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# Management of Aphthous Ulceration with Topical Quercetin: A Randomized Clinical Trial

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## Abstract

**Aim:** Recurrent aphthous ulceration is the most commonly known oral mucosal disease. Quercetin is a useful therapeutic agent for the treatment of colitis and gastric ulcer. The objective of this study was to determine the effect of topical application of quercetin in the treatment of minor aphthous ulcers.

**Methods and Materials:** Forty male patients with no known pathology of the oral mucosa other than minor aphthous ulcers were enrolled in this study. Patients were randomly divided into two groups, each consisting of 20 patients. Group 1 (control group) patients used a benzydamine hydrochloride mouthwash three times daily. Group 2 patients placed two to three dabs of quercetin three times daily directly on their ulcers. Clinical evaluation of patients included assessment of ulcer size, pain measure, and interviews regarding the topical application of quercetin in terms of consistency, taste, local tolerability, and ease of application.

**Results:** The topical application of quercetin cream to minor mouth ulcers relieved pain and produced complete healing in seven of the Group 2 patients (35 percent) in 2–4 days, 18 patients (90 percent) in 4–7 days, and 20 patients (100 percent) in 7–10 days. When comparing the mean ulcer size after 10 days, lesions in the Group 2 patients were smaller than those in Group 1, and the size difference between the two groups was significantly different ($p<0.004$). Also, 90 percent of patients responded that they appreciated the ease of application when using the topical quercetin, and they did not object to its consistency or taste.


**Conclusion:** Quercetin is a safe, well-tolerated, and highly effective promising new, adjunctive treatment for healing common aphthous ulcers.

**Clinical Significance:** Although aphthous ulcers typically resolve on their own in one to two weeks, the daily topical application of quercetin may be useful in accelerating the healing process of minor aphthous ulcers.

**Keywords:** Quercetin, aphthous ulcer, canker sores, healing

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## Introduction

Recurrent aphthous ulceration is the most commonly known oral mucosal disease with a prevalence of up to 25 percent in the general population and a three-month recurrence rate as high as 50 percent.[1–3] These lesions typically are round or oval in shape with a yellow or gray floor surrounded by an erythematous halo of inflamed mucosa. They can cause considerable pain and may interfere with eating, talking, and swallowing.[4,5]

Aphthous ulcers (also referred to as "canker sores") can be classified into three different types: minor, major, and herpetiform.

***Minor ulcers:*** The minor type is by far the most common ulcer, representing an estimated 80–87 percent of these lesions. They have a diameter of <1 cm, usually occur on the nonkeratinized oral mucosa, have a good prognosis, and generally do not persist for more than two weeks.

***Major ulcers:*** The major type, also termed Sutton disease, constitutes an estimated 10–15 percent of all aphthous ulcers. These lesions generally are larger in size (>1 cm in diameter) with deeper ulceration. Healing is slow and may take weeks, if not months, to resolve, and often with scarring.

***Herpetiform ulcers:*** The herpetiform type constitutes only 5–10 percent of all aphthous ulcers and consists of clusters of multiple, pinpoint-type lesions that are 1–3 mm in diameter.


Although the entire cycle of formation to healing may take only three to four days, new lesions may develop during this time, extending the cycle of these ulcers for as much as one month.[5–8]

The pathophysiology of aphthous ulcers is still poorly understood,[5,7,8] but these lesions more commonly affect young adults. Some cases have a familial and genetic basis, but most patients seem to be otherwise healthy.[9,10] Attacks may be precipitated by local trauma, stress, food intake, drugs, hormonal changes, gastrointestinal track (GIT) diseases, immunological factors, and vitamin and trace element deficiencies. In HIV-seropositive patients, mouth ulcers occur more frequently, may be larger, take longer to heal spontaneously, and produce more painful symptoms than in immunocompetent persons.[2,7,8–11]

Treatment for oral aphthous ulcers can include antibacterial, anti-inflammatory, and analgesic mouth rinses; immunomodulatory therapy; hormones; and $CO_2$ laser. In most patients, topical agents, including over-the-counter preparations such as antiseptic mouthwashes, are recommended. In patients with frequent exacerbations or more severe forms of aphthous ulcers that are unresponsive to topical treatments, systemic agents such as corticosteroids, colchicines, dapsone, or antibacterials are indicated.[10,11] However, the treatment of aphthous ulcers remains unsatisfactory largely because both topical and systemic therapies are palliative, reducing the severity of the ulceration; yet neither therapy results in permanent remission. Moreover, the lack of predictability of the efficacy of a particular treatment reflects the etiology of the condition. A substantial need exists for an effective and well-tolerated agent that can promote complete ulcer healing within a short period of time.[11,12]

