Evaluation of the Effects of Three Plant Species (Myrtus Communis L., Camellia Sinensis L., Zataria Multiflora Boiss.) on the Healing Process of Intraoral Ulcers in Rats

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Original Article

Introduction

Traditional medicine has been used to relieve human sufferings for a very long period of time and is still one of the most inspiring sources of providing medicines. [1-2] Recently, the use of herbal medicines has increased markedly by patients who seek traditional treatment modalities and has been approved by patients and physicians. [3-4] There are several factors that affect patients’ tendency to use traditional medicine including easy access and patients’ interest in self-
traditional treatments are available easily. Furthermore, their benefits in treatment skin and stomach wounds are proven according to different several studies. [7-10] So, in the present study, an attempt is made for investigating the effects of these plants in wound curing. It is worth mentioning that the present investigation is continuously doing on other plants, and the main goal is making the best mucosa patch for treatment of oral ulcers.

Materials and Method
In this study, the procedures of all steps were based on international protocols for animal care under the supervision of the Ethics Committee of Medical Kerman University (#256.93.k)

Leaves and stems of Zataria multiflora Boiss. stems and seed of Myrtus communis L. and leaves of Camellia sinensis L. are collected in spring and summer.

In the present research work, an attempt was made to investigate the authentication of herbal materials according to macroscopic and microscopic examinations. Macroscopic examination involved the comparison of morphological characters that are visible with the naked eye or under low magnification with descriptions of the plant or botanical drug in floras or monographs. Characters such as size, shape and color of leaves (or leaf fragments), and also flowers or fruits are commonly used in macroscopic identification. Microscopic examination is focused on anatomical structures in the plant material that are visible only with the help of a microscope such as trichome (hair) shape and structure, the arrangement of stomata in the epidermis, the presence or absence of compounds such as mucilage, starch or lignin, or the presence of tissues with characteristic cells. The plant was collected from Kerman (Baft, Iran), dried in shade, and powdered by mechanical grinder. The voucher samples were preserved for reference in the Herbarium of Pharmacognosy Department, School of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran.

The plant powder was extracted using aqueous in fusion and maceration with ethanol. For the aqueous infusion, 1000 ml of hot water was added to 100 g leaves powder, boiled for 15 min, and filtered through cloth. For ethanolic extraction, the plant powder was macerated in 500 ml ethanol (80%, v/v) for 72h and the mixture was subsequently filtered and concentrated in
vacuum at 40°C. By distillation technique, the extracts were concentrated in vacuum and stored at -20°C. [11]

A total of 60 healthy white Spraque-Dawley rats weighing 250-300 g were selected in this study. The animals were randomly divided into 5 groups of 12. 12 rats were placed in the control group and 48 rats were equally divided into Z. multiflora, M. communis, C. sinensis and the basic material groups.

The animals were kept in a well ventilated room at the animal laboratory of the Neuroscience Research Center, while the temperature and moisture were under control. A standard 12-hour cycle of day and night was established in the room. Standard food and water were provided for these rodents with equal dietary conditions for all the animals.

The hand and legs of the animals were tied to the dissection table and a buckle-shaped clamp was fastened on the upper incisor tooth to keep the mouth open. The animals were divided into 5 groups of 12 and numbered. The animals in each group were kept in separate cages, while the food regime was the same for all the animals, with consumption of soft food stuffs.

On the first day, all the 60 animals underwent a general anesthesia procedure with ketamine at a dose of 60 mg/kg and Xylazine (Rompun®), as a muscle relaxing agent at a dose of 7.5 mg/kg. A #2 punch was used to create a wound in the hard palate in the oral cavity, measuring 2×2 mm, with a depth of 2-3 mm; therefore, the wound included the whole epithelium and the connective tissue, (Figure 1). [30] After controlling hemorrhage and the formation of a clot, the animals were divided into 5 groups of 16, including group C in which animals did not receive any medication, group Z in which the animals received the methanolic extract of Z. multiflora, group M in which the animals received the methanolic extract of M. communis, group CS in which the animals received the methanolic extract of C. sinensis and group B in which the animals received the basic material.

In the present study, materials were prepared in the form of mucous patch. The medications were placed on the wounds at certain concentrations and volumes in 48 animals and the remaining 12 animals were considered as the controls (group C). Mucosa patch was used one time daily during eight days. All the animals were weighed every day using an accurate weighing machine. [31] The wounds were clinically evaluated during the whole period of study (8 days) before re-administration of medications. The animal underwent a general anesthesia procedure every day and the depth and width of the ulcers were measured using slide calipers, [32-33] by an operator who was blinded to animal groupings.

