in tissue engineering and wound dressings, biomaterials for drug delivery, due to their unique mechanical and physical properties. The transparency property is the major advantage of hydrogels which makes the user to visually monitor the wound without the removal of the dressing. The wound healing is accelerated due to the diffusion of oxygen and vapour produced by hydrogels bearing high water content. In 2016 hydrogel with antimicrobial property was synthesized using poly (vinyl alcohol) and poly(methyl vinyl ether-*alt*-maleic anhydride) for the purpose of wound care applications by cola et al. The hydrogels developed had a eccentric properties like adhesiveness to skin, excellent swelling ability, intrinsic antimicrobial activity and good mechanical strength (Cal et al., 2016). The activity of hydrogels was tested against *Staphylococcus aureus* and cost-effective. The focusing concept of the article is that the hydrogels did not require the usage of silver or iodine to exhibit activity which represents a significant advantage in wound management application (Cal et al., 2016).

In recent years the use of synthetic packaging films had lead to alarming ecological issues due to non-biodegradability. As a result the use of biodegradable polymers like polylactic acid, chitosan, polylactide etc., is blooming rapidly due to their less negative impact on environment (Castillo-ya et al., 2017; Lucera et al., 2012; Zhou et al., 2010; Lagarón et al., 2011; Kenawy and Worley, 2007). The addition of copolymers boosts the miscibility between the components of films and thus represents a novel approach in the field of active packaging. Antibacterial films for food packaging was developed by Maria et al. in 2016 by poly (L-lactic acid)/poly(L-lactic acid) grafted maleic anhydride/epigallocatechin gallate blends. The miscibility between poly (L-lactic acid) and epigallocatechin gallate was increased by adding maleic anhydride grafted poly(L-lactic acid)was added as a compatibilizer agent. The antimicrobial activity was tested against two foodborne bacteria: *S. aureus* and *Pseudomonas* spp. Thus the copolymer and epigallocatechin gallate can be used as an active additive in food packaging applications (Castillo-ya et al., 2017). Yet another terpolymer prepared from N-vinyl-2-pyrrolidone, maleic anhydride and styrene was by Ajithkumar et al. in 2016 was further grafted with 2,4-dichlorophenol. Generally, chlorine-containing compounds exhibit antibacterial activity and 2,4-dichlorophenol is one of the major constituent used for preparing various derivatives exhibiting antibacterial activity (Ajithkumar et al., 2017). The grafted terpolymer exhibited activity against *E coli* and *S. epidermidis*. Various low molecular antimicrobial agent containing phenolic gropus were reacted with maleic anhydride polymers through esterification to result in antimicrobial polymers. The list of polyhemiesters are tabulated in Table 3.

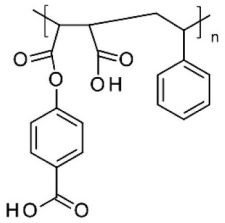
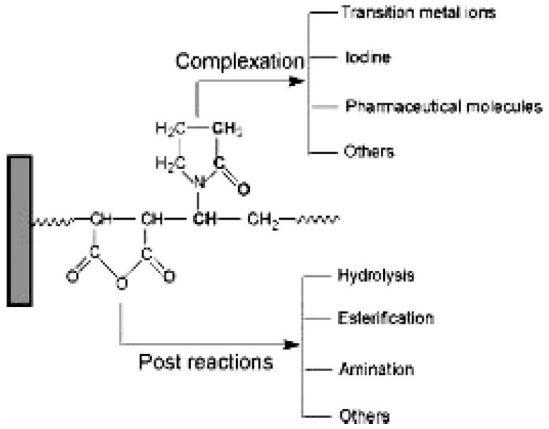
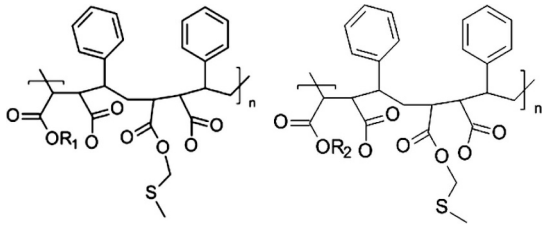
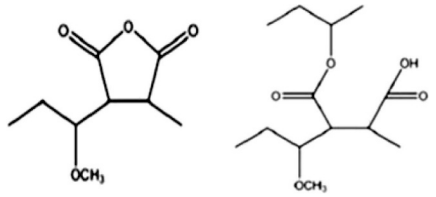
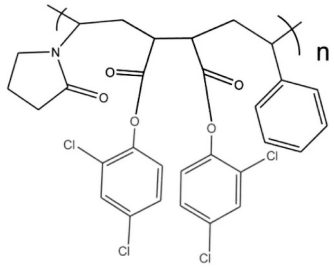
## 5. Maleic anhydride polymers with quaternary ammonium salts