Phytogenic agents (phytochemicals from fruits and vegetables) have traditionally been used by herbalists and indigenous healers for the prevention and treatment of peptic ulcer.[13–15] Quercetin is an important dietary flavonoid derived from whole onion and apple extracts.[16–19] The uptake of quercetin aglycon and quercetin 3-glucoside was recently found to accelerate cutaneous lesion healing in rats when applied topically once daily.[14] Calvo et al.[14] showed that a single oral administration of quercetin (250 mg/kg once daily) potently stimulates gastric epithelial cell proliferation that contributes to the accelerated

healing of gastric ulcers. The antioxidant activity of quercetin was mentioned by Suzuki et al.,[20] Janisch et al.,[16] Sun et al.,[21] and Hämäläinen et al.[22] They determined that quercetin had free radical–scavenging activities, through inhibition-inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production, and also modulated low-density lipoprotein (LDL) oxidation.

The healing properties of quercetin were found to be associated with enhanced myofibroblast and epithelial cell growth, both of which are involved in granulation tissue formation.[16] Because the formation of granulation tissue is a key process in healing aphthous ulcers, the present study was undertaken to determine the potential healing properties and tolerance of quercetin in otherwise healthy patients presenting with the minor form of aphthous ulcers.

## Methods and Materials

Forty male patients ranging in age from 18 to 41, with a mean age 24.8 years, were selected from the outpatient clinic of Oral Medicine, Periodontology, and Oral Diagnosis Department, Faculty of Dentistry, Minia University, Minia, Egypt. Patients were chosen who presented with minor aphthous ulcers of one to two days' duration and had no other known pathology of the oral mucosa. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Dentistry, Minia University. The rules of this committee are in compliance with the Declaration of Helsinki (1964), and the study was conducted in accordance with the guidelines for Good Clinical Practice. Patients were informed of the nature and objectives of the study, expressed willingness to participate, and agreed to apply topical treatment from the beginning of the study until complete ulcer healing. All participants read, approved, and signed a written informed-consent form.

Patients with either major or herpetiform aphthous ulcers were excluded from the study. Those who were accepted had to be otherwise healthy and symptom free according to the Cornell Medical Index, a well-known health questionnaire.[23] Patients were randomly divided into two groups of 20. Individuals assigned to Group 1 (control group) were instructed to use a benzydamine hydrochloride mouthwash three times daily.


Patients in Group 2 received quercetin (Rootage skin cream "quercetin, glycol, EBC, Zn, Myristica" by Elsi-Si) and were instructed to apply two to three dabs of quercetin cream three times daily as directed on their ulcer. Patients in both groups were asked to continue daily treatment until complete healing had occurred.

The following measures and scales were used for the clinical evaluation of patients in both groups:

1. **Pain measure using Visual Analog Scale:**[1]
   Score 0 = no pain
   Score 1 = pain with rough aggravation
   Score 2 = pain with moderate aggravation
   Score 3 = pain with slight aggravation
   Score 4 = constant pain
   Score 5 = severe pain
   Patients were told that aggravation was anything that moved or touched the ulcer area. Note that pain associated with only gentle touching was awarded a higher score than that of pain accompanying rough handling.
2. **Assessment of the ulcer's size:** For accurate evaluation of affected areas, the patients were subjected to the following assessment process:
   A. With the patient sitting upright in good lighting, the ulcer area on the cheek was dried carefully.
   B. A transparent plastic sheet was cut to permit its introduction intraorally and its direct application on the ulcer.
   C. Using a Faber Multimark 1513 permanent waterproof marker, the margins of the ulcer

were traced on the plastic sheet.

D. The tracing was then placed on graph paper and the numbers of square millimeter ($mm^2$) units included inside the drawn areas were counted.
E. Ulcers were assessed five times: pretreatment (baseline), at 2 days, at 4 days, at 7 days, and at 10 days.
F. The sizes of the lesions were plotted in a table and compared statistically using paired t-test within the group and ANOVA test between two groups.