Three animals from each group were euthanized on days 2, 4, 6 and 8, [32-33] respectively by using ether. Each wound was removed by a #5 punch, a periosteum elevator and a scalpel blade, consisting of adjacent muscles and 1 mm of the healthy peripheral tissues and fixed in 10% formalin. The samples were sent to the pathology laboratory. They were embedded in paraffin, stained with H&E and evaluated by a pathologist blinded to the status of each sample. The histopathologic criterion for the evaluation of wounds was tissue inflammation (Table 1).

In addition, the wounds were histopathologically graded from 1 to 5 for re-epithelialization (Table 2). [34] Two-way ANOVA was used to compare mean wound sizes, the maximum ulcer diameter, animal weights in different groups and re-epithelialization degree. The criteria $p<0.05$ was considered significant, and the statistical analysis was performed by the SPSS 21 software.

Figure 1a and b: A N2 punch which was used to create a wound in the hard palate in the oral cavity, measuring 2×2 mm, with a depth of 2-3 mm; to include whole epithelium and the connective tissue.
Table 1: Histopathological scores to evaluate inflammation

| Score | Description |
|-------|-------------|
| 0     | No acute inflammation |
| 1     | Perivascular scattered acute inflammatory cells |
| 2     | Submucosal band-like inflammatory infiltrate, less than 1/4 of one power field |
| 3     | Submucosal band-like inflammatory infiltrate, between 1/4 and 3/5 of one power field without tissue necrosis |
| 4     | Submucosal band-like inflammatory infiltrate, more than 3/5 of one power field with tissue necrosis |

Table 2: Histopathological grading to evaluate re-epithelialization

| Score | Description |
|-------|-------------|
| 1     | Re-epithelialization at the edge of the wound |
| 2     | Re-epithelialization covering less than half of the wound |
| 3     | Re-epithelialization covering more than half of the wound |
| 4     | Re-epithelialization covering the entire wound, irregular thickness |
| 5     | Re-epithelialization covering the entire wound, normal |

Results
The average weights of the animals in the 5 groups (M, CS, Z, B, and C) at the beginning of the study were 220, 215, 222, 218, and 225 g, and after 4 days with oral ulcer were decreased to 215, 205, 209, 210, and 220 g, respectively. There were no significant differences between groups in the reduction of weight (p > 0.05). Comparison of clinical wound size showed that group M had the greatest reduction in wound size on days 4, 6, and 8, which was significantly different from the other groups (p < 0.05) (Figure 2).

In relation to the residual wound area, group M showed the lowest values among all the treatment groups at all the intervals (p < 0.05). Furthermore, clinical examination of the wounds in groups M and CS showed gradual healing over time in all the groups. Slow wound healing was observed on days 3 and 4 days postoperatively. Macroscopically, bone was covered with a sero fibrinous layer. Margins of the wound became irregular and started to migrate towards the center of the wound. The area of fibrin covering the base of the wound decreased rapidly from day 3 to day 4. On the day 4, the defect was largely covered with epithelium. At the end of experiment (day 8), most of the defects were healed with minimal central depression.

The highest thickness of epithelium was observed in groups M and CS on days 6 and 8, which was significantly different from the other groups (p < 0.05). In addition, group C had the lowest thickness of epithelium, which was significantly different from the other groups at all the intervals (p < 0.05) (Figure 3 and 4).

![Figure 2: Clinical photographic of the palate wound that showed healing of the wound in the group M.](image-url)

![Figure 3: Mean clinical wound size (μm) for every day.](image-url)

![Figure 4: Mean epithelium thickness (μm) during the period of experiments.](image-url)
There were significant differences between re-epithelialization results. Group M showed the highest values on days 6 and 8 ($p < 0.05$), while the groups C and B showed the lowest values at all the intervals (Figure 6). According to two-way ANOVA, a higher count of polymorphonuclear cells (PMNs) was observed on days 2 and 4 in groups Z, B and C, with significant differences from groups M and CS ($p < 0.05$). A lower score was observed in group M at all the intervals, with significant differences from other groups ($p < 0.05$).

This study showed a lower mononuclear cell counts in group M on days 6 and 8 compared to others, which was statistically significant; the counts were lower in groups Z, B and C on days 2; while, the difference was not significant ($p < 0.05$).

Discussion

Wounds are common conditions of the oral cavity, afflicting 12-20% of the population. [35] A large number of chemical compounds used for healing of oral ulcers and wounds after oral surgeries have been evaluated. Maintaining a high level of oral hygiene and plaque control determine the success of oral cavity surgeries, [36] which is especially important in the case of some specific wounds such as wounds induced in the palate for free graft of soft tissues, in which a large amount of tissue is lost; because they go through secondary intention healing process. [37]

The results of this study showed that M. communis has the greatest effect on wound healing process. This plant resulted in a decrease in neutrophil counts and an increase in the number of fibroblasts and improved epithelialization process. C. sinensis, Z. multiflora ranked second to third in relation to their effect on wound healing. Studies by Sharififar et al. [7-10] and Hosseinzadeh et al. [11] have shown the strong anti-inflammatory, antioxidative and antibacterial properties of these plants and in some cases they can have significant effects on wound healing.

