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MINI-REVIEW

Antimicrobial additives for poly(lactic acid) materials and their applications: current state and perspectives

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Abstract

Poly(lactic acid)-based antimicrobial materials received considerable attention as promising systems to control microbial growth. The remarkable physicochemical properties of PLA such as renewability, biodegradability, and US Food and Drug Administration (FDA) approval for clinical use open up interesting perspectives for application in food packaging and biomedical materials. Nowadays, there is an increasing consumer demands for fresh, high-quality, and natural foods packaged with environmentally friendly materials that prolong the shelf life. The incorporation of antimicrobial agents into PLA-based polymers is likely to lead to the next generation of packaging materials. The development of antimicrobial PLA materials as a delivery system or coating for biomedical devices is also advantageous in order to reduce possible dose-dependent side effects and limit the phenomena of antibiotic resistance. This mini-review summarizes the most recent advances made in antimicrobial PLA-based polymers including their preparation, biocidal action, and applications. It also highlights the potential of PLA systems as efficient stabilizers-carriers of various kinds of antimicrobial additives including essential oils and other natural compounds, active particles and nanoparticles, and conventional and synthetic molecules.

Keywords Poly(lactic acid) · Antimicrobial agents · Processing · Food packaging · Delivery systems

Introduction

Microbial contamination is a great concern in several fields, ranging from food packaging to medical devices (Lau and Wong 2000; Darouiche 2004). Various kinds of polymers are usually sterilized by means of either dry/wet heat or ionizing radiation (Kenawy et al. 2007). However, these materials are able to be colonized by microbial cells (Sousa et al. 2011) and give rise to infection if they are exposed to the atmosphere or other contaminating environments. For instance, they can come into contact with microorganisms usually present on foods or wounds (Lau and Wong 2000). Therefore, there is a definite need for new antimicrobial materials able to inhibit the microbial growth and to prevent the subsequent colonization and proliferation (Nostro et al. 2010, 2012, 2013; Liu et al. 2016; Scaffaro and Lopresti 2018).

In this context, poly(lactic acid) (PLA) can be considered one of the most attractive biopolymers due to its physical properties, renewability, biodegradability, and biocompatibility (Tawakkal et al. 2016; Scaffaro et al. 2017a). The great advantages of PLA are due in part to its ability to degrade into the naturally occurring lactic acid under physiological conditions, but other exceptional qualities such as low immunogenicity and good mechanical properties must also be considered (Llorens et al. 2015). Moreover, PLA can be processed adopting a large number of techniques and it is commercially available in a wide range of grades making it suitable for several applications (Scaffaro et al. 2016, 2017a, c).

Over recent years, several additives, including natural compounds, peptides, enzymes, metals, chelating agents, and antibiotics, were incorporated into PLA polymeric matrix to provide antimicrobial activity (Tawakkal et al. 2014). The incorporation of antimicrobial additives into PLA is a promising way to overcome microbial proliferation (Scaffaro et al. 2018). The most common methods to prepare PLA-based antimicrobial materials can be divided in two main approaches:

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melt processing and wet processing, each one presenting its own advantages and disadvantages. Melt processing has the advantage to involve equipment commonly used to process thermoplastic materials, thus ensuring easy scale up of the production volumes and solventless environments. These features reduce the overall environmental impact and the production costs; furthermore, they minimize the presence of solvents in the final device (Scaffaro et al. 2013). On the other hand, high temperature (PLA requires melting and molding temperature of 160–190 °C) can be a problem for those drugs that undergo thermodegradation or in presence of highly volatile compounds (Nostro et al. 2015). In these cases, wet processing can be preferred since it is carried out at ambient temperature (Scaffaro and Lopresti 2018). Furthermore, polymer solutions used in wet processing can enhance the dispersion in case of active particles or insoluble drugs, i.e., dispersed as separated phase.

This review focuses on the recent advances (from 2015 to date) on antimicrobial additives for PLA-based materials including their preparation, biocidal action, and application, thus updating previous reviews released on the same (Jamshidian et al. 2010; Pawar et al. 2014; Tawakkal et al. 2014) or different polymer (Appendini and Hotchkiss 2002; Kuorwel et al. 2011; Palza 2015; Huang et al. 2016). Among the reported studies, some evaluated the antimicrobial activity by the in vitro test in solid and liquid media; some others investigated the efficacy in a food model. Conversely, the antibiofilm efficacy and the in vivo assays received little attention. The potential of PLA was particularly investigated for use in antimicrobial food packaging and biomedical applications. The first section will be devoted to the essential oils (EOs), their components, and other compounds of natural origin that are the most investigated additives for PLA. Another section will be dedicated to active particles and nanoparticles such as silver or zinc oxide. Finally, the last section will focus on conventional and synthetic molecules added into PLA polymer. Figure 1 reports the schematic representation of the topic that will be discussed in the following sections.

Essential oils, their components, and other compounds of natural origin

The EOs are complex mixtures of plant secondary metabolites with high inhibitory potential against a wide spectrum of microorganisms. The most important limitations of their direct use, namely high hydrophobicity and volatility, can be overcome by their incorporation into polymeric materials. Table 1 reports the processing for the incorporation of different EOs and other compounds of natural origin into PLA polymer such as melt mixing (Chieng et al. 2015; Llana-Ruiz-Cabello et al. 2016; Râpă et al. 2016; Moustafa et al. 2017; Tawakkal et al. 2017), extrusion (Llana-Ruiz-Cabello et al. 2015; Moreno-Vásquez et al. 2017; Wang et al. 2017), solvent casting (Bonan et al. 2015; Qin et al. 2015; Ahmed et al. 2016a; Javidi et al. 2016; Liu et al. 2016; Yahyaoui et al. 2016; Yang and Song 2016; Ahmed et al. 2016b, c; George et al. 2017; Muller et al. 2017; Rezaeigolestani et al. 2017; Shavisi et al. 2017; Arfat et al. 2018; Milovanovic et al. 2018; Niu et al. 2018), and electrospinning (Jiang et al. 2015; Wen et al. 2016; Adomavičiute et al. 2017; Gomaa et al. 2017; Liu et al. 2017; Scaffaro et al. 2018). In some cases, the presence of additives such as β-cyclodextrin (β-CD) (Wen et al. 2016; Wang et al. 2017), chitosan (CS), nanoparticles (Liu et al. 2017), cellulose nanocrystals (George et al. 2017), maleic

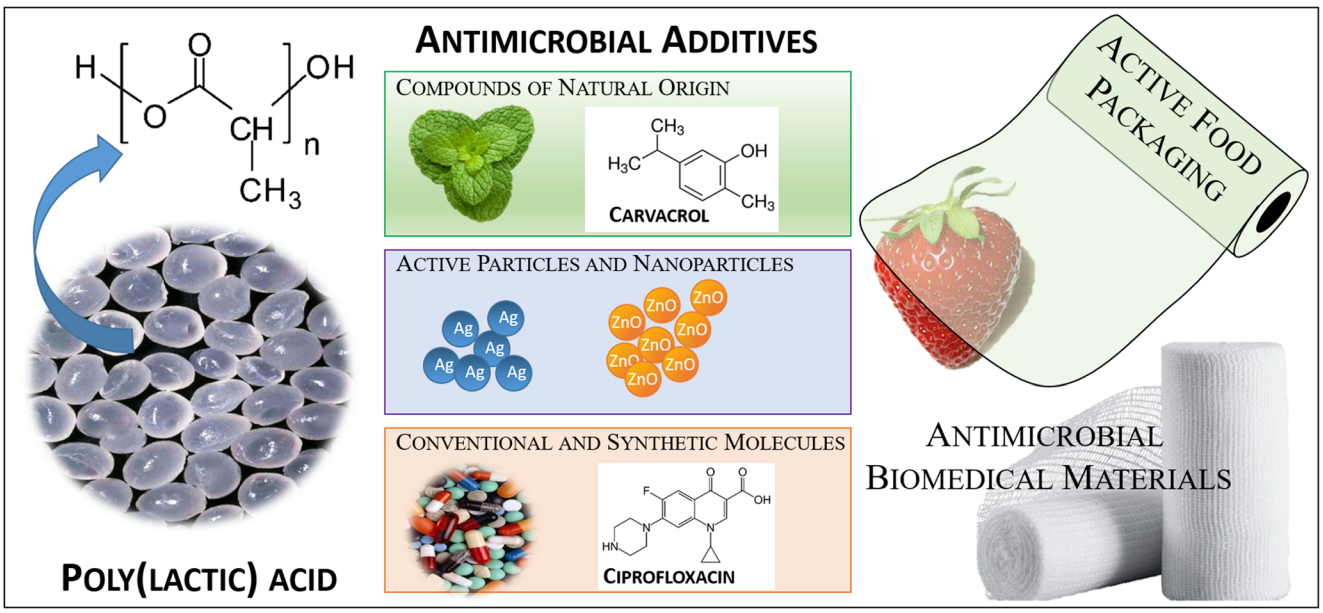

Fig. 1 Schematic representation of the topic of this review

Table 1 Processing and antimicrobial activity of PLA containing essential oils, their components, and other "compounds of natural origin"

