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ORIGINAL ARTICLE

Assessment of antioxidant and cutaneous wound healing effects of *Falcaria vulgaris* aqueous extract in Wistar male rats

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Abstract

Treatment of wounds by ethnomedicinal plants which have fewer side effects than chemical drugs has been on the rise. In this experiment, we evaluated cutaneous wound healing potential of aqueous extract of *Falcaria vulgaris* in Wistar male rats. DPPH free radical scavenging test was used to examine the antioxidant effect of *F. vulgaris* aqueous extract, which indicated high antioxidant activity compared to butylated hydroxy toluene (BHT) as the positive control. In our study, after creating the cutaneous wound on the back of the rats, the animals were randomly divided into four groups; untreated control, treatment with Eucerin ointment, treatment with 3% tetracycline ointment, treatment with 3% *F. vulgaris* aqueous extract ointment. The groups were treated for 30 days. For histopathological and biochemical analysis of the cutaneous wound healing trend, a 3 × 3 cm section was prepared from all dermal thicknesses at days 10, 20, and 30. The use of *F. vulgaris* aqueous extract ointment in the treatment groups led to significant decrease ($p < 0.05$) in the levels of wound area, total cells, lymphocyte, neutrophil, macrophage, and significant enhance ($p < 0.05$) in the levels of wound contracture, hydroxyproline, hexosamine, fibrocyte, fibroblast, and the rate of fibrocyte to fibroblast as compared to the control and basal ointment groups. According to the results, *F. vulgaris* aqueous extract ointment can treat the cutaneous wound.

Keywords *Falcaria vulgaris* · Aqueous extract · Ointment · Wound healing potential

Introduction

The wound is defined as a disruption of the continuous physical structure due to injuries induced by physical-chemical and biological agents (Johnston 1990; Jarrahi and Emami Abarghuee 2008; Jarrahi et al. 2009). Since ancient time, Egyptian, Greek, Indian, and European physicians have continued to develop effective therapies to cure wounds in the shortest time with the least complications (Souba and Wilmore 1999; Townsend 2001). Numerous drugs and ointments have been used for wound healing, each having frequent limitations and deficiencies (Sewall et al. 2003). Currently, disinfectants like betadine, acetic acid, physiologic serum, antibiotic ointments, and hydrocortisone are being used for wound healing. But, new studies have shown that many disinfectants like betadine, acetic acid, iodophore, and hydrogen peroxide for fibroblasts, lymphocytes, and cells required for wound healing are toxic (Kramer 1999; Khan and Naqui 2006; Hunt and Hopf 1997; Thomas et al. 2009; McCauley et al. 1992; Singer and Dagum 2008). Moreover, numerous methods such as dressing, drug consumption (as systemic and topical), low-energy laser, ultrasound, high-pressure oxygen, cutaneous substitutes, growth factors, electric stimulation, and even gene therapy are being used to accelerate amelioration of chronic wounds, each of which has strengths and weaknesses (Allahtavakoli et al. 2010).

In Iranian traditional medicine, many attempts have been made to find herbal medicines to accelerate would healing such as *Lawsonia inermis* L. (Leaf), *Hypericum perforatum* L. (Leaf), *Myrtus communis* L. (Leaf/fruit), *Malva sylvestris* L. (Leaf), *Malva neglecta* Wallr. (Leaf), *Olea europaea* L. (Fruit), *Sesamum indicum* L. (Seed/seed oil), *Iris* sp. (Leaf/bulb),

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Lilium candidum L. (Leaf/ bulb), *Pinus pinea* L. (Bark/leaf), *Beta vulgaris* L. (Leaf), *Galium verum* L. (Flower), *Boswellia carteri* Birdw. (Oleogum resin), *Arnebia euchroma* (Royle) I.M.Johnst. (Root), *Convolvulus arvensis* L. (Leaf), *Narcissus tazetta* L. (Bulb), *Indigofera tinctoria* L. (Leaf), *Ocimum basilicum* L. (Leaf), *Ocimum minimum* L. (Leaf), *Hedera helix* L. (Flower/leaf), *Punica granatum* L. (Flower), *Scrophularia deserti* (Stem), *Scrophularia striata* (aerial parts), *Amygdalus communis* L. (Leaf), *Chenopodium botrys* L. (Leaf), and *Stevia rebaudiana* Bertoni. (Leaf) (Fahimi et al. 2015; Ghasemi-Pirbalouti et al. 2012; Sayyedrostami et al. 2018; Goorani et al. 2018; Ghashghaii et al. 2017). But due to the failure to introduce a definitive drug to enhance the wound healing process, studies on medicinal plants and their effects on the wound healing process are continuing. One of the most important herbal medicines which are widely used by many people for wound healing in Iran is *Falcaria vulgaris* from *Plantae* kingdom, *Apiales* order, *Apiaceae* family, and *Falcaria* genus. In Iran, people use *F. vulgaris* as food. In fact, *F. vulgaris* is a good source of low-cost food and is a perfect part of the Iranian diet (Zangeneh et al. 2018c; Zangeneh et al. 2018d). Also, it is added to the dairy as a flavoring. In medicine, *F. vulgaris* applied as a medicinal plant has been used for its anti-inflammatory, antioxidant, antibacterial, antifungal, antiviral, and bleeding inhibitor activities (Jivad and Bahmani 2006; Jaberian et al. 2013; Zangeneh et al. 2018c, d; Shakibaie et al. 2007). It has a long history of use in traditional medicine, but there is a little evidence to reveal it is useful to treat the cutaneous wound. We attempted to survey the remedial activity of *F. vulgaris* on the cutaneous wounds in rats.