The widely used chemical sanitizers in food industries is quaternary ammonium compounds (QACs) since they are effective against L. *monocytogenes.* In quaternary ammonium compounds, usually organic radical is cation and halogens (chlorine) is anion (Temiz et al., 2006) and are highly active against gram-positive bacteria *S. aureus* and are less active against Gram-negative bacteria such as *E. coli*. Temizet al. in 2006 worked on the synthesis of poly (N-vinyl-pyrrolidone-*alt*-maleic anhydride) copolymer and grafted with polyethyleneimine and tested their activity against *Listeria monocytogenes, Staphylococcus aureus, Enteritidis* and *Escherichia coli* and recommended the use in the food industry and biomedical applications (Temiz et al., 2006).

Natural antimicrobial peptides act as a defense when organisms are attacked by bacterial pathogens and these peptides have broad-spectrum antimicrobial activity (Lienkamp et al., 2008; Timofeeva and Kleshcheva, 2011; Michl et al., 2015; Siedenbiedel and Tiller, 2012). Most of the living organisms like animals, humans, invertebrates and plants bear antimicrobial peptides within. Due to the favorable characteristics, the research is focused on the mimicking antimicrobial peptides made of peptoids, synthetic polymers, α – and β -amino acids and aromatic oligomers (Huang et al., 2016; Liu et al., 2006; Talu et al., 2010b; Ganewatta et al., 2014; Miquel et al., 2016; Lienkamp et al., 2008). The robust resin acid-derived antimicrobial agents were synthesized from natural resin that exhibits excellent antimicrobial activities against a six Gram-positive and seven Gram-negative bacteria with selective lysis of microbial membranes over mammalian membranes. The article describes that the high antimicrobial activity was due to the hydrophobicity and unique structure of resin acids (Wang et al., 2012).

The antimicrobial materials was derived from an unlikely yet abundant natural source and offered a novel alternative to currently-used approaches and developed effective natural resin acid-based polymers and cationic antimicrobial compounds against Methicillin-

**Table 3**
List of authors synthesized various polymaleates/hemiesters and tested their antimicrobial activity on various pathogenic microorganisms.

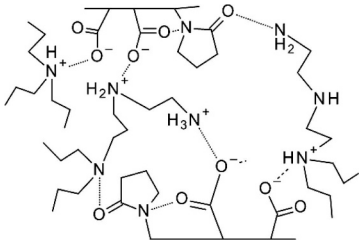
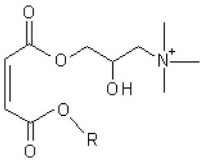
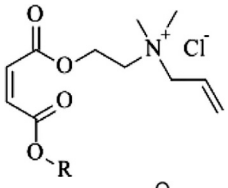
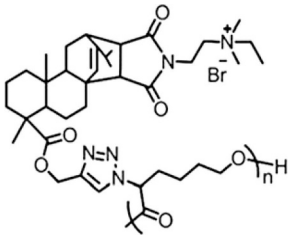
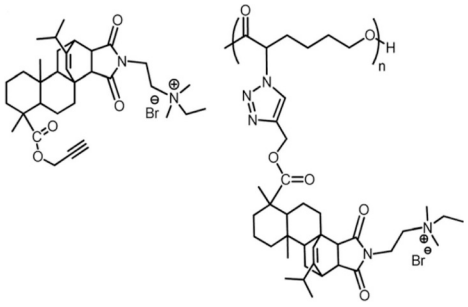
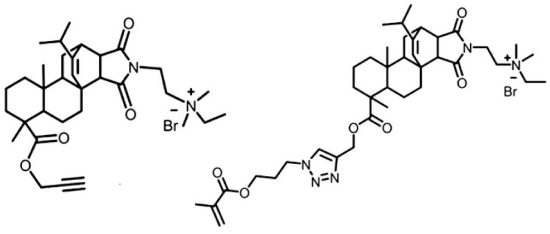
| Polymaleates/ hemiesters | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Jeong et al. |  | *E. coli* and *S. aureus* | (Jeong et al., 2001) |
| Chang et al. |   | *E. coli, S. aureus* and *C. albicans* | (Xing et al., 2005) |
| Ravish et al. |  | *E. coli* | (Rajput et al., 2009) |
| Cal et al. |  | *S. aureus* | (Cal et al., 2016) |
| Maria et al. | Poly(L-lactic acid)/poly(L-lactic acid) grafted maleic anhydride(copolymer)/epigallocatechin gallate (EGCG) | *S. aureus* and *Pseudomonas spp* | (Castillo-ya et al., 2017) |
| Ajithkumar et al. |  | *E coli* and *S. epidermidis* | (Ajithkumar et al., 2017) |