Antimicrobial additive	Other additive	PLA grade	Processing	Nominal amount	Microbial strain	Activity	Method	Application	Reference
Allyl isothiocyanate	β-cyclodextrin	NatureWorks® Ingeo4032D	Blown extrusion	0.16–8 wt%	*Bacillus subtilis* *Escherichia coli* *Salmonella* *Staphylococcus aureus* *Penicillium* *Aspergillus niger*	Growth inhibition 85–98% (Bacteria) Growth inhibition 88–94% (Molds)	VC	Food packaging	(Wang et al. 2017)
Carvacrol		NatureWorks® Ingeo2002D	Electrospinning	14–28 wt%	*Staphylococcus aureus* ATCC 6538 *Candida albicans* ATCC 10231	Log reduction 3.8–5 (Single cultures) Log reduction 2.5–4.5 (Mixed cultures) Biofilm reduction >80%	VC, BA, FM	Wound healing	(Scaffaro et al. 2018)
Chitosan	Tributyl o-acetyl citrate	NatureWorks® Ingeo2002D	Melt compounding	1–3 wt%	*Escherichia coli* CCUG 10979 *Staphylococcus aureus* CCUG 1828 *Aspergillus brasiliensis* ATCC 16404 *Fusarium graminearum* G87 *Penicillium corylophilum* CBMF1	Log reduction 2.7–2.8 Log reduction 5.5 IR 99–100% IR 84.16–100% IR 94.5–100%	VC, GI	Food packaging	(Râpă et al. 2016)
Cinnamaldehyde	Poly(trimethylene carbonate	NatureWorks® (280 kDa)	Solvent casting	3–12 wt%	*Escherichia coli* *Staphylococcus aureus*	Log reduction 2 Log reduction 1.2	VC	Food packaging	(Qin et al. 2015)
Cinnamaldehyde			Supercritical impregnation	8–13 wt%	*Escherichia coli* O157:H7 *Staphylococcus aureus* ATCC 25923	Log reduction >4.7 Log reduction >4.2	VC	Food packaging	(Villegas et al. 2017)
	Starch Polyethylene glycol	NatureWorks® Ingeo4060D	Solvent casting Compression molding	7.6 wt%	*Escherichia coli* CECT 101 (*Ec*) *Listeria innocua* CECT 910 (*Lm*)	Log reduction ~ 4 (*Ec*) (monolayer films) Growth delay (*Lm*) (monolayer films) No inhibition (*Ec, Lm*) (bilayers films)	VC	Food packaging	(Muller et al. 2017)
Cinnamon EO	Chitosan	Self-made (15,000 g/mol)	Electrospinning	1–2.5% v/v	*Escherichia coli* ATCC 29522 (*Ec*) *Staphylococcus aureus* ATCC 29523 (*Sa*)	CFU reduction 99.3% (*Ec*) CFU reduction 98.4% (*Sa*)	VC	Food packaging	(Liu et al. 2017)
	Polyethylene glycol	NatureWorks® Ingeo4043D	Solvent casting	25–50 wt%	Total viable count (T) Lactic acid bacteria (L) Total coliform (C) *Pseudomonas* spp. (*Pspp*)	Log reduction 4–5 (T, L, C, *Pspp*) Log reduction ~ 1.5 (*Lm*) Log reduction ~ 3 (*Se*)	VC, FM	Food packaging	(Ahmed et al. 2016b; Ahmed et al. 2016c)

Table 1 (continued)

Antimicrobial additive	Other additive	PLA grade	Processing	Nominal amount	Microbial strain	Activity	Method	Application	Reference
					Listeria monocytogenes ATCC 19114 (*Lm*) *Salmonella enterica sv* Typhimurium ATCC 14028 (*Se*)				
	β-Cyclodextrin		Electrospinning	0–2 wt%	*Escherichia coli* *Staphylococcus aureus*	MIC 1 mg/ml; MBC 7 mg/ml Growth delay		Food packaging	(Wen et al. 2016)
Cinnamon EO (CEO) Garlic EO (GEO) Clove EO (ClEO)	Polyethylene glycol	NatureWorks® Ingeo4043D	Solvent casting	0.25–1 ml/g	*Campylobacter jejuni* ATCC 33291 (*Cj*) *Staphylococcus aureus* ATCC 6538 (*Sa*)	Inhibition zone ≥ 45 mm (*Cj*) Inhibition zone 5–10 mm (*Sa*) Log reduction 7 with CEO and ClEO (*Cj*) Log reduction 1 with CEO and ClEO (*Sa*) No inhibition with GEO	DT, VC	Food packaging	(Ahmed et al. 2016b)
Clove EO	Graphene oxide Polyethylene glycol	NatureWorks® Ingeo 4043D	Solvent casting	15–30 wt%	*Escherichia coli* ATCC 25922 (*Ec*) *Staphylococcus aureus* ATCC 6538 (*Sa*)	Log reduction ~ 6 (*Ec*) Log reduction ~ 7 (*Sa*)	VC	Food packaging	(Arfat et al. 2018)
Copaiba oil	Polyvinylpyrrolidone	NatureWorks® (66,000 g/mol)	Solution blow spinning	20 wt%	*Staphylococcus aureus* ATCC 25923	Inhibition zone 20.3–21.5 mm		Biomedical	(Bonan et al. 2015)
E14LKK magainin-class peptide	Cellulose nanocrystals	N/A	Solvent casting	0.25–1.25%	*Escherichia coli* O159:H7 ATCC35150 *Klebsiella pneumonia* ATCC4352 *Listeria monocytogenes* ATCC13932 *Salmonella* Tiphymurium ATCC14028	Log reduction ≥ 8	VC	Food packaging	(George et al. 2017)
Epigallocatechin gallate	Maleic anhydride	NatureWorks® Ingeo4042D	Extrusion	0.03–10 wt%	*Pseudomonas* spp. ATCC 13867 (*P*) *Staphylococcus aureus* ATCC 25923 (*Sa*)	Growth inhibition 28% (*P*) Growth inhibition 56% (*Sa*)	DT, VC, OM	Food packaging	(Moreno-Vásquez et al. 2017)
Lemongrass EO		NatureWorks® Ingeo4032D	Solvent casting	1–3%	*Listeria monocytogenes* ATCC 19111	Inhibition zone 11.8–30.7 mm Log reduction 1.47	DT, VC, FM	Food packaging	(Yang and Song 2016)
Nisin	Phosphorylated Soybean protein Zirconium dioxide	Self-made (25,000 g/mol)	Electrospinning	3–15 wt%	*Staphylococcus aureus*	Inhibition zone 28–29 mm Growth inhibition ~ 80%	DT, GI	Drug delivery Food packaging Wound dressing	(Jiang et al. 2015)

Table 1 (continued)

