J Food Sci Technol (November 2020) 57(11):4211–4219
https://doi.org/10.1007/s13197-020-04459-6

ORIGINAL ARTICLE

Effect of two different delivery systems of honey on the healing of oral ulcer in an animal model

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Revised: 7 April 2020 / Accepted: 15 April 2020 / Published online: 22 April 2020

Abstract Honey had several healing properties which includes antibacterial, anti-inflammatory and antioxidant properties. Hence, the aim of this study was to evaluate the effect of two different systems of honey on the healing of experimentally created traumatic oral ulcers in rats. Traumatic ulcers were created on the lower labial mucosa on male rats using 50% acetic acid. The rats were subsequently divided into three groups; in group one and two, the ulcers were treated with honey gel and honey adhesive respectively, whereas the third group received no treatment. The ulcers were macroscopically and microscopically studied. A statistical significant difference was observed in macroscopic investigation among the three groups in the 3rd and 7th day ($p < 0.05$). However, there were no statistical significant findings by the 15th day although a complete clinical healing was virtually observed in most of the cases. Histological examination shows a statistical significant difference within each of the three groups over time ($p < 0.05$). On the other hand, the mean rank values for the honey gel group were significantly higher in comparison to the other groups over time ($p < 0.05$). The therapeutic value of honey gel appears to be more effective than the mucoadhesive form in shortening the duration of wound healing.

Keywords Oral mucosal ulcer · Wound healing · Honey · Mucoadhesive film

Introduction

Honey is a sweet, viscous and natural liquid which is produced by honeybees after the absorption of the nectar from the flowers (Czipa et al. 2019). In many ancient cultures, it is used as a food and even as a natural remedy for several diseases (Ismail et al. 2015). Honey is obtained from several natural sources but its main biological source is *Apis mellifera* (honeybee) (Czipa et al. 2019; Selvaraju et al. 2019). Honey's healing properties have been endorsed across ancient cultures and by the most influential religions. However, from the late nineteenth century until present, it had only gained scientific interest (Lee et al. 2011). Honey contains several chemical constituents including "sugars (40% fructose, 30% glucose, and 10% maltose), oligosaccharides, minerals, carbohydrates, amino acids, vitamins, enzymes, and phytochemicals such as flavonoids, and ferulic and caffeic acids, and water" (Oskouei and Najafi 2013; Oroian et al. 2018). The presence and formation of 5-hydroxymethyl-2-furaldehyde has also been reported in honey (Yang et al., 2019). Various volatile components were also found in honey (da Silva et al. 2020). The supported antibacterial and antioxidant

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13197-020-04459-6) contains supplementary material, which is available to authorized users.

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activity of honey is attributed to its chemical and physical properties (Goslinski et al. 2020; Liang et al. 2020). The concentration of the honey affects the bacteriostatic and bactericidal activity. Its high osmolality inhibits the bacterial growth by absorbing moisture from the surrounding environment, which will dehydrate bacteria. It also has a low pH, in the range of 3.2–4.5, which can inhibit microbial growth (Leyva-Jimenez et al. 2019). Moreover, hydrogen peroxide produced by the reaction of glucose oxidase that is added by the bees to the nectar contributes to honey's antibacterial activity as well. The amount of hydrogen peroxide decreases with the increase of honey concentration. The other honey constituents, enzymes and phytochemical factors are also reported to have antibacterial action. Honey has additionally shown antifungal and antiviral effects. It is worth mentioning that honey does not cause antimicrobial resistance, and the allergy to honey is rare (Al-Waili et al. 2011; Mandal and Mandal 2011; Oskouei and Najafi 2013). Flavonoids and phenolic acids have antioxidant effect against the free radicals produced by the hydrogen peroxide. There is a correlation between the darkness of honey's color and its antioxidant activity, the darker the honey the higher phenolic content. In addition, honey has the ability to reduce the concentration of prostaglandins in plasma. This anti-inflammatory effect reduces wound edema and exudates (Vallianou et al. 2014).

