








## Article

# Development of *Inula graveolens* (L.) Plant Extract Electrospun/Polycaprolactone Nanofibers: A Novel Material for Biomedical Application

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**Abstract:** Recently, there has been a growing interest in research on nanofibrous scaffolds developed by electrospinning bioactive plant extracts. In this study, the extract material obtained from the medicinal plant *Inula graveolens* (L.) was loaded on polycaprolactone (PCL) electrospun polymeric nanofibers. The combined mixture was prepared by 5% of *I. graveolens* at 8% (PCL) concentration and electrospun under optimal conditions. The chemical analysis, morphology, and crystallization of polymeric nanofibers were carried out by (FT-IR) spectrometer, scanning electron microscopy (SEM), and XRD diffraction. Hydrophilicity was determined by a contact angle experiment. The strength was characterized, and the toxicity of scaffolds on the cell line of fibroblasts was finally investigated. The efficiency of nanofibers to enhance the proliferation of fibroblasts was evaluated in vitro using the optimal *I. graveolens*/PCL solutions. The results show that *I. graveolens*/PCL polymeric scaffolds exhibited dispersion in homogeneous nanofibers around  $72 \pm 963$  nm in the ratio 70/30 (V:V), with no toxicity for cells, meaning that they can be used for biomedical applications.

**Keywords:** electrospun; *Inula graveolens* (L.); polycaprolactone; scaffolds; cell culture

## 1. Introduction

*Inula graveolens* (L.) belongs to the family of Asteraceae, which is traditionally used in some medicines and food additives [1,2]. It is an annual herbaceous genus of plant species that usually grow in Iraq, Southwest Asia, and Mediterranean regions [3]. Recent studies indicated that the methanol extract of this plant has antioxidant and antimicrobial activities [4]. In recent years, electrospun technology based on nanofibers has attracted a huge deal of interest because it is simple and can be easily controlled. It could also produce new polymeric material scaffolds that support or replace impaired weak cells and tissues from natural parts of plant materials [5,6].

Electrospinning is an evolving nanofiber manufacturing technique that has attracted attention due to its versatility and relatively low cost. Electrospinning is widely used in

tissue engineering for biomedical purposes, such as possible injury healing and scaffolding to replace damaged tissues, support cell growth, and support interactions that can mimic the body's environment [7–9]. A variety of criteria, such as biodegradation, biocompatibility, mechanical properties, scaffolding architecture, and manufacturing technology, are considered when designing or assessing a tissue engineering scaffold [10]. Such new biomaterials with desired properties will fulfill the requirement of fabric engineering that minimizes the secondary effects of other materials. Natural polymers from green plants are renewable [11,12]. Electrospinning of a polycaprolactone (PCL)/gelatin(Gel)/hyaluronic acid(HA) blended solution composite scaffold has been shown in recent studies to be an efficient technique for modifying PCL nanofibrous scaffolds for 3D glioblastoma cell culture [13]. Polycaprolactone (PCL), silver nitrate (AgNO<sub>3</sub>) and zinc oxide (ZnO) were used for the fabrication of a multilayered antibacterial nanocomposite material using coaxial electrospinning (CAE) as described by Guner CETIN et al. [14]. It was indicated that electrospun plants and their derivatives' nanofibers such as polysaccharides provide unique characteristics which will lead to enhancing wound healing, such as good biocompatibility, liquid absorption, strong durability, minimum toxicity, and antibacterial activities. Lacob et al. [15]. The impact of the aligned and randomly orientated PCL scaffolds was studied by Abbasi et al. [16] on quantitative gene expression during neural stem cell differentiation by real-time polymerase chain reaction (RT-PCR). An investigation by Jahani et al. [17] studied the production of nerve cells from mesenchymal stem cells through PCL nanofibrous scaffolds as a 3D matrix to induce cell proliferation and differentiation. In addition, co-electrospun collagen with poly (vinyl alcohol) (PVA)/N-[(2-hydroxy-3-trimethyl-ammonium)-propyl] chitosan chloride) (HTCC) has been shown to develop a scaffold with good biocompatibility, and mechanical properties. as described by Khalaji et al. [18]. A biodegradable polymer such as poly( $\epsilon$ -caprolactone) has been extensively applied in the electrospinning method and has multiple biomedical applications due to its interesting mechanical properties and biocompatibility [19,20]. However, because of its hydrophobicity, it is not easy to provide an ability for cell adhesion, development, and proliferation. The combination of plant and synthetic polymers by electrospinning is, therefore, a promising way of overcoming these challenges [21]. On the other hand, *I. graveolens* is cheap and readily available, and it is possible to produce scaffolds at a low cost.