Antimicrobial additive	Other additive	PLA grade	Processing	Nominal amount	Microbial strain	Activity	Method	Application	Reference
Oregano EO		NatureWorks® Ingeo2002D	Solvent casting	0.5–1.5 wt%	*Escherichia coli* ATCC 1330 *Listeria monocytogenes* ATCC 19118 *Salmonella enteritidis* ATCC 138 *Staphylococcus aureus* ATCC 25923 *Enterobacteriaceae* (*E*) Lactic acid bacteria (L) Psychrotrophic bacteria (P) Total viable count (T)	Inhibition area 230–722 mm^2 (DT), 147–248 mm^2 (VA) Growth delay (*E*, L, P, T)	DT, VA, VC, FM	Food packaging	(Javidi et al. 2016)
	Trimethylene carbonate	NatureWorks® (280 kDa)	Solvent casting	3–12 wt%	*Escherichia coli* (*Ec*) *Listeria monocytogenes* (*Lm*)	Log reduction 3.6 (*Ec*) Log reduction 3.5 (*Lm*)	DT, VC, FM	Food packaging	(Liu et al. 2016)
Origanum vulgare L. virens EO		NatureWorks® Ingeo2003D	Melt compounding	2–10 wt%	*Escherichia coli* *Enterococcus faecalis* *Listeria monocytogenes* *Staphylococcus aureus* *Staphylococcus carnosus* *Salmonella enterica* *Yersinia enterocolitica* Aerobic bacteria (A) *Enterobacteriaceae* (E) Yeasts (Y) Molds (M)	Log reduction ~ .5–1 (Bacteria) No inhibition (A, E) Growth delay (Y, M)	VC, FM	Food packaging	(Llana-Ruiz-Cabello et al. 2016)
Palm oil (Epoxidized)	Polyethylene glycol Graphene nanoplatelets	NatureWorks® Ingeo4042D	Melt compounding	0.1–1 wt%	*Escherichia coli* *Listeria monocytogenes* *Salmonella typhimurium* *Staphylococcus aureus*	Log reduction enhancing by adding the graphene nanoplatelets	VC	Medical Food packaging	(Chieng et al. 2015)
Proallium® based on *Allium* spp. extract		NatureWorks® Ingeo2003D	Extrusion	2–6.5 wt%	*Staphylococcus aureus* *Yersinia enterocolitica* *Listeria monocytogenes* *Enterococcus faecalis* *Salmonella enterica* *Staphylococcus carnosus* *Escherichia coli* O157:H7 *Listeria ser.* 1/2a *Campylobacter jejuni* *Clostridium perfringens*	No inhibition zone Log reduction 3–4.95 Log reduction (A, *E*, Y, M)	DT, VC, FM	Food packaging	(Llana-Ruiz-Cabello et al. 2015)

Table 1 (continued)

Antimicrobial additive	Other additive	PLA grade	Processing	Nominal amount	Microbial strain	Activity	Method	Application	Reference
					Zygosaccharomyces bailii *Candida humicola* *Fusarium oxysporum* *Penicillium expansum* Aerobic bacteria (A) *Enterobacteriaceae* (E) Yeasts (Y) Molds (M)				
Propolis Silver nanoparticles		NatureWorks® Ingeo6202D (98% L-lactid)	Electrospinning	10–20 wt% 5 wt%	*Bacillus cereus* ATCC 11778 *Escherichia coli* ATCC 25922 *Proteus mirabilis* ATCC 12453 *Pseudomonas aeruginosa* ATCC 27853 *Staphylococcus aureus* ATCC 25923 *Staphylococcus epidermidis* ATCC12228 *Candida albicans* ATCC 10231	No quantified inhibition zone	DT, CA	Wound healing	(Adomavičiute et al. 2017)
Propolis ethanolic extract (PEE) *Zataria multiflora* EO (ZME) Cellulose nanofibers (CNF)		FkuR kunststoffm GmbH (197,000 g/mol)	Solvent casting	0.5–2% v/v	*Listeria monocytogenes* ATCC 19111 *Staphylococcus aureus* ATCC 25923 *Escherichia coli* O157:H7 ATCC 43895 *Vibrio parahaemolyticus* ATCC 43996 Aerobic bacteria (A) Lactic acid bacteria (L) Psychrotrophic bacteria (P) *Enterobacteriaceae* (E) *S. aureus (Sa)* Yeasts (Y) Molds (M)	No inhibition zone PPE Inhibition zone ZME 29–39 mm Inhibition zone ZME/CNF 28–39 mm Inhibition zone ZME/PEE 30–39 mm Inhibition zone ZME/CNF/PEE 30–38 mm Growth delay (A, L, P) Log reduction: below the detection limit (< 1 log) (E, *Sa*, Y, M)	DT VC, FM	Food packaging	(Rezaeigolestani et al. 2017)
			Solvent casting	1–2 wt%	*Bacillus cereus* ATCC 11774	Inhibition zone PEE 2.22–6.22 mm	DT	Food packaging	(Shavisi et al. 2017)

Table 1 (continued)

Antimicrobial additive	Other additive	PLA grade	Processing	Nominal amount	Microbial strain	Activity	Method	Application	Reference
Propolis ethanolic extract (PEE) *Ziziphora clinopodioides* EO (ZEO)		PLA powder (Sigma-Aldrich, UK			*Bacillus subtilis* ATCC 6633 *Escherichia coli* O157:H7 *Listeria monocytogenes* ATCC 19118, *Salmonella enterica* serovar Typhimurium ATCC 14028 *Staphylococcus aureus* ATCC 6538	Inhibition zone ZEO 8.24–14.84 mm Inhibition zone PEE/ZEO 8.2–16.88 mm			
Rosemary EO Myrtle EO Thyme EO		NatureWorks® Ingeo3051D	Solvent casting	0.5–5 wt%	*Aspergillus niger* Tiegh MB284309	Log reduction ~ 0.5–0.7 Growth inhibition (%) depending on EO	VC	Food packaging	(Yahyaoui et al. 2016)
Rosin	Poly(butylene adipate--coterephthalate) Nanoclay	NaturePlast PLE 003	Melt compounding	N/A	*Pseudomonas aeruginosa* *Staphylococcus aureus* *Candida albicans*	Inhibition zone 10–22 mm	DT	Food packaging	(Moustafa et al. 2017)
Rosin-modified cellulose nanofiber	Chitosan	NatureWorks® Ingeo2003D	Solvent casting	2–10 wt%	*Bacillus subtilis* ATCC 6633 *Escherichia coli* ATCC 9677	Inhibition zone 8.09–10.88 mm Growth delay	DT, VC	Food packaging	(Niu et al. 2018)
Terpinen-4-ol	Polyethylene glycol	Biomater (1.25×10^5 g/mol)	Solution blow spinning	40 wt%	*Aggregatibacter actinomycetemcomitans* ATCC 00078	Biofilm viability inhibition > 80–90%	FMA, BA	Periodontal infection	(Nepomuceno et al. 2018)
Thymol	Kenaf	NatureWorks® Ingeo7001D	Melt compounding	10–30 wt%	*Escherichia coli*	Inhibition zone 7.5–20.6 mm Log reduction ~ 2 Death rate ~ 0.19/day IR 100%	DT, VC, VA, FM	Food packaging	(Tawakkal et al. 2017)
	Poly(ε-caprolactone)	NatureWorks® Ingeo3052D	Supercritical impregnation	9–35.8 wt%	*Bacillus subtilis* *Escherichia coli*	Viability reduction based on ATP level ≥ 80%	LA, GI	Food packaging	(Milovanovic et al. 2018)
Thymoquinone	Cellulose acetate	NatureWorks® Ingeo4043D	Electrospinning	3%	*Escherichia coli* *Staphylococcus aureus*	Inhibition zone 17–33 mm Prevention of bacterial infection	DT, IVA	Wound dressing	(Gomaa et al. 2017)

VC, viable count; BA, biofilm assay; FM, food model; GI, growth inhibition; IR, percentage of the film surface on which the mycelia was not present; CFU, colony-forming unit; O, essential oil; DT, diffusion test; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; OM, optical microscopy; VA, vapor assay; FMA, fluorescence microscope assay; LA, luminescence assay; IVA, in vivo assay; N/A, not available

anhydride (Moreno-Vásquez et al. 2017), and nanoclays (Moustafa et al. 2017) were proposed in order to achieve higher thermal stability; reduce volatility of the active compound, masking unpleasant odors in the case of food packaging applications; and to control the release of drugs and flavors. In other cases, additives such as graphene oxide (GO) (Arfat et al. 2018) and kenaf (Tawakkal et al. 2017) were used to enhance the tensile strength of the material. In other circumstances, polymers such as tributyl o-acetyl citrate (ATBC) (Râpă et al. 2016), trimethylene carbonate (Qin et al. 2015), polyethylene glycol (PEG) (Chieng et al. 2015; Ahmed et al. 2016a, b; Muller et al. 2017; Arfat et al. 2018; Nepomuceno et al. 2018), poly(ε-caprolactone) (PCL) (Milovanovic et al. 2018), and cellulose acetate (Gomaa et al. 2017) were used as plasticizers to improve the processability and the ductility of the final material.