Traumatic ulcer is a common oral lesion in all age groups, especially in males. It is commonly located in the tongue, gingiva, and buccal mucosa, floor of the mouth, palate, and lip. It may be due to acute or chronic trauma; which arises from chemical, electrical, thermal or mechanical damage to oral mucosa (Neville 2009; Lester 2011). It appears as an erythematous area with a central yellow movable fibrinopurulent material. Some cases may develop a rolled white margin. Histopathologically, traumatic ulcer is a mixture of fibrin and neutrophils, while the epithelial edges are normal or hypertrophic with or without hyperkeratosis. The core of traumatic ulcer is granulation tissue with endothelial proliferation and a mixture of inflammatory cells such as lymphocytes, histiocytes, neutrophils, and plasma cells that may extend to nearby muscles (Neville 2009).

Treatment of traumatic ulcer consists of removing the possible cause of the injury. Hydroxypropyl cellulose film or topical anesthetic is applied on the ulcer to relieve pain. The use of corticosteroids as a treatment of traumatic ulcer is controversial, as it may delay healing, while some reported its effectiveness (El-Haddad et al. 2014). If the ulcer does not heal, histopathological examination is indicated to rule out the lesion (Lester 2011). Since long time, honey is being used in treating wounds and other skin disorders (Jull et al. 2015). Honey has also been found efficacious in improving healing times in superficial and partial thickness burns, however the evidence for efficacy in other conditions is not yet confirmed. Numerous dressings and gels comprising honey are now available (Evans and Flavin 2008; Iftikhar et al. 2010; Jull et al. 2015) but its influence on the wound healing parameters had not yet studied well in literature. Since, the oral mucosa offers unique challenges for topical application, the present research was undertaken to study the effect of two delivery systems of honey i.e. honey gel and honey mucoadhesive films on the healing of experimentally created traumatic oral ulcers in rats.

Materials and methods

Materials

Sodium carboxy methylcellulose (SCMC; purity 99.0%) was obtained from "Sigma-Aldrich (St Louis, MO, USA)". Propylene glycol (PG) (purity 99.6%) and methyl paraben (pharmaceutical grade) were obtained from "BDH Chemicals Ltd. (Poole, England)". Deionized water was collected from "Milli-Q Water Purification Unit" in the laboratory. Acacia honey was purchased from local market in Riyadh, Saudi Arabia.

Honey formulations

The type of honey used was acacia honey. It is commercially available with certified quality, produced by honeybees from *Acacia modusta* flowers. All the components and their respective amounts for each honey formula used in the present study are displayed in Table 1.

Preparation of honey gel

Honey solution was prepared by dissolving 20% w/w of accurately weighed honey in the required quantity of hot deionized water containing 0.2% w/w of methyl paraben in 5% w/w solution of PG. Accurately weighed 2.5% w/w of SCMC was added gradually to the honey solution with gentle stirring (at 120 rpm) using a magnetic stirrer. The remaining amount of water was added in order to obtain 100% w/w of total gel. Stirring was continued until no lump formations were observed and then the contents were left overnight at refrigerator (4 °C) to allow complete swelling in order to obtain gel formation (Febriyenti et al. 2014).

Preparation of honey mucoadhesive films

Mucoadhesive films of honey were prepared by solvent casting technique (Febriyenti et al. 2014). Specified

Table 1 Components of the honey gel and mucoadhesive formula

Honey components	Honey gel formula (% w/w)	Honey mucoadhesive formula for 28 cm^2 area
Honey	20	120 mg
SCMC	2.5	500 mg
Propylene glycol	5	30 mg
Methyl paraben	0.2	70 mg
Deionized water to	100	25 ml

weights of SCMC, honey and other excipients were progressively transferred to a 100 ml beaker containing 20 ml of the casting solvent (deionized water). The final volume was adjusted to 25 ml with deionized water and the beaker was covered with aluminum foil paper to prevent the evaporation of the solvent. The casting solution was subjected to gentle stirring for 1 h using magnetic stirrer (Bibby, L32, Staffordshire, UK). The casting solution was transferred into a previously cleaned and dried Teflon coated plate (area = 28 cm^2). The solvent was allowed to evaporate for 72 h at room temperature (25 °C); the film was then removed from the Teflon plate and was allowed to dry in a desiccator at least for 48 h before evaluation. The patches were wrapped in an aluminum foil (to maintain the integrity and elasticity of the films) and were lastly kept in a dry place at ambient room temperature. The films were subjected to evaluation within one week of their preparation. PG and methyl paraben were used as plasticizer and preservative, respectively. The films were prepared in a concentration of 4.2 mg/cm^2. The resulted films were punched into 5.0 mm discs each containing honey 2.1 mg/disc to become ready for biological evaluation (Febriyenti et al. 2014).