In this study, the electrospinning technique was used to produce polymeric scaffolds from a natural polymer derived from *I. graveolens* loaded with biocompatible PCL polymer, which was chosen as a carrier for its favorable surface properties to produce a novel material scaffold with better characterization for biomedical applications.

There are different ratios of both *I. graveolens* and PCL that were used via electrospinning methods, and we selected the sample with *I. graveolens*/PCL ratio of 3:7 (V:V), and the sample with ratios was adapted depending on the properties of the resulting fibers. Then, we carried out several tests to investigate morphological features of nanofibers and beads, including FT-IR for the analysis of functional groups in scaffold, and a contact angle test was used to detect the hydrophilicity of the scaffold, and the tensile strength was observed. Finally, suitable conditions of the prepared polymeric scaffold for fibroblast cells were obtained.

## 2. Materials and Methods

### 2.1. Plant Extract

*I. graveolens* was obtained from Basrah governorate, Iraq, during October 2020. The samples were identified and deposited in the Herbarium Department, Science College, Basrah University, Iraq. The aerial parts of a plant extracted with a Soxhlet Instrument after cleaning and drying. In short, 100 g was soaked in 80% methanol at room temperature for 24 h. The methanolic extract was filtered and evaporated to dryness under reduced pressure in a rotary evaporator to afford 10 g of dry extract.

PCL polymer with a molecular weight of  $M_n = 80,000$ , acetic acid, and formic acid was provided by Sigma-Aldrich, the Dimethyl sulfoxide (DMSO), phosphate buffer saline (PBS), Dulbecco Modified Eagle's Medium (DMEM) Culture medium, MTT agent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and other supplements were obtained from Invitrogen.

## 2.2. Fabrication of PCL/*I. graveolens* Solution and Suspension

Firstly, various amalgamations of PCL and *I. graveolens* with several ratios and concentrations were prepared and subjected to the electrospinning. The 3/7 ratio was ultimately selected for the combination of *I. graveolens*/PCL polymer.

A PCL solution (8 wt.%) was prepared separately by dissolving 0.08 g of PCL in 1 mL in acetic/formic acid (1:2 w/w) under magnetically stirring at room temperature. A solution of *I. graveolens* concentration of 5 wt.% was acquired by dissolving 0.05 g of *I. graveolens* in in acetic/formic acid (1:2 w/w). The homogenous mixtures of *I. graveolens*/PCL were obtained with a ratio of 3/7 (V:V).

## 2.3. Electrospun

The feeding rate and the distance between the needle and the collector were set at 0.5 mL/h and 20 cm, respectively; the optimum voltage was 8 kV, and the polymer feed rate was 0.5 mL/h. The aluminum sheet was used for collecting the fibers. Electrospinning was performed at a temperature of 25 °C and a relative humidity of 20%.

## 2.4. Characterization

SEM tested the morphological characteristics of the generated nanofibers of *I. graveolens*/PCL scaffold by coating the surface of nanofibers with a thin layer of 5 mA gold undercurrent and voltage of 6 kV and the morphology of the fibers was tested.

## 2.5. FT-IR

Various electrospun specimens with FTIR were analyzed. Chemical analysis of the prepared nanofibers was conducted. The spectrum was scanned at a resolution of  $4\text{ cm}^{-1}$  over a spectrum of  $500\text{--}4000\text{ cm}^{-1}$ .

## 2.6. XRD

For XRD measurements, for PCL nanofibers and *I. graveolens* extract, loaded PCL nanofibers were obtained using Philips apparatus at an angle of  $(2\theta)$  around  $10^\circ$  and  $80^\circ$ , with Cu as a reference at wavelengths of  $1.5406\text{ \AA}$  ( $\lambda$ ).

## 2.7. Tensile Strength

The analysis was performed according to ASTM D 5035 (Standard Test Method for Breaking Force and Elongation of Textile Fabrics (Strip Method)) to estimate tensile strength. Samples were measured with a width of 2.54 cm, and 5 cm each was constructed in a warp direction, the weft direction, with a length of 15 cm.

