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Natural okra-based hydrogel for chronic diabetic wound healing

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ABSTRACT

As a representative of chronic wounds, the long-term high levels of oxidative stress and blood sugar in chronic diabetic wounds lead to serious complications, making them the biggest challenge in the research on wound healing. Many edible natural biomaterials rich in terpenes, phenols, and flavonoids can act as efficient antioxidants. In this study, okra extract was selected as the main component of a wound dressing. The okra extracts obtained *via* different methods comprehensively maintained the bioactivity of multiple molecules. The robust antioxidant properties of okra significantly reduced intracellular reactive oxygen species production, thereby accelerating the wound healing process. The results showed that okra extracts and their hydrogel dressings increased cell migration, angiogenesis, and re-epithelization of the chronic wound area, considerably promoting wound remodeling in diabetic rats. Therefore, okra-based hydrogels are promising candidates for skin regeneration and wider tissue engineering applications.

Chronic wounds are a serious global problem with high morbidity, mortality, and recurrence rates; of these wounds, diabetic foot ulcers are the most common [1–4]. In contrast to acute/normal wounds, chronic wound healing is attenuated and disordered. Instead of proceeding through four classical overlapping phases, diabetic wounds typically fail to proceed and remain in the inflammation phase [5–7]. Sustained stimulation from excess inflammatory cytokines and hyperglycemia continue to destroy the extracellular matrix, which consequently induces high concentrations of reactive oxygen species (ROS) in the trauma microenvironment [8,9]. The imbalance of redox levels subsequently exacerbates metabolic disorders, heavily interrupting neovessel construction and tissue regeneration [10,11]. Considering the close correlation between hyperglycemia and oxidative stress during chronic injury repair, it is believed that diabetic cutaneous wound healing practices that simultaneously control blood glucose levels and eliminate excessive free radicals will represent an effective solution to these problems.

The concept of the "homology of medicine and food" has been developed for thousands of years in Chinese medicine [12–14]. Many small molecules and biomacromolecules extracted from natural resources have already been noted as novel therapeutic products with high compatibility and low toxicity; these include alginate, cellulose, collagen, and curcumin [15,16]. Food-borne biomaterials have been widely explored and have demonstrated potential for tissue engineering applications [17,18]. Furthermore, they can be applied as an entity to realize more comprehensive biomedical functions. Okra is one of the most popular functional edible vegetables. It contains abundant polysaccharides, polyphenols, phenolic acids, vitamins, minerals, and so on [19–21]. A great deal of research has shown that these multiple nutritional components significantly support the antioxidant properties of okra fruits [22–26]. Furthermore, the hypoglycemic effect of okra polysaccharides has also been confirmed and reported [27–33]. Therefore, okra can be expected to function as a multifunctional active substance that can be directly applied in severe diabetic chronic wound treatments.

Because okra-derived wound dressings lack systematic tissue regeneration studies, in this work, okra extracts are obtained to improve dysfunctional diabetic wounds (Scheme 1). The experimental results show that hot water extraction can yield okra

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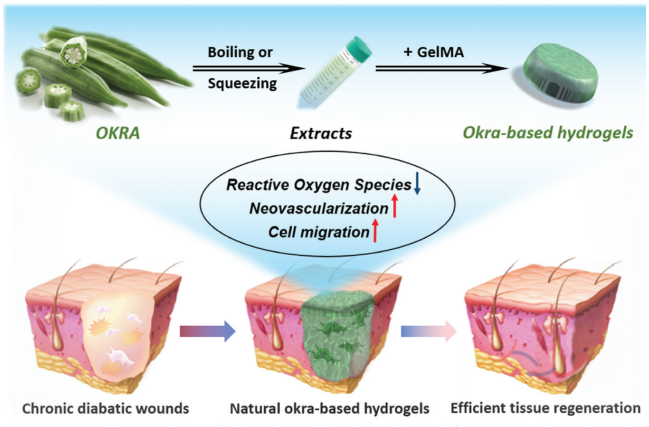

Scheme 1. Illustration of okra-based hydrogel used for promoting chronic diabetic wound healing.