Materials and methods

Extract preparation method

F. vulgaris was collected from Kermanshah city. Then, the leaves of the plant were dried in shadow, and after grinding, each time 150 g of the obtained powder was dissolved in 1500 cc distilled water and put in Soxhlet extractor for 8 h. The collected extract was filtered by Whatman filter paper no 1 and steamed in a glass container at the solvent temperature. The remaining dried extract was poured into a glass container and weighed. The powder of the obtained extract weighed (Zangeneh et al. 2018a, b; Moradi et al. 2018).

Antioxidant assay

In this study, 11 dilutions of *F. vulgaris* aqueous extract (1000, 500, 250, 125, 62, 31, 15, 7, 3, 2, and 1 μg/mL) were analyzed. Two hundred microliter 2, 2-diphenyl-1-picrylhydrazyl (DPPH) were dissolved in ethanol, and the equal volume of DPPH was added to each concentration. After mixing, the solution was incubated in darkness for 30 min, and its absorption was read at the wavelength of 517 nm. BHT was used as positive control, and trapping activity of free radicals was calculated by the following formula (Hosseinimehr et al. 2011). The experiment was repeated three times.

Experimental design

This experimental study was conducted on 60 Wistar male rats with the weight of 200 ± 5 g that were kept in individual cages for 10 days to adapt to the environment. During the experiments, the temperature of the animal house was adjusted at 22 ± 3 °C under a 12-h dark/light cycle. At the beginning of the surgery, the rats were anesthetized by administration of ketamine (60 mg/kg body weight) and xylazine (1 mg/kg body weight) with 3:1 ratio, respectively. After hair removal, skin-marking excision wound with the plastic mold of 2 cm^2 to mark the skin, located on the dorsal medial line of the animal, using 1 cm below the transverse line connecting the lower angle of the scapula as the cranial limit. Then incision made with a scalpel blade around the marked tissue. Dissection of the excised skin did in the suprafascial plane with tweezers and Mayo scissors, respecting the muscular fascia (2 mm deep) and resection of the skin segment demarcated. After the above levels, cleaning of excision wound with sterile gauze soaked in saline solution (Fig. 1).

Then, the animals were randomly divided into four groups, 15 animals in each group:

Group I: Untreated control
Group II: Treatment with Eucerin ointment
Group III: Treatment with 3% tetracycline ointment
Group IV: Treatment with 3% *F. vulgaris* aqueous extract ointment (3 g of *F. vulgaris* aqueous extract +97 g base ointment).

At days 10, 20, and 30, five rats from each group were anesthetized with ketamine (60 mg/kg body weight) and xylazine (1 mg/kg body weight) with 3:1 ratio, respectively. To calculate the cutaneous wound surface, the wound shape was drawn on a transparent sterile plastic by a special marker. Using a negatoscope and Video Image Analyze software, the wound area and shrinkage percentage were accurately calculated as follows:

Percentage of the remaining wound

$$= \text{area of the remaining wound in the sampling day} / \text{area of the remaining wound in day zero} \times 100$$

Percentage of wound contractures

$$= 100 - \text{percentage of the remaining wound}$$

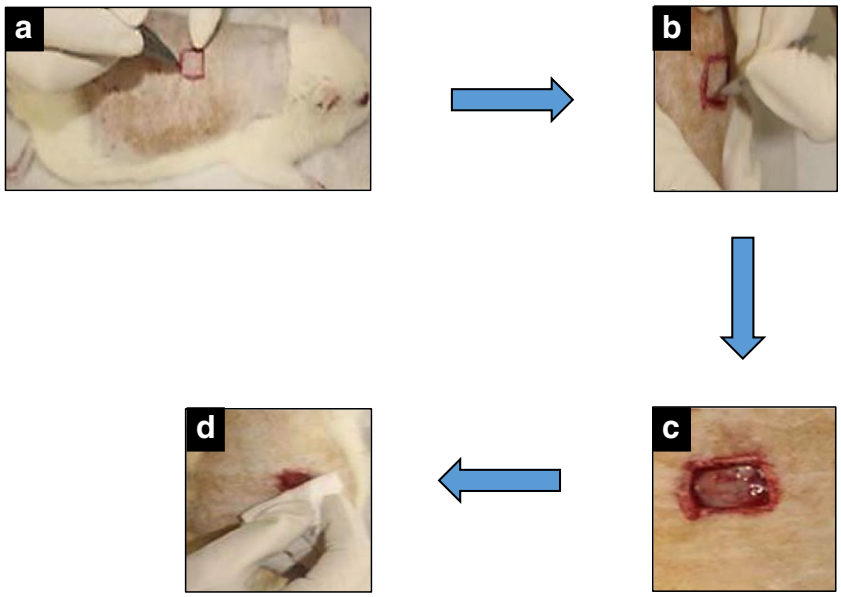

Fig. 1 Surgical procedure for creating the cutaneous wound. (A) After hair removal, skin-marking excision wound with plastic mold of 2 cm^2 to mark the skin, located on the dorsal medial line of the animal, using 1 cm below the transverse line connecting the lower angle of the scapula as the cranial limit. (B) Incision with a scalpel blade around the marked tissue. (C) Resection of the skin segment demarcated. (D) Cleaning of excision wound with sterile gauze soaked in saline solution

For histopathological and biochemical analysis of the cutaneous wound healing trend, a 3 × 3 cm section was prepared from all dermal thicknesses. The samples were divided into two halves in the middle; a part of them fixed in 10% formalin buffer and the other part used for biochemical studies. Having ensured the tissues were completely fixed, the samples were processed in an Autotechnicon tissue processor, and paraffin sections were stained by hematoxylin-eosin staining technique and studied under the optic microscope (Ghashghaii et al. 2017).