## 2.8. Water Contact Angle

A sessile drop water angle approach was used to test the weight ability of an electrospun fibrous scaffold using the OCA 20 surface analyzing system (GmbH, Filderstadt, Germany). Distilled water was used as a solvent to generate a droplet on the nanofiber surface. The touch angle captured the images and processed them. For each sample, triple testing and mean  $\pm$  SD values were conducted.

## 2.9. Cell Culture

The fibroblasts' (rat dermal) cell line was obtained from (Sigma- Aldrich, Hamburg, Germany). Fibroblasts cells were cultured by Dulbecco's modified Eagle medium, enriched

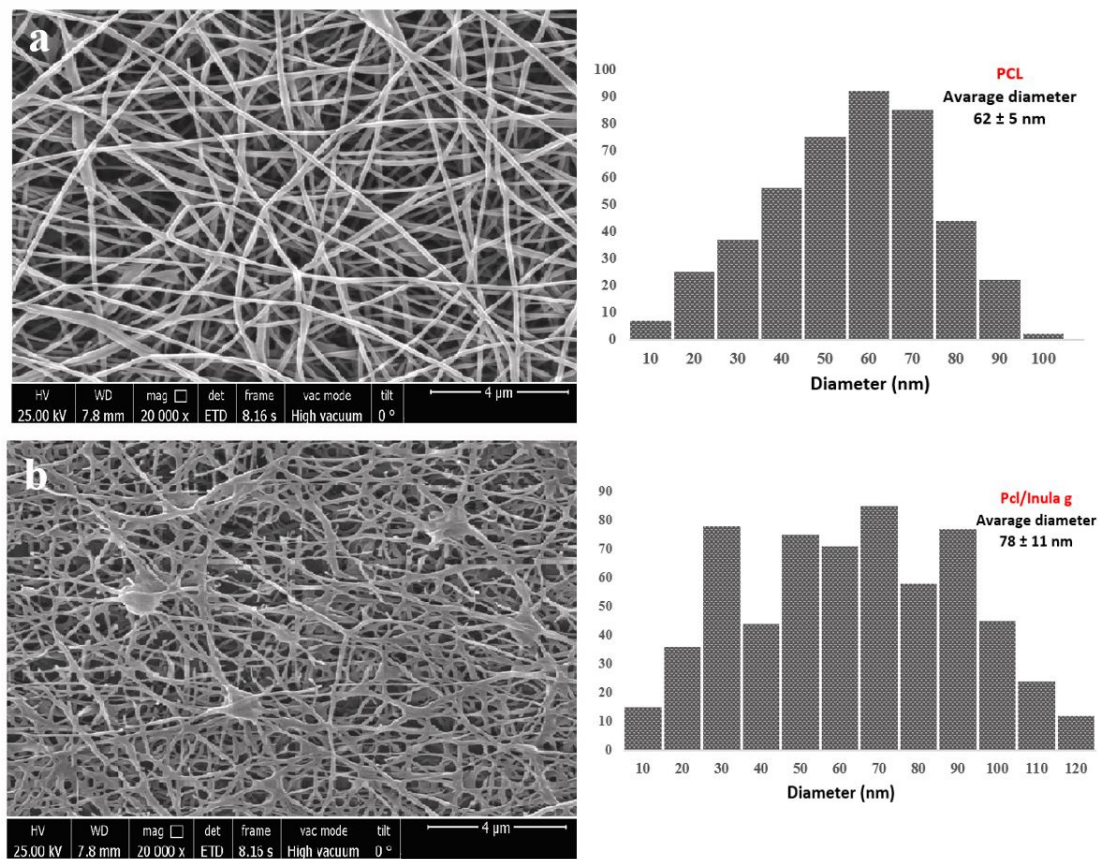
with 15% fetal bovine serum, streptomycin (100 µg/mL) and penicillin (100 µg/mL) and humidified incubator, which contains 5% CO<sub>2</sub>, at 37 °C.

### 2.10. MTT

Fibroblast cells were grown in DMEM cultured medium supplemented by 10 % FBS with 1 % penicillin/streptomycin and incubated at 37 °C in a humidified Incubator of 5 % CO<sub>2</sub> according to last studies previously described by Phaiju, S. et al. and Phaiju, S. et al. [22,23]. Briefly, 5 mg/mL of reagent (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was obtained in PBS in a well-plated 96 fibroblasts cell line by seeding density of  $2 \times 10^4$  at 37 °C in 5% CO<sub>2</sub> incubator. Cell-containing microplates that were centrifuged to separate cells, residues and plates at 3500 RPM were dried, followed by applying 160 and 20 µL of glycine buffer.