Different antimicrobial EOs such as cinnamon (Ahmed et al. 2016a, b, c; Wen et al. 2016; Liu et al. 2017), garlic (Ahmed et al. 2016a), clove (Ahmed et al. 2016a; Arfat et al. 2018), copaiba (Bonan et al. 2015), epoxidized palm oil (Chieng et al. 2015), lemongrass (Yang and Song 2016), rosemary, myrtle, thyme (Yahyaoui et al. 2016), and oregano (Javidi et al. 2016; Liu et al. 2016; Llana-Ruiz-Cabello et al. 2016) or their major active constituents including carvacrol (Scaffaro et al. 2018), cinnamaldehyde (Qin et al. 2015; Muller et al. 2017; Villegas et al. 2017), terpinen-4-ol (Nepomuceno et al. 2018), thymol (Tawakkal et al. 2017; Milovanovic et al. 2018), and thymoquinone (Gomaa et al. 2017) were incorporated in PLA. Considering the high number of variables such as kind and amount of EO, processing method, microbial strain, and antimicrobial test, it is very difficult to compare the different data.

Several papers documented the antimicrobial properties of oregano essential oil (OEO) added to PLA (Liu et al. 2016; Javidi et al. 2016; Llana-Ruiz-Cabello et al. 2016). Specifically, PLA/poly (trimethylene carbonate) films containing OEO exhibited strong antioxidant and antimicrobial activity against *Escherichia coli* and *Listeria monocytogenes* (log reduction of 3.5–3.6) (Liu et al. 2016; Javidi et al. 2016; Llana-Ruiz-Cabello et al. 2016). Javidi et al. (2016) reported the higher inhibition area of PLA films containing 1.5 wt% OEO detected by direct contact than that observed by vapor phase assay and described the significant delay of bacterial growth (reduction of colony-forming units/g) on rainbow trout fillets. Llana-Ruiz-Cabello et al. (2016) studied the greater antimicrobial activity of PLA films containing OEO 5–10 wt% against yeasts and molds and suggested a new active packaging for use in ready-to-eat salads. Similarly, a significant decrease in different microbial counts was observed in lettuce packaged in active ethylene-vinyl alcohol copolymer (EVOH)-coated polypropylene (PP) films containing OEO 7.5 wt% (Muriel-Galet et al. 2013). Regarding the OEO constituents, composite PLA films containing kenaf fibers (20 wt%) and thymol (30 wt%) significantly killed *E. coli* on chicken slice samples by direct food contact and also were effective against naturally occurring fungi by indirect food contact (Tawakkal et al. 2017). The death rate of *E. coli* in the presence of the PLA/kenaf/thymol was related to the concentration of thymol in the formulation and was higher than that detected for the PLA/thymol films. The population of *E. coli* decreased upon increasing the thymol concentration from 10 to 30 wt%, with a death rate of ca. 0.19/day. Recently, innovative supercritical fluid technology was employed to impregnate PLA/PCL films with thymol and thyme extract for potential use in packaging against *Bacillus subtilis* and *E. coli* (Villegas et al. 2017; Milovanovic et al. 2018) or to impregnate PLA films with cinnamaldehyde against *E. coli* and *Staphylococcus aureus* (Villegas et al. 2017). This technology exploits supercritical carbon dioxide allowing the addition of volatile compounds avoiding the limitations of the conventional methods such as the evaporation of the active substance (Milovanovic et al. 2018).

Among the EOs, also cinnamon essential oil (CEO) (Ahmed et al. 2016a, b, c; Wen et al. 2016; Liu et al. 2017) or its major component cinnamaldehyde (Qin et al. 2015; Muller et al. 2017; Villegas et al. 2017) incorporated into PLA-based materials showed antimicrobial activity. Liu et al. (2017) successfully encapsulated cinnamon essential oil into CS nanoparticles subsequently added in a PLA solution and electrospun together for active packaging applications. The nanoparticles enhanced the EO stability and retained the antimicrobial activity of the compound. Overall, 75% more cinnamon essential oil was released from the fiber with the highest concentration exhibiting a diffusion-swelling controlled process. Muller et al. (2017) developed antibacterial monolayer and bilayer films with PLA (NatureWorks® Ingeo4060D)/cinnamaldehyde and starch by compression molding of previously solvent casted films with a loading efficiency of 87%. The authors studied the release kinetics of the active compound into food simulants of differing polarities finding that Fick's model fitted to the experimental points in each simulant. Occasionally, the inclusion of β-CD stabilized and improved the antimicrobial activity of PLA polymers containing CEO or allyl isothiocyanate (AITC) (Wen et al. 2016; Wang et al. 2017) despite the high polymer-processing temperature. Ahmed et al. (2016b, c) documented the efficacy of PLA (NatureWorks® Ingeo4043D)/CEO composite films also in a real food system such as chicken samples. The efficacy of PLA/CEO films was measured by evaluation of general indicators of microbial quality by the poultry industry such as total viable counts (TVC), lactic acid bacteria (LAB), *Pseudomonas* spp., and total coliform. The TVC, LAB, *Pseudomonas*, and total coliforms in the chicken samples wrapped with antimicrobial PLA/CEO films were less

than 1.0 log colony-forming unit (CFU)/g during the entire storage period (day 0 to day 20). The efficacy of PLA/CEO films was also evaluated by performing a challenge test in chicken sample inoculated with *L. monocytogenes* and *Salmonella enterica* Typhimurium and storage at 4 °C for 17 days. The counts were reduced by 1.5 and 3 log cycles for *L. monocytogenes* and *S. enterica* Typhimurium, respectively. Additionally, a synergistic effect was observed between high-pressure treatment and the PLA/CEO films on survival of *L. monocytogenes*. CEO and clove oil-based PLA films exhibited higher activity against *Campylobacter jejuni* (approximately 7 log reduction) compared to the garlic oil-based films suggesting their use for preservation of poultry meats (Ahmed et al. 2016a). In a recent paper, Arfat et al. (2018) developed composite PLA (NatureWorks® Ingeo4043D) films with excellent antibacterial activity against *S. aureus* and *E. coli* by incorporating clove EO (CLO) (15–30 wt%) and graphene oxide nanosheets (1 wt%). After 7 days of incubation, about 7 log reductions of *S. aureus* and 6 log reductions of *E. coli* were achieved for films containing 30% CLO.

Other antimicrobial natural compounds such as plant extracts (Llana-Ruiz-Cabello et al. 2015), epigallocatechin gallate (Moreno-Vásquez et al. 2017), propolis (Rezaeigolestani et al. 2017; Shavisi et al. 2017), and rosin (Moustafa et al. 2017; Niu et al. 2018) were used to develop PLA polymeric materials for food packaging applications. Llana-Ruiz-Cabello et al. (2015) demonstrated the inhibiting activity of PLA (NatureWorks® Ingeo2003D) films containing Proallium®, a commercial product based on *Allium* spp. extract, against *Enterobacteriaceae*, aerobic bacteria, yeasts, and molds on ready-to-eat lettuce salads. Moreno-Vásquez et al. (2017) prepared antimicrobial PLA (NatureWorks® Ingeo4042D) films through extrusion incorporating a certain amount of PLA grafted maleic anhydride (PLA-gr) as a compatibilizing agent to increase the miscibility between neat PLA and epigallocatechin gallate (EGCG). EGCG diffusion from PLA films followed a Fickian behavior and after 7 days, the release of EGCG for PLA–EGCG and PLA-gr–EGCG was 2.40 and 3.01 wt%, respectively. For the authors, this result could indicate that the EGCG distribution in PLA-gr–EGCG was more homogeneous than PLA–EGCG, such that the surface contact between EGCG and deionized water was higher. Also, propolis in association with EOs or nanoparticles was successfully incorporated in PLA (FkuR kunststoffm GmbH, 197,000 g/mol) materials. In particular, combinations of propolis ethanolic extract (PEE) with *Zataria multiflora* Bioss. essential oil (ZME 1% v/v) (Rezaeigolestani et al. 2017) or *Ziziphora clinopodioides* essential oil (ZEO 1–2 wt%) (Shavisi et al. 2017), containing carvacrol and thymol as the most abundant constituents, included into PLA polymer showed higher antibacterial effects against Gram-positive and Gram-negative bacteria than those obtained with each single ZEO or PEE (Shavisi et al. 2017) or increased the shelf life in vacuum-packed cooked sausages (Rezaeigolestani et al. 2017).

