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Electrospinning of polylactic acid fibres containing tea tree and manuka oil

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ABSTRACT

Here the effect of tea tree and manuka essential oils (EOs) on the mechanical properties and antibacterial activity of electrospun polylactic acid (PLA) fibres is investigated. It is found that the essential oils work as plasticisers for PLA, lowering the glass transition temperature of the resulting composite fibres up to 60% and increasing elongation-at-break and tensile strength up to 12 times. Manuka EO is particularly successful in blocking the formation of biofilms of *Staphylococcus epidermidis* that is typically involved in nosocomial infections associated with implanted devices. The results demonstrate that natural extracts can be used to control the mechanical behaviour of PLA fibres and to confer antibacterial activity.

1. Introduction

The recent health concerns associated with the side effects of synthetic additives used in pharmacy, cosmetics, agriculture and the food industry have stimulated a consumer demand for natural alternatives [1]. There is therefore a growing interest in plant extracts with biological activity, such as essential oils (EOs). They are complex mixtures of volatile compounds that possess, among other characteristics, antimicrobial, antioxidant, anti-inflammatory, antifungal and anticancer properties [2].

Nanostructured systems containing EOs, mainly produced by electrospinning, have so far been proposed for wound management and food packaging applications [3–16]. For instance, electrospun scaffolds made of a blend of chitosan/poly(ethylene oxide) (PEO) and cinnamon essential oil have been developed for the treatment of infections caused by *Escherichia coli* and *Pseudomonas aeruginosa* [3]. The efficacy against *E. coli* of cinnamon oil has also been demonstrated when cellulose acetate was used as the polymer matrix for nanofibrous dressings [4]. Moreover, in the food sector the antibacterial activity of cinnamon EO has been exploited to fabricate packaging materials that avoid microbial contamination of food and consequently food spoilage [5]. Cinnamon EO and β-cyclodextrin inclusion complex were incorporated into polylactic acid (PLA) fibres, and the inhibition of the growth of *E. coli* and *Staphylococcus aureus* was analysed. Another EO that has been electrospun is lavender oil. Nanofibers of polyacrylonitrile (PAN) [6] and sodium alginate [7] combined with lavender EO were used for preventing bacterial colonisation of skin wounds (*S. aureus* and *Klebsiella pneumonia*). Furthermore, it was demonstrated that dressings made of sodium alginate and lavender oil exhibit anti-inflammatory properties, reducing the production of pro-inflammatory cytokines both *in vivo* and *in vitro* [7]. Electrospun fibres containing thyme [8], peppermint and lemongrass have also been produced [4].

Recently, essential oils have been incorporated into electrospun fibres not only to achieve bioactivity but also to control the thermal properties of the resulting mats [17,18]. Souza et al. have reported 18% reduction of the glass transition temperature (T_g) of PLA fibres when 20% of Linalool was used [17]. In another study, the incorporation of Candeia EO into PLA fibres induced a T_g reduction of 30% (15% of EO) [18]. In both cases, the natural extracts act as plasticisers for PLA, affecting the mobility of the polymer chains and lowering chain-to-chain interactions, as also demonstrated for PLA-EOs films [19].

In this study, the electrospinning of PLA fibres containing essential oils derived from *Melaleuca alternifolia* (Australian Tea Tree oil) and *Leptospermum scoparium* (New Zealand manuka oil) is demonstrated. The EOs extracted from these two different species of Myrtaceae are typically used in aromatherapy and for the treatment of microbial infections. This study investigates the effect that diverse EO concentrations (from 2.5 to 15.0% v/v) have on fibre morphology, thermal and mechanical properties. It is shown that both oils are strong plasticisers for PLA. The glass transition temperature (T_g) of PLA fibres containing Tea Tree and Manuka EO was up to 40 °C lower than the T_g of pristine PLA fibres. Differently from previous studies [17,18], the mechanical

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properties of the composite fibres are also characterised, demonstrating that both elongation at break and tensile strength at break increase by increasing the amount of EO, with values that are up to 12 times higher than those of PLA fibres without EO. PLA/Manuka fibres also possess antibacterial activity, being able to inhibit the growth of *Staphylococcus epidermidis*, which is one of the main causes of biofilm formation on implanted medical devices [20]. The mechanical properties and the bioactivity of the composite PLA/EO mats make them promising as infection-resistant materials for biomedical applications.