3. With the aid of a questionnaire, patients were asked to comment on the topical application of quercetin in terms of consistency (excellent, good, unsatisfactory), taste (excellent, good, unsatisfactory), local tolerance (none, slight, moderate), and ease of application (very easy, easy, difficult).

## Results

The mean and standard deviation of the size of the ulcer ($mm^2$) and pain scores are presented in Table 1. Analysis of variance of the size of the ulcer and the pain score appears in Tables 2 and 3 for both patient groups. Of the 20 Group 2 patients treated with topical quercetin, 7 (35 percent) achieved complete ulcer healing in 2–4 days, 18 (90 percent) had complete healing in 4–7 days, and all 20 patients (100 percent) had complete healing in 7–10 days (Table 4). In contrast, of the 20 Group 1 patients treated with topical benzydamine hydrochloride mouthwash, none achieved complete healing prior to 7 days and only 12 of the 20 patients (60 percent) experienced complete ulcer healing in 7–10 days.

**Table 1. Mean and standard deviation of the size of the ulcer ($mm^2$) and the pain score in both patient groups.**

| | Pre-therapy | | 2 Days | | 4 Days | | 7 Days | | 10 Days | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 |
| Size of ulcer | 59.6±11.69 | 61.85±13.58 | 43.9±12.47 | 20.35±6.74 | 20.55±5.96 | 3.65±3.54 | 9.45±2.92 | 0.2±0.69 | 1.8±2.46 | 0±0 |
| Pain score | 3.2±0.61 | 3.2±0.61 | 1.7±0.57 | 1+0.72 | 1.2±0.76 | 0.3±0.47 | 0.45±0.51 | 0±0 | 0.3±0.47 | 0±0 |

**Table 2. Analysis of variance of the size of the ulcer in both patient groups.**

| | Group 1 (pre-therapy vs. 10 days) | Group 2 (pre-therapy vs. 10 days) | Group I vs. Group 2 (at 10 days) |
|---|---|---|---|
| *t* value | 26.563 | 20.366 | 3.269 |
| *p* value | <0.05 | <0.001 | <0.004 |
| Degrees of freedom | 19 | 19 | 19 |
| Significance | significant | significant | significant |

**Table 3. Analysis of variance of the pain score in both patient groups.**

| | Group 1 (pre-therapy vs. 10 days) | Group 2 (pre-therapy vs. 10 days) | Group I vs. Group 2 (at 10 days) |
|---|---|---|---|
| *t* value | 20.241 | 23.247 | 2.853 |
| *p* value | <0.05 | <0.001 | <0.01 |
| Degrees of freedom | 19 | 19 | 19 |
| Significance | significant | significant | significant |

**Table 4. Correlations (*R*) between the mean size of the ulcer and the mean pain score in both patient groups.**

| | | | Mean Size of Ulcers | |
|---|---|---|---|---|
| | | | Group 1 | Group 2 |
| Mean pain score | Pre-therapy | *R* | 0.653 | 0.650 |
| | | *p* value | <0.05 | <0.05 |
| | After 2 days | *R* | 0.519 | 0.415 |
| | | *p* value | <0.05 | <0.05 |
| | After 4 days | *R* | 0.386 | 0.217 |
| | | *p* value | <0.05 | >0.05 |
| | After 7 days | *R* | 0.305 | 0.112 |
| | | *p* value | <0.05 | >0.05 |
| | After 10 days | *R* | 0.207 | 0.00 |
| | | *p* value | >0.05 | >0.05 |

When questioned about the topical application of quercetin, in terms of consistency, taste, local tolerability, and ease of application, the majority of patients (90 percent) reported that quercetin was very easy or easy to apply, was nonirritating, and had a good or moderate consistency and taste.


## Discussion

Aphthous ulcers are a common and painful problem, but their pathophysiology is still not fully understood. Currently used topical or systemic antibacterial, anti-inflammatory, immunomodulatory, or symptomatic treatments for the condition are neither 100 percent reliable nor efficacious.[6–8,14] Most patients with aphthous ulcers are likely to treat their lesions with over-the-counter products and antiseptic mouthwashes primarily.[3,8,14] There is currently no single, well-established treatment for these common mouth ulcers,[6,8,11,14] and none of the existing treatments accelerate the healing process. The aim of the present study was, therefore, to determine the potential healing properties of quercetin in the treatment of minor aphthous ulcers.