polysaccharide with a relatively low molecular weight and high unmethylated galacturonic acid content, which helps to improve its antioxidant activity [34,35]. Direct extraction methods are convenient and quick, though the solution may contain more impurities than other methods. Therefore, two different extraction methods (boiling and squeezing) were used, and two formulations (a pure okra extraction dressing and okra-incorporated hydrogels) were prepared. In addition to excellent biocompatibility, different types of okra exhibited high ROS-scavenging activity and remarkably promoted cell migration and vascularization *in vitro*; of these two groups, the okra-based hydrogel group was superior. In the animal model of diabetic rats, the wounds of the experimental groups [especially the boiled okra-derived hydrogel (B-OKRA/GelMA) treatment group] showed superior repair performances with increased collagen fiber deposition, hair follicle regeneration, granulation tissue formation, and epithelialization. To summarize, ultra-natural okra-based hydrogel dressings prepared *via* a simple and feasible route have a promising potential in diabetic wound repair.

Before the biocompatibility tests, the physicochemical properties of the hydrogels were characterized. SEM images showed that the GelMA hydrogels exhibited many irregular porous structures (Fig. S1 in Supporting information), and the pore size of the hydrogel increased after the addition of B-OKRA; this may lead to a higher water vapor permeability (Fig. S2 in Supporting information). The experimental results showed that S-OKRA/GelMA had a higher compression modulus (Fig. S3 in Supporting information) and swelling rate (Fig. S4 in Supporting information), which may be attributable to the addition of more fibers and polysaccharide molecules.

Biocompatibility and biological safety are essential for dressings that come into direct contact with wounds. Biocompatibility is essential for cell proliferation, migration, and numerous physiological functions. Therefore, the cytotoxicity and blood compatibility of the different groups of okra solutions were tested using 3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyl-2*H*-tetrazolium bromide (MTT) and hemolysis assays. First, we conducted MTT experiments at 24 h and 48 h, to test the cytocompatibility of okra solutions. As shown in Fig. 1a, after 24 h of treatment, the survival rate of NIH 3T3 cells in all groups exceeded 87%. Furthermore, the cell viability of the groups treated with S-OKRA (50 mg/mL) and B-OKRA (50 mg/mL) exceeded 147% and 132%, respectively, indicating that okra not only has good cytocompatibility but also an excellent ability to promote cell proliferation. After 48 h of incubation, the survival rate of all cell groups exceeded 98% (Fig. 1b). The cell survival rates of the B-OKRA groups were generally higher than those of the S-OKRA groups, which may be because low-temperature dipping could retain more nutrients (*e.g.*, sugars and amino acids) in the okra.

