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Production, characterization, and antioxidant activity evaluation of *Rheum Ribes* L. extract-loaded PLA/PEG nanofibers

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ABSTRACT: The use of natural compounds such as biocompatible and non-toxic plant extracts, without undesired side effects, in tissue engineering applications, is highly preferred compared to chemical drugs. In recent years, many studies have been carried out to produce nanofibrous materials produced by electrospinning of bioactive plant extracts. Electrospun nanofibers have very large surface area, controllable pore size, and tunable drug release profiles. Several biocompatible polymers with excellent biocompatibility and biodegradability including poly ethylene glycol (PEG) and poly-lactic acid (PLA) have been widely used for the synthesis of nanofibers using the electrospun technique. The ethanol-water extract of the root parts of the *Rheum ribes* L. plant has antioxidant, antimicrobial, and antiurease effects. In this study, the characterization and performance of electrospun Rheum ribes L.-loaded (20 mg, 40 mg, and 60 mg in 20mL) poly (lactic acid) (PLA) (8%, w/v) /Polyethylene glycol (PEG) (1%, w/v) /Tween 80 (3%, w/v) nanofibrous mats for skin tissue engineering were investigated. Morphological (SEM), molecular interaction (FT-IR), thermal analysis (DSC), antioxidant activity and physical analysis were carried out after the production process. According to the results obtained, *Rheum ribes* L.- loaded PLA/PEG nanofibers have smooth fiber morphology in fine structure without beads, proper tensile strength and antioxidant activity. Consequently, Rheum ribes L.-loaded nanofibrous mats are suitable for skin tissue engineering applications.

KEYWORDS: Electrospinning; r*heum ribes* L.; nanofibers; polylactic acid; antioxidant activity; tissue engineering.

1. INTRODUCTION

Antioxidants can be defined as active compound that has reduced the harmful effects caused by free radicals or could delay some mechanisms. Phenolic substances constitute the most important groups of natural antioxidants and they are important sources of antioxidant activity [1]. Phenolic compounds which are synthesized by plants play a major role in protecting the biochemical components of the human body from oxidative stress conditions. However, disease conditions lead to oxidative stress, causing damage to cells. Synthetic chemicals can inhibit oxidative damage but they are also associated with unfavorable side effects. Plant extracts have advantages over prescription drugs; not only are they more cost-effective, easier to produce and process, more available, and more effective, but they also tend to have fewer adverse effects [2]. Therefore, the therapeutic uses of antioxidant drugs made from natural food components are attracting attention due to their non-toxic nature.

Rheum ribes L. (RR), which belongs to the family of Polygonaceae, is one of the most important medicinal Mediterranean plants. *R. ribes* L. which was the subject of many researchers, has a great deal of useful phenolic compounds [3,4]. In addition, extract, which is obtained from RR, is one of the most effective natural compounds in order to destroy free radicals that cause diseases and adverse effect on human health. For this reason, many studies conducted on its antiviral [5,6], antimicrobial [6], antibacterial [7,8], antioxidant [9-11], and anticancer [12].

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Nanotechnology has progressed significantly in a scientific and industrial areas. Over the past few decades application of electrospun nanofiber has attracted a high interest because it has high production rate and simplicity. Based on the method, the spinning conditions, and the polymer solution ambient temperature affect the electrospinning process. With the increasing popularity of nanomaterials in this century, plant extracts with polymers by using electrospinning the technique are gradually becoming widely used in various medical fields. It could also produce new polymeric material scaffolds that support or replace impaired weak cells and tissues from natural parts of plant materials [13,14]. These plants have shown promising potential in pharmacological practices due to their naturally occurring compound that exhibits good antioxidant effects [15].

As we mantioned in our previous study, we evaluated the highest antioxidant activity in correlation with the method of extraction for RR [16]. According to the results, it was concluded that ethanol extracts obtained from the roots of the plant can be used as a natural antioxidant and extraction conditions can be preferred during the encapsulation stage in light of the information obtained.

In this electrospinning approach, fiber can be produced from either natural or synthetic polymers Polylactic acid (PLA) is a biodegradable, biocompatible and ecological polymer. However, PLA nanofiber has the disadvantages of poor flexibility, high brittleness, and low mechanical properties [17]. Therefore, it is important to improve the mechanical properties of PLA nanofiber for application. Poly(ethylene glycol (PEG), an effective plasticizer for PLA and the combined use of, can be preferred, as it provides a large increase in elongation at break [18,19].