2. Experimental section

2.1. Electrospinning process

Solutions for electrospinning were prepared by dissolving PLA (Ingeo™ 4060D supplied by Natureworks LLC) in acetone at 15% w/v concentration. PLA 4060D is an amorphous polymer with an L-lactide content of around 88 wt% and a weight average molecular weight (M_w) as determined by gel permeation chromatography (GPC) of 1.15×10^5 g/mol. The optimum concentration for defect-free nanofibre production is between 2 and 2.5 times the critical chain entanglement concentration (C_e) and the value of C_e for PLA/acetone was found to be 6% w/v [21,22]. Hence the concentration of 15% w/v was chosen.

Tea Tree oil (*Melaleuca alternifolia*) or manuka oil (*Leptospermum scoparium*) were added to the PLA/acetone solution at different concentrations: 2.5, 5.0, 7.5, 10.0 and 15.0% v/v. Tea Tree oil is mainly constituted by terpinen-4-ol, γ-terpinene, α-terpinene and 1,8-cineole; Manuka oil contains triketones, sesquiterpenes and *p*-cymene [23–25]. PLA, PLA/Tea Tree EO (PLA/TT EO) and PLA/Manuka EO (PLA/M EO) solutions were loaded into a 3 mL plastic syringe capped with one 18-gauge needle. The solutions were injected at a constant flow rate of 2 ml/h that was generated by a pump system (PHD ULTRA, Harvard Apparatus). A voltage of 18.5 kV was applied between the needle and an aluminium planar collector, placed at a relative distance of 15 cm. The electrospinning process was conducted at 20 °C, using the Spraybase® Electrospinning equipment.

2.2. Characterisation of the fibrous mats

The morphology of the electrospun fibres was observed using a scanning electron microscope (SEM), with a field emission gun system LEO1530VP. A gold/palladium coating was deposited onto the fibrous mats before imaging using an Emitech SC7640 sputter coater (90 s sputter time).

The chemical analysis of the fibres with and without the essential oils, and of the pristine essential oils was carried using Raman spectroscopy. Raman measurements were performed in a confocal back-scattering configuration with a HORIBA LabRAM HR spectrometer equipped with an Olympus microscope, a liquid-nitrogen cooled Charge-Coupled Detector and a He-Ne laser (excitation wavelength of 633 nm). The laser power on the sample surface was 3.75 mW.

Thermal characterisation of the mats was conducted using differential scanning calorimetry (DSC Q200, TA Instruments Calorimetric Analyser, USA) in a nitrogen atmosphere with a flow rate of 50 ml/min. Approximately 8 mg of each type of mat was sealed in an aluminium pan and heated from − 20 to 100 °C at 10 °C/min. Empty aluminium pans were used as reference. Data were analysed using the TA universal analysis software. All the reported values are the average of 3 samples.

For analysis of mechanical properties, the fibrous mats were detached from the aluminium foil and cut using an ISO527-2/5A die. Tensile tests were carried out using a single column table top Instron system at room temperature. The rate of extension was set at 2 mm/min for the preload stage and at 3 mm/min for the test. Side action grip clamps with flat jaw faces were used.

2.3. Antibacterial tests

The antibacterial activity of the nanofibrous mats containing Tea Tree oil or Manuka oil, was tested against *Staphylococcus epidermidis*. PLA nanofibers without essential oils were used as control. Bacterial cultures were prepared in 2.5 mg/100 ml water LB broth, according to the manufacturer's instructions, and incubated at 37 °C overnight. 11.1 mg LB Agar was dissolved in 300 ml of water and then heated at 120 °C for 15 min. Agar plates were then prepared and inoculated with 1 ml of bacteria culture. The electrospun mats (weight 45 mg) were placed on top of the plates and incubated at 37 °C for two days. Photos of the plates were taken and the zone of inhibition was measured.

3. Results and discussion

The solubility of PLA, Tea Tree oil and Manuka oil in acetone allowed homogeneous solutions to be obtained, which gave good dispersion of the essential oils in the polymer matrix. This had a positive effect on the morphology of the electrospun fibres.