In this study, microscopic, biochemical, and histopathologic parameters were studied at the wound site.

Measurement of biochemical parameters during wound healing

Hydroxyproline measurement

First, the cutaneous wound sample was transferred to 5 ml Eppendorf. Then, 0.3 ml hydrolysate, 2.5 ml N NaOH, 0.01 M $CuSO_4$, and 6% H_2O_2 were added to each Eppendorf. Next, the Eppendorf tubes were transferred to 80 °C bain-marie. After 15 min, the Eppendorf tubes were cooled in cold water for 5 min. After that, 0.6 ml 5% paradimethyl amino-benzaldehyde and 1.2 ml 3 NH_2SO_4 were added to the Eppendorf. Following

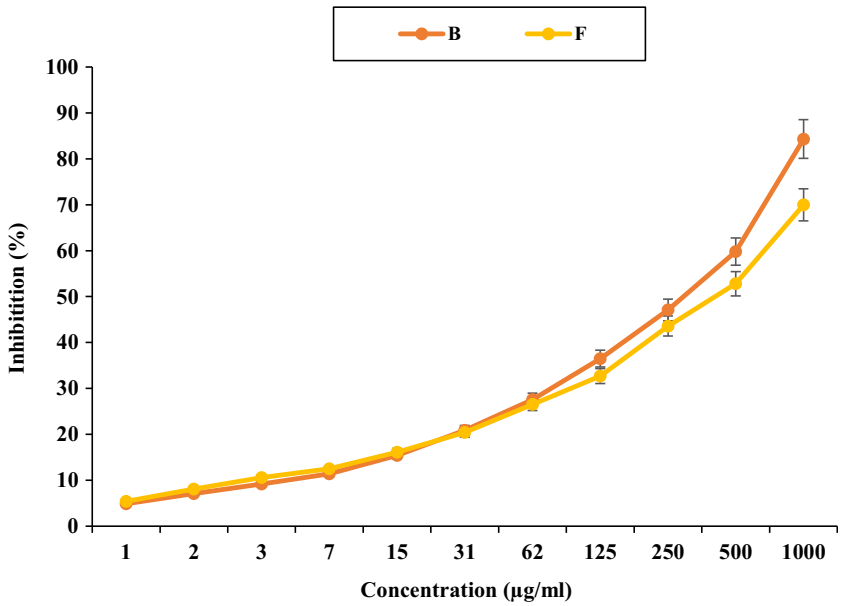

Fig. 2 Antioxidant activity of *Falcaria vulgaris* aqueous extract. F: *Falcaria vulgaris* aqueous extract, B: Butylated hydroxy toluene

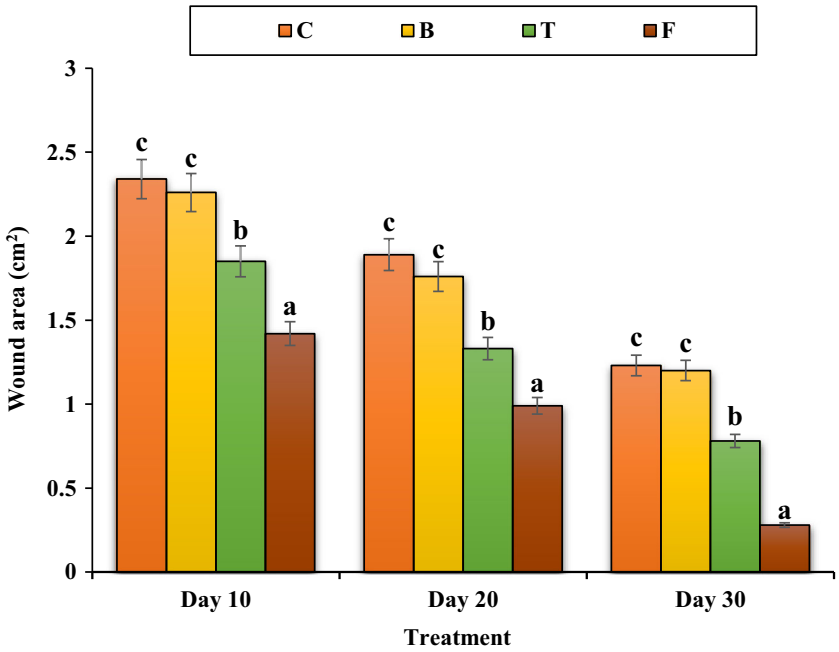

Fig. 3 Wound area level in several groups. C (control group), B (treated group with basal ointment), T (Treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

this, the Eppendorf tubes were put in 75 °C bain-marie for 15 min and transferred then to cold water for 5 min. Finally, hydroxyproline level was measured by a spectrophotometer at 540 nm wavelength (Caetano et al. 2016).