To the best of our knowledge, to date there is no report on the development of PLA/PEG incorporated with extract from RR leaf extract. Hence In this study, nanofibers were obtained by adding RR extract at different concentrations into PLA/PEG by electrospinning technique. Pure PLA /PEG and *Rheum Ribes* L. plant extract in three different concentrations were added to mixed solvents. The morphological structures of nanofibers produced in the first step of the study were investigated by Scanning Electron Microscope (SEM). The tensile stress of fibers is an important parameter for designing and sizing nanofibrous structures in this reason the tensile test results were compared to scanning electron micrographs. In the second stage of the study, FT-IR, and DSC tests were performed to identificate different functional groups and bond structures of the fibers. In the last part of the study, a view of the existing methods to measure antioxidant activity and give a general discussion on the meaning of the different values of antioxidant activity [20,21].

2. RESULTS and DISCUSSION

2.1. Morphology of electrospun nanofibers

Processing parameters such as applied voltage, the distance between needle and collector, solution flow rate, temperature, and relative humidity affect the transformation of polymer solutions into fibers in the electrospinning process [22]. The morphological structure of the produced nanofiber samples was examined using electron microscopy. All nanofiber samples have smooth fiber morphology in a thin structure without beads. The mean fiber diameter of the PLA-PEG-Tween 80 sample was determined as ϕ=1681.14 ± 530,918 nm (Figure 1). A significant thinning of the mean fiber diameters was experienced with the inclusion of the plant extract. Average fiber diameters of plant extract- loaded nanofiber mats; It was measured as ϕ=759.32±150.986 nm for 20 mg RR; ϕ=688.85±121.04 nm for 40 mg RR and ϕ=567.26±130.85 nm for 60 mg RR. Consequently, plant extract-loaded nanofiber mats indicated smaller diameters compared to PLA/PEG/Tween 80 nanofibers. A similar observation was reported by Cam et. al. [23].

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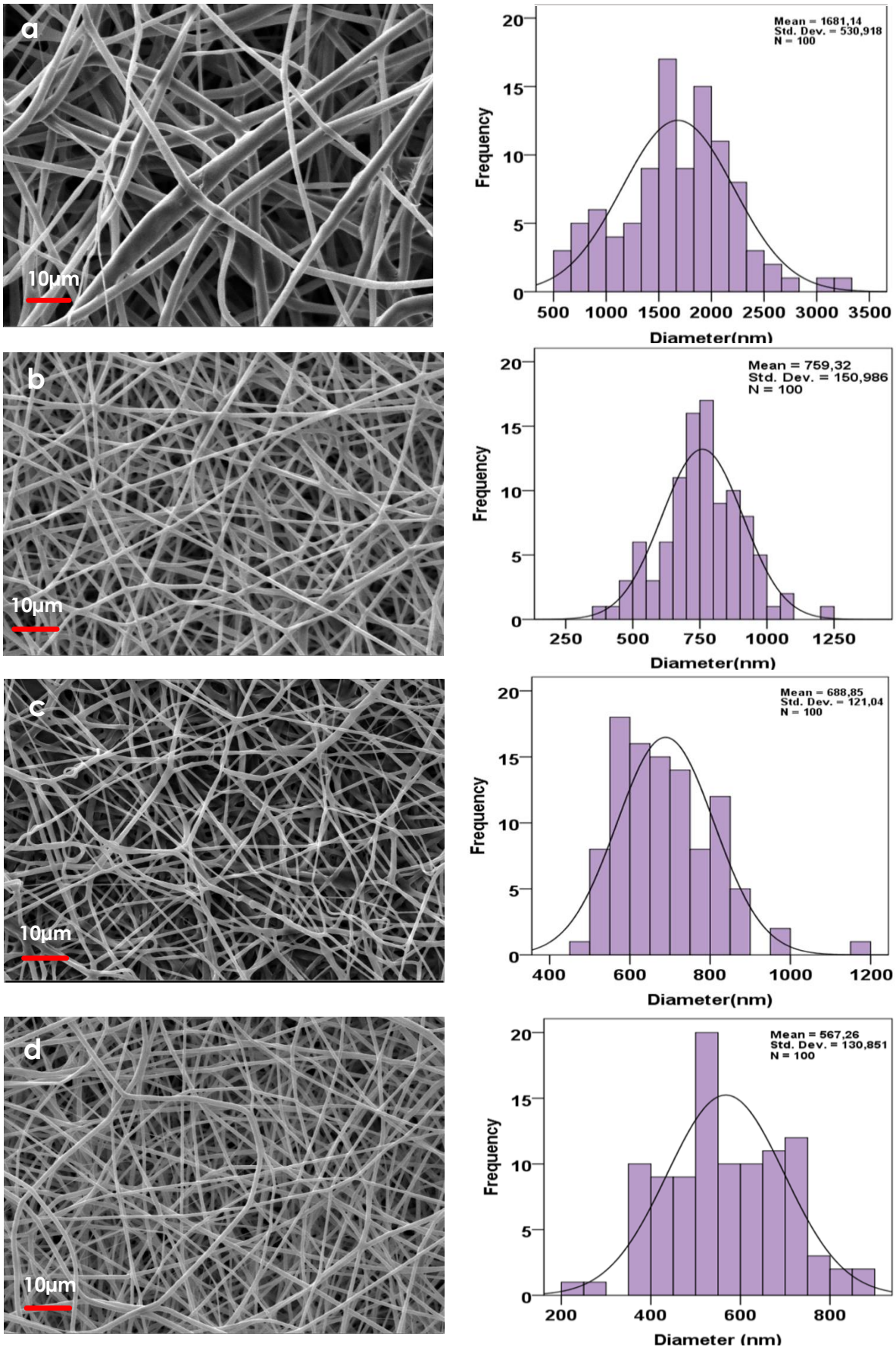