As shown in Fig. 1, SEM analysis of the fibrous mats revealed the absence of defects and beads. Fibres produced from PLA solution without EOs (Fig. 1a) showed a cylindrical and well-defined shape, with overlapping but not merged fibres. The addition of 5% v/v of Tea Tree EO to PLA/acetone solution gave rise to the formation of junctions where fibres merged together, as shown in Fig. 1b and highlighted by the blue circle in the inset of Fig. 1b. The extent of this inter-fibre bonding further increased with the increase of Tea Tree EO concentration, as seen in the inset of Fig. 1c for PLA fibres elecrospun from solutions containing 10% v/v of Tea Tree EO. Two or more fibres have fused together and formed bundles. When the concentration of EO reached 15% v/v, mats with highly interconnected fibres were produced. The fibrous structure is still visible but fibres have merged together and lost their cylindrical shape (Fig. 1d and inset).

The effect of oil concentration was less evident for fibres produced from PLA/Manuka EO solutions (Fig. 1e–g). Only at EO concentration of 15% v/v, the morphology of the fibrous mat changed, with extended regions of contact between fibres but without fusion (Fig. 1g and relative inset). The phenomenon of fibre coalescence has been already reported in the literature. For example, interconnected networks of Fe-N/C Polyvinylpyrrolidone can be formed as a consequence of water absorption [26]; Electrospun fibres of nitrile butadiene rubber tend to fuse together if the crosslinking degree is insufficient [27]. In the case of PLA and EOs, the changes observed in fibre morphology can be attributed to the thermal properties of the composite fibres, as discussed below.

The chemical properties of the mats were characterised by Raman spectroscopy. The Raman spectra of pure Tea Tree (dashed green curve) and Manuka essential oil (dashed magenta curve), and the spectra of the pure PLA fibres (continuous grey curve), PLA/TT EO (continuous green curve) and PLA/M EO (continuous magenta curve) fibres are shown in Fig. 2. The spectrum of PLA exhibits the characteristic band of C═O with one peak at 1770 cm^{-1} and a shoulder at 1754 cm^{-1} [28]. The peaks at 1454 cm^{-1}, 1387 cm^{-1} and 1129 cm^{-1} are assigned to CH_3 asymmetric and symmetric wagging, and bending modes respectively; whereas, the peaks at 1182 cm^{-1} and 1096 cm^{-1} correspond to the OCO stretching mode. The CH bending, C-CH_3 stretching, C-COO stretching and C═O deformation appear at 1297 cm^{-1}, 1045 cm^{-1}, 875 cm^{-1}, and 745 cm^{-1}, respectively [29].

The Raman spectrum of Tea Tree oil (*Melaleuca alternifolia*) in Fig. 2a is characterised by bands assigned to terpinen-4-ol, which is one of the main components of this essential oil [23]. Particularly, the peaks