Hexosamine measurement

First, 0.5 ml acetyl acetone was added to the Eppendorf of cutaneous wound sample, and Eppendorf tubes were placed in 75 °C bain-marie for 20 min to heat, and were transferred to cold water for 5 min afterward. Then, 1.5 ml 95% alcohol and 0.5 ml Ehrlich solution were added to the samples. After 30 min, the hexosamine level was measured at 530 nm wavelength (Dwivedi et al. 2017).

Statistical analysis

All data were analyzed by one-way variance analysis (ANOVA), using the SPSS 18 software package. Data were considered statistically significant at $p \leq 0.05$.

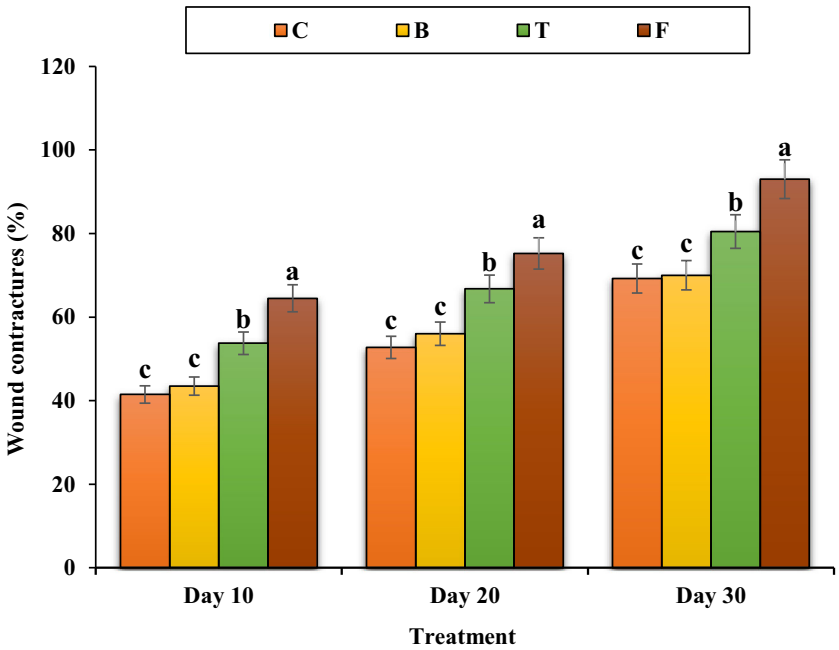

Fig. 4 Wound contracture level in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

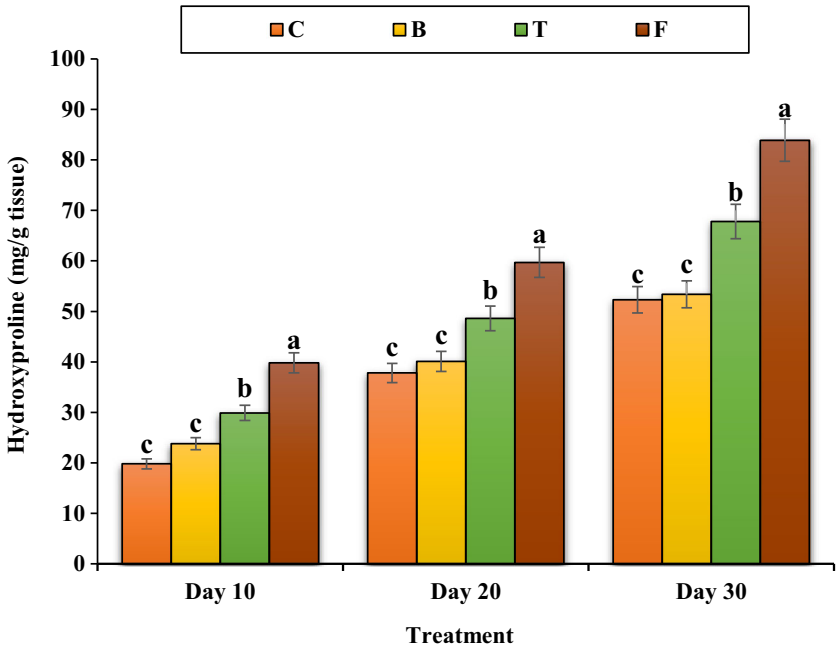

Fig. 5 Hydroxyproline level in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

Results

Antioxidant activity of *F. vulgaris* aqueous extract

DPPH free radical scavenging effect of the present *F. vulgaris* aqueous extract indicated effective inhibition in comparison with BHT as a positive control (Fig. 2). As shown, the free radical scavenging activity of *F. vulgaris* increased as a result of an increase in a dose-depended manner. The findings indicated the antioxidant effect for *F. vulgaris*.

Effect of *F. vulgaris* aqueous extract ointment on the macroscopic parameters

As shown in Figs. 3 and 4, *F. vulgaris* aqueous extract and tetracycline ointments decreased significantly ($p \leq 0.05$) the level of the wound area and increased significantly ($p \leq 0.05$) the percent of wound contracture as compared to the control and basal ointment groups. *F. vulgaris* ointment ameliorate significantly ($p \leq 0.05$) the levels of the wound area and wound contracture in comparison of the tetracycline ointment.