Animals

Forty-five Sprague–Dawley male rats (weighing 250–300 g) were acquired from the center of Laboratory Animals and Experimental Surgery (CLAES) at King Khaled University Hospital, King Saud University, Riyadh, Saudi Arabia. The animals were kept under standardized conditions with free access to laboratory chow and water.

All the procedures for animal care were performed in compliance with the guidelines for proper conduct of animal experiments after the approval of the ethical committee and support of the College of Dentistry Research Centre, King Saud University, Riyadh, Saudi Arabia (Research project # IR 0139).

The rats were randomly assigned into three equal treatment and control groups (n = 15) as follows: group I was treated with honey oral gel, group II was treated with honey impregnated mucoadhesive film, whereas group III served as control where no treatment was applied. Topical or any other systematic therapy was not used apart from the honey.

Surgical procedure

Prior to the creation of the ulcer, all the animals were anesthetized using an intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg). After the anesthetic stage was reached, each animal was placed on a surgical table in dorsal decubitus and restrained with adhesive tape. The ulcer model used in the present study was a modified adaptation from Fujisawa et al. (2003). Standardized cotton tips (5 mm in diameter) soaked in 15 µl of 50% acetic acid was used to cause aseptic tissue necrosis. In order to create round ulcers, the acid soaked cotton tips were pressed onto the lower labial mucosa of the rats for 60 s. The surgical procedures were performed by one examiner. The created labial ulcers were covered 24 h after ulcer initiation (day 1) with the honey oral gel and the honey impregnated mucoadhesive film, whereas the control group did not receive any treatment. The honey gel and adhesive film were placed twice daily, until the day of scarification. Healing time was evaluated for all three groups. Five animals from each group were sacrificed by an overdose of ether after 3, 7 and 15 days, respectively.

Macroscopic observation

The created mucosal ulcers of each group were measured after the excision of the lesion in the third, seventh and fifteenth days using a metal gauge caliper as shown in supplementary Fig. 1 (Fig. S1) to calculate the surface area. In addition, the specimens were examined to detect any infection or changes in the ulcer shape.

Microscopic observation

The area of the surgical wound was subsequently excised and fixed in 10% neutral buffered formalin. The specimens were then accordingly processed by the conventional methods for paraffin embedding, 4-µm thickness serial sections were cut and stained with Hematoxylin and Eosin (H & E) and Masson Trichrome for light microscopic