Interestingly, novel perspectives in biomedical area such as drug release systems, treatment of periodontitis, and wound healing were suggested by PLA materials containing PPE and silver nanoparticles (Adomavičiute et al. 2017), copaiba oil (Bonan et al. 2015), epoxidized palm oil (Chieng et al. 2015), or thymoquinone (Gomaa et al. 2017). Combination of PPE and silver nanoparticles loaded in PLA (NatureWorks® Ingeo6202D) provided efficient antimicrobial protection and maintained viability of HaCaT cells indicating a possible application for wound healing (Adomavičiute et al. 2017). Bonan et al. (2015) added polyvinylpyrrolidone (PVP) in order to prepare PLA (NatureWorks®, 66,000 g/mol)/PVP electrospun blends containing copaiba oil. The authors demonstrated that the EO increased the diameter of the fibers, reduced the contact angle, and showed activity against *S. aureus* (inhibition zone of 20.3–21.5 mm) suggesting a potential use in controlled drug system. In addition, plasticized PLA-based (NatureWorks® Ingeo4042D) nanocomposites filled with graphene nanoplatelets and containing PEG and epoxidized palm oil exhibited potentiated antimicrobial activity (log reduction enhancing by adding the graphene nanoplatelets) against *E. coli*, *S. typhimurium*, *S. aureus*, and *L. monocytogenes* (Chieng et al. 2015). Gomaa et al. (2017) proposed thymoquinone (TQ)-loaded PLA (NatureWorks® Ingeo4043D)/cellulose acetate nanofibers for wound dressing applications. The authors demonstrated a loading efficiency of TQ in PLA ranging from 80 to 90.5% and the efficacy of this system to prevent bacterial infection and to accelerate the rate of in vivo wound closure reepithelialization.

Microbial biofilms represent a serious problem because microorganisms embedded in a self-produced extracellular polymeric substance are less susceptible to conventional treatment (Fux et al. 2005). Although several publications focused on PLA as a suitable matrix for the incorporation of antimicrobial compounds, there are limited reports on the effects of PLA containing natural compounds against microbial biofilm. As reported in Fig. 2, Scaffaro et al. (2018) studied the efficacy of PLA (NatureWorks® Ingeo2002D)/carvacrol electrospun membranes against *S. aureus* and *Candida albicans* up to 144 h and suggested the potential of nanofibers as new tools for skin and wound polymicrobial infections. The gradual release of carvacrol from PLA membranes (up to 90% of carvacrol released after 144 h with respect of the nominal CAR loaded in PLA) resulted in the antimicrobial activity for all the investigated time and reduced the biofilm production of *S. aureus* and *C. albicans* in single and mixed cultures (> 80%). Nepomuceno et al. (2018) proposed solution blow spinning as a particular approach to prepare PLA/poly(ethylene glycol) nanofibers containing terpinen-4-ol (up to 40 wt%)

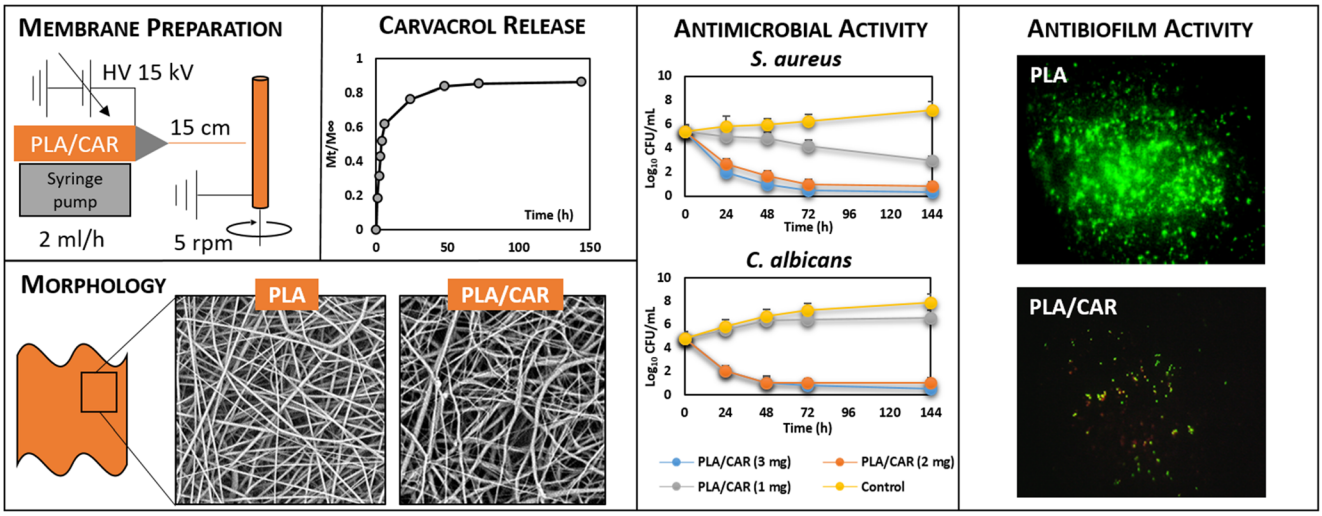

Fig. 2 Schematic representation of the preparation and characterization of antimicrobial PLA/CAR electrospun membranes

or chlorhexidine gluconate (up to 0.12 wt% used as control) and demonstrated their antimicrobial and antibiofilm activity (> 80–90%) against *Aggregatibacter actinomycetemcomitans* for potential treatment of aggressive periodontitis.

Antimicrobial peptides are another broad class of naturally occurring molecules that can be incorporated into PLA polymer. In particular, nisin is a bacteriocin approved as a food preservative because of its negligible toxicity and antibacterial effectiveness (Nostro et al. 2010; Scaffaro 2012). Jiang et al. (2015) described the *S. aureus* inhibition by nisin loaded into phosphorylated soybean protein isolate/PLA/zirconium dioxide nanofibrous membranes and suggested their use as a potential material in drug delivery, food active packaging, and wound dressing. Notably, PLA fortified with cellulose nanocrystals and E14LKK (a 14 residue, magainin-class peptide) or silver nanoparticles (control) were studied for their inhibitory effects against microorganisms (log reduction ≥ 8) commonly encountered in the food industry (George et al. 2017).

Active particles and nanoparticles

The processing approaches for the preparation of antimicrobial PLA-based polymer containing active particles and nanoparticles are reported in Table 2. For these systems, the particle dispersion is a crucial parameter for the performances of the material such as biocidal efficacy, mechanical properties, and barrier properties. In order to improve filler dispersion in solvent-based processing such as solvent casting (De Silva et al. 2015; Huang et al. 2015; Chu et al. 2017; Li et al. 2017) and electrospinning (Quirós et al. 2015; Adomavičiute et al. 2017), sonication of the polymeric solution is usually proposed (Huang et al. 2015; Quirós et al. 2015; Adomavičiute et al. 2017; Li et al. 2017). On the other hand, improvement of the particles dispersion in melt processing such as melt mixing (Tsou et al. 2017; Nootsuwan et al. 2018) and extrusion (Marra et al. 2016; Yang et al. 2016) is generally achieved by using masterbatch of PLA and particles (Marra et al. 2016) or by PLA functionalization (Yang et al. 2016).