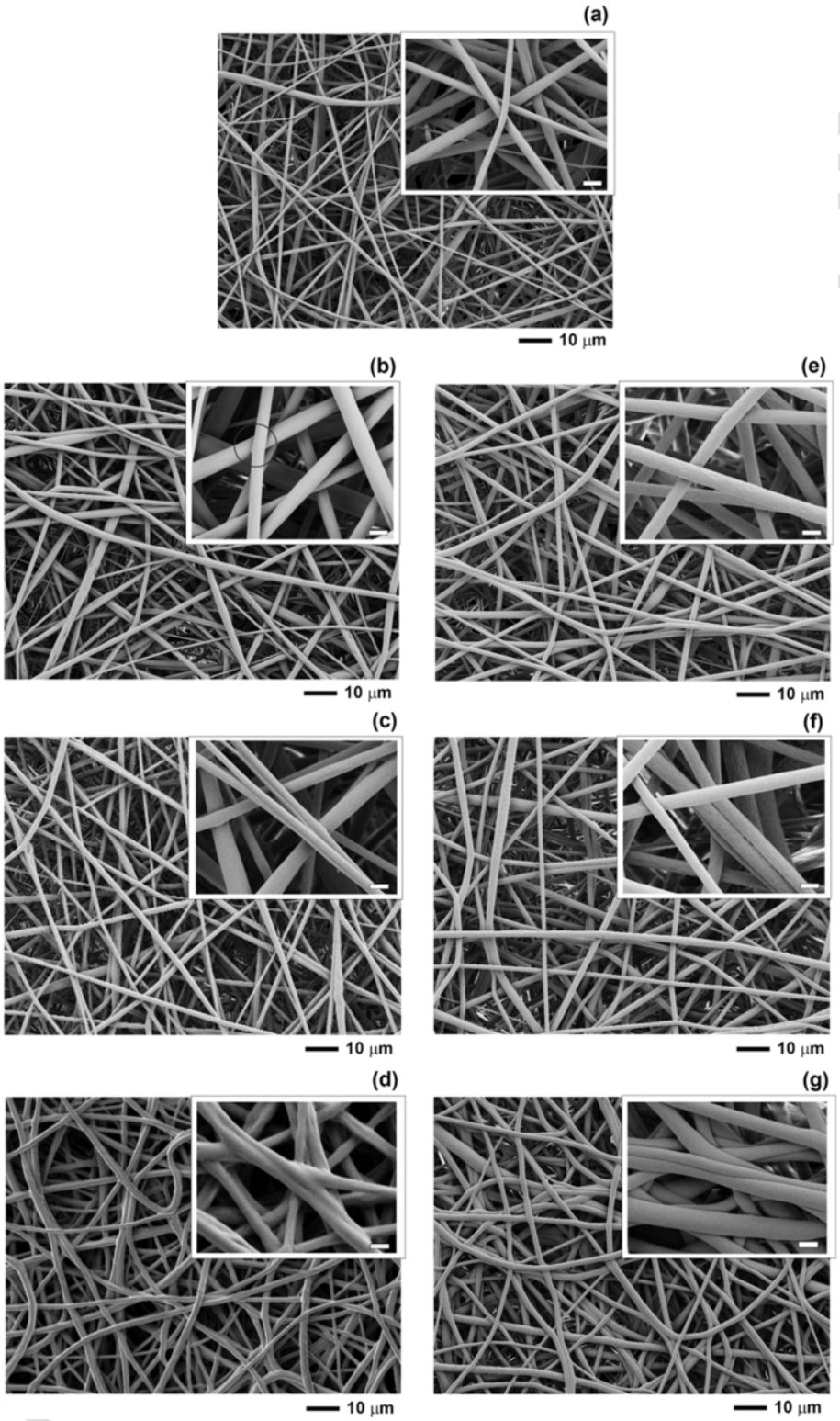

Fig. 1. SEM images of electrospun fibres of (a) PLA, (b) PLA/TT EO (5% v/v), (c) PLA/TT EO (10% v/v), (d) PLA/TT EO (15% v/v), (e) PLA/M EO (5% v/v), (f) PLA/M EO (10% v/v) and (g) PLA/TT EO (15% v/v). Insets: SEM images at higher magnification. Scale bar = 2 μm.

at 1678 cm^{-1}, 1376 cm^{-1}, 1307 cm^{-1} and 730 cm^{-1} correspond to C═C stretching modes of terpinen-4-ol. The presence of γ-terpinene and α-terpinene, which are two other components of Tea Tree EO, is confirmed by the peaks at 1702 cm^{-1} (C═C stretching of γ-terpinene), 1612 cm^{-1} (C═C stretching of α-terpinene), 1425 cm^{-1} (C—H bending of γ-terpinene), 756 cm^{-1} (ring deformation of γ-terpinene). The bands at 1445 cm^{-1} and 652 cm^{-1} are assigned to CH_3/CH_2 bending mode and to 1,8-cineole, respectively. The analysis of the PLA/TT EO fibres reveals the presence of the characteristic peaks of PLA and a reduction of the intensity of some of the bands of Tea