## 3. Results and Discussion

This study concerned the development of *I. graveolens*/PCL nanofibrous scaffolds using an electrospinning technique. The scaffolding conditions are improved by adjusting the electrospinning parameters, which include the needle measurement, the collector, the voltage, and the pumped polymer quantity. After optimization of conditions [24], bead-free fibers with a minimum diameter were obtained. To that end, the needle's distance to the collector was 20 cm, the voltage was 8 kV, and the polymer flow was 0.5 mL/h, and a blend of 8% PCL and 5% *I. graveolens* were found to be suitable. The polymeric materials, becoming smaller in scale with a large surface area to volume ratio, can provide the plant extracts with improved properties such as chemical and antimicrobial activity [25]. The major benefit of plant scaffolding is the obvious simplicity with which it can be produced and handled; the design of a variety of sizes and shapes is entirely foldable, easy to cut, shaped, rolled, or stacked. They can also be reused, are easy to use, and are relatively cheap [26]. The principle of plant material Electrospun comprising therapeutic characteristics especially wound healing on the polymer matrix, is impressive. In Figure 1, the SEM micrographs of PCL Electrospun nanofibers and *I. graveolens*/PCL nanofibers showed that nano-scaled fibrous structures without beads were present. It was acquired under the controlled spinning conditions used in this research. The scaffold nanofibers derived from the *I. graveolens*/PCL combination were illustrated with micrographs of the SEM in Figure 1. As seen in the pictures, the fiber diameter decreases when natural polymers are increased. Fiber diameters were  $72 \pm 963$  nm in the PCL/*I. graveolens* ratio 70/30 (V:V). In a similar study, Suryamathi and his coworkers reported that the average fiber diameter of PCL nanofibers was increased with the encapsulation of Tridax Procumbens Extract [27]. A natural *I. graveolens* polymer is also a polyelectrolyte polymer, which can release ionic groups such as carboxyl groups in the solution. The addition of anionic and cationic polyelectrolytes increases the electric conductance of the solution of electrospinning [28].



**Figure 1.** SEM micrographs of (a) Electrospun PCL nanofibers and (b) *I. graveolens* extract loaded PCL nanofibers.

### 3.1. FTIR Results

FTIR was performed to inspect the functional groups found in pure PCL and *I. graveolens*/PCL nanofibers scaffolds which were clarified in (Figure 2). The FTIR spectrum presents a number of peaks at curve regions from about  $3400$  to  $650\text{ cm}^{-1}$ . Areas on the curve of *I. graveolens* lead to the O-H stretching, stretching (CH, CH<sub>2</sub>, and CH<sub>3</sub>), C=O stretching, C-C intraloop stretching, C-H bending, C-O-C stretching, C-O stretching, carboxylic acid bending O-H, and C-H bending, respectively. On the PCL curve, which corresponds to stretching CH<sub>2</sub>, stretching C-H, stretching C=O, stretching C=C, bending C-H C-H rock, C-H wag, C-O of carboxylic acid, bending OH of carboxylic acid, and aromatic C-H, respectively, some peaks can also be found in  $2900$  to  $740\text{ cm}^{-1}$  region. We can observe peaks corresponding to PCL when analyzing the *I. graveolens*/PCL curve, which is indicative of the lack of any chemical reactions between *I. graveolens* and PCL.

### 3.2. XRD

Figure 2 shows the corresponding XRD graph for PCL, *I. graveolens*, and a mixture of 7/3 with a PCL/*I. graveolens* ratio. As can be noted, there are two distinctive peaks in the PCL curve; by observing the XRD pattern, the loading of *I. graveolens* extract into the PCL nanofibrous scaffolds has been verified. The XRD of PCL nanofibers (Figure 3) shows peaks at  $2\theta$  19, 21.3, 24.6, and 42 indicate crystallinity of the PCL nanofibers. The peaks underwent a blue shift and appeared at  $2\theta$  18.8, 23.9, and 41.4 with PCL nanofibers loaded with increased intensity for *I. graveolens*. The rise in strength provides a higher degree of crystallinity. The XRD pattern means that the *I. graveolens* extract has been successfully loaded into PCL nanofibers.