Figure 1. SEM images and fiber diameter distribution of (a) Pure PLA/PEG (b) PLA/PEG/20mg RR (c) PLA/PEG/40 mg RR (d) PLA/PEG/60 mg RR

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2.2. Fourier transform infrared spectroscopy

The chemical bond structure for PLA/PEG and RR-loaded nanofiber mats was investigated by FT-IR spectroscopy. The results of the FTIR analysis of the molecular structure are shown in Figure 2. The characteristic absorption bands of PEG were observed in the -CH_2- group stretching vibration at 2884 cm^{-1}, C-O-C group stretching vibration at 1248 cm^{-1}, 1113 cm^{-1} and 963 cm^{-1} [24]. The characteristic absorption bands of PLA were observed in the C-O vibration peak at 1749 cm^{-1}, CH_3 asymmetrical scissoring at 1453 cm^{-1}, C–O, C–O–C stretch at 1080 cm^{-1}, C–CH_3 stretching at 1042 cm^{-1} and The C–COO stretch peak at 867 cm^{-1} [23]. In the FTIR spectrum of RR, the peaks of organic compounds at 3217, 2919, 1429 to 1675 and 1009 cm^{-1} belonging to the O-H, C-H, C=C, C=O, and C-O bond confirm the linkage of RR secondary metabolites [25]. Similar types of peaks with different intensities were obtained in the FTIR spectra for RR-loaded nanofibers. These results indicate successful formulation and encapsulation.

