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Dong, W-H, Liu, J-X, Mou, X-J et al. (6 more authors) (2020) Performance of polyvinyl pyrrolidone-isatis root antibacterial wound dressings produced in situ by handheld electrospinner. Colloids and Surfaces B: Biointerfaces, 188. 110766. ISSN 0927-7765

https://doi.org/10.1016/j.colsurfb.2019.110766

Title page

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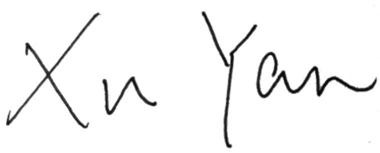
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Performance of Polyvinyl Pyrrolidone-Isatis Root Antibacterial Wound Dressings Produced *in situ* by Handheld Electrospinner

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Abstract

Antibacterial dressings are an increasingly important tool for the prevention and management of wound infections, particularly in light of concerns surrounding conventional drug-resistant antibiotics. Handheld electrospinning devices provide opportunities for the rapid application of antibacterial dressing materials to wounds, but spinning formulations need to be compatible with live biological surfaces. We report the development of a new antibacterial formulation compatible with handheld electrospinning, and its manufacture directly on a wound site. Nanofibrous dressing mats were produced from polyvinyl pyrrolidone (PVP) containing isatis root (Indigowoad root or Ban-Lan-Gen), a traditional Chinese medicine, commonly used for the treatment of infectious disease. The resulting wound dressing mats of PVP/isatis root exhibited well-defined fibrous structures and excellent surface wetting, and permeability characteristics. The presence of isatis root conferred antibacterial activity against gram negative and gram positive strains. Moreover, in a Kunming mouse skin injury model, direct electrospinning of PVP/isatis root formulations on to wound sites produced near complete wound closure after 11 days and epidermal repair in histological studies.

Keywords: *In situ* electrospinning; PVP fibers; *isatis* root; wound dressing.

Introduction

Among the main requirements of a wound dressing are the control of microbial and enzymatic activity, conformance to the wound bed, low adhesion and the promotion of a moist wound healing environment, necessitating effective fluid management and control of gaseous exchange [1-3]. If designed appropriately, electrospun nanofibrous mats have the potential to meet many of these requirements, and to be used as wound contact layers due to their large surface-area-to-volume ratio, small pore size and high porosity, as well as their ability to incorporate antimicrobials [4-13].

During the past two decades, electrospinning is fast developing to coaxial [14], modified coaxial [15], tri-axial [16], side-by-side [17] and multiple fluid [18] processes. Meanwhile, creation of nanofibers on a large scale for potential commercial application is very popular [19]. However, the production of nanofibers *in situ* using a low-cost handheld device has been demonstrated to be a very useful manner for promoting the commercial application of nanofibers [20, 21]. Besides, electrospinning, as an electrohydrodynamic method [22-25], is extremely sensitive to the working parameters when an electrospinning system is exploited [26]. Most recent investigations have disclosed more parameters that exerted their influences on the production processes [14, 15, 27]. In contrast, the handheld electrospinner had less these concerns [20].

Therefore, electrospinning of dressings *in situ*, directly on to wounds, using a handheld spinner, together with carefully pre-formulated spinning solutions, is a potential route to customization of dressings according to individual patient needs, whilst improving conformance to the wound bed and reducing pain [20, 28-31]. Several antibacterial spinning formulations compatible with handheld or portable electrospinners have been investigated for the production of wound dressings, including Poly-ε-caprolactone (PCL) loaded with silver nanoparticles (AgNP)[28] and poly(vinyl pyrrolidone) (PVP) combined with iodine (I)[29].