Silver is known to have antibacterial effects since ancient times (Silver and Phung 1996) and its use in antimicrobial packaging is attracting intense interest in recent times. In this context, silver nanoparticles were incorporated into PLA polymer in order to provide antimicrobial efficacy (Adomavičiute et al. 2017; Chu et al. 2017; Li et al. 2017; Tsou et al. 2017; Nootsuwan et al. 2018). Li et al. (2017) described PLA (NatureWorks®, 280 kDa) nanocomposite films with different amounts of nanosilver (0.5 wt%) and nanotitanium dioxide (1–5 wt%) particles and demonstrated their good antimicrobial activity (CFU reduction > 4.5) toward *E. coli* and *L. monocytogenes*. The author also studied the migration of the nanoparticles into different media. For Ti nanoparticles, the maximum migration ratios for 3% (w/v) aqueous acetic acid were 2.19, 2.36, 3.12, and 3.5 μg/kg for PLA/Ti1%, PLA/Ti1%/Ag, PLA/Ti5%, and PLA/Ti5%/Ag, respectively. For 50% (v/v) aqueous ethanol, the maximum migration ratio amounts were 0.593, 0.72, 0.80, and 0.99 μg/kg. For the 50% (*v*/*v*) aqueous ethanol, the 3% (*w*/*v*) aqueous acetic acid shows a higher amount of Ti migration. This result was explained by dissolution experiments, which show that an acidic solution could more easily dissolve Ti or TiO_2, compared to an organic solution. Tsou et al. (2017) added nanosilver-doped multiwall carbon nanotube (MWCNT-Ag) as active PLA (Cargill-Dow Biopolymer 4032D) filler to avoid the use of organic solvents, to improve tensile strength, thermostability, and antimicrobial activity in order to obtain novel materials for biomedical applications (Tsou et al. 2017). In a recent study, Nootsuwan et al. (2018) developed biodegradable hybrid materials between PLA- (NatureWorks® Ingeo2003D)

Table 2 Processing and antimicrobial activity of PLA containing active particles and nanoparticles

Antimicrobial additive	Other additive	PLA grade	Processing	Amount	Microbial strain	Activity	Method	Application	Reference
Cellulose Lignin nanostructured		NatureWorks® Ingeo3251D	Extrusion	1–3 wt% 1–3 wt%	*Pseudomonas syringae* pv. *tomato Xanthomonas arboricola* pv. *pruni Xanthomonas axonopodis* pv. *vesicatoria*	Reduction of bacterial survival/multiplication	VC	Food packaging	(Yang et al. 2016)
Cobalt frameworks (Co-SIM-1) particles		NatureWorks® Ingeo2002D	Electrospinning	2–6 wt%	*Pseudomonas putida* ATCC 12633 (*Pp*) *Staphylococcus aureus* ATCC 6538P (*Sa*)	Inhibition zone 23.6 mm (*Pp*) Inhibition zone 25.4 mm (*Sa*) CFU reduction ~ 60% (*Sa*) CFU reduction ~ 40% (*Pp*) Presence of VBNC Biofilm reduction ~ 30–40%	DT, VC, BA	Biomedical	(Quirós et al. 2015)
Silver nanoparticles	Carbon black	NatureWorks® Ingeo2003D	Compounding	5–20 phr	*Staphylococcus aureus* ATCC 25923 (*Sa*) *Bacillus subtilis* ATCC 6633 *Micrococcus luteus* ATCC 9341 *Escherichia coli* ATCC 25922 *Pseudomonas aeruginosa* ATCC 2785 *Candida albicans* ATCC 10231 (*Ca*)	Inhibition zone 13–25 mm (Bacteria and *Ca*) CFU reduction 99.86% (*Sa*)	SEM, FMA	Novel antielectrostatic antimicrobial materials	(Nootsuwan et al. 2018)
Silver nanoparticles doped multiwall carbon nanotube MWCNT		Cargill-Dow Biopolymer 4032D	Melt compounding	0.03–0.1 wt%	*Staphylococcus aureus*	CFU reduction enhancing by increasing the MWCNT-Ag content	DT, VC	Biomedical	(Tsou et al. 2017)
Silver nanoparticles Propolis		NatureWorks® Ingeo6202D	Electrospinning	10–20 wt% 5 wt%	*Bacillus cereus* ATCC 11778 *Escherichia coli* ATCC 25922 *Proteus mirabilis* ATCC 12453 *Pseudomonas aeruginosa* ATCC 27853 *Staphylococcus aureus* ATCC 25923 *Staphylococcus epidermidis* ATCC12228 *Candida albicans* ATCC 10231	No quantified inhibition zone	VC, CA	Wound healing	(Adomavičiute et al. 2017)
Silver nanoparticles Titanium Dioxide nanoparticles		NatureWorks® (280 kDa)	Solvent casting	0.5 wt% 1–5 wt%	*Escherichia coli* (*Ec*) *Listeria monocytogenes* (*Lm*)	CFU reduction > 4.5 CFU (*Ec*) CFU reduction > 4.5 CFU (*Lm*)	DT	Food packaging	(Li et al. 2017)
Silver nanoparticles Zinc oxide nanoparticles		NatureWorks® (280 kDa)	Solvent casting	0.5–1 wt% 1–3 wt%	*Escherichia coli*	CFU reduction ~ 2–3 CFU	VC	Food packaging	(Chu et al. 2017)
Zinc oxide particles			Extrusion	1–5 wt%	*Escherichia coli* DSM 498	CFU reduction 99.99%	VC	Food packaging	

Table 2 (continued)

Antimicrobial additive	Other additive	PLA grade	Processing	Amount	Microbial strain	Activity	Method	Application	Reference
		NatureWorks® Ingeo4032D							(Marra et al. 2016)
Zinc oxide nanoparticles loaded on Graphene oxide (GO-ZnO)		Zhejiang Haizheng Biological Materials PLA290	Solvent casting	0.2–1 wt%	*Escherichia coli* ATCC 25922 (*Ec*) *Staphylococcus aureus* ATCC 29213 (*Sa*)	CFU reduction 52.3% (Dark) 97.6 (Light) (*Ec*) CFU reduction 83% (Dark) 99.2 (Light) (*Sa*)	VC	Food packaging	(Huang et al. 2015)
Zinc oxide nanoparticles deposited halloysite nanotubes (ZnO-Hal)		NatureWorks® Ingeo3051D	Solvent casting	1–10 wt%	*Escherichia coli* ATCC 25922 *Staphylococcus aureus* ATCC 29213	Antibacterial activity enhanced by increasing the ZnO and ZnO-Hal Log reduction > 6 with ZnO and ZnO-Hal 7.5–10 wt%	VC	Food packaging	(De Silva et al. 2015)

VC, viable count; CFU, colony-forming unit; DT, diffusion test; BA, biofilm assay; SEM, scanning electron microscope; FMA, fluorescence microscope assay; VBNC, viable but non-culturable microorganism

and nanosilver-coated carbon black with good mechanical properties, electrical conductivity, and antimicrobial activity (inhibition zone 13–25 mm) toward *S. aureus* (CFU reduction 99.86%), *B. subtilis*, *Micrococcus luteus*, *E. coli*, *Pseudomonas aeruginosa*, and *C. albicans* and suggested a different application as novel materials for computer keyboards.

Other metal particles were proposed as additives in PLA-based antimicrobial food packaging. Marra et al. (2016) prepared PLA (NatureWorks® Ingeo4032D) filled with nano zinc oxide (ZnO) particles in a twin-screw extruder. PLA/ZnO masterbatch was first prepared with the aim to improve the dispersion of the filler within the PLA matrix. The addition of ZnO increased the Young modulus and the stress at yield point and decreased the O_2 and CO_2 permeability. Specifically, PLA film with 5 wt% of ZnO showed excellent activity against *E. coli*, with a bacterial reduction of 99.99% after 24 h. Chu et al. (2017) compared the effect of nano-Ag and nano-ZnO on PLA (NatureWorks®, 280 kDa) films prepared by solvent casting and demonstrated that the higher the content of nano-ZnO, the more white particles aggregated. This phenomenon affected the mechanical properties that resulted in lower elastic modulus and maximum strength than that of neat PLA as well as the water vapor permeability and opacity that were enhanced with respect to neat PLA film. Nevertheless, nano-Ag and particles nano-ZnO added alone and in combination into PLA films significantly improved the antimicrobial activity against *E. coli*. Again, ZnO nanoparticles deposited halloysite nanotubes incorporated into PLA matrix (NatureWorks® Ingeo3051D) as a reinforcing filler simultaneously increased the mechanical and the antimicrobial properties, reducing *E. coli* and *S. aureus* counts by more than 99% (De Silva et al. 2015). Huang et al. (2015) reported that graphene oxide loaded with ZnO nanoparticles (0.2 wt%) was mixed with PLA (Zhejiang Haizheng Biological Materials PLA290) to prepare nanocomposite films with strong ultraviolet resistance and antibacterial activity against *S. aureus* and *E. coli*, both in dark conditions and under light irradiation. In addition, the release of metal contained in the structure of metal-organic frameworks (MOF) gave rise to antimicrobial materials. In this context, a cobalt-MOF, Co-SIM-1, successfully embedded in PLA (NatureWorks® Ingeo2002D) electrospun matrix decreased the bacterial colonization and biofilm formation up to 30–40% of the surface of mats by *P. putida* and *S. aureus* (Quirós et al. 2015). The authors also found that the time profile for metal release took place during the first 24 h. For mats loaded with a lower amount of Co-SIM-1, the metal was released at a higher rate (Quirós et al. 2015).