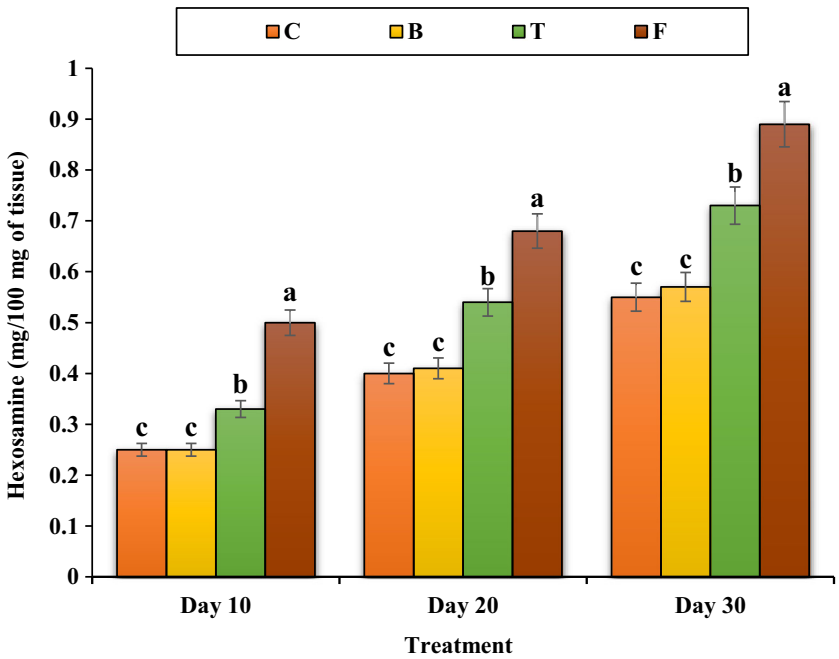

Fig. 6 Hexosamine level in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

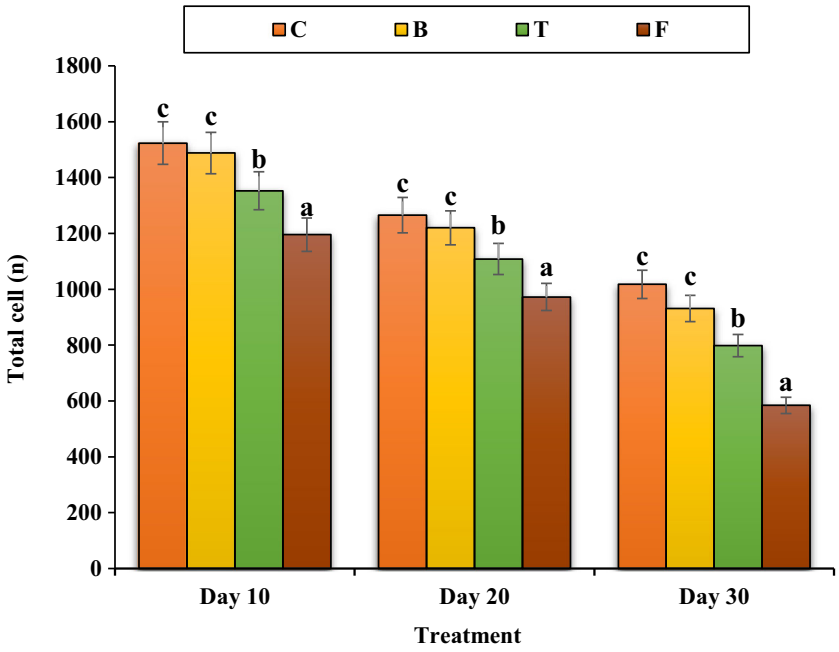

Fig. 7 Total cell number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

Also, there were not remarkable changes ($p \leq 0.05$) in the above parameters between control and basal ointment groups.

Effect of aqueous extract of *F. vulgaris* on the biochemical parameters

The levels of the hydroxyproline and hexosamine increased significantly ($p \leq 0.05$) in *F. vulgaris* aqueous extract and tetracycline groups as compared to the control and basal ointment groups. *F. vulgaris* ointment increased significantly ($p \leq 0.05$) the levels of hydroxyproline and hexosamine in comparison of the tetracycline ointment. Also, no remarkable changes ($p \leq 0.05$) were found between control and basal ointment groups in the above parameters (Figs. 5 and 6).

Effect of aqueous extract of *F. vulgaris* on the microscopic parameters

F. vulgaris aqueous extract and tetracycline ointments decreased significantly ($p \leq 0.05$) the number of total cells, lymphocyte, neutrophil, macrophage, and increased significantly ($p \leq 0.05$) the number of fibrocyte, fibroblast, and the rate of