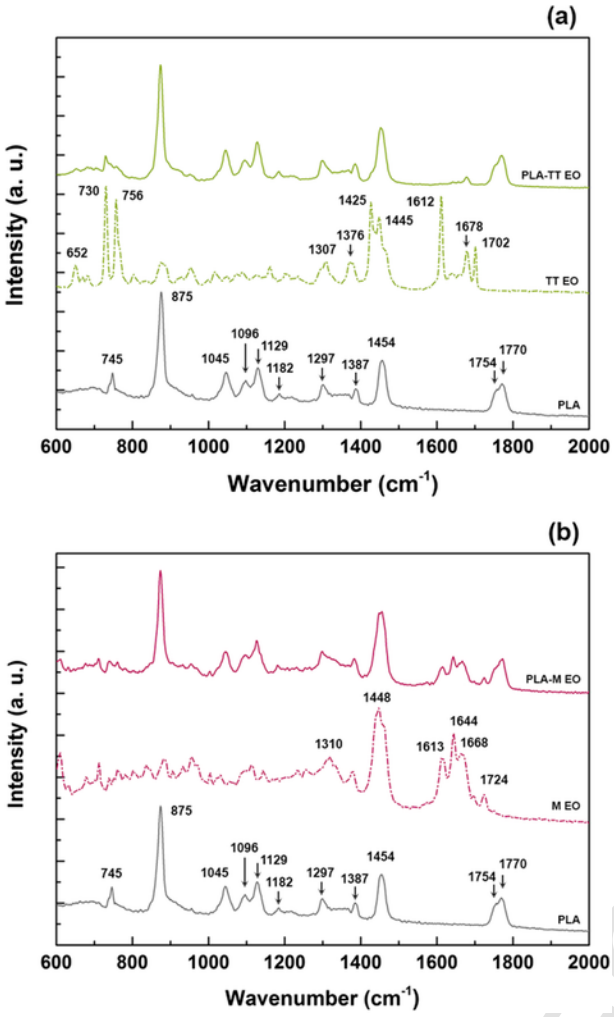

Fig. 2. Comparison of the Raman spectra of PLA electrospun fibres (continuous grey line), essential oils and composite PLA/EOs fibres: (a) pristine Tea Tree oil (dashed green line) and PLA/TT EO (10% v/v) fibres (continuous green line); (b) pristine Manuka essential oil (dashed magenta line) and PLA/M EO (10% v/v) fibres (continuous magenta line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Tree oil, particularly those associated with γ-terpinene and α-terpinene. This can be due to the evaporation of the oil during the electrospinning procedure. The bands of terpinen-4-ol are visible.

The main constituents of *M. alternifolia* oil are not present in Manuka essential oil (*Leptospermum scoparium* from New Zealand), for which the relevant compounds are flavonoids, triketones (such as leptospermone and flavesone), sesquiterpenes (α-copaene and calamenene) and monoterpenes (α-pinene, myrcene, and *p*-cymene) [24,25]. In Fig. 2b, the Raman spectrum of the Manuka EO exhibits bands of triketones at 1724 cm^{-1}, 1668 cm^{-1}, 1448 cm^{-1}, and 1310 cm^{-1} [30,31]. The peaks at 1644 cm^{-1} and 1613 cm^{-1} can be ascribed to C═C stretching mode and ring stretching mode of *p*-cymene, respectively [32]. Those bands are still visible in the spectrum of PLA/M EO electrospun mats together with the peaks of PLA. Therefore, Manuka oil and particularly triketones, which are responsible for the antibacterial activity of this EO [31], are contained inside the fibres.

DSC analysis was performed in order to evaluate the glass transition temperature (T_g) of PLA, PLA/TT EO and PLA/M EO fibres. As shown in Fig. 3, the T_g of PLA fibres (grey bar) was (53 ± 1)°C, in agreement with previous reports [33]. However, PLA/TT EO (light green bars)

