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The Efficacy of *Hypericum perforatum* Extract on Recurrent Aphthous Ulcers

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According to anti-inflammatory and anti-nociceptive effects of *Hypericum perforatum* (St. John's wort), the aim of this study was to evaluate the efficacy of *Hypericum perforatum* extract on the management of Recurrent Aphthous Ulcers (RAU). Thirty patients with RAU participated in a randomly, placebo controlled double blind trial during three episodes of RAU to evaluate the efficacy of the topical hypericum containing mouthwash (0.5%). After a no-treatment run-in phase, patients were asked to use placebo mouthwash or hypericum mouthwash randomly. The diameters of ulcer and inflammatory halo (with 0.1 mm precision) and ulcer duration (day) were recorded and associated pain (Visual Analog Scale) were recorded by patients during each episode. Hypericum mouthwash resulted in a significant reduction of pain of RAU ($p<0.05$). Healing time was reduced in hypericum mouthwash group in comparison to other episodes ($p = 0.052$). Other indices did not show any significant differences. *Hypericum perforatum* extract in form of mouthwash (0.5%), may be of benefit in reduction of pain of RAU and has relative effect on reduction of healing time.

Key words: Recurrent aphthous ulcers, *Hypericum perforatum*, mouthwash, management

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INTRODUCTION

Recurrent Aphthous Ulceration (RAU) is a common inflammatory condition of unknown etiology, although a variety of predisposing and risk factors have been identified (Greenberg and Glick, 2003). Due to the often-uncertain etiology of recurrent aphthous ulceration and the unpredictable course of the disease, the primary goals of therapy are to control the pain of ulcers, promote ulcer healing and prevent recurrence (Greenberg and Glick, 2003; Scully *et al*., 2003; Barrons, 2001). Although topical agents do not prevent ulcer recurrence they are the most commonly used treatment modality. A multitude of topical agents are available for symptomatic relief including antibiotics (commonly topical tetracycline) (Gorsky *et al*., 2007; McBride, 2000), local anesthetics (such as lidocaine gel) (Greenberg and Glick, 2003; Scully *et al*., 2003), antihistamines (such as Diphenhydramine mouthwash) (Greenberg and Glick, 2003; Scully *et al*., 2003; Saxen *et al*., 1997; Edres *et al*., 1997) and NSAIDs. In multiple ulcerations or major aphthous lesions corticosteroids commonly use topically or systematically (Greenberg and Glick, 2003; Scully *et al*., 2003; Barrons, 2001). Because of the side effects that occur in long-term application of corticosteroids, other agents commonly apply, even though the efficacy of many of these agents has not been fully evaluated in adequate designed and controlled clinical trials and contradictory results are reported in the literature.

Hypericum perforatum (St. John's wort) extracts have become popular natural medicines for the treatment of mild-to-moderate depression and anxiety disorders (Sanchez-Reus *et al*., 2007; Anghelescu *et al*., 2006; Grundmann *et al*., 2006; Harrer *et al*., 1999; Schrader, 2000; Szegedi *et al*., 2005; Wheatley, 1997; Woelk, 2001). Its topical and systemic effects have proved as an anti-oxidant, anti-inflammatory, anti-viral, anti-bacterial and anti-nociceptive agent (Abdel-Salam, 2005; Herold *et al*., 2003; Tedeschi *et al*., 2003; Avato *et al*., 2004; Rabanal *et al*., 2005; Schempp *et al*., 2003; Dell' Aica *et al*., 2007; Breyer *et al*., 2007; Savikin *et al*., 2007) and have effect on wound healing (Öztürk *et al*., 2007). Due to those effects of hypericum; this study has designed to investigate the efficacy of *Hypericum perforatum* extract in form of mouthwash preparation on management of RAU.

MATERIALS AND METHODS

Study design: This double-blinded, placebo controlled clinical trial conducted on 30 subjects (17-37 years old), with no history of systemic diseases from March 2006 to June 2007. Other entry criteria included a clear history of RAU occurring at least once in two months and suffering from only one ulcer in buccal or labial mucosa at the time of entry. Patients were excluded if they exhibited any underlying systemic disorders, taking anti-inflammatory or immunosuppressant drugs and oral contraceptives, had a history of probable sensitivity to mouthwash or toothpaste and had multiple or major aphthous lesions.