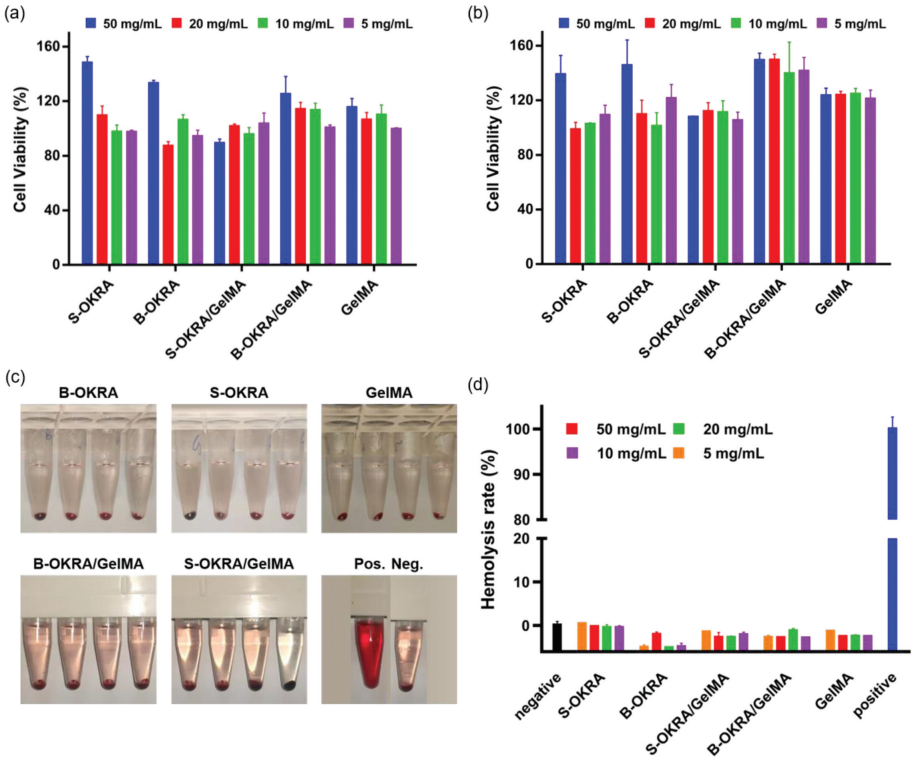

Fig. 1. The biocompatibility of different concentrations of B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA extracts (50, 20, 10 and 5 mg/mL) *in vitro*. (a, b) MTT assay used to detect the cell survival rate after 24 h and 48 h treatment ($n = 3$). (c) Images of red blood cells after treatment with different concentrations of okra solutions (from left to right, the concentrations are 50, 20, 10 and 5 mg/mL), water (positive) and saline solution (negative). (d) Hemolysis ratio analysis ($n = 3$).

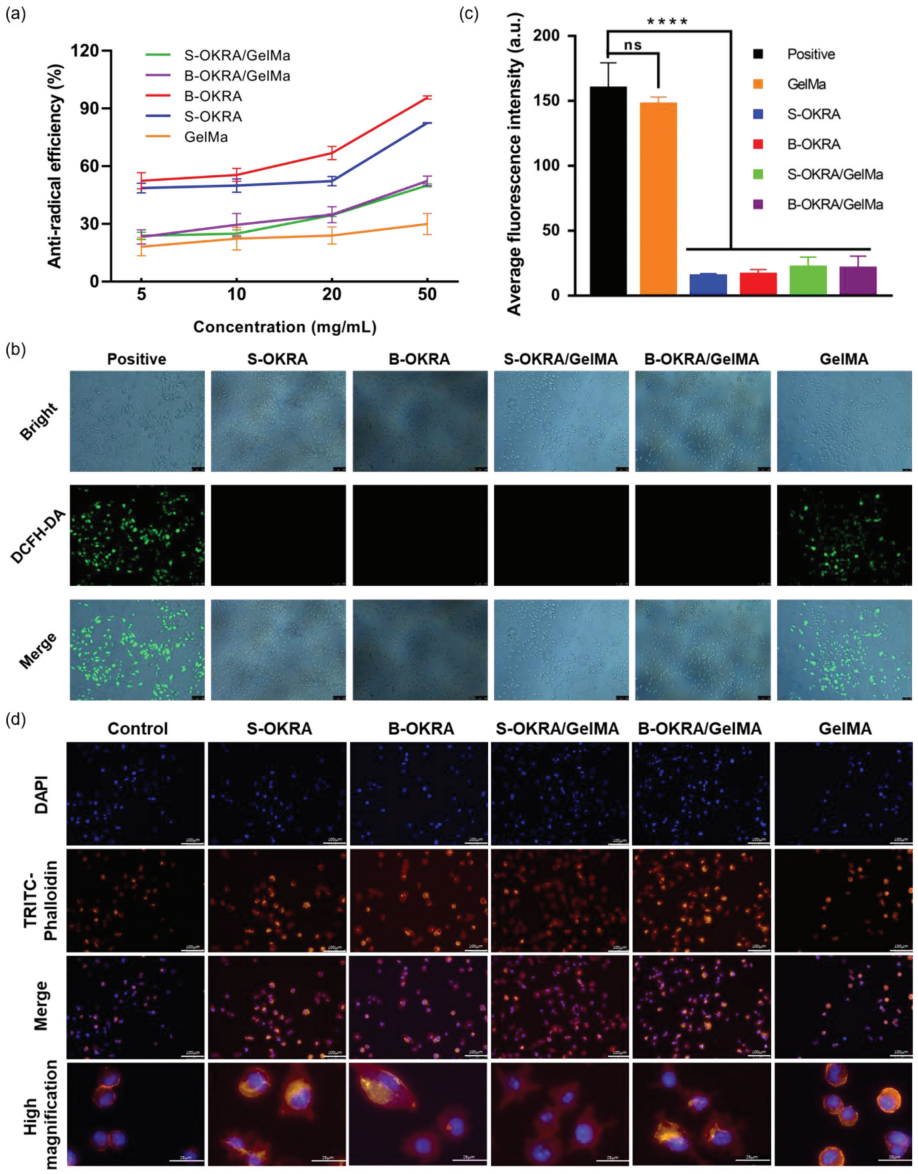

Fig. 2. The free radical scavenging capacity of different concentrations (50, 20, 10 and 5 mg/mL) for B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA and GelMA extracts. (a) Hydroxyl radical scavenging rate. (b) The ROS scavenging capacity for 50 mg/mL of each solution, as detected by DCFH-DA. The scale is 100 μm. (c) Semi-quantitative analysis of the average fluorescence intensity of the pictures in (b). (d) Representative fluorescence images of RAW264.7 cells after incubation for 48 h. The scales are 100 μm and 25 μm.