With respect to bactericidal function, plant extracts are cultivated in various countries due to their relatively low cost and reported long-term anti-inflammatory and antimicrobial effects [31-35]. Among the multitude of plant-based antimicrobials reported in the literature, dried Isatis indigotica Fort. root, also known as Indigowoad root or

Ban-Lan-Gen, is a well-known traditional Chinese medicine for the treatment of infectious diseases [36-43]. According to ancient Chinese literature and the Pharmacopeia of the PRC, Isatis root is used to treat inflammatory diseases, particularly those associated with skin [36], and is reported as 'possibly effective' for the treatment of psoriasis[37, 38]. Several studies have shown that isatis root has good antibacterial and anti-inflammatory activity [39-43].

Herein, we studied the manufacture and physical properties of wound contact layers comprising electrospun PVP/isatis root fibers, produced by a handheld electrospinner, in relation to wound healing. The morphology, chemical structure, wettability, gas permeability, antibacterial properties and wound healing capability of the as-spun dressings were investigated.

Material and methods

Materials

Polyvinylpyrrolidone (PVP, 250 kDa, Sinopharm Chemical Reagent Co., Ltd., China) was dissolved in absolute alcohol (Sinopharm Chemical Reagent Co., Ltd, China) at 13% (wt/wt). *Isatis* root extract (Henan zhongguanjianye Biotechnology Co., Ltd, China) was added into the PVP/alcohol solutions at 5 %, 8 % and 10 % (wt/wt) and then agitated at room temperature under constant stirring for at least 24 h before electrospinning.

Handheld electrospinning process

The prepared solutions were loaded into a 5 mL syringe equipped with a stainless steel nozzle of 0.2 mm diameter. Then, the syringe was placed into the handheld portable electrospinning apparatus (HHE-1, Qingdao Junada Technology Co., Ltd), as shown in Fig. 1a. This unit operated with a fixed voltage of 10 kV [44]. During the formation of the dressing, the electrospinning process is operated by hand with electrospinning distances about 5-8 cm. The as-spun fibers could also be directly formed in to a coherent wound dressing *in situ*, as suggested in Fig. 1b.

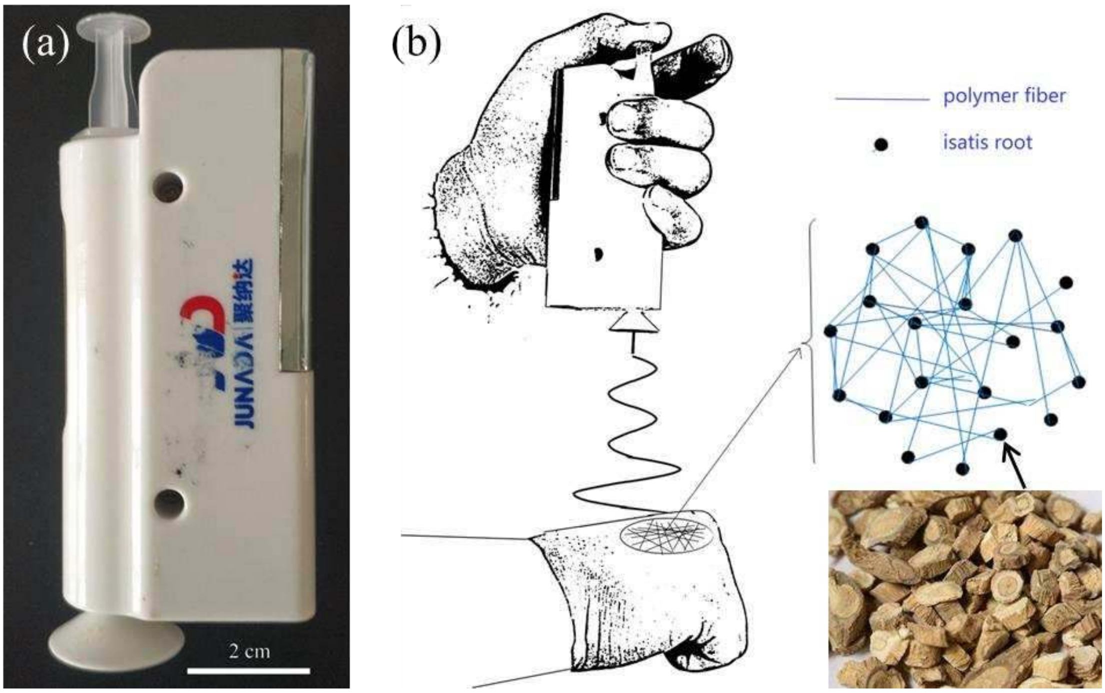

Figure 1 (a) Image of the handheld electrospinner. (b) Illustration of electrospinning PVP/isatis root solution to form a dressing fabric in situ on a biological site.