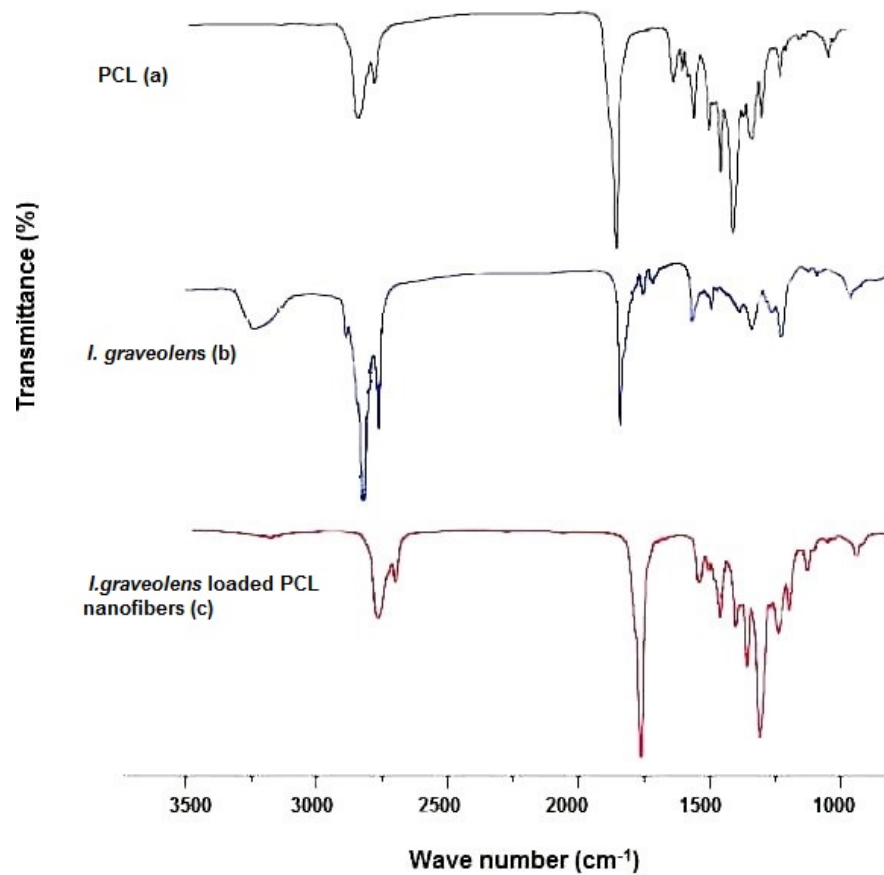


Figure 2. FTIR spectrum of PCL (a), *I. graveolens* (b), and (c) *I. graveolens* loaded PCL nanofibers.