Next, the blood compatibility of the okra solution was verified *via* a hemolysis test. As shown in Fig. 1c, similar to the negative control group, solutions of various concentrations of B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA extracts were mixed with blood cells, and the supernatant after centrifugation was clear and transparent, indicating that no hemolysis occurred. In contrast, the supernatant of the positive control group (water-treated) was red, indicating that many blood cells burst. Fig. 1d shows the quantitative analysis results for the hemolysis rates of the supernatant in each group. The results showed that the hemolysis rates of the experimental and control groups were below 0.7%, suggesting the excellent blood compatibility of okra solutions.

Hydroxyl radical scavenging experiments were performed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution, to explore the free radical scavenging abilities of the okra solutions. As shown in Fig. 2a, under an increasing concentration, the free radical scavenging efficiency of the okra solutions increased. It is noteworthy that the DPPH clearance rate of the 50 mg/mL S-OKRA solution exceeded 82%, and the rate of the 50 mg/mL B-OKRA solution reached 94%. The DPPH clearance rates of B-OKRA/GelMA and S-OKRA/GelMA extracts were lower than those of B-OKRA and S-OKRA, possibly because the substances related to free radical scavenging in okra solutions (*e.g.*, flavonoids) were not fully released, and some remained in the hydrogel. Next, 50 mg/mL solutions from each group were used for the intracellular ROS scavenging experiment (Figs. 2b and c). Fluorescence images and the semi-quantitative analysis of fluorescence intensity showed that after stimulation with H_2O_2, most cells in the positive control group were stained with green fluorescence by dichloro-dihydro-fluorescein diacetate (DCFH-DA), which indicated high intracellular ROS levels. Similar to the negative control group without H_2O_2 stimulation, no obvious fluorescence was observed in cells stimulated by H_2O_2 and incubated for 24 h with B-OKRA, S-OKRA, B-OKRA/GelMA, or S-OKRA/GelMA extracts. This suggested that B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA extracts had

good scavenging abilities for intracellular ROS. B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA extracts exhibited high intracellular reactive oxygen scavenging activity and antioxidant properties, which could further potentially reduce the inflammatory response caused by oxidative stress, promote cell growth, and accelerate tissue regeneration. The strong fluorescence observed in the GelMA extract group indicated that GelMA itself does not have a good scavenging ability for ROS; this was consistent with the results shown in Fig. 2a.

Studies have shown that macrophages affect the entire wound healing process. Macrophages can be categorized into classically activated macrophages (M1) and replacement-activated macrophages (M2) [36,37]. The activation of M1 type macrophages helps to release inflammatory factors and activate and recruit immune cells. M2 macrophages are particularly important in the later stages of wound repair [38]. They secrete cell growth factors, promote cell proliferation at the wound site, and accelerate wound healing. In this study, the effects of B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA extracts on RAW264.7 cells were investigated. As shown in Fig. 2d, RAW264.7 cells still maintained their classic spherical shape after being cultured in PBS for 48 h. After incubation with separate GelMA extracts, the morphology did not change. However, after culturing with B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA extracts, the shape of these macrophages became irregular and many strands appeared, which is the classic M2 type macrophage morphology. These results indicate that OKRA has a lighter immunogenicity and can induce macrophages to differentiate into the M2 phenotype. This helps to accelerate the transition of the wound site from the inflammatory to the proliferative phase, increase wound closure speeds, and improve the wound healing effect.

Scratch experiments were performed to evaluate the ability of each group to promote cell migration. As shown in Figs. 3a and b, the wound healing rate in the PBS group was very slow, reaching only 27% after 24 h of culturation. In contrast, after 24 h of incubation with S-OKRA/GelMA extract, the wound healing rate exceeded 92%, and the wound was almost completely healed after 24 h in cells incubated with B-OKRA/GelMA extract. GelMA had a weak promotion effect on cell migration, whilst B-OKRA and S-OKRA had stronger promotion effects on cell migration, with 24-h wound healing rates reaching 72%–78%. The results of the wound healing migration tests showed that B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA effectively promoted cell migration, which is useful for tissue regeneration and wound healing.