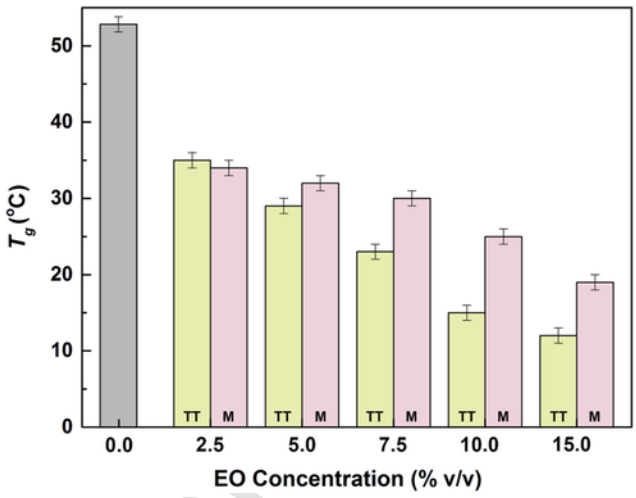

Fig. 3. Glass transition temperature of PLA (grey bar), PLA/TT EO (light green bars) and PLA/M EO (light pink bars) fibres as a function of the EO concentration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and PLA/M EO (light magenta bars) electrospun mats exhibited a lower T_g, which decreased with increasing EO concentration. Fibres produced from PLA solutions with 2.5 and 5.0% v/v of Tea Tree and Manuka EO were characterised by similar values of T_g: around 35 °C and around 30 °C for 2.5 and 5.0% v/v, respectively. For concentrations ranging from 7.5 to 15.0% v/v, the difference in T_g between PLA/TT EO and PLA/M EO fibres became statistically significant, with Tea Tree EO having a greater effect on T_g than Manuka EO. When fibres were elecrospun from PLA solutions with 7.5, 10.0 and 15.0% v/v of Tea Tree EO, T_g values of (23 ± 1)°C, (15 ± 1)°C and (12 ± 1)°C were recorded, respectively. On the other hand, for Manuka EO, T_g dropped to (19 ± 1)°C when 15% v/v of oil was used. Values of T_g in the range of 17–35 °C have been reported for PLA plasticised with low molecular weight molecules (less than 2000 g/mol), such as citrates or terpenes [34,35]. Tea Tree and Manuka oil are compounds with low molecular weight (lower than 500 g/mol) and rich in terpenes [2]. Like plasticisers, they are able to drastically lower the T_g of PLA by enhancing polymer chain mobility and increasing polymer free volume [34,36,37]. The difference in thermal properties between PLA/TT EO and PLA/M EO fibres can be ascribed to the different chemical composition of the two essential oils, as previously demonstrated by Raman spectroscopy.

The thermal properties of the PLA/EOs mats had an impact on their morphology. As previously discussed (Fig. 1c, d and g), inter-fibre bonding was observed for high concentrations of Tea Tree and Manuka EO (10 and 15% v/v). At those concentrations, the samples produced had T_g in the range of 12–25 °C, which was comparable or slightly lower than room temperature (the electrospinning process was conducted at room temperature). As demonstrated in the literature, when electrospun fibres are annealed at a temperature close to their T_g, motions of the polymer chains at the fibre surface or in the bulk of the fibre, depending on the annealing temperature and polymer, give rise to fusion at the fibre-fibre junctions and eventually formation of collapsed structures [38–41]. Therefore, it can be assumed that PLA/TT EO mats exhibited more evident inter-fibre bonding than PLA/M EO fibres because their T_g was much lower than the temperature at which the electrospinning process was carried out.

The plasticising effect of Tea Tree and Manuka oil on PLA also affected the mechanical properties of the composite fibres. PLA fibres exhibited tensile elongation at break (ε_b) and strength at break (σ_b) of (0.3 ± 0.1) and (2.4 ± 0.5) MPa, respectively, in agreement with previous studies (Fig. 4) [40,42]. The incorporation of Tea Tree and Manuka