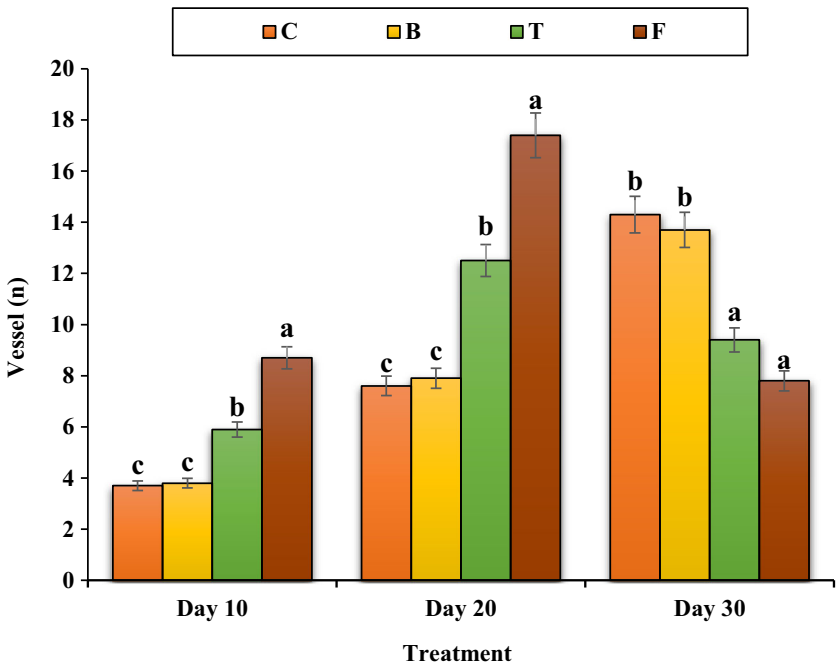

Fig. 8 Vessel number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

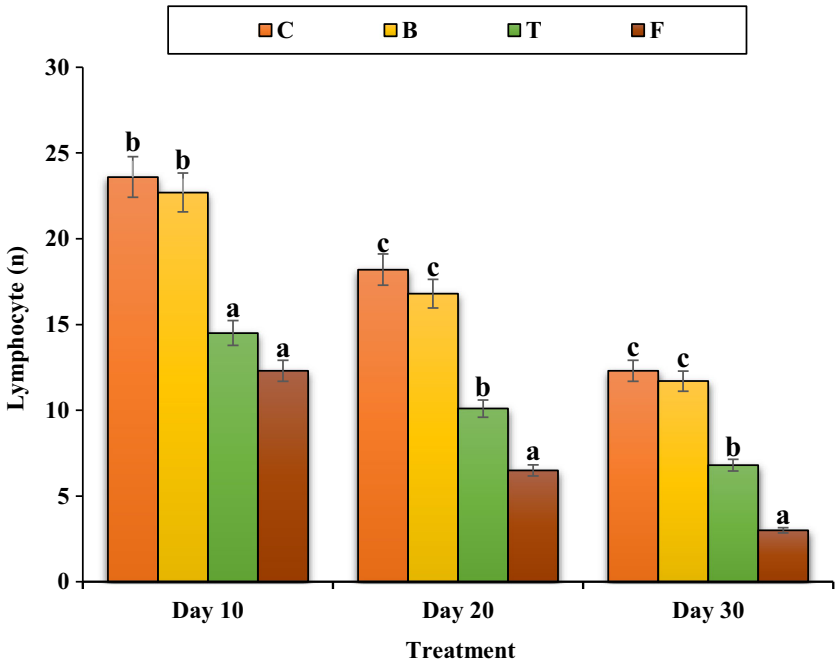

Fig. 9 Lymphocyte number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

fibrocyte to fibroblast as compared to the control and basal ointment groups. Also, there were not remarkable changes ($p \leq 0.05$) in the above parameters between control and basal ointment groups (Figs. 7, 8, 9, 10, 11, 12, 13, 14).

Discussion

In Iran, there are many medicinal plants with tremendous therapeutic effects. These herbs are used in traditional medicine to prevent, control, and treat several diseases includes anorexia, nasopharyngitis, diabetes, hypertension, nephrotoxicity, hepatotoxicity, hemorrhoid, anemia, rheumatism, atherosclerosis, cancer, Alzheimer, gastroduodenal ulcers, fatty liver disease, cutaneous wound, etc. (Sharafzadeh and Alizadeh 2012; Ghashghaii et al. 2017; Hagh-Nazari et al. 2017; Sherkatolabbasieh et al. 2017; Hamelian et al. 2018; Farzaei et al. 2018). One of the herbs used in Iranian traditional medicine to treat the cutaneous wound is *F. vulgaris*.