Characterization

The morphology and diameter (n=40) of the as-spun fibres was examined by a Scanning Electron Microscope (SEM, Phenom Pro, Thermo Fisher Scientific) at 10 kV. Fourier Transform Infrared Spectroscopy (FTIR) spectra were obtained from a Thermo Scientific Nicolet iS10 spectrometer. The air permeability of the electrospun mats was determined (Textest FX3300) at a fixed pressure of 200 Pa, based on ASTM D 737. The pore size of the as-spun membranes was determined using a capillary flow porometer, (Pore Size Meter, PSM 165-Germany, Topas GmbH, PSM 165), based on n=5 replicates. Contact angle measurements (n=3 per sample) were conducted using simulated body fluid (SBF) at a drop volume of 2 μL and an optical tensiometer (Attension Theta, Biolin Scientific, Germany) after ten seconds.

Escherichia coli (E. coli, ATCC 10536) and Staphylococcus aureus (S. aureus, ATCC 25923) bacteria were selected to examine the antibacterial behaviour of the as-spun dressings according to the standard methods BS EN ISO 20645:2004 (Textile fabrics-Determination of antibacterial activity, agar diffusion plate test) [45], Chinese Standards GB/T 20944.1-2007 (Textiles - Evaluation for antibacterial activity-Part 1: Agar diffusion plate method) [46] and following procedures reported in a previous study [12].

All *in vivo* procedures were conducted according to the protocol approved by the Institutional Animal Care and Use Committee of Hospital of Qingdao University and in agreement with the Regulation on the Administration of Laboratory Animals (2017 Revision) (CLI.2.293192). Fifteen Kunming mice (10 weeks old, male, SPF, Jinan Pengyue Laboratory Breeding Co., Ltd.) were housed in three groups (without treatment, in situ electrospun PVP wound dressing and in situ electrospun PVP/*isatis* root (10 wt%) dressing). Before experimentation, all the mice were housed for 7 days, replenishing their food and water provisions. After experimental wounding, animals were housed in individual cages (cage size 290×178×160 mm with sawdust bedding, changed two times per week) at 23 °C with 12 hour light/dark cycles. Animals were provided with food (Standard Rodent Diet) and water *ad libitum*. Hematoxylin and eosin (H&E) staining was employed to evaluate the histological recovery during wound closure.