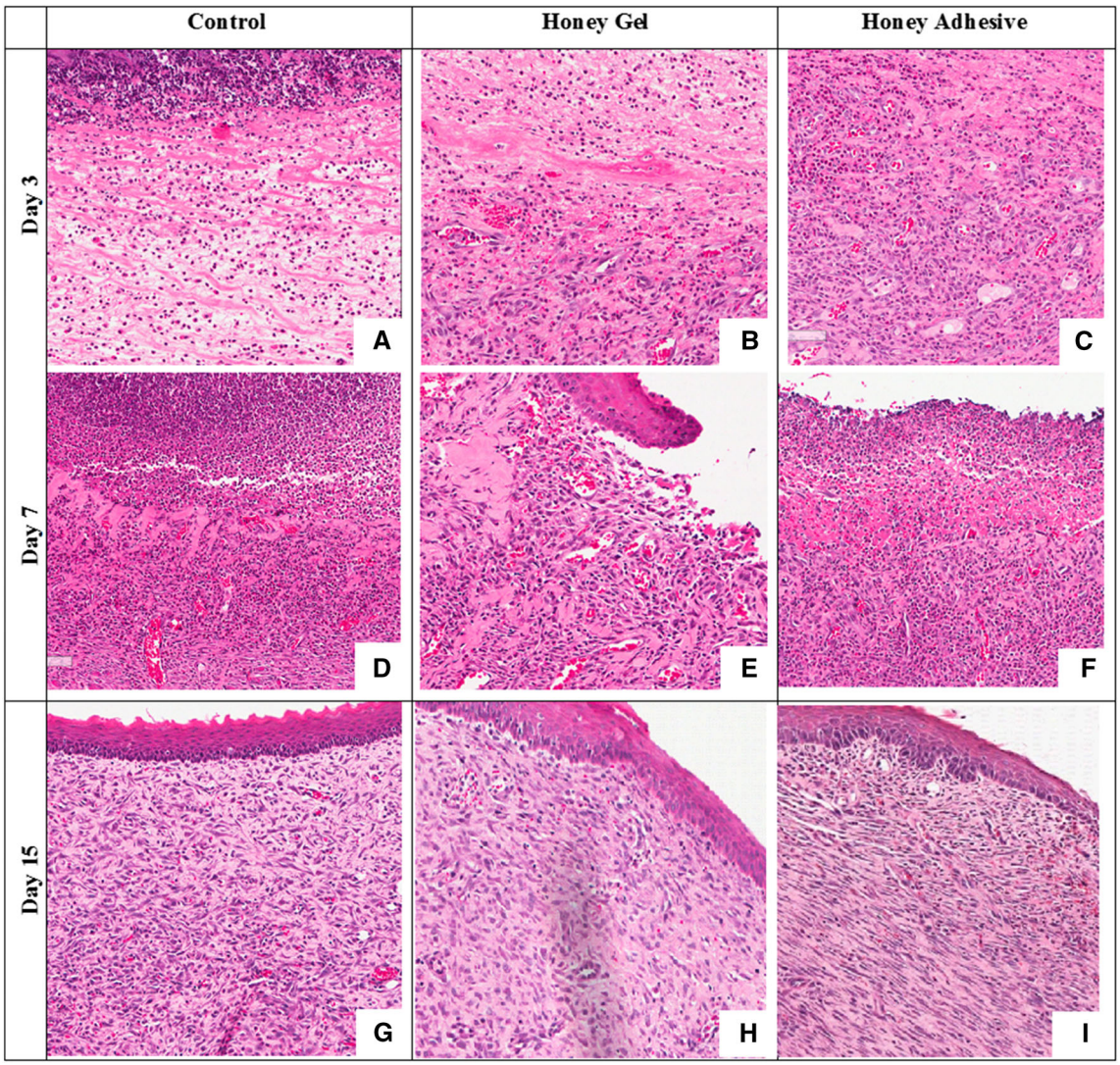

Fig. 1 Histological presentation of the ulcer areas in the three groups at the 3rd (A: control group, B: honey gel group and C: honey adhesive group), 7th (D: control group, E: honey gel group and F: honey adhesive group) & 15th (G: control group, H: honey gel group and I: honey adhesive group) day (H & E X 200)

histological investigation using a pre-established histological healing score (Karavana et al. 2011) as shown in Table S1.

Statistical analysis

The collected data were analyzed using "SPSS® Statistics, Version 21.0 software (IBM Corp., Armonk, NY, USA)". Descriptive statistics (mean, standard deviation, median and inter quartile range) were used to describe the quantitative and categorical variables. One-way analysis of variance was used followed by Tukey's test for multiple comparisons. A non-parametric Kruskal–Wallis-H test was used to compare the mean ranks of categorical outcome variables in relation to the categorical study variables (study groups). The p-value less than or equal to 0.05 was considered to be statistically significant.

Results

Macroscopic observation

During the first three days, the created ulcer area in the labial mucosa of the rats was clinically visible and crateriform. By the third day of the experiment, clinical measurement of the ulcer crater revealed a marked variation in size among the three groups, with statistical significance ($p < 0.05$). By the seventh day, the ulcer sizes were reduced with statistical significant variations between the groups ($p < 0.05$). By the fifteenth day, the complete

clinical healing was virtually observed in most of the cases with no significant difference between the groups as indicated in Table 2. The surgical procedures were satisfactory and all wounds healed without infection. All animals remained alive except for one rat from the control group who died by the 10th day.