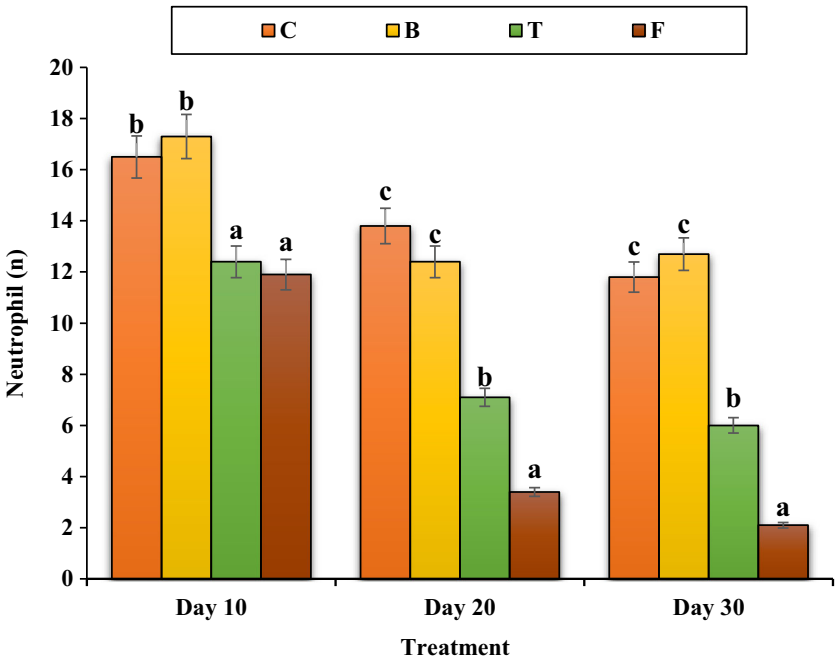

Fig. 10 Neutrophil number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

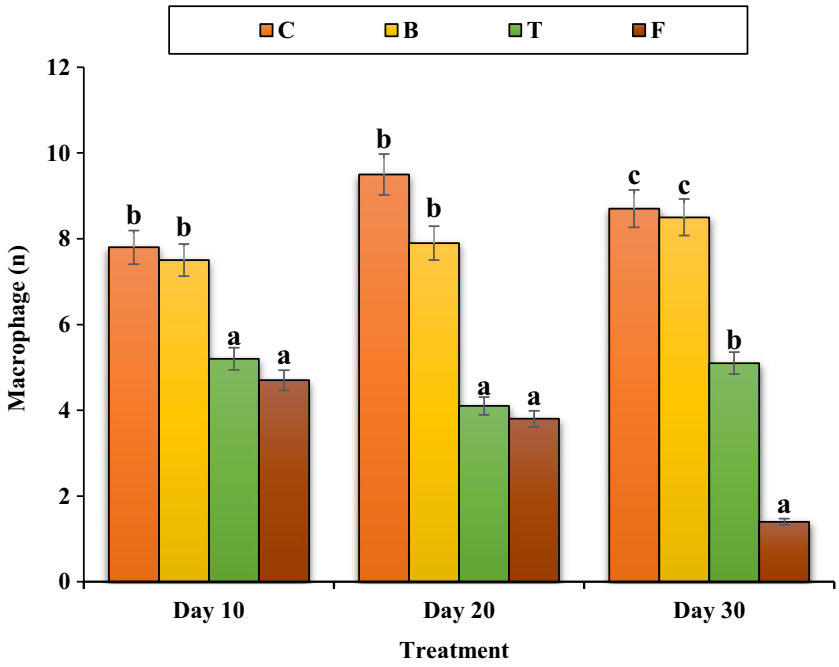

Fig. 11 Macrophage number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

Wound healing is a restorative process that occurs after skin and soft tissue injury (Ayyanar and Ignacimuthu 2009; Ruszczak and Schwartz 2000; Stavrou 2008). After histological impairments, platelets present abundantly at the wound site, many cytokines release from the site and neutrophils migrate to the injured site and initiate phagocytosis (Lazarus et al. 1994; Phillips et al. 1991). As a part of the inflammatory phase, macrophages appear and initiate phagocytosis and secretion of a series of growth-stimulating factors, the wound site is cleaned and fibroblasts migrate to the given site, secrete the extracellular matrix, which includes collagen, and organize at the site (Oryan et al. 2012; Nayak et al. 2007). Hydroxyproline is one of the components of collagen and, along with hexosamine, results in the continuous production of extracellular matrix (Caetano et al. 2016; Dwivedi et al. 2017). Despite dramatic developments in the treatment of surgical wounds, pus has remained one of the noticeable causes of post-operative mortality. The pus is caused by the excessive migration and activity of inflammatory cells includes neutrophils, macrophages, and lymphocytes at the wound site (Koh and DiPietro 2011; Guo and DiPietro 2010;