Results and discussion

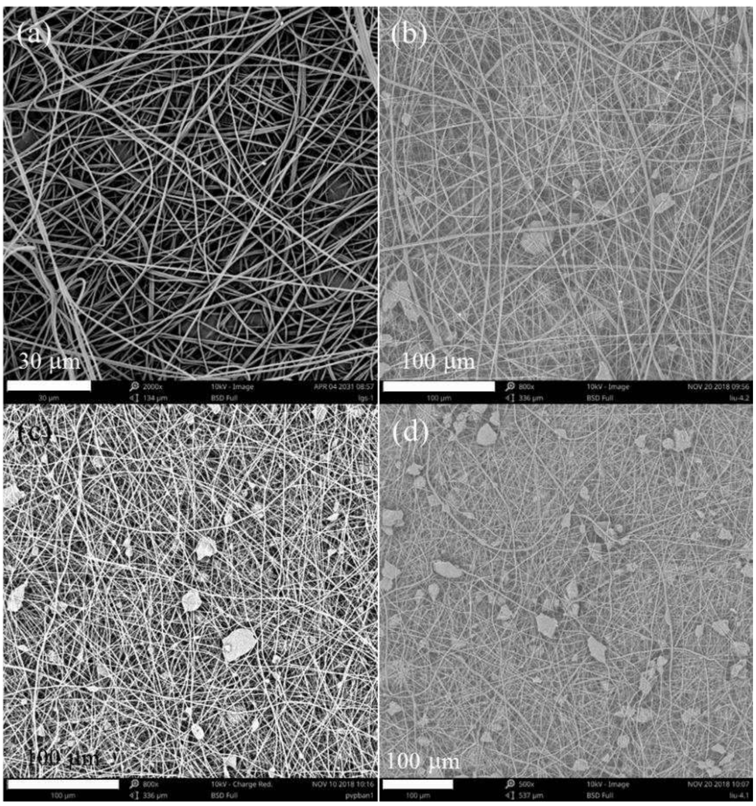

Figure 2 SEM images of the handheld electrospun PVP dressings (a), electrospun PVP/isatis root dressing mats with isatis root concentrations of 5 % (b), 8 % (c), and 10 % w/w (d), respectively.

The SEM analysis of the 100% PVP fibres and the PVP/isatis root fibres with the lowest *isatis* content (5 wt%) revealed smooth fibre morphologies, as shown in Fig. 2a-b. As the concentration of *isatis* root increased in the spinning solution, there was a higher prevalence of solid *isatis* root particles distributed across the surface of the fibrous network, as can be seen from Fig. 2c-d. The increasing addition of *isatis* root in the spinning solution resulted in progressively larger mean fiber diameters, as evidenced by Fig. 3a-d due to reduced attenuation of the polymer stream during electrospinning. Moreover, the PVP/*isatis* root fibres exhibited a hierarchical structure with a wider fiber diameter distribution, which given that the area density of the mats remained fixed throughout at ~ 17 g/m^2, resulted in a larger mean pore size, and higher gas permeability, Fig. 3e-f.

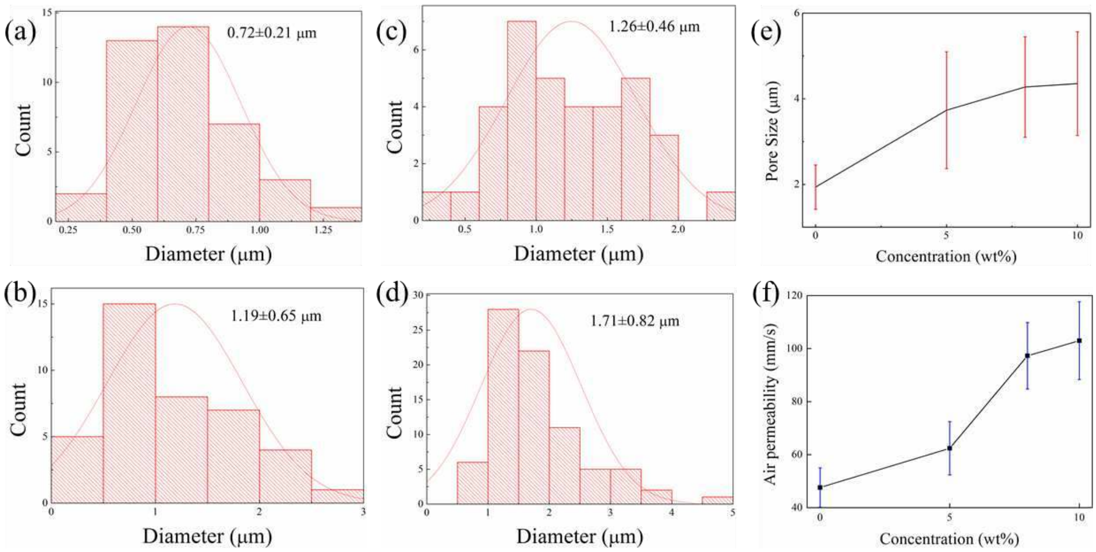

Figure 3 Fiber diameter distribution of electrospun PVP fibers (a), electrospun PVP/isatis root fibers with isatis root concentrations of 5 % (b), 8 % (c), and 10 % w/w (d). The mean pore size (e) and air permeability (f) of the as-spun dressing mats produced with different isatis root concentrations.