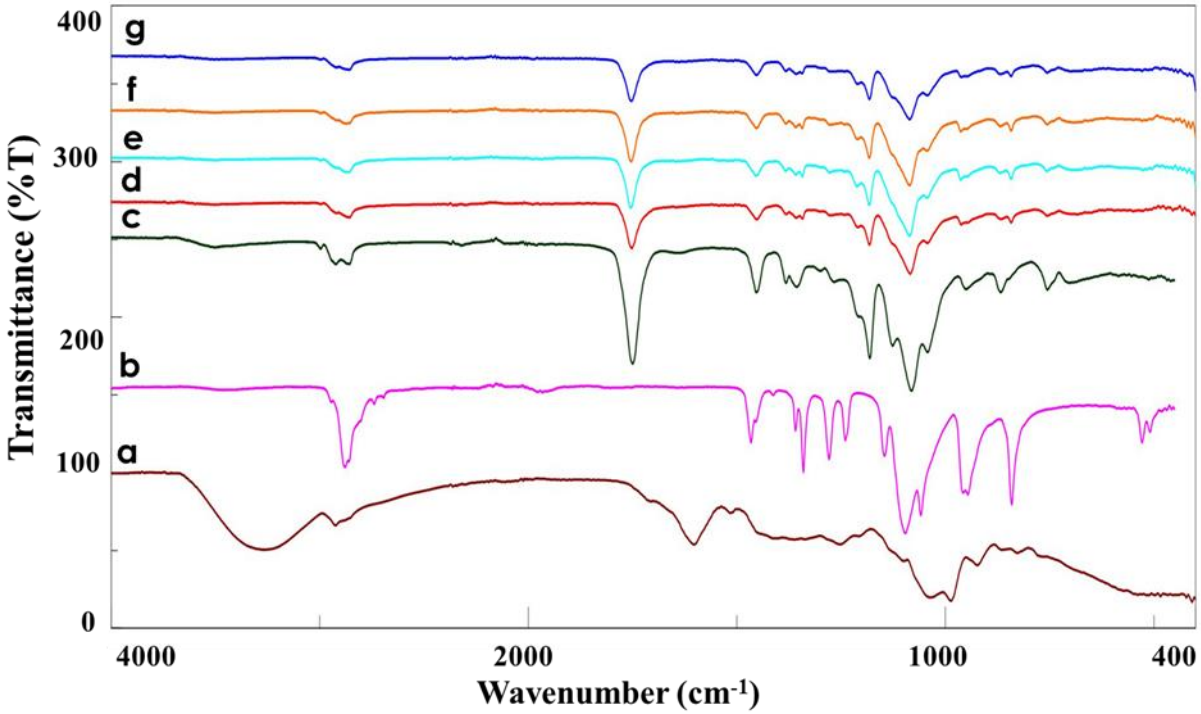

Figure 2. FTIR spectra of the (a) RR extract, (b) PEG, (c) PLA, (d) PLA-PEG-Tween 80 nanofiber, (e) PLA/PEG/20 mg RR nanofiber, (f) PLA/PEG/40 mg RR nanofiber and (g) PLA/PEG/60 mg RR nanofiber

2.3. Differential scanning calorimetry analysis

In the thermogram obtained as a result of the thermal analysis using a differential scanning calorimeter device, sharp endothermic peaks were observed indicating that the crystal structure of the polymer chains was disrupted. These peaks indicate the melting curve of polymers. The main thermal transitions and heating processes of the nanofibers were analyzed by DSC, respectively, as shown in Figure 3. The DSC results show that cold crystallization is in a highly amorphous form in pure PLA/PEG, while decreasing cold crystallinity is associated with an increase in the RR ratio [23]. Considering all DSC data, loading of RR affects the molecular chain mobility of PLA/PEG nanofibers and causes a change in the thermal behavior of the material.

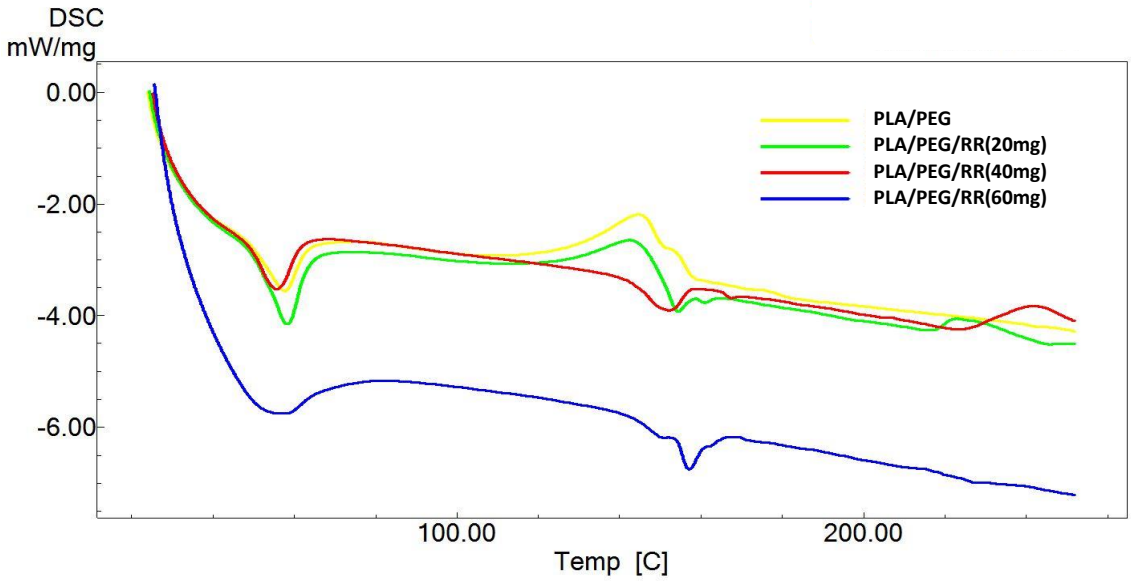

Figure 3. DSC thermogram of pure PLA/PEG and RR-loaded nanofibrous mats in three different concentrations (20, 40, and 60 mg)