resistant *Staphylococcus aureus* (MRSA) in 2014 by Mitra et al. Both the polymer and small molecule can be used as a medicine for Methicillin-resistant *Staphylococcus aureus* with minimal side effects.

The authors continued to synthesize surface immobilized resin acid-derivatives compounds bearing quaternary ammonium and polycations with properties like biocompatible, antibiofilm and antibacterial. Surface immobilization was performed by two chemical methods: (1) copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition click reaction and (2) surface-initiated atom transfer radical polymerization. The antibiofilm and antibacterial activities were tested against *S. aureus* and *E. coli*. The article described that the immobilized surface is effective in combating bacteria, prevent biofilm formation and is biocompatible which leads application in the biomedical field (Ganewatta et al., 2015; Ganewatta et al., 2014).

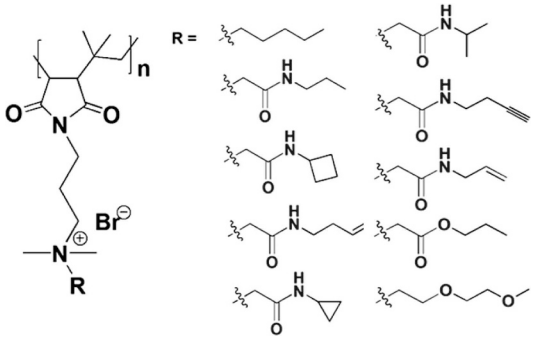
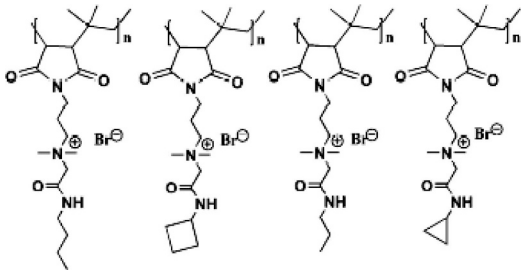
The QAS molecules with long alkyl chain have got antimicrobial property. Hence most of the disinfectants, sanitizers, cosmetics, and hand washes have got the QAS molecules in their formulations (Dominic et al., 2015; Alamri et al., 2012). Hence they do cause severe environmental problems. There is a need to introduce degradable QAS molecules. The bacteria which are exposed to below inhibitory

**Table 4**
List of authors synthesized various quaternary polymaleates/polyamides/polyimides and tested their antimicrobial activity on various pathogenic microorganisms.

| Polyanhydrides with quaternary ammonium salts | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Temiz et al. |  | *L. monocytogenes*, *S. aureus, S. enteritidis* and *E. coli* | (Temiz et al., 2006) |
| John et al. |  | *E. coli* | (Dominic et al., 2016) |
| John et al. |  | Ampicillin resistant recombinant *E. coli* | (Dominic et al., 2015) |
| Wang et al |  | *P. aeruginosa, E. coli, K. pneumoniae, Proteus vulgaris, E. agglomerans, S. typhimurium, A. faecalis, S. aureus, B.cereus, S. pyogenes, M. luteus, M. smegmatis, Corynebacterium xerosis* | (Wang et al., 2012) |
| Mitra et al |  | Methicillin-resistant *Staphylococcus aureus* (MRSA) | (Ganewatta et al., 2015) |
| Mitra et al |  | *S. aureus* and *E. coli* | (Ganewatta et al., 2014) |