Since surface wettability is important in terms of maintaining contact with the wound bed and promoting exudate management, contact angle measurements were made using SBF. As shown in Fig. 4a-d and video S1, the PVP/*isatis* root dressings produced small SBF contact angles, reflecting the relatively high hydrophilicity of 100% PVP [29, 47] and the water solubility of the *isatis* root [39, 43]. The addition of *isatis* root to PVP did not markedly affect the contact angle measurements.

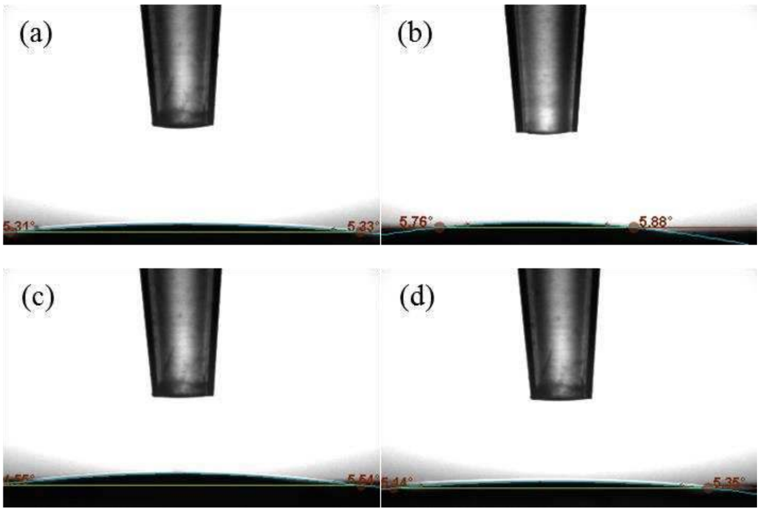

Figure 4 Contact angles of SBF on the handheld electrospun PVP/*isatis* root dressing mats, with *isatis* root concentrations of 0 wt% (a), 5 wt% (b), 8 wt% (c) and 10 wt% (d), respectively.

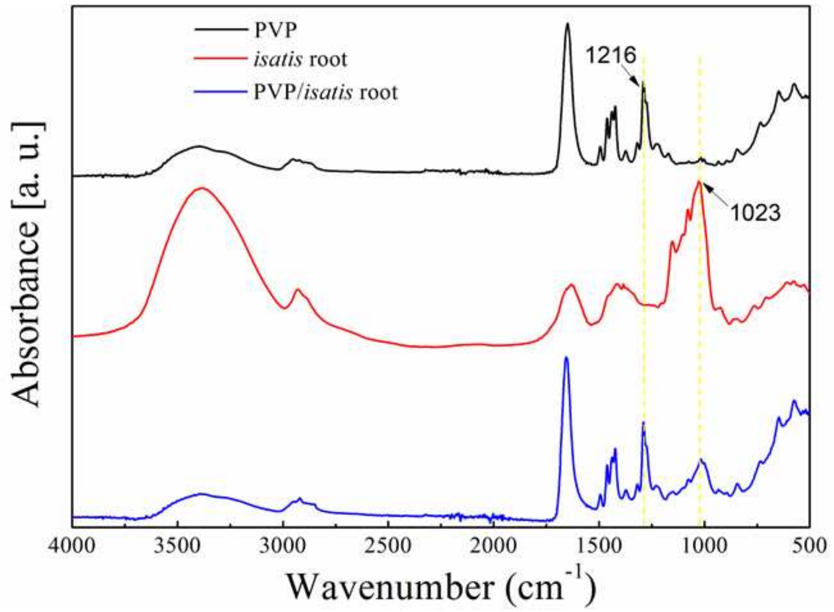

Figure 5 FTIR spectra of the as-spun fibers and *isatis* root extract alone.