2.4. Mechanical Properties

The tensile strength and strain at break for each nanofiber sample are indicated in figure4. When we look at the tensile strength and strain at break measurement results when R.R. extract was added to the PLA/PEG combination, it was observed that strain at break values increased proportionally with the concentration of R.R. extract but the tensile strength values decreased proportionally with the concentration of R.R. extract (Figure 4) [26].

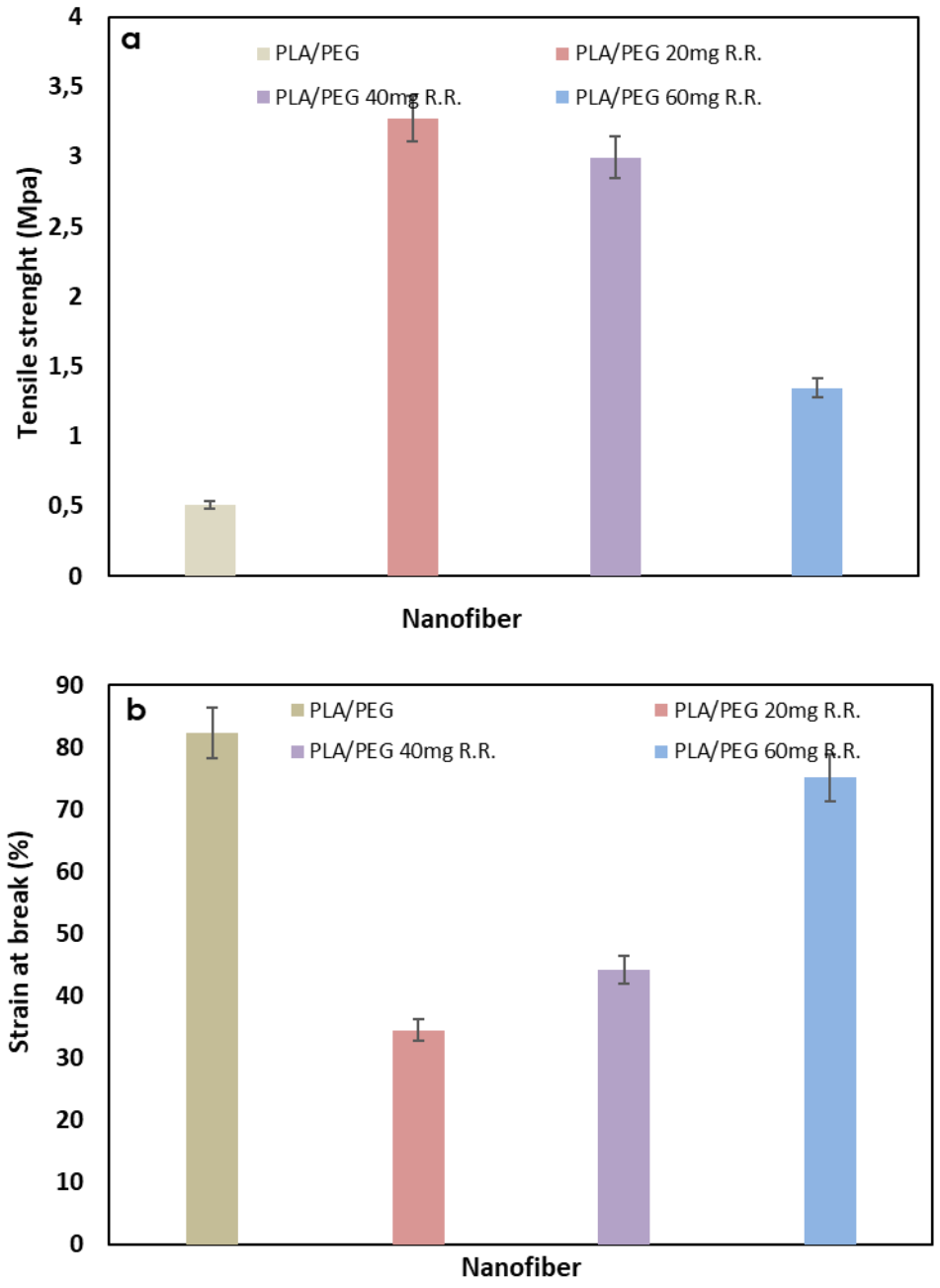

Figure 4. Physical parameters of nanofiber mats: (a) tensile strength and (b) strain at break