(*continued on next page*)

**Table 4** (*continued*)

| Polyanhydrides with quaternary ammonium salts | Macromolecule | Activity | Reference no |
|---|---|---|---|
| Uppu et al. |  | *E. coli* and *S. aureus* | (Uppu and Haldar, 2016) |
| Uppu et al. |  | Methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococci* (VRE) and multi-drug resistant clinical isolates of *A. baumannii* | (Uppu et al., 2016) |

concentrations of the QAS molecules are capable of getting resistance towards the molecules. John et al. in 2015 found a novel route to synthesize QAS molecules from maleic anhydride (MA), epichlorohydrin, fatty alcohols and trimethyl amine.

The length of the alkyl chain is directly related to the antimicrobial properties. The degradation studies show that these QAS molecules are degradable and hence would not be any damage towards the environment when disposed in sewages. The antimicrobial property of synthesized QAS was tested against *E. coli*. The author continued to synthesize polymerizable quaternary ammonium dialkyl maleates and copolymerized with methyl methacrylate in the year 2016 and tested activity against recombinant *E. coli* which is resistant to ampicillin which showed lethal antimicrobial behaviour (Dominic et al., 2016; Dominic et al., 2015). Mimicking the function of natural peptides was done by incorporating hydrophobicity and cationic charges to the synthetic polymer. The synthesized cationic-amphiphilic antibacterial polymers bear endotoxin neutralization properties which are not been reported elsewhere. The article reports synthetic amphiphilic polymers with antibacterial, endotoxin neutralizing as well as anti-inflammatory properties. The antibacterial activity of various amphiphilic polymers were tested against *E. coli* (Gram-negative) and *S. aureus* (Gram-positive) and also against highly pathogenic MRSA and VRE. The non-quaternized polymer, in its protonated state (soluble in water), does not have potent antibacterial efficacy against *E. coli* and *S. aureus* respectively and hence quaternization was performed to improve the antibacterial activity by Uppu et al. in 2016 (Uppu and Haldar, 2016).

Novel cationic polymers were synthesized by Uppuet al. in 2016 where maleic anhydride polymer was grafted by various amide side chains. The polymers also exhibited efficient activity against vancomycin-resistant *Enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant clinical isolates of *A. baumannii*. The article also describes the mechanism of cell lysis. Even after various passages, the polymer was efficient in preventing the development of drug resistance bacteria. The membrane-active properties of cationic polymers were determined by assessing the permeabilization, cytoplasmic membrane depolarization and ATP leakage against *E. coli*, *S. aureus* and *A. baumannii*. All the synthesized cationic polymers exhibited an efficient and similar extent of membrane depolarization against both *E. coli* and *S. aureus* (Uppu et al., 2016). To enhance the antimicrobial activity of synthesized maleic anhydride polymers, the polymers were treated with various alkyl group (different alkyl chain length) and Table 4 contains the list of maleic anhydride antimicrobial polymers with quaternary ammonium salts.

## 6. Conclusion

The intensified serious health threats by microorganisms have become a daunting challenge to modern society. Antimicrobial polymers receive significant attention in finding an effective solution which leads to gain interest in both academia and industry. This review summarizes the development and advances in the area of antimicrobial polymers using maleic anhydride. The detailed discussion on different categories of maleic anhydride based antimicrobial polymers namely copolymers/terpolymers, polymaliamides/maleimides, polymaleats/polyhemiesters and macromolecule with quaternary ammonium groups are included in this article in a systematic way. The unique property of maleic anhydride makes the macromolecule scatter in diverse commercial applications like surface coatings/ immobilization/functionalization/modification, water purification system/biological water treatment, drug carriers, food packaging, hydrogels in wound management, biomedical application and so forth.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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