Topical applications of quercetin cream to minor mouth ulcers produced complete healing in 35 percent of the test patients (Group 2) in 2–4 days, in 90 percent in 4–7 days, and in all 20 patients (100 percent) in 7–10 days (Tables 1 and 4). The control patients treated with topical benzydamine hydrochloride mouthwash showed no evidence of ulcer healing before 7 days, and only 60 percent of patients showed complete ulcer healing in 7–10 days, compared to 100 percent of those in Group 2.

On comparing the mean of the ulcer size obtained at 10 days, there was a statistically significant difference ($p<0.004$) between the two treatment modalities. In fact, the Group 2 patients receiving quercetin had significantly smaller lesions (Table 1).

In terms of the effects of the two treatments on pain, there also was a significant difference ($p<0.01$) between the two groups at 10 days. In fact, the Group 2 patients reported no pain at 7 days and 10 days, while the mean pain score for the Group 1 controls was 0.45±0.51 and 0.3±0.47, respectively.

Taken together, the results of this study suggest promising beneficial effects from quercetin on aphthous ulcer healing, such as accelerated healing

and earlier relief from pain and discomfort. More importantly, complete ulcer healing occurred in two to four days for 35 percent of the patients receiving quercetin. In contrast, none of the Group 1 patients using topical benzydamine hydrochloride mouthwash had healing before 7 days and only 12 (60 percent) subjects achieved complete healing after 10 days.

The rapidity of lesion healing in the mucous membrane is dependent upon competition between bacterial multiplication, which retards healing, and the growth of myofibroblast and epithelial cells, which are needed for tissue repair.[13,14] The healing properties of quercetin on GIT ulcers have been reported by many authors,[24–26] who found that quercetin up-regulated vascular endothelial growth factor (VEGF), an ulcer healing factor. The anti-ulcerative effect of quercetin also could be attributed to its antiperoxidative, antioxidant, anti-inflammatory, and antihistaminic activity favoring wound healing.

The induction of iNOS in response to excessive cytokine production is a nonspecific event that will occur in a wide variety of cell types. In inflammatory/ulcerative diseases, proinflammatory cytokines induce the formation of large amounts of NO by iNOS from macrophages, and compounds that inhibit NO production have anti-inflammatory and antioxidant effects.[27] Onions are one of the best sources of antioxidants, especially the compound quercetin, which is found in high concentrations in the skin of onions. Quercetin inhibited the activation of nuclear factor-kappa B (NF-kappa B), which is a significant transcription factor for iNOS. It also inhibited the activation of the signal transducer and activator of transcription 1 (STAT-1), another important transcription factor for iNOS.[26]

Prevention of dermal enzyme degradation, cutaneous lipid peroxidation, and enhanced wound-healing properties have been described for quercetin.[16] Accelerated ulcer healing also requires removal of bacterial contamination from the wound to provide favorable grounds for mucosal cell growth and repair. The combination of quercetin and glycol would appear to be particularly adapted to topical treatment of minor oral aphthous ulcers. Glycol is commonly employed for the storage and preservation of biological materials such as skin. Although glycol is not generally considered to be antiseptic, a physicochemical role for glycol in removing bacterial contamination from the wound is likely. A hypertonic glycol solution may create an osmotic gradient on the mucosal surface of the ulcer that favors plasma exudation from inside the ulcer down its osmotic gradient and into the buccal cavity, thus extruding contaminating bacteria, and consequently promoting wound healing.[14] Newly formed cells occupy space in the wound, leading to extracellular matrix deposition and neovascularization. Quercetin is reported to accelerate intercellular matrix regeneration and experimental cutaneous wound healing in rats.[14]

## Conclusion

Topical application of quercetin to minor aphthous ulcers in otherwise healthy patients produced complete healing in 35 percent of cases within two to four days, and within four to seven days for the majority of cases (90 percent) compared to patients who received topical benzydamine hydrochloride mouthwash. Nearly all the patients (90 percent) appreciated the ease of application of the quercetin, and they did not object to its taste or consistency.

## Clinical Significance

Although aphthous ulcers may resolve on their own in one to two weeks, daily topical application of quercetin may be useful in accelerating that healing process for minor aphthous ulcers in otherwise healthy individuals.

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