2.5. Phenolic content and antioxidant properties

The total phenolic content of Rheum ribes L. loaded nanofibers was determined with Folin-Ciocalteu reagent and the free radical scavenging activity of nanofibers was determined using DPPH. radical. In Figure 5, it is seen that PLA/PEG/Tween 80 fiber (control) has very weak DPPH. antioxidant activity and reducing capacity, while PLA/PEG/Tween80/RR fibers exhibit significant antioxidant activity. This indicates that exposure to high voltage during the electrospinning process does not affect the antioxidant activities. As expected, pure PLA/PEG/Tween80 did not show any antioxidant effect; however, it served as a reservoir and protection system for the antioxidants found in the RR investigated [27].

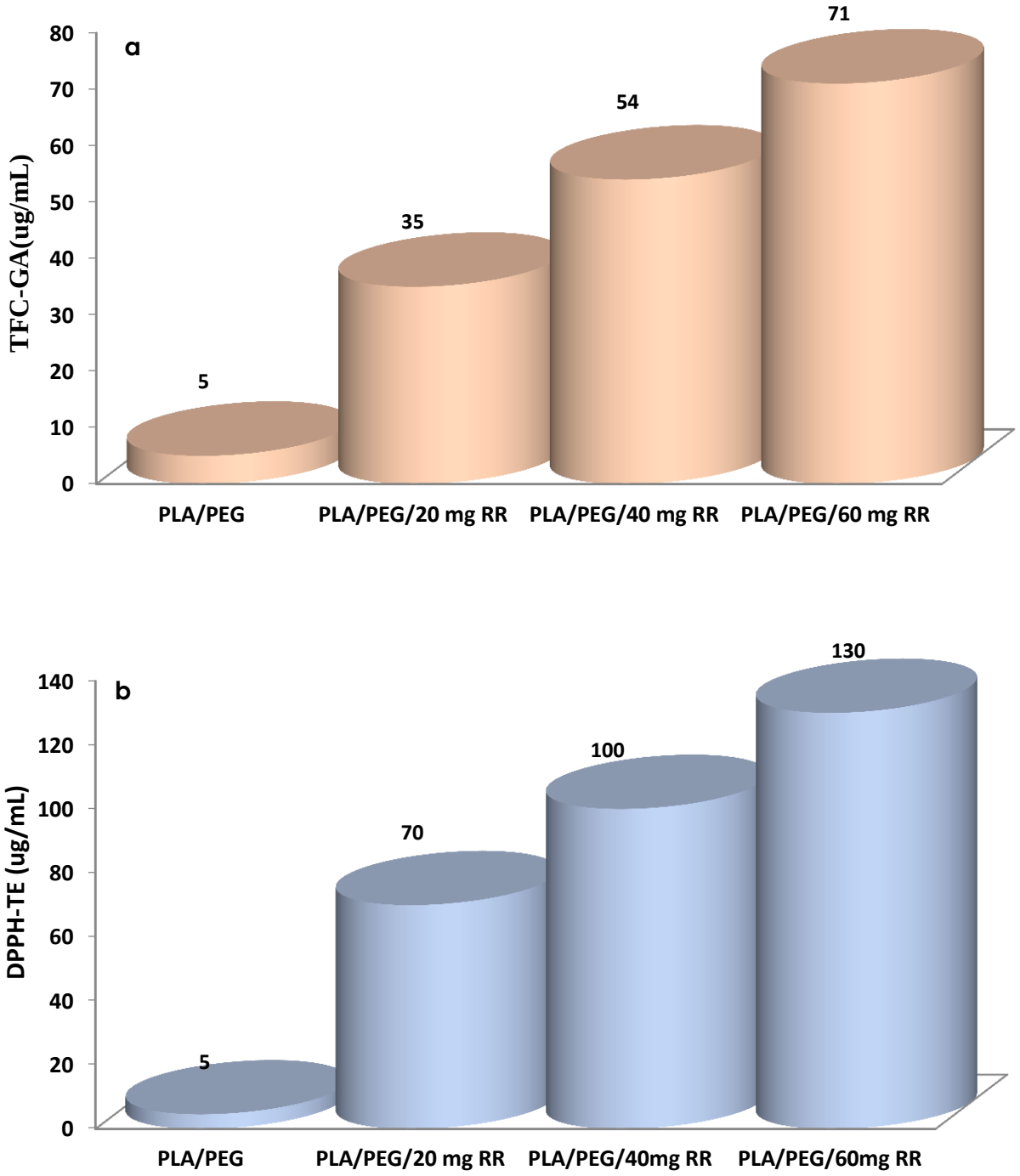

Figure 5. Total phenolic content and antioxidant activity of nanofiber mats: (a) Folin-Ciocalteu reagent, (b) DPPH· radical

3. CONCLUSIONS

In this study, nanofibers loaded with R. Ribes extract, which will increase biocompatibility and bioactivity, together with PLA/PEG polymers were produced using electrospinning methods. The morphological, chemical, thermal and mechanical properties of all fiber samples formed by the electrospinning method were examined and the results were evaluated. Characterization tests showed that different concentrations of RR were successfully loaded on PLA/PEG/Twen 80 nanofiber mats by the electrospinning method. Characteristic chemical bonds of PLA and PEG were observed in the FTIR analysis, confirming successful fiber production. In addition, considering the SEM results of the fiber samples

produced, it was observed that the nanofibers produced by electrospinning were nano-scale, beadless, and regular fibers. Consequently, the tensile test observed that adding RR to the PLA/PEG combination increased the stress at break. As a result of thermal characterization, it has been shown that the fibers can be used at body temperature (35-38°C) without any degradation or phase change. Considering all the results, it is concluded that RR-loaded nanofibers have promising potential for biomedical applications.

4. MATERIALS AND METHODS

4.1. Materials