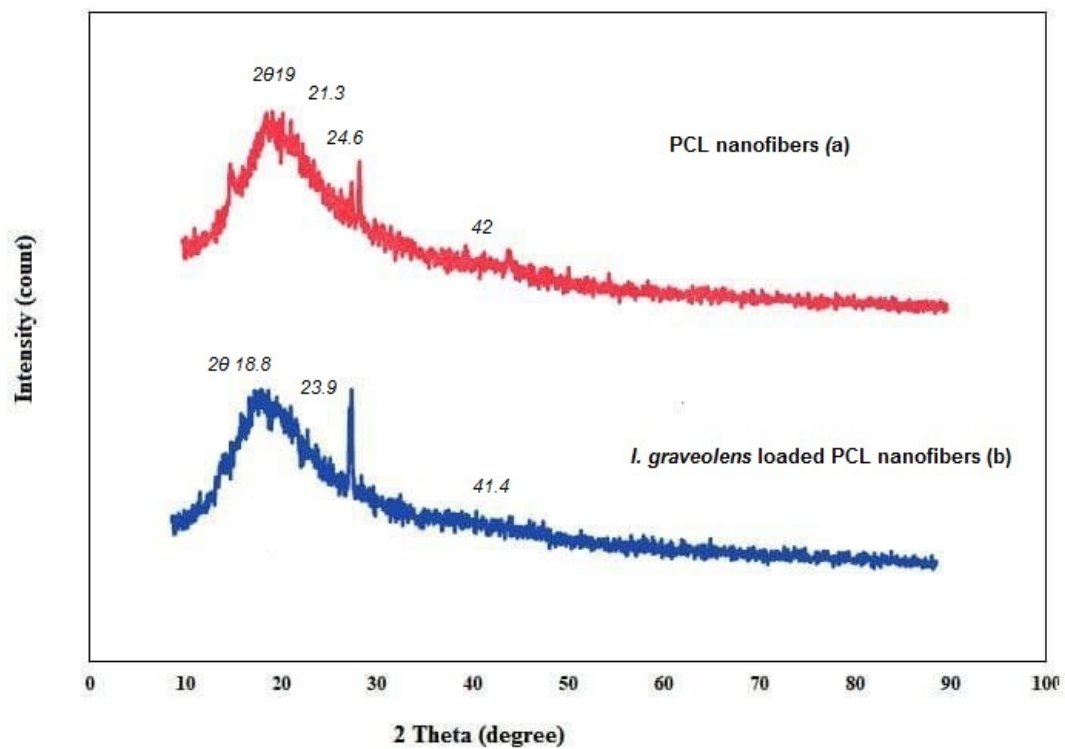


Figure 3. XRD pattern of PCL nanofibers and *I. graveolens* loaded PCL nanofibers.

### 3.3. Hydrophilicity Test

The hydrophilicity of scaffolds is one of the most important parameters in the manufacture of scaffolds to make it possible for cells to adhere to and develop [29]. Via the contact angle test, the hydrophilicity of the scaffold was evaluated [30]. In the PCL, the water touch angle is around  $118.4^\circ \pm 2.0^\circ$ . The contact angle of the scaffold composed of PCL and *I. graveolens* with a ratio of 7/3 obtained was about  $51.4 \pm 2.0^\circ$  (Table 1). The addition of *I. graveolens* to the polymer solution dramatically increases the scaffold hydrophilicity, resulting in better adhesion of cells to the scaffold. The results of present study are agreement with those of previous studies indicated the adding natural plant extract, improved the hydrophilic behavior of PCL nanofibrous scaffold [31]. Similar results by Agnes Mary et al. [32] showed that there was a lower contact angle value for PCL scaffolds containing natural plant extract (*Aloe vera* (AV)).

**Table 1.** Samples' codes, compositions, and electrospinning conditions of the Electrospun nanofibers.

Sample	Solutions:Ratio	Contact Angle ( $^\circ$ ) (Hydrophilicity)	FR (mL/h)	TCD (cm)	Voltage (kV)
PCL	-	$118.4^\circ \pm 2.0^\circ$	0.5	18	20
PCL/ <i>I. graveolens</i>	70:30	$51.4 \pm 2.0^\circ$	0.5	18	20

### 3.4. Tensile Strength

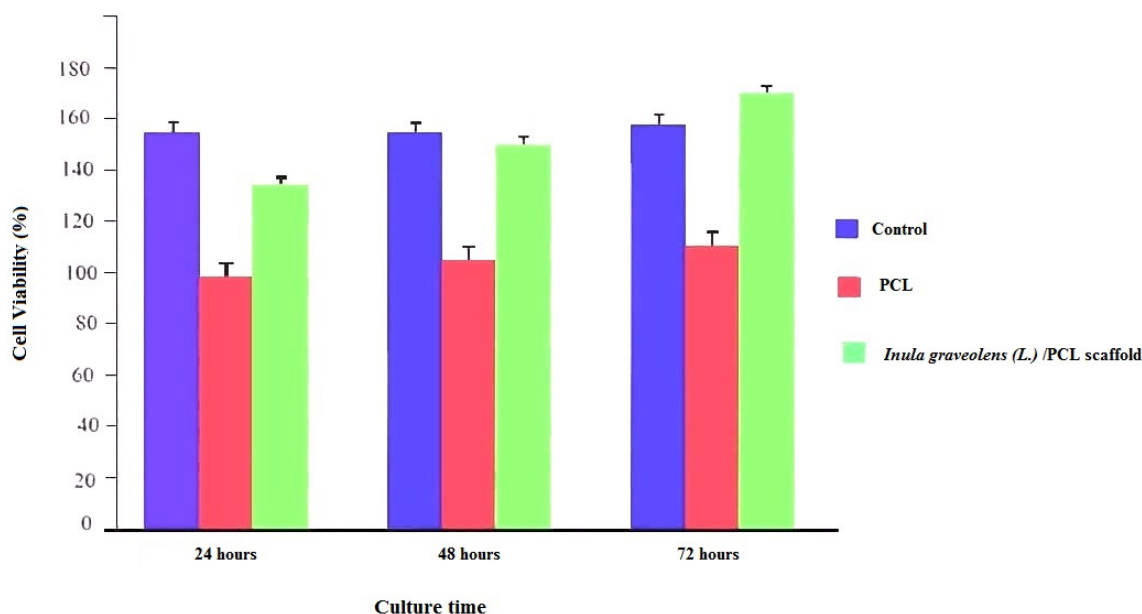
Mechanical properties are among the most relevant characteristics of a scaffold. Suitable stability, elasticity, and adequate resistance to external mechanical forces should be given for the scaffold. Table 2 displays the mechanical properties of the nanofibrous Electrospun scaffolds. Compared to PCL nanofibers  $1.6 \pm 0.1$  MPa alone, the tensile strength of the *I. graveolens* nanofibers was  $5.2 \pm 0.7$  MPa, which is increased as *I. graveolens* extract incorporated, and this finding agrees with the literature [33].