Microscopic observation

The histological evaluation was carried out based on the pre-established histological healing score (Karavana et al. 2011) as shown in Table S1 and presented in Figs.1 and 2. During the third day, all the groups showed profound inflammatory cell infiltration and excessive granulation tissue with an interrupted epithelization as well collagen fiber deposition in a mesh like pattern as shown in Figs.1 and 2A–C but they differed in the new blood capillary formation. Angiogenesis with proliferation of the endothelial cells with attempts of excessive blood vessel formation was found in the honey gel and adhesive groups respectively (Figs.1B–C and 2 B–C). On the other hand, the control group (Figs.1A and 2A) was devoid of new blood vessels. By the seventh day, prominent chronic inflammatory cell infiltration with a slight increase in the number of the blood vessels was evident at the base of the ulcer. Granulation tissue still persisted under an incompletely epithelized ulcer at the surface in the control group as presented in Figs.1D and 2D. Collagen bundles showed mild organization, yet with delayed collagen build up compared to the honey gel and honey adhesive groups where they displayed decreased signs of inflammation and granulation tissue, with the appearance of new blood vessels reaching the surface with beginning of re-epithelialization as illustrated in Figs.1E–F and 2E–F.

During the fifteenth day of the experiment, all the groups showed almost complete epithelization covering the surface as demonstrated in Figs.1G–F and 2G–F with clearance of all inflammatory cells and normal vascularity. Granulation tissues were no more evident with apparent reorganization of the collagen fibers with few areas showing a mixed horizontally oriented and mesh like pattern of collagen organization (Fig. 2G-I). By the end of the experiment, all animals had a healing score of 5 except 1 animal in the honey adhesive group and 4 rats from the control group as shown in **Fig. 3.** A statistical significant difference was observed in the histological findings within each of the three groups over time where the control, honey gel and honey mucoadhesive presented improved healing with re-epithelization ($p < 0.001$). A statistical significant difference was observed between the study groups at 3, 7 and 15 days ($p < 0.05$). Where the mean rank values for the honey gel group were significantly higher in comparison to the other groups over time as shown in Table 3.

Discussion

Honey is a traditional medication which is used to treat infected wounds. It has recently been rediscovered by the medical profession for the treatment of microbial infections, particularly where regular present therapeutic agents fail due to microbial resistance (Mandal and Mandal 2011). The present study was conducted to assess the effect of two delivery systems of honey on the healing of experimentally created traumatic oral ulcers in rats. Both clinical ulcer size and histological healing evaluation were assessed to provide detailed information 15 days following tissue injury. The experimental time period of 15 days was chosen because most wounds even if untreated or infected would show complete healing by the end of this time period (Karavana et al. 2011; Ali and Dahmoush 2012). The use of rats as an animal model in the present study had some advantages over other animals. Among these advantages is the resemblance between the oral mucosa of rats and humans, which in turn allow us to analyze the aspects of oral mucosa that would not be easily studied in humans. The choice of male rats also cancelled the effect of sex hormones on wound healing. Sex hormones likely

Table 2 Mean ulcer surface area values at the three-time point in each of the 3 study groups and among the three groups at each of the 3 time points (n = 15)

Time point	Groups (Mean ± SD)			F-value	*p*-value
	HC	HG	HA		
Day3	1.168 (± 0.25)	1.644 (± 0.12)	1.338 (± 0.34)	4.53	0.034*
Day7	0.534 (± 0.17)	0.860 (± 0.29)	0.994 (± 0.20)	5.56	0.020*
Day 15	0.352 (± 0.41)	0.356 (± 0.34)	0.468 (± 0.43)	0.13	0.877
F-value	10.82	29.37	9.44	–	–
p-value	0.003*	< 0.001*	0.003*	–	–