Polylactic acid (PLA) 2003D was purchased from Nature Works LLC, Minnetonka, MN. Polyethylene glycol 4000 (PEG 4000) Mw ¼ 3500–4500 g/mol, Acetic acid (CH3COOH), Chloroform and Tween 80 (viscous liquid), Citric acid, 1,1-Diphenyl-2-picrylhydrazyl radical (DPPH); 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox); 2,4,6-tri(2-pyridyl)-s-triazine (TPTZ), Folin-Ciocalteu phenol reagent, gallic acid (GA), Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), sodium carbonate, PBS (phosphate-buffered saline) pH 7.4 solution were purchased from SigmaAldrich.

4.2. Preparation of plant extracts

The root parts of Rheum ribes L. plant were collected from Bingöl province in June. The extraction procedure was described by Alkaya et al.2019 [16]. The dried material was ground in a blender and turned into fine powder. 2 g of powdered Rheum ribes L. roots were then extracted in an ultrasonic extraction device at 60°C with 70% ethanol for 1 hour and three consecutive extractions. The extract was filtered with Whatman blue band filter paper and evaporated to dryness in the Evaporator at 50°C under reduced pressure. The resulting residues (crude extracts) were weighed, then transferred to bottles and kept at +4°C. These crude extracts were dissolved in DMSO and used for the evaluation of nanofiber production.

4.3. Preparation and characterization of electrospinning solutions

PLA was dissolved in chloroform at magnetic stirring (IKA, RCT, Germany) for about 2 h to obtain the concentration of 8% (w/v) at room temperature. Than 3% by weight of Tween 80 was added to the PLA solution and mixed for an additional 15 minutes. After mixing, 1% PEG was added to this solution and this mixture was stirred for 10 minutes [28].

To prepare electrospinning solutions containing RR plant extract, RR extracts solutions prepared in ethanol (70:30, v/v) at different concentrations (20 mg/20 mL, 40 mg/20 mL, and 60 mg/20 mL) were added to the PLA/PEG/Twin 80 mixture and this solution was stirred for 20 minutes, separately. Pure nanofiber (PLA/PEG/Twinn 80), PLA/PEG/Twinn 80/RR (prepared in 3 different concentrations by electrospinning at ambient conditions (25 ^{o}C).