The FTIR spectra of the as-spun fibers and *isatis* root extract in Fig. 5 reveal the main differences in the 100% PVP and *isatis* root extract relate to the absorbance peaks at wavenumbers of 1261 cm^{-1} (PVP only) and 1023 cm^{-1} (*isatis* root only). As a result, the electrospun PVP/*isatis* root dressing showed both absorbance peaks at both 1261 cm^{-1} and 1023 cm^{-1}, which indicated that the *isatis* root was present in the as-spun mats. *Isatis* root extract has been reported to have antibacterial functionality [39-43], and fibrous dressings containing the material may therefore be expected to have utility in the prevention and treatment of wound infections. Consequently, the antibacterial function of the as-spun mats was assessed in relation to typical pathogenic bacteria, such as S. aureus and E. coli after 24 h incubation, as shown in Fig. 6 a-d. Zones of inhibition over 1 mm were observed for samples containing 10 wt% *isatis* root, but not for the 100% PVP control. The contact zone underneath the samples revealed no evidence of bacterial growth below the *isatis* root samples. Therefore, in the absence of *isatis* root, there was insufficient antibacterial functionality in the dressing mats to restrict microbial growth. These results confirm the toxicity of *isatis* root against both common gram positive and gram negative strains of bacterium.

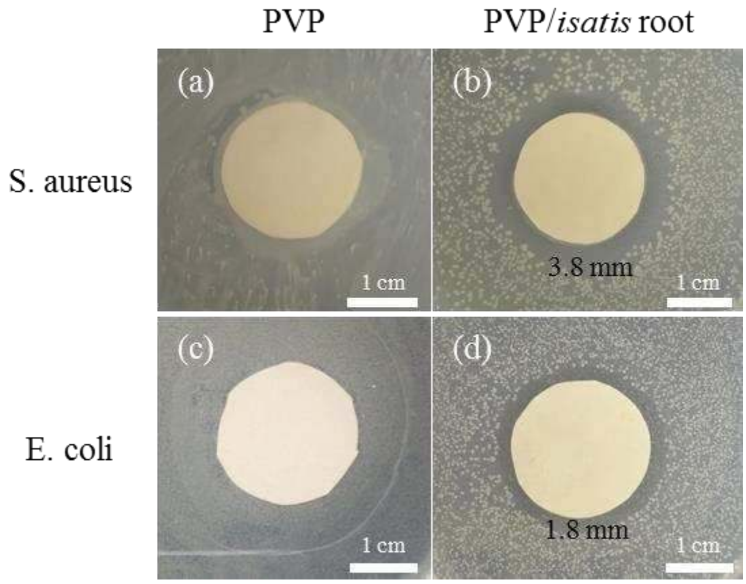

Figure 6 Antibacterial assessment of the handheld electrospun PVP and PVP/*isatis* root dressing mats (10 wt%), for S.aureus (a), (b) and E. coli (c), (d), respectively.

The wound healing performance of PVP/*isatis* root (10 wt%) dressing mats, applied by *in-situ* deposition to a pre-prepared wound site, was examined based on a Kunming mouse model, as shown in Fig. 7 and video S2. In this procedure, no manual manipulation of the dressing or contact with the wound site was involved, and fibres were deposited directly using the handheld electrospinner to provide a protective covering layer (Fig. 7a and video S2). Rapid layer-by-layer deposition of fibres in this way, to produce a nonwoven dressing, is also likely to result in good conformance to the wound bed. Results for a 100% PVP sample and an untreated wound control were evaluated together with a PVP/*isatis* root fabric sample. The application time to the wound site was identical for the 100% PVP and PVP/isatis (10%wt) samples to ensure comparable area densities. The appearance of the wounds and histology for each group was observed at 11 days after treatment.