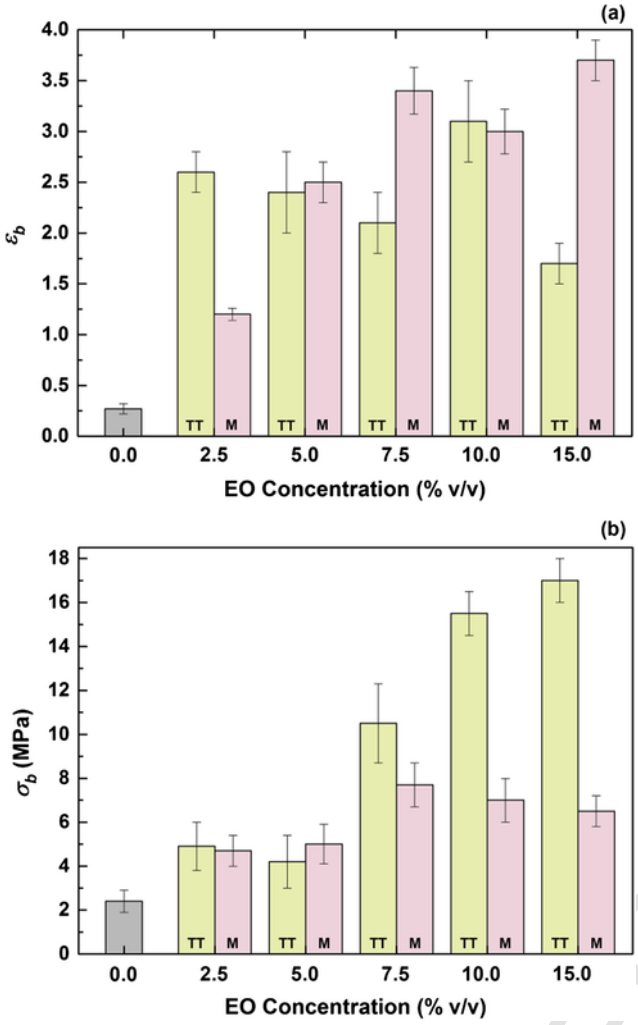

Fig. 4. (a) Elongation-at-break and (b) tensile strength of PLA (grey bar), PLA/TT EO (light green bars) and PLA/M EO (light pink bars) fibres as a function of the EO concentration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

EOs resulted in a significant increase in both ε_b and σ_b. For PLA/TT EO fibres (Fig. 4a), ε_b reached values of (2.6 ± 0.2) when the lowest oil concentration was used (2.5% v/v), namely 8.7 times higher than the ε_b of PLA fibres. Then, with increasing TT EO concentration (up to 10.0% v/v), ε_b remained almost constant with values between 2.1 and 3.1. However, a drop in ε_b was recorded for fibrous mats produced from PLA solutions with 15.0% v/v of TT EO. While the high values of elongation at break (particularly for EO concentrations from 2.5 to 10.0% v/v) are mainly due to the plasticising effect of TT EO, the decrease of ε_b observed for 15.0% v/v concentration can be attributed to the morphology of the fibrous mat. Previous studies have found that incorporating EOs in PLA films leads to increase in elongation at break and the increase tends to be directly proportional to the amount of oil used, as expected for plasticising agents [19,33,44]. In the case of fibres electrospun from 15% v/v PLA/TT EO solution, inter-fibre adhesion, shown in the morphological analysis in Fig. 1d, limits the sliding of fibres on top of each other during tensile deformation, resulting in a lower elongation. Similar behaviour has been observed, for example, for Polyethersulfone electrospun membranes after thermal treatment and for composite Polycaprolactone, collagen and elastin fibres [45,46]. Once tight cohesion between the fibres has been established, the elongation at break of the electrospun mat decreases, contrary to the tensile strength, which increases.

As shown in Fig. 4b, the addition of Tea Tree EO resulted in an increase of σ_b: values of (4.9 ± 1.1) MPa and (4.2 ± 1.2) MPa were measured for fibres electrospun from PLA solutions with 2.5 and 5.0% v/v oil, respectively. The effect of Tea Tree EO on the σ_b was much more evident for EO concentrations higher than 7.5% v/v, (10.5 ± 1.8) MPa, with the highest value reported for concentration of 15.0% v/v, (17.0 ± 1.0) MPa, as expected, due to the morphology of these mats. A previous study on thermally treated PLA electrospun membranes has demonstrated that, as a consequence of the temperature increase, the fibres undergo changes in morphology and fibre-fibre junctions become bonded [47]. Fibre coalescence increases as a function of the temperature together with the tensile strength of the membranes.

Tensile tests conducted on PLA/M EO electrospun samples also showed an increase of ε_b and σ_b with oil concentration (Fig. 4). Differently from PLA/TT EO fibres, ε_b gradually increased from (1.2 ± 0.1) at 2.5% v/v EO concentration to (3.4 ± 0.2) at 5.0% v/v. Then, ε_b remained almost constant, with the highest value of (3.7 ± 0.2) at 15.0% v/v EO concentration. The trend observed for σ_b also differed from that of PLA/TT EO samples, with values in the range of 4.7–6.5 MPa, which were significantly lower than those of the PLA/TT EO samples, and without a large incremental change between the different EO concentrations. The lack of fibre coalescence in PLA/M EO mats can be the reason for the difference in mechanical properties observed for the two types of composite fibres, particularly at higher EO concentrations.