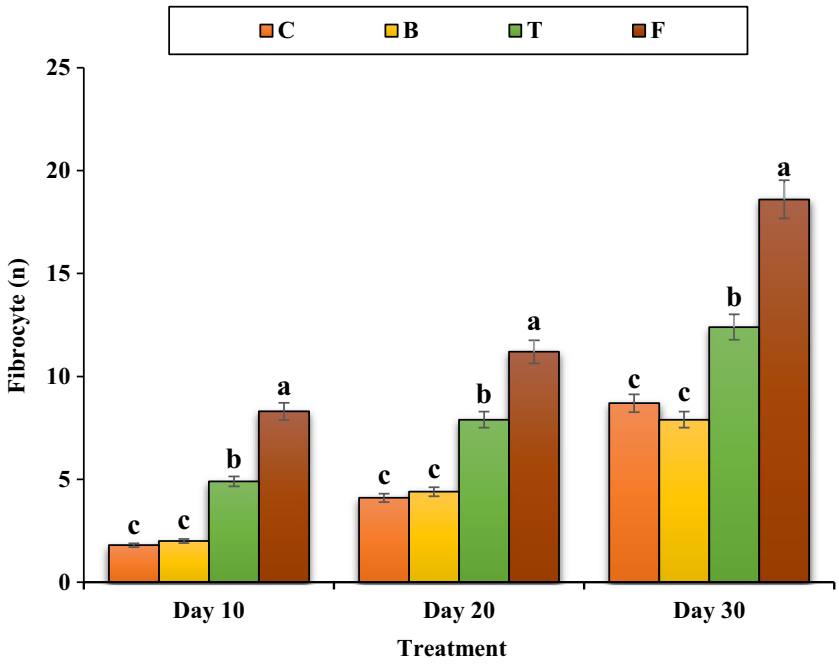

Fig. 12 Fibrocyte number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

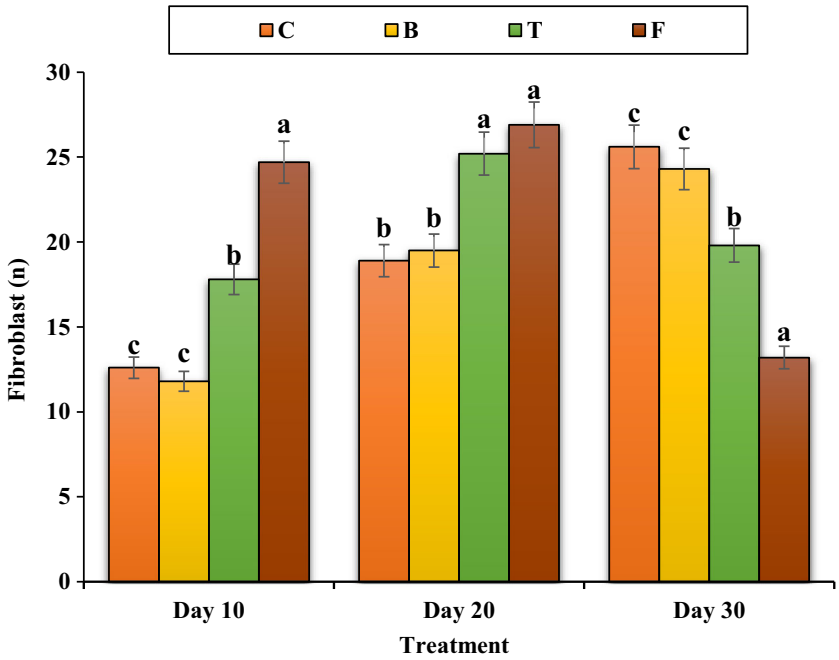

Fig. 13 Fibroblast number in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

Dong et al. 1993). In agreement with the above studies, the results of biochemical and histopathological parameters of our study demonstrated that aqueous extract of *F. vulgaris* significantly ($p \leq 0.05$) increased the levels of wound contracture, hydroxyproline, hexosamine, fibrocyte, fibroblast, and the rate of fibrocyte to fibroblast, and decreased the levels of wound area, total cells, lymphocyte, neutrophil, and macrophage as compared to the control and basal ointment groups. In recent study, the evidence of pus accumulation, fibrin deposition, polymorphonuclear cells infiltration or edema were not seen in the lesions of animals in *F. vulgaris* group, but were seen in control and basal ointment groups.

Free radicals that were found abundant at the wound site intensify production of the pus and decrease the rate of wound healing (Foschi et al. 1988). Other studies indicated that medicinal plants rich in antioxidant and anti-inflammatory compounds significantly reduced production of pus and increased wound healing process (Geethalakshmi et al. 2013; Robards et al. 1999). In our study, we determined that *F. vulgaris* had strong antioxidant activity. In the study of the Jaberian et al.

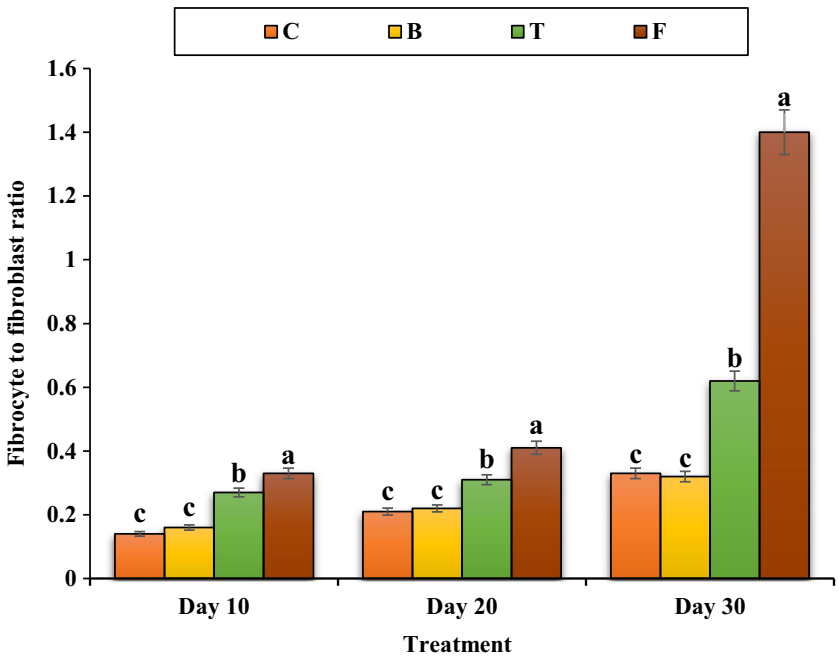

Fig. 14 Fibrocyte to fibroblast ratio in several groups. C (control group), B (treated group with basal ointment), T (treated group with tetracycline ointment), and F (treated group with *Falcaria vulgaris* aqueous extract ointment). Non-like letters show a remarkable change between the several groups ($p \leq 0.05$)

(2013), it is reported that *F. vulgaris* were rich in antioxidant compounds including alkaloid, anthraquinone, flavonoid, phenolic, saponin, steroids, and tannin. In another study, Khanahmadi and Shahrezaei (2008) revealed that spathulenol and carvacrol (antioxidant compounds) were the main compounds of *F. vulgaris*. Also in the study of the Ebrahimi Monfared et al. (2012), it is indicated that *F. vulgaris* with phenolic compounds had good DPPH radical scavenging activity. So it was normal that the plant had wound healing potential.

Conclusion

It concludes that *F. vulgaris* aqueous extract revealed significant wound healing potential. This extract also demonstrated improvement in biochemical and histopathological parameters and so might be of value in wound treatment.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

Ethic approval All institutional and national guidelines for the care and use of laboratory animals were followed.

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