*Statistically significant P < 0.05

HC Control group; *HG* Honey Gel group; *HA* Honey Adhesive group

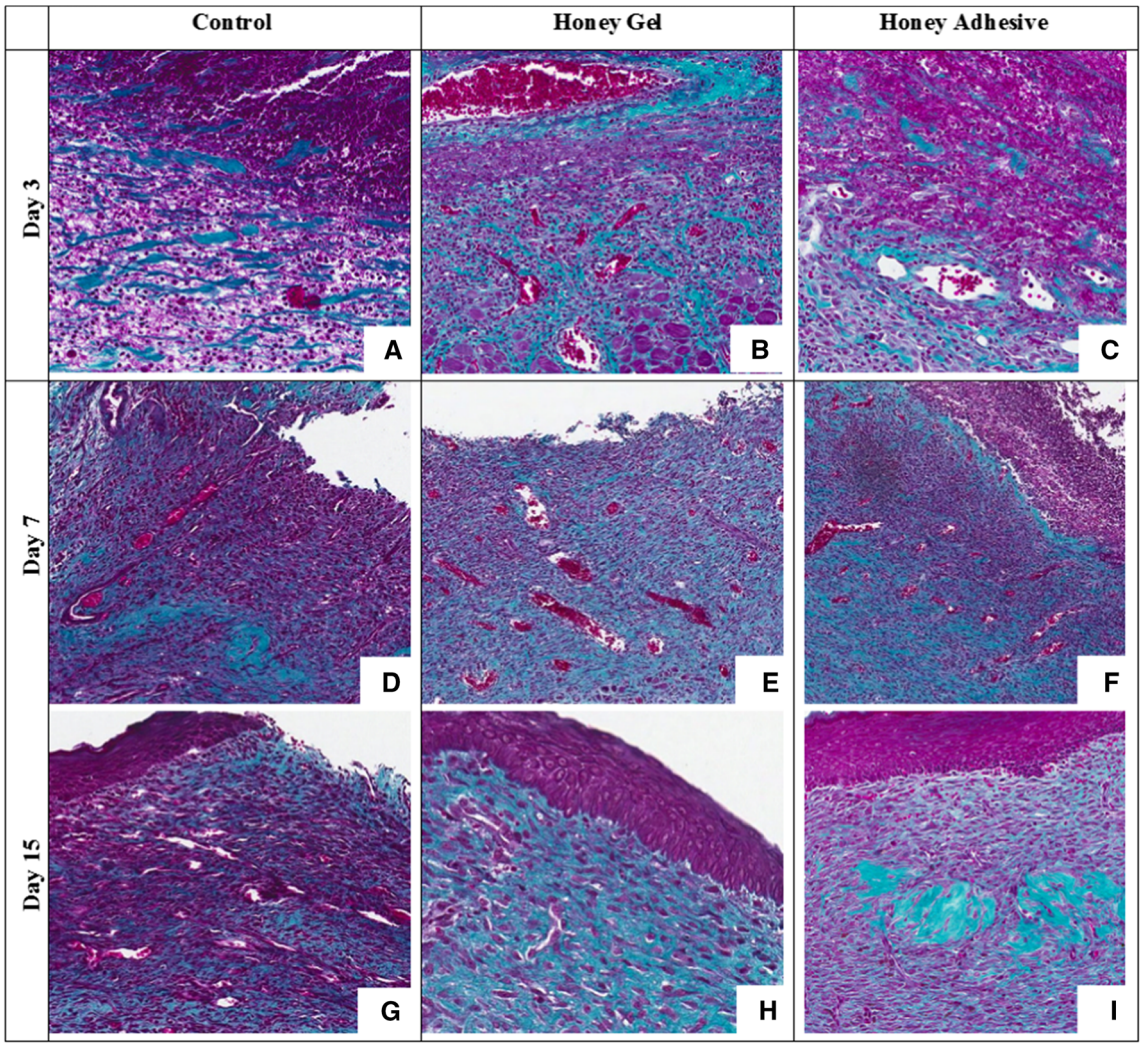

Fig. 2 Histochemical presentation of the ulcer areas in the three groups at the 3rd, 7th & 15th day (Masson Trichrome X 200)