4.4. Fabrication of Electrospun Nanofibers

The electrospinning method was utilized for the fabrication of nanofibers. The experimental setup composes a syringe pump (NE-300, New Era Pump Systems, Inc., USA), a single brass needle (diameter of 1.63 mm), a high voltage power supply connected to the needle, and a laboratory scale electrospinning unit (NS24, Inovenso Co., Turkey). The homogeneous polymer solutions were filled into 10 ml plastic syringes. For electrospinning, the solutions were delivered with a constant flow rate of 2 ml/h using a syringe pump. The voltage was subjected to about 18 kV. The working distance between the needle tip and the oily paper-coated circular collector was set to 120 mm. All the experiments were performed at ambient conditions (25 0C) and humidity (%40-45) [29].

4.5. Characterization of Nanofibers

4.5.1. Scanning electron microscopy

The morphology of nanofibers was observed by scanning electron microscope (SEM) (EVO LS 10, ZEISS) after being coated with gold-palladium for 120 seconds. The applied accelerating voltage was 10 kV. The diameters of the electrospun nanofibers were measured by the image analysis software (Olympus AnalySIS, USA) by choosing 100 fibers from each SEM image randomly. The collected data were transferred to SPSS software for further analysis.

4.5.2. Fourier transform infrared spectroscopy (FTIR)

Fourier-transformed infrared spectroscopy (FTIR) analysis was used to qualitatively characterize the functional groups of electrospun nanofibers (Jasco FT/ IR-4700). Each spectrum was recorded between 4000 and 400 cm-1 and averaged over 32 scans with 4 cm-1 resolution.

4.5.3. Differential scanning calorimetry (DSC)

The main thermal transitions and the heating runs of nanofibers were analyzed by DSC (Shimadzu DSC-60 Plus). Temperature ranges were adjusted from 25 ◦C to 300 ◦C for all electrospun nanofiber groups (scanning rate of 10 ◦C/min.).

4.5.4. Mechanical Properties

Before the testing, each different sample was sectioned into five rectangular-shaped samples which are 5 cm in length and 1 cm in width and the thickness of the nanofibrous meshes of different types was calculated using a digital micrometer (Mitutoyo MTI Corp., USA). The mechanical properties were analyzed with a tensile testing machine (Shimadzu Corporation, EZ-LX, Kyoto, Japan). For each group, three different samples were tested.

4.5.6. Total phenolic content

The total polyphenols content of RR-loaded nanofibers was determined by the Folin Ciocalteu method [30]. Firstly, nanofiber samples (0,01g) were extracted with %70 ethanol (v/v) using a orbital shaker-incubator (BIOSAN ES-20) at a constant stirring speed (200 rpm, at 37 °C) for 1 hour. Briefly, 100 µL of each sample was mixed with 4 mL water and 100 µL of Folin-ciocalteu reagent. Then, 100 µL of sodium carbonate (6%) was added to each sample. The absorbance was measured between 685-760 nm after 30 min reaction by using a spectrophotometer (Shimadzu UV-1601, Japan). The calibration curve was prepared using gallic acid standard, in the concentration range of 62.5 – 1000 µM (y = 0.0018 x- 0.0079, r2 = 0.9998). Results were expressed as gallic acid equivalents (GAE/mL). All measurements were repeated three times.

4.5.7. Determination of radical scavenging ability by using DPPH. method

DPPH radical scavenging activity of RR-loaded nanofibers was determined according to Ayaz Seyhan [21]. Briefly, 1,5 mL of each sample was mixed with 1,5 mL DPPH. radical solution (100µM) using an orbital shaker-incubator (BIOSAN ES-20) at a constant stirring speed (200 rpm, at 37 °C) for 30 min. The absorbance was measured between 515-528 nm by using a spectrophotometer (Shimadzu UV-1601, Japan). The calibration curve was prepared using trolox standard, in the concentration range of 62,5 – 1000 µM (y =- 0.06 x + 0.6164, r2 = 0.9954). Results were expressed as the trolox equivalents (TE/mL). All measurements were repeated three times.

4.5.8. Statistical analysis

The statistical analyzes of the data obtained as a result of the measurements were made using a single-factor ANOVA analysis program. Diameter measurements of nanofibers were made using the SPSS analysis program. All results are given as the mean ± STD. Statistical significance was defined as $p < 0.05$.

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