**Table 2.** Physical properties of the PCL/*I. graveolens* Electrospun nanofibers after cross-linking (\*:  $p < 0.05$ ).

Sample	Ultimate Tensile Strength (MPa)	Contact Angle ( $^\circ$ ) (Hydrophilicity)
PCL	$1.5 \pm 0.1$	$118.4 \pm 2.0$
PCL/ <i>I. graveolens</i>	$5.2 \pm 0.7$	$122.4 \pm 2.0$

### 3.5. Cell Viability

MTT assay was achieved to evaluate the toxicity and biocompatibility of *I. graveolens*/PCL nanofibers on Fibroblast cells (Figure 4) that shows cell viability cultures at different times 24, 48, and 72 h, respectively, of incubation. The growth rate on the scaffold of the PCL/*I. graveolens* is higher than on the scaffold made of PCL, as is evident on the graph, and also surpassed that of the control group at the end of the third day. The results showed that nanofiber scaffolds of PCL/*I. graveolens* exhibit no cytotoxicity on Fibroblast cells. The fabricated nanofibers of captured *I. graveolens*/PCL were obtained by Electrospun, with attractive amplified surface area and density, pore size properties, that advanced by optimization by adjusting some important variables such as the distance between needle and collector, electrical voltage, and also the amount of the polymer after being pumped. Nanofibers have gained considerable importance in biotechnology due to their promising applications due to a large surface area that could be turned into an ideal matrix for cellular activities [34]. Nanofibers form a chain of biomaterial interactions within cell cultures. Therefore, it is necessary to make use of biocompatible materials for this matter [35].



**Figure 4.** Cytotoxicity results of PCL and *I. graveolens*/PCL nanofibers on fibroblast cell culture by MTT assay, after 24, 48, and 72 h of cell seeding. ( $p < 0.05$ ); represent significant differences between the same sample at a different time ( $p < 0.05$ ).

#### 4. Conclusions

In summary, PCL fibers functionalized with plant extract *I. graveolens* were successfully obtained through the electrospinning process using PCL as polymer, in acetic/formic acid (1:2 w/w) as an organic solvent to prepare the polymeric solutions. The fibers produced by electrospun from the spinning *I. graveolens*/PCL were nanofibers with ribbon-like twisted forms and have no toxic effect on cell cultures. Our study has demonstrated that electrospinning is an encouraging progress for the manufacture of scaffolds consisting of nanofibers containing a potent natural polymer such as polymer derived from *I. graveolens* that has medicinal applications with synthetic biodegradable PCL polymer with a suitable choice for fibroblast cell culture at a 7/3 (V:V) ratio. Evaluating the Tensile strength hydrophilicity test, as well as, cell toxicity and biocompatibility, indicated that *I. graveolens*/PCL scaffold could be a potential candidate for tissue regeneration and wound healing applications.

**Author Contributions:** Conceptualization and methodology, W.J.A.-K., S.A., A.J.M.A.-F.; formal analysis, H.K.A.-K., S.M.A.-M. and G.M.S.; investigation and data curation, W.J.A.-K., S.A., A.J.M.A.-F., S.M.A.-M., and G.M.S.; validation Y.H.D., M.S.A. and D.A.S.; visualization, all authors; writing—original draft preparation, W.J.A.-K., S.A., A.J.M.A.-F., S.M.A.-M., and G.M.S.; writing—review and editing, Y.H.D., M.S.A., and D.A.S.; supervision, S.A. and G.M.S.; project administration, S.A. All authors gave approval to the final version of the manuscript.

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