The antimicrobial properties of Tea Tree and Manuka EOs are attractive for preventing microorganism colonisation and biofilm formation [8,48]. As reported in literature, the mechanism of action of essential oils against bacteria is mainly due to the hydrocarbons partition into the bacteria membrane [49]. This induces damages to the cytoplasmic membranes, with disruption of its functions and eventually cell lysis. The effectiveness of the composite fibres produced was tested against *S. epidermidis*. This bacterium is abundant on human skin and often responsible for infections and formation of biofilms on indwelling medical devices [20]. As shown in Fig. 5, PLA mats without EO (Fig. 5a) and with Tea Tree oil (Fig. 5b) were not able to inhibit the proliferation of *S. epidermidis*, and the presence of the biofilm was visible in the agar medium. On the other hand, an inhibition zone of 2 cm in di-

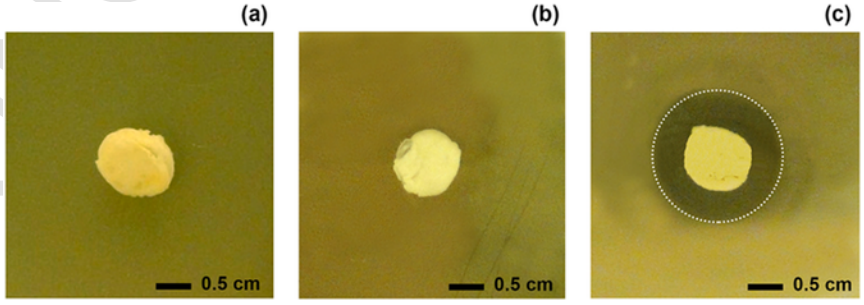

Fig. 5. Photographs of the *in-vitro* test for analysing the activity of (a) PLA, (b) PLA-TT EO (10% v/v) and (c) PLA-M EO (10% v/v) electrospun mats against *S. epidermidis*.

ameter was detected for PLA fibres containing Manuka oil (Fig. 5c), indicating the antibacterial activity of those mats. Although Tea Tree oil is used for the treatment of skin infections induced by *S. epidermidis* [20], in this case its efficacy was limited. This was probably due to the low amount of terpinen-4-ol, and α-terpinene available after the electrospinning process, as demonstrated by Raman spectroscopy. Conversely, Manuka oil was more stable during electrospinning, and the electrospun fibres still contained the compounds that confer antimicrobial properties on this essential oil (triketones) [31]. The glass transition temperature of the fibrous mats had also an effect on the release and diffusion of the active compounds inside the agar gel, leading to the inhibition zone observed. It is known that the use of plasticisers for polymer-based drug delivery systems promotes the release of bioactive agents [50].

4. Conclusions

In conclusion, it is demonstrated that essential oils of Tea Tree and Manuka can be used for enhancing the properties of PLA electrospun fibres, in terms of both mechanical and antibacterial characteristics. Chemical analysis of the fibres through Raman spectroscopy showed that the main components of Manuka oil were stable after the electrospinning process. This was different from Tea Tree oil in which a strong reduction in the intensity of the characteristic peaks was detected. Consequently the antibacterial activity of the composite PLA mats against *S. epidermidis* was affected. PLA/M EO fibres exhibited an inhibition effect against this pathogen, whereas PLA/TT EO mats were ineffective in preventing biofilm formation. Nevertheless, both EOs worked as plasticizers for PLA. In fact, the glass transition temperatures of PLA/TT EO and PLA/M EO fibres were reduced compared with the control PLA fibres. An increase in elongation-at-break as well as in tensile strength was observed for the composite fibres, and it was dependent on the EO concentration used. These results demonstrate that the PLA/EOs combinations studied have the potential to be exploited for the development of biomedical devices of which the mechanical behaviour and bioactivity can be controlled by using natural plant extracts.

Uncited reference

[43]

Acknowledgements

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