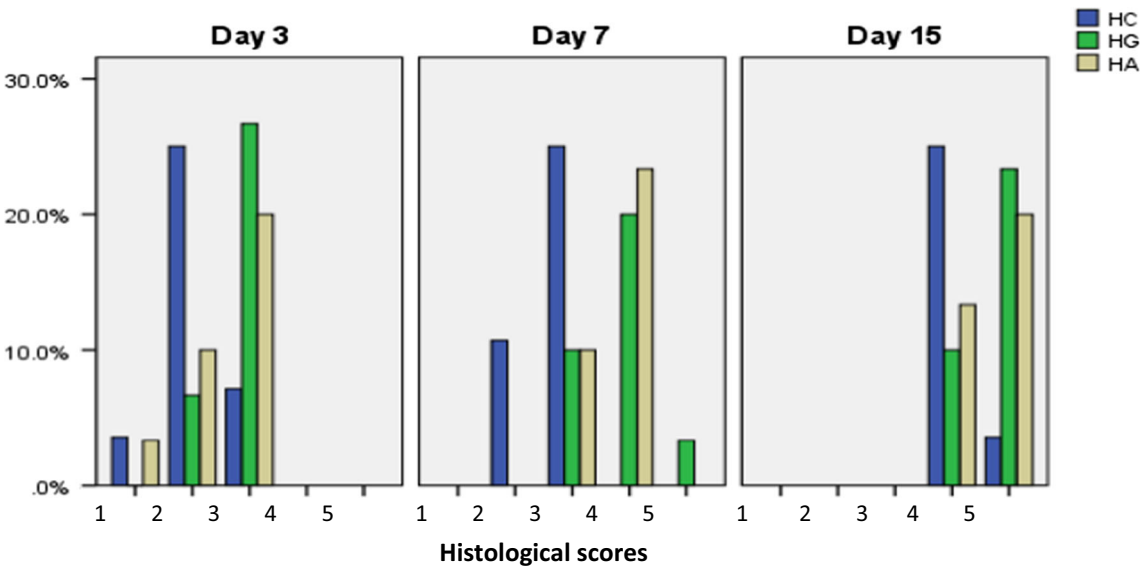

Fig. 3 The histological evaluation scores among and within the three study groups in each of the 3 time points

Table 3 Comparison of the mean ranks of the histological evaluation scores among the three study groups at each of the 3 time points (n = 15)

Groups	Time points					
	Day3		Day7		Day15	
	Median (IQR)	Mean Ranks	Median (IQR)	Mean Ranks	Median (IQR)	Mean Ranks
HC	2(0)	10.60	3(1)	7.60	4(0)	9.25
HG	3(0)	19.70	4(1)	19.80	5(1)	17.30
HA	3(1)	16.20	4(1)	19.10	5(1)	15.90
p-value		0.031*		0.001*		0.044*

*Statistically significant $P < 0.05$

HC Control group; *HG* Honey Gel group; *HA* Honey Adhesive group; *IQR* Interquartile range

modulate oral mucosal healing in accordance to previous investigations (Ali and Dahmoush 2012). The macroscopic analysis of the ulcerated areas had a tendency for linear regression with time and the injury in the labial mucosa was virtually healed by the end of the 15th day period. Over the whole observation period, honey gel treated animals had higher healing scores than the honey mucoadhesive and control groups. The honey gel application seemed to increase the retention time of the drug at the application site with high cohesion and mucoadhesion due to its high water content and may have in turn improved the treatment outcome by providing sustained faster release of the honey. On the other hand, mucoadhesive film is prepared by drying the honey gel to form a thin layer which sequentially provides slower release based on the dissolution of medication over a longer period of time (Febriyenti et al. 2014).