Angiogenesis experiments were performed to test the ability of B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA to improve the formation of blood vessels via human umbilical vein endothelial cells (HUVECs). As shown in Fig. 3c, the cells cultured with the B-OKRA/GelMA and S-OKRA/GelMA extracts formed numerous nodes and grid lumens after 4 h of co-culturation. The groups treated with B-OKRA and S-OKRA formed slightly fewer nodes and grids than the aforementioned two groups, and the control and GelMA-treated groups formed the fewest. After 8 h of incubation, the area of a single grid formed by HUVECs cultured with B-OKRA/GelMA and S-OKRA/GelMA extracts was significantly enlarged, and the number of nodes that could be observed under the same field of view was reduced. This phenomenon is consistent with the results of the statistical analysis in Figs. 3d-f. From Fig. 3c, it can also be observed that the grid area of the B-OKRA and S-OKRA treatment groups was enlarged, though the area was smaller than those of the B-OKRA/GelMA and S-OKRA/GelMA extract-treated groups. No change occurred in the control and GelMA-treated groups. As shown in Fig. 3f, although the grid area formed by the cells cultured with B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA extracts increased (and the number of nodes correspondingly decreased) over time, the connection length of the cells in the field of view changed very little, indicating that some active ingredients of okra (*e.g.*, polyphenols and flavonoids) could promote cell self-assembly to form lumens. In short, the tube formation experiment demonstrated that B-OKRA, S-OKRA, B-OKRA/GelMA, and S-OKRA/GelMA extracts (especially B-OKRA/GelMA and S-OKRA/GelMA extracts) had pro-angiogenic effects *in vitro*. This is of great significance for vascular regeneration, nutrient transport, and tissue regeneration at wound sites.