Essential oils of M. communis leaves are used in France as an antiseptic. In addition, they have been used in hospitals in Paris in respiratory and certain urinary bladder conditions and have been recommended for local procedures in local conditions. [38-41] Its fruit has been used in diarrhea, dysentery, internal wounds, rheumatism, [38-39] foot ulcers, malodorous wounds, aphthous stomatitis, sinusitis, hair loss, bleeding, bronchitis, etc. [42] The antimicrobial and antioxidant properties of compounds produced by M. communis have been reported in some studies. [43-44] M. communis L. extracts profile constitutes polyphenolic compounds.
phenolic acids, tannins and flavonoids. Some results have indicated that phenolic compounds significantly contributed to the wound healing. [43] This activity may be attributed to the enzyme inhibition by the more oxidized phenolic compounds possibly through reaction with sulphhydryl compounds or through more nonspecific interactions with the protein. [44]

Findings of Ramezani et al. [45] revealed that in experimental group (Myrtus Communis cream) in comparison to control group, a significant increase was seen in wound closure, hair follicle numbers, and blood vessel numbers. Also increased skin thickness and diameter of collagen fibers were observed. These findings showed the acceleration of wound healing in the treated samples. [45] Also, Rezaie et al. showed that Myrtus communis has considerable effect on healing of the experimental skin wounds on rats compared with zinc oxide. [46] Sumbul et al. showed that oral administration of aqueous extracts of M. communis significantly reduced the ulcer index in all models of gastric ulcers (ethanol, indomethacin and pyloric ligation). Also this plant reduced the gastric juice volume, total acidity and increased the gastric pH and gastric wall mucus content in all the models of ulcers. [47]

Green tea contains large amounts of C. sinensis that is a polyphenols and the concentrations progressively decrease in produced tea and in some tea products, such as black tea, their concentrations reach zero. Polyphenols are achromatic water-soluble substances and have a great role in human health, including antimicrobial, antineoplastic and anti-allergic properties, preventive effects on cardiovascular diseases and a strengthening effect on the human immune system. Antimicrobial effects of polyphenols include an inhibitory effect on the growth of various bacteria and viruses and fermenting bacteria. [23, 48]

According to previous studies, the anti-neoplastic and anti-mutational effects of epicatechins of green tea leaves [27] and the inhibitory effect of extract of green tea on some carcinogenic chemical agents have been proved. [49] The anti-ulcerative effects of the extract of black tea leaves on various wounds and ulcers, including stress-induced peptic ulcers, have been confirmed. [49-50] Hamaishi et al. [51] showed that green tea may primarily protect rat gastric mucosa from acute gastric mucosal injury and promote the healing of chronic gastric ulcers by its antioxidant activity and gastric mucus-increasing actions. The study of Chatterjee et al. [52] reported that green tea relieved pain in a manner similar to diclofenac sodium, which is an indication of the anti-inflammatory effect of this plant. Eshghpour et al. [53] showed that green tea mouthwash could be an appropriate and safe choice to control postoperative pain after third molar surgery, which is an indication of the anti-inflammatory effect of this plant. Scoparo et al. [54] in their study found that green tea reduces the gastric lesions induced by ethanol and protects the gastric mucosa. In addition, the maintenance of gastric mucus and reduced glutathione levels was involved with the polysaccharides gastroprotection. [54]

Z. multiflora is traditionally used in various foodstuffs, especially in yoghurt, to add flavor and as an appetizer and antiflatulent. It is also used to alleviate pains due to premature pregnancies and ruptures. In addition, the extracts of top branches of Z. multiflora have exhibited anti-inflammatory effects in acute and chronic inflammatory conditions. [27-28] This plant species has been used in traditional medicine as an antiseptic, antispasmodic and anti-inflammatory agent. [27] Moreover, it was showed that the aqueous and methanolic extracts of top branches of Z. multiflora have definite anti-inflammatory effects in acute and chronic inflammation. [28]

**Conclusion**
The results of the present study showed that Myrtus communis L. have significant effects on oral wound healing processes. These favorable results might introduce a new group of material or medicine which has been derived from this plant. Moreover, Camellia sinensis L. and Zataria multiflora Boiss. had no significant effect on wound healing.

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**Conflict of Interest**
Authors declare no conflict of interest.
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