Particular efficacy against plant pathogens, namely *Xanthomonas axonopodis* pv. *vesicatoria* and *X. arboricola* pv. *pruni*, was demonstrated by using a ternary system composed of cellulose and lignin filled into PLA (NatureWorks®

Ingeo3251D) grafted with glycidyl methacrylate (Yang et al. 2016). The effectiveness of the reactive melt grafting and the high value of disintegration rate of the composites after 10 days revealed the potential to prevent the hazard of microbial contamination from post-harvest phases to the final users.

Conventional and synthetic molecules

The local treatment of microbial infections is clinically advantageous as it could reduce systemic drug administration and then avoid widespread harmful effects. The development of antimicrobial delivery systems based on localized antibiotic release at the site of infection is claimed as a way to limit antibiotic resistant strains, to prevent the appearance of biofilm and avoid secondary infection (Luo et al. 2017).

As reported in Table 3, PLA compounding with conventional and synthetic drugs is often carried out by incorporation of the drug during electrospinning (Llorens et al. 2015; Jiang et al. 2016; Moslem et al. 2016; Luo et al. 2017; Shahi et al. 2017). Electrospinning process permits the fabrication of nonwoven mats composed of continuous fibers ranging from micro to nanometer diameters. The remarkable physicochemical properties of nanofibers such as high levels of flexibility, porosity, gas permeation, and surface-to-volume ratio make them ideal materials to be applied in the biomedical field. Another interesting approach is 3D printing that focuses on the on-demand production of anti-infective and chemotherapeutic filaments that can be used to create discs, beads, catheters, or any medical construct using a 3D printing system (Weisman et al. 2015; Hall Barrientos et al. 2017) and solvent casting(Weisman et al. 2015). Solvent casting approach was adopted for preparing both dense and porous antimicrobial films by eventually, addition of PEG into PLA as a water-soluble porogen agent (Concilio et al. 2015; Chitrattha and Phaechamud 2016). Moslem et al. (2016) reported that electrospun membranes of chitosan/PLA (Sigma-Aldrich, 59,800 g/mol)/imipenem were effective against the growth of *E. coli* (inhibition zone of 10–14 mm), allowed good proliferation of the fibroblast cells, and maintained up to 1 week the released imipenem. The system containing imipenem was indicated as a novel biocompatible and antibacterial scaffold used for wound and burns dressing. PLA matrix (Sigma-Aldrich, GF45989881) loaded and electrospun with levofloxacin or irgasan (triclosan) and collagen type I were examined. PLA systems were effective in inhibiting the growth of *E. coli* and *S. aureus* (inhibition zone equal to 21 mm for levofloxacin and 10 mm for irgasan) except PLA-collagen-levofloxacin which showed a regrowth of bacteria after 48 h (Hall Barrientos et al. 2017). Weisman et al. (2015) proposed a new class of bioactive 3D printing filaments using gentamicin sulfate (GS) for bone infection treatment and methotrexate (MTX) for inhibition of osteosarcoma. The author found that both molecules retained the antibacterial activity (inhibition zone 12.9–21.35 mm for GS) and the cancer growth-inhibiting cytostatic activity (inhibition of 65% of osteosarcoma cells proliferation for MTX) throughout the manufacturing process despite the heat required for this method. Moreover, the composite showed superior combination of strength, versatility, and enhanced drug delivery. Chitrattha and Phaechamud (2016) also documented the efficacy of PLA (NatureWorks® Ingeo2002D) film loaded with gentamicin sulfate against a wide variety of Gram-positive and Gram-negative microorganisms (inhibition zone of 27.17–35.67 mm) whereas PLA with metronidazole inhibited only *Bacteroides fragilis* (inhibition zone of 54–55 mm). They sustained the antimicrobial activity for a week indicating that PEG 400 filled in PLA enhanced the drug release of films. The authors explained this result considering the porous structure of the films and the high water solubility of PEG likely able to enhance the diffusivity of water and drug into the drug-loaded films. Scaffaro et al. (2017b) prepared antimicrobial PLA (NatureWorks® Ingeo2002D) sheets containing ciprofloxacin (CFX), chosen as model molecule since its melting temperature is higher than that of PLA processing temperature. The incorporation of graphene nanoplatelets (GnPs) improved the stiffness of the system and affected the release of ciprofloxacin without hindering the antimicrobial activity (inhibition zone of 42 mm for CFX and 35 mm for CFX/GnPs). In particular, the presence of GnPs reduced the burst release effect thus suggesting the potential ability of GnP for controlled drug release applications (Scaffaro et al. 2017b). PLA-based materials containing chitosan were also carriers for tetracycline with activity against *S. aureus* (inhibition zone of 11–35 mm) (Jiang et al. 2016). The concentration of *S. aureus* decreased rapidly (absorbance values from 0.9 to 0.04) with increasing Tet content (20%) at first, and then decreased slightly at Tet content beyond 20% (absorbance values from 0.04 to 0.02).

Microbial infections associated with medical devices represent a significant public health challenge (Darouiche 2004). The presence of biofilm-forming microorganisms increases this problem (Fux et al. 2005). Antibiotic-containing fibers hold great potential as an antibacterial and antibiofilm implant coating. Innovative biodegradable PLA-based films, containing different percentages of antimicrobial azo dyes, showed qualitative colorimetric biofilm inhibition against *S. aureus* and *C. albicans* and were indicated for biomedical and antimicrobial active packaging applications (Concilio et al. 2015). Shahi et al. (2017) deposited antibiotic-containing PLA (NatureWorks® Ingeo4060D) nanofibers on titanium dental implants. The authors first studied the in vitro antimicrobial properties against a multispecies peri-implantitis-relevant biofilm such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomita*, and then evaluated its effects on a pre-clinical animal model.

Table 3 Processing and antimicrobial activity of PLA containing conventional and synthetic molecules