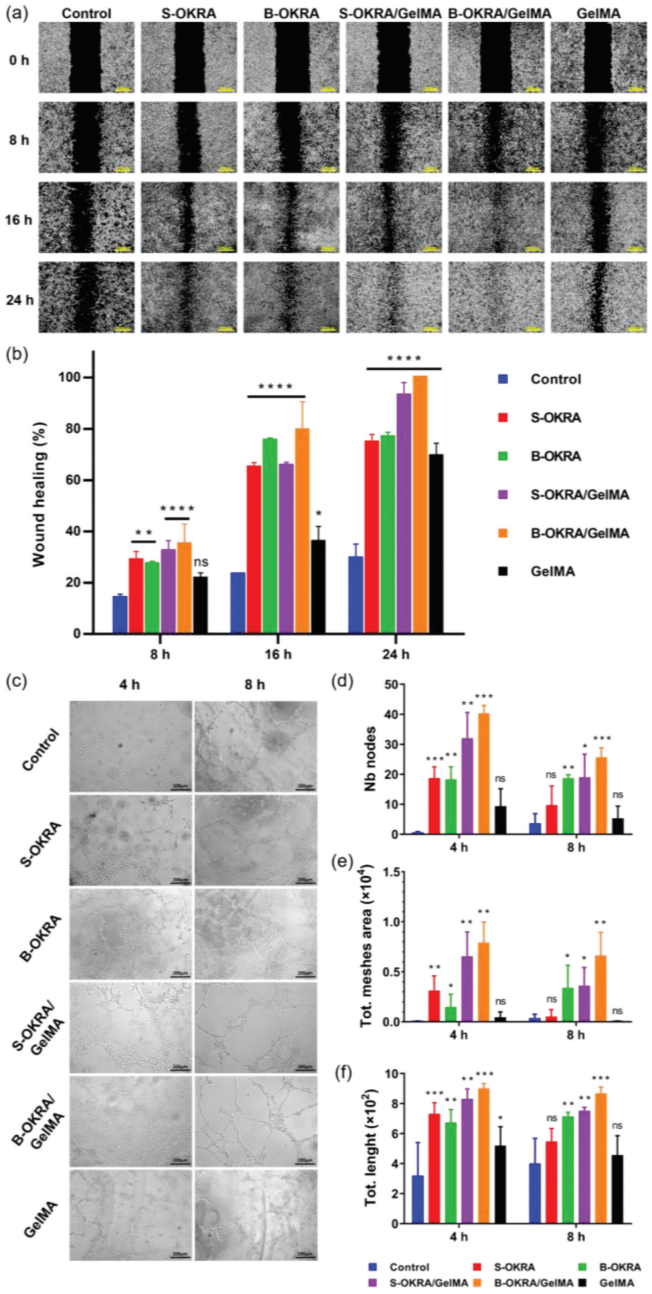

Fig. 3. (a) Representative images of wound healing after incubation with PBS, B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA extract at 50 mg/mL and (b) wound healing rate at different time points. The scale is 200 μm. (c) Tube-formation abilities of HUVECs treated with B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA extracts at 50 mg/mL and (d-f) quantitative evaluation of typical parameters of the pro-angiogenesis potential. The scale is 200 μm. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$ compared to the control group; ns means no significant difference.

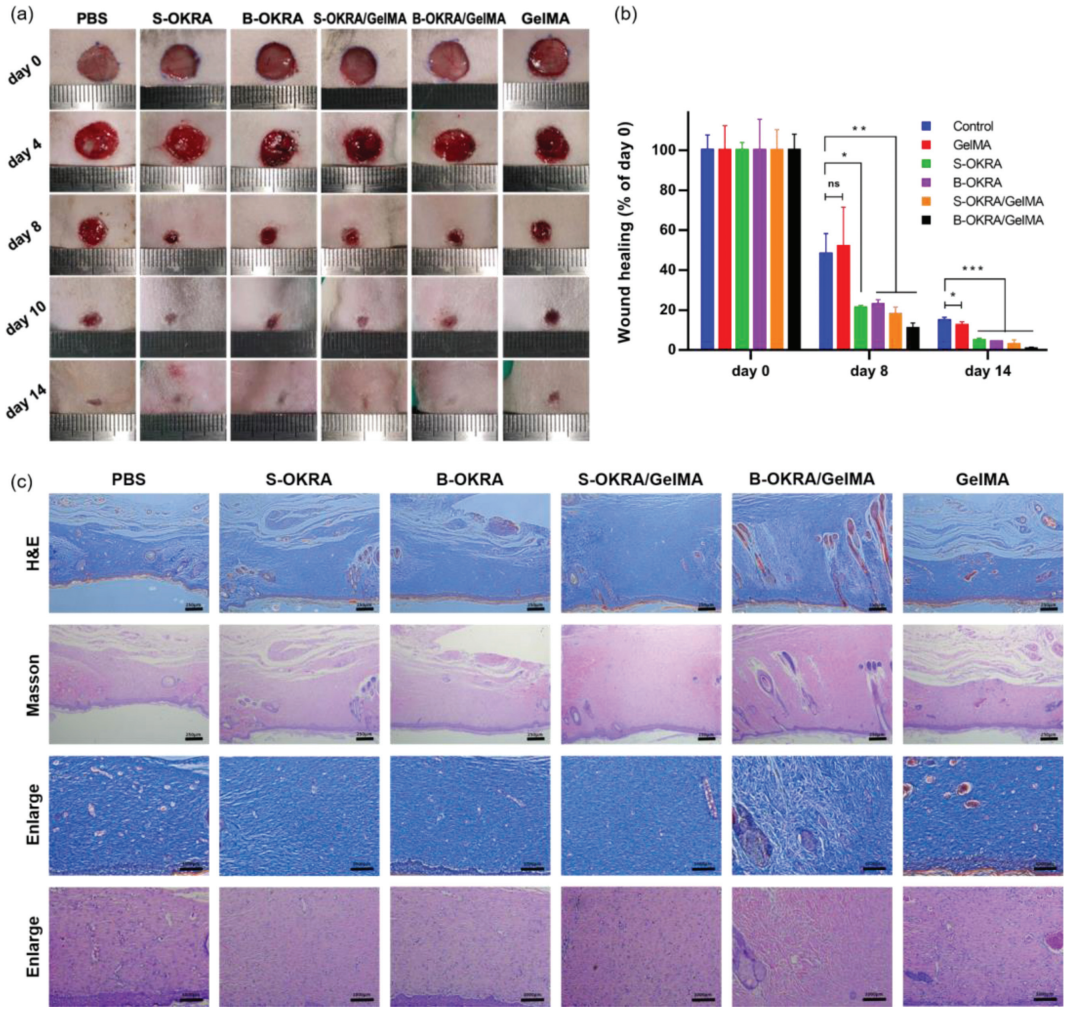

Fig. 4. Promotional effect of B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA at 50 mg/mL on wound healing *in vivo*: (a) images of skin wounds and (b) changes to wound area in each group. (c) H&E and Masson's trichrome staining of the granulation tissue on the 28th day of wound healing in different groups. The scale is 1000 μm.