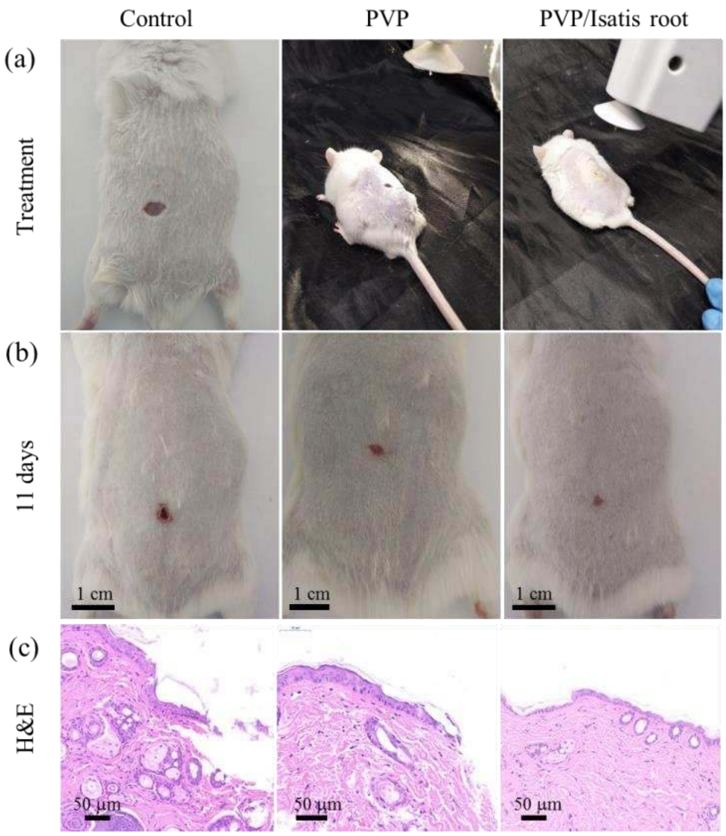

Figure 7 Effect of PVP and PVP/*isatis* root dressing mats produced in situ on wounds in a Kunming mouse model. (a) from left to right: untreated wound control, 100% PVP control; and PVP/*isatis* (10 wt%) root dressing fabric, respectively. (b) Wound closure at 11 days after injury. (c) HE staining histological images 11 days after injury.

As is evident in Fig. 7b, closure of the skin wound was most rapid for the PVP/*isatis* root dressing fabric 11 days after injury, with almost complete closure, compared to the 100% PVP and untreated control group. The histological analysis using H&E staining [28,48,49] (Fig. 7c), revealed an almost intact epidermis in the PVP/*isatis* root dressing fabric, while the untreated and 100% PVP controls exhibited somewhat fragmentary epidermal layers. The degree of epidermal repair for the 100% PVP sample was intermediate between untreated control and PVP/*isatis* root dressing fabric. Based on the wound closure and histological studies, it appears that the addition of *isatis* to PVP fibres in a dressing is beneficial in terms of wound healing.

Conclusions

Naturally occurring *isatis* root extract can be successfully incorporated in to PVP spinning solutions to provide an antibacterial formulation capable of being directly applied to wounds via a simple handheld electrospinning device to provide a protective wound contact layer. The PVP/*isatis* root dressing mats produced a nanofibrous structure with air permeability sufficient to allow gaseous exchange, good surface wetting characteristics and antibacterial functionality against common gram positive and gram negative bacteria (PVP/*isatis* (10 wt%)). Moreover, direct formation on the wound site of electrospun dressings containing PVP/*isatis* (10 wt%) results in more rapid wound healing, compared to untreated and 100% PVP controls, and nearly complete wound closure, 11 days following injury. Handheld electrospinning combined with new customised spinning solutions based on PVP provides a promising strategy for the management and prevention of wound infections.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (51703102, 51973100 and 51673103) and the Innovation and Entrepreneurship Training Program for College Students of Qingdao University (X2018110650078).

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