The histological characteristics of healing depends on the orderly collagen formation at different stages of wound healing as noticed in all groups starting in the early stage of wound healing increasing with time until reaching a maximum mature arrangement by the 15th day in accordance to the observations of Ali and Dahmoush (2012). In addition to re-vascularization where new blood vessels returned to the damaged tissue when treated with honey was unexpectedly faster than that observed in the control group. The honey group had better histological healing scores than the control group, which may be due to the positive effect of covering the ulcer surface. This is partly in agreement with Yilmaz et al. research (2009) where they stated that the wounds of all their studied groups were covered by new mucosa and were similar to the normal epithelium on day 7 and 14 confirming the present findings. Acceleration of re-epithelization results from honey's high osmotic pressure, which dehydrates tissue edema and holds the wound edges together, and by the existence of hydrogen peroxide which stimulates the growth of epithelial cells (Iftikhar et al. 2010). Additionally, Molan (2006) claimed that honey gel healing effect may have been partly through systemic absorption, which can explain why honey gel was more effective. Wound healing represents a dynamic physiological process initiated and influenced by many factors (Diegelmann and Evans 2004). A number of studies have provided histological data for wound healing and reported that honey can help wounds heal faster (Al-Waili et al. 2011; Peimani and Eslammanesh 2014). The bioactivity of honey promotes wound healing by simulating cytokine production, which starts the healing process (Tonks et al. 2003). Some studies have demonstrated that the amount of angiogenesis, epithelization, and granulation tissue increases with the administration of honey (Simon et al. 2009). Furthermore, honey causes significantly greater wound contraction than controls, stimulating tissue growth (Molan 1998; Al-Waili et al. 2011). In addition, honey does not adhere to wounds and can easily be removed from the wounds without damage to the new tissue (Molan 2006) as seen within the present findings. Many studies are in accordance to our findings where they have reported different kinds of honey to have noticeable benefits in healing diverse wounds in humans and rats (Iftikhar et al. 2010; Al-Waili et al. 2011; Lee et al. 2011; Ismail et al. 2015). A clinical randomized controlled trial by El-Haddad et al. (2014), who studied the efficacy of honey as a topical treatment of recurrent minor aphthous ulceration as compared to topical corticosteroid and orabase treatment, concluded that honey was more effective in ulcer size and erythema reduction, as well as pain relief. The mean number of days for reduction of ulcer size and healing for the honey treated group was 2.73 ± 0.57 days versus 5.91 ± 0.91 and 7.14 ± 0.92 for triamcinolone treated and orabase control groups, respectively. Another controlled clinical study, however, with a small sample size (n = 20), confirmed that topical application of honey in comparison to triamcinolone had accelerated the healing of oral minor aphthous ulcers (Gichki et al. 2012). Al-Waili (2004) had found that the mean duration of labial herpes attacks with topical honey was shorter when compared to acyclovir treatment in the same subjects. The mean duration of pain and occurrence of crust with honey treatment were better than with acyclovir treatment as well. Honey application

resulted in two cases of aborted attacks in labial herpes. None of those studies reported any adverse effects of topical honey use for recurrent aphthous ulcer or herpes labialis lesions. Treatment options for oral ulcers include topical or systemic application of anti-inflammatory agents, antimicrobials, and corticosteroids (Hullah 2014). The adverse effects of those agents, especially when administered systemically are well documented. While honey use is reported to be safe with no adverse effects, aside from momentary stinging in some cases. Allergy to honey is rare, but there could be an allergic response to either the pollen or the bee proteins in honey. Analyses of honeys from various regions have revealed that up to 26% of unrefined honeys and 5% of commercial honeys are contaminated with *Clostridium botulinum*, which can be overcome by the use of gamma irradiated honey, which destroys clostridial spores in honey without loss of any of the antibacterial activity (Molan 1998; Lee et al. 2011). Conclusively, the present experiment corroborates that honey, as has been documented, has a positive effect on improving the healing times in mild to moderate superficial and partial thickness oral ulcers compared with other conventional dressings. The honey gel promoted faster wound healing than the mucoadhesive film, however, there did not seem to be a statistically detectable difference in their effectiveness on the clinical and histological parameters. Owing to the small number of animal in each group during each observation time, the overall assessed outcomes did not reveal statistically significant variations. Further investigation on a larger and more robust clinical randomized controlled trials are needed to study the effectiveness of the different delivery systems of honey on humans rather than the conventional treatment modalities.

Conclusion

In the present study, two different delivery systems namely honey gel and mucoadhesive film were studied to evaluate the potential of natural honey in the treatment of ulcerative oral mucosal lesions in rat models. The novel honey gel and mucoadhesive film delivery systems are considered natural candidates for the topical management and healing of ulcerative oral mucosal lesions. The therapeutic value of honey gel appeared more effective than the mucoadhesive film in shortening the duration of wound healing. The proposed delivery systems can be explored in suitable human subjects for future studies.

Supplementary materials

This manuscript contains supplementary materials which can be found online. The picture of gauze caliper for the measurement of the size of the ulcer is presented in Fig. S1. The scoring protocol of histological level of healing is summarized in Table S1.

Acknowledgements "Authors are thankful the College of Dentistry Research Center (CDRC) and Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia for supporting and approving this study".

Compliance with ethical standards

Conflict of interest "Authors report no conflict of interest associated with this manuscript".

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