Before conducting the animal experiments to test the effect of OKRA on wound treatment at the individual level, we evaluated its biological safety *in vivo*. After 21 days of treatment, the serum from each group of rats was used for biochemical blood analysis. As shown in Fig. S5a (Supporting information), no statistical difference was observed between the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) in the control group and the B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA groups, indicating that B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA did not affect liver function in rats. Meanwhile, no difference was observed in urea nitrogen (BUN) and creatinine (Cre) levels between the experimental groups and control group, indicating that okra did not cause kidney damage. The results for tissue sections are consistent with the above conclusions (Fig. S5b in Supporting information). The figures show no difference in the slices of the heart, liver, spleen, lung, and kidney between the experimental groups and control group, which means that okra was not toxic to the main organs of rats and did not affect their normal functions. In general, okra does not produce toxicity in rats and has reliable *in-vivo* biological safety.

Full-thickness skin defect models of diabetic rats were established to test the effect of each material on wound healing. Animal experiments have been approved by the Institutional Animal Care and Use Committee of Sun Yat-sen University (Approval number: SYSU-IACUC-2021–000418). B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA (at concentrations of 50 mg/mL) were sprayed or applied to the wound surface. The dressing was changed regularly, and images were taken to observe wound healing. As shown in Fig. 4a, the wounds treated with B-OKRA/GelMA and S-OKRA/GelMA were closed after 14 days, whereas clear wounds were still observable in the control and GelMA-treated groups. The statistical analysis data in Fig. 4b are in accordance with the results in the images. The wound healing rates of the B-OKRA/GelMA and S-OKRA/GelMA groups were highest, and those of the B-OKRA and S-OKRA groups were slightly slower; however, all exceeded 93%. This may be due to the strong antioxidant activity and pro-angiogenic ability of okra.

Remarkable wound healing outcomes were also confirmed *via* hematoxylin and eosin (H&E) and Masson's staining. From Fig. 4c, it could be seen that the wound treated with B-OKRA/GelMA regenerated thick skin. Abundant collagen deposition, increased hair follicles, and other appendages were observed at the wound site. The wound surface treated with S-OKRA/GelMA showed relatively fewer hair follicles; however, many collagen fibers, well-constructed wound granulation tissues, and sufficiently thick new skin still remained. In contrast, wounds treated with B-OKRA and S-OKRA had less collagen fiber deposition and almost no hair follicle regeneration. In the control and GelMA-treated groups, the regenerated skin was thinnest, without considerable collagen deposition. The *in-vivo* wound repair results showed that okra solutions

have excellent potential for promoting diabetic skin wound repair; of these, B-OKRA/GelMA exhibited the best therapeutic effect.

To summarize, okra solutions prepared *via* different methods showed great potential in diabetic wound treatment, mainly attributable to their rich biologically active ingredients. The experimental results revealed that B-OKRA, S-OKRA, B-OKRA/GelMA, S-OKRA/GelMA, and GelMA exhibited efficient free radical scavenging and antioxidant activities *in vitro*. They promoted the differentiation of macrophages towards anti-inflammatory activity, thereby accelerating the transition of the wound from the inflammatory to the proliferative phases and accelerating the healing process. Meanwhile, okra solutions had a strong capability to promote cell migration and enhance pro-angiogenesis; B-OKRA/GelMA and S-OKRA/GelMA were superior in this respect. The results of animal experiments further confirmed that, compared with the control group, the wounds of the experimental group (especially the B-OKRA/GelMA treatment group) exhibited better therapeutic effects with elevated collagen fiber deposition, increased skin appendage regeneration (*e.g.*, hair follicles), faster neovascularization, and more granulation tissue formation and epithelialization. This may be attributable to the continuous release of more bioactive components in the B-OKRA/GelMA hydrogel (*e.g.*, okra polysaccharides, flavonoids, phenolic acids, and small-molecule nutrients). In addition, studies into improving wound repair using the bioactive ingredients of natural okra extracts are expected to be further extended to other aspects of antibacterial, anti-inflammatory, and immunomodulatory effects. This study explores new biological materials from the natural world; these might provide ideas for the development of other biomaterials.

Declaration of competing interest

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.108125.

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