Antimicrobial additive	Other additive	PLA grade	Processing	Amount	Microbial strain	Activity	Method	Application	Reference
Azo compound A3 Azo compound A4 Azo compound A5		NatureWorks® Ingeo4060D	Solvent casting Melt compounding	0.01 wt% 0.05 wt% 0.1 wt%	*Staphylococcus aureus* A170 *Candida albicans*	Qualitative colorimetric biofilm inhibition	BA	Biomedical packaging	(Concilio et al. 2015)
Chlorhexidine		NatureWorks® Ingeo2002D	Electrospinning	0.5–5 wt%	*Escherichia coli* DH5a	Inhibition zone 10–16 mm Growth turbidity inhibition	DT, GI	Infection treatment	(Luo et al. 2017)
Ciprofloxacin	Graphene nanoplatelets	NatureWorks® Ingeo2002D	Melt compounding	5 wt%	*Micrococcus luteus* ATCC 10240	Inhibition zone 35 mm	DT	Medical device packaging	Scaffaro et al. (2017b)
Gentamicin sulfate		NatureWorks®	3D Printing	1–2.5 wt%	*Escherichia coli*	Inhibition zone 12.9–21.35 mm Total growth inhibition	DT, GI	Drug delivery system Medical device	(Weisman et al. 2015)
Gentamicin sulfate (GS) Metronidazole (MZ)	Polyethylene glycol	NatureWorks® Ingeo2002D	Solvent casting	3 wt% 15 wt%	*Bacteroides fragilis* ATCC 25285 (*Ba*) *Proteus mirabilis* TISTR 100 (*Pm*) *Pseudomonas aeruginosa* TISTR 781 (*Pa*) *Staphylococcus aureus* ATCC 6538P (*Sa*)	Inhibition zone GS 27.17–35.67 mm (*Ba, Pm, Pa, Sa*) Inhibition zone MZ 54–56 mm (*Ba*)	DT	Wound healing	(Chitrattha and Phaechamud 2016)
Imipenem Chitosan	Polyethylene oxide	Sigma-Aldrich (59,800 g/mol)	Electrospinning	0.3–2.5 wt% 2 wt%	*Escherichia coli* ATCC 35401(*Ec*) *Staphylococcus aureus* ATCC 6538 (*Sa*)	Inhibition zone 10–14 mm (*Ec*) No inhibition zone (*Sa*)	DT	Skin burn infection	(Moslem et al. 2016)
Levofloxacin (LEVO) Irgasan (IRG)	Collagen	Sigma-Aldrich, GF45989881	3D printing	1%, 2.5 wt%	*Escherichia coli* ATCC 8739 *Staphylococcus aureus* ATCC 29213	Inhibition zone LEVO 21 mm, IRG 10 mm Inhibition zone collagen/IRG 4–11 mm	DT	Medical	(Hall Barrientos et al. 2017)
Tetracycline	Polycaprolactone Gelatin	Lactel Absorbable Polymers	Electrospinning	5–25 wt%	*Porphyromonas gingivalis* ATCC 33277 (*Pg*) *Fusobacterium nucleatum* ATCC 10953 (*Fn*) *Prevotella intermedia* ATCC 25611 (*Pi*) *Aggregatibacter actinomycetemcomitans* ATCC 33384 (*Aa*)	Biofilm log reduction ~ 3–4 (*Pg*) Biofilm log reduction > 4.6 (*Fn*) Biofilm log reduction > 5.1 (*Pi*) Biofilm Log reduction 2.7 > 3.7 (*Aa*)	BA, SEM	Dental implant coating	(Shahi et al. 2017)
Tetracycline Chitosan		Self-made (35 kDa)	Electrospinning	3–30 wt%	*Staphylococcus aureus* ATCC 6538	Inhibition zone 11–35 mm Absorbance reduction from 0.9 to 0.02	DT, GI	Drug delivery	(Jiang et al. 2016)
Triclosan (TCS) Ketoprofen (KTP)		NatureWorks® Ingeo2002D NatureWorks® Ingeo4032D	Electrospinning	1 wt% 3 wt%	*Escherichia coli* (*Ec*) *Micrococcus luteus* (*Ml*)	Growth inhibition TCS and TCS/KTP 90–95% (*Ec*), 80–90% (*Ml*) Growth inhibition KTP ~ 10–55% (*Ec, Ml*) Adhesion inhibition TCS and TCS/KTP > 90% (*Ec*), > 75% (*Ml*) Ahesion inhibition KTP < 25% (*Ec, Ml*)	GI, AA	Medical	(Llorens et al. 2015)

BA, biofilm assay; DT, diffusion test; GI, growth inhibition; SEM, scanning electron microscope; AA, adhesion assay

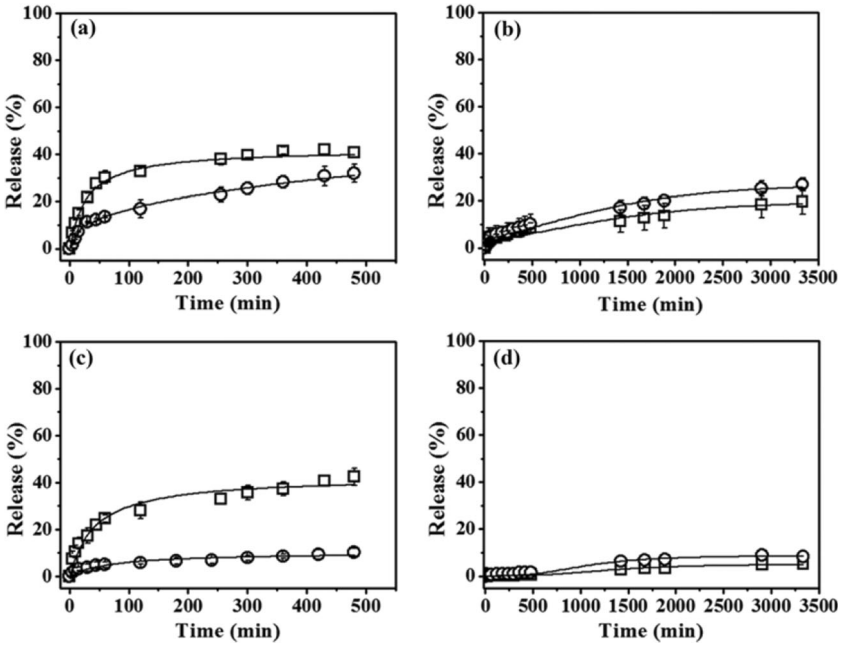

Fig. 3 Release curves in PBS medium of TCS (□) and KTP (○) from single drug-loaded (**a**, **c**) and dual drug-loaded (**b**, **d**) PLA 2002D (**a**, **b**) and PLA 4032D (**c**, **d**) electrospun scaffolds. Reprint with permission of Springer Nature (Llorens et al. 2015)

PLA electrospun microfibers filled with triclosan (TCS), ketoprofen (KTP), or their combination to obtain multifunctional scaffolds with anti-inflammatory and bactericide activities against *E. coli* and *M. luteus* were prepared (Llorens et al. 2015). Specifically, the authors studied the influence of different ratios between L- and D-lactide units on the polymer matrix crystallinity and on the release behavior (NatureWorks® Ingeo4032D and Ingeo2002D). In particular, release of TCS and KTP was found to be dependent on the stereoregularity of the polymer matrix and also on the intermolecular interactions potentially established in dual drug-loaded scaffolds. More in detail, PLA 2002D microfibers showed the highest release percentages, probably as a consequence of the decrease in trapping efficiency caused by their lower molecular orientation and less dense molecular arrangement if compared with PLA 4032D. In fact, TCS and KTP from PLA 2002D scaffolds after 8 h of exposure to PBS medium rose to 40 and 30%, respectively, while these percentages decreased to 30 and 5% for a similar exposure time when PLA 4032D (Fig. 3). Furthermore, a decrease of the release percentage and the release rate for both drugs was detected in the binary system. This feature demonstrates the potential interest of the studied binary system since the intrinsic cytotoxicity of TCS could be suppressed while the bactericide activity could be maintained (growth inhibition of 80–95%).

Luo et al. (2017) proposed a novel no cytotoxic system consisting of electrospun PLA (NatureWorks® Ingeo2002D) fiber with sustained antibacterial properties (inhibition zone equal to 35 mm) filled with uncoated or encapsulated chlorhexidine (0.5 and 1% wt/wt). The encapsulation of chlorhexidine spheres by polyelectrolytes had a fundamental influence on the chlorhexidine release kinetics in H_2O lowering the diffusion of the drug. The use for the treatment of persistent infections in medicine and dentistry was suggested.

Conclusion and future perspectives

PLA-based antimicrobial systems received considerable attention in both academic and industrial research. This mini-review summarizes the recent advances made in antimicrobial PLA-based polymers and highlights the potential of PLA systems as efficient stabilizers–carriers of various kinds of molecules.

Nowadays, there is an increasing consumer demands for fresh, high-quality, and natural foods packaged in environmentally friendly materials that prolong the shelf life. The physicochemical properties of PLA coupled to beneficial properties of incorporated molecules open up interesting perspectives and are likely to lead to the next generation of food packaging materials.

The antimicrobial PLA materials offer novel perspectives also in biomedical area such as drug release systems, wound healing, or coating for medical devices. The antimicrobial-releasing systems can be advantageous to reduce possible dose-dependent side effects and limit the phenomena of antibiotic resistance.

Despite the substantial progress on PLA polymers, further studies on their antibiofilm activity and in vivo studies are needed in order to design promising effective antimicrobial systems. A better understanding of this information will pave the way toward more applications in the near future.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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