Informed consent was taken from all eligible patients and they filled out a questionnaire included personal details and some demographic information. After a no-treatment run-in episode, subjects were investigated in two other episodes, in which individual ulcer in labial or buccal mucosa that appeared less than a day, was evaluated in ten days. During all three episodes, studied parameters included ulcer duration (day), the diameters of ulcer and inflammatory zone (0.1 mm precision) in days 0, 1, 3, 5 and 7 that were recorded by clinical examiner with standard guage (Iwonson) and associated pain by using Visual Analog Scale (VAS) in ten days recorded by subjects. To standardized pain stimulation during different episodes, patients recorded the pain three times a day after using mouthwash and after applying sugar-free orange juice on the ulcer by a swab. Ultimately median of three VASs that were recorded by subjects for each day, considered as the pain score of that day in patient's documents.

Hypericum dried extract was made from commercial standard drop named Hypiran (Pursina, Tehran, Iran) in Pharmacology Department of Babol University of Medical Science. Hypericum mouthwash was a suspension of hypericum dried extract in pure water with 0.5% concentration. Pure water was used as placebo mouthwash. Bottles were filled with the mouthwashes and they were all coded. After no-treatment run-in episode, during two next episodes, subjects were asked to use placebo mouthwash or hypericum mouthwash randomly for seven days. They were trained to use one filled bottle cap of mouthwashes, four times a day, after meals, for 30 sec and then spill it out and not to eat or drink for one hour. Subjects were examined on days 0, 1, 3, 5 and 7 for recording the diameter of ulcer and inflammatory zone. VAS was recorded by subjects for 10 days and healing time was confirmed by examiner.

Statistical analysis: Repeated measures were used to test for significant association observed between, before and after pain scores and the VAS scores of the 10 days and also One-way ANOVA were used to test differences in pain experience with and without treatments in both groups. To test differences in healing time in trial groups, Friedman test was used. $p<0.05$ was considered statistically significant.

Table 1: Mean (±SD) of VAS in three episodes of study

	Days										
Group	0	1	2	3	4	5	6	7	8	9	10
No-treatment	1.5 (1.19)	2.0 (1.58)	3.0 (1.77)	4.3 (1.23)	4.6 (1.18)	4.3 (1.84)	3.5 (2.29)	2.6 (2.06)	1.7 (1.83)	1.0 (1.51)	0.6 (1.23)
Placebo mouthwash	2.2 (0.77)	2.4 (0.64)	3.4 (0.83)	4.7 (0.88)	4.8 (1.06)	4.4 (0.99)	4.0 (1.39)	3.2 (1.37)	1.8 (1.13)	0.8 (1.19)	0.3 (0.82)
Hypericum mouthwash	2.0 (0.65)	2.3 (0.81)	2.2 (0.70)	2.8 (0.86)	3.1 (0.74)	2.8 (0.74)	2.5 (0.91)	1.6 (0.91)	0.8 (1.20)	0.4 (0.73)	0.1 (0.35)
p-value	0.12	0.59	0.03	0.0001	0.0001	0.002	0.04	0.02	0.09	0.35	0.25

Table 2: Mean (±SD) of diameter of ulcers in three episodes of study

	Days				
Groups	0	1	3	5	7
No-treatment	39.3 (17.37)	46.7 (18.69)	53.0 (19.29)	51.9 (19.02)	49.0 (20.51)
Base bioadhesive	36.3 (11.66)	45.2 (9.25)	52.3 (7.57)	55.0 (8.44)	50.13 (11.02)
Hypericum bioadhesive	32.9 (7.61)	41.9 (8.08)	49.0 (9.36)	52.8 (10.25)	53.9 (13.91)
p-value	0.45	0.66	0.73	0.81	0.90

Table 3: Mean (±SD) of inflammatory zone of ulcers in three episodes of study

	Days				
Groups	0	1	3	5	7
No-treatment	19.6 (8.08)	24.3 (7.19)	29.3 (8.78)	30.0 (10.4)	30.6 (13.74)
Base bioadhesive	23.2 (6.97)	29.5 (5.83)	34.1 (4.19)	38.2 (7.9)	37.1 (10.91)
Hypericum bioadhesive	21.5 (4.87)	28.1 (4.78)	35.7 (7.2)	40.8 (11.06)	39.7 (13.49)
p-value	0.36	0.26	0.03	0.01	0.16

RESULTS

All of subjects included 21 male and 9 female (mean±SD Age 24.66±3.12) were finished three consecutive RAU episodes.

Comparison of VAS in different episodes of RAU: The evaluation of the trend of VAS was significant in each episode (Repeated-measures test, $p<0.0001$), but did not show any significant differences between episodes ($p>0.05$). Significant decrease was observed in the mean of VAS of hypericum mouthwash episode in day 3 to 5 compared with no-treatment episode and on day 2 to 7 compared with placebo mouthwash episode (one-way ANOVA test, $p<0.05$) (Table 1).

Comparison of the diameter of ulcers, in different episodes of RAU: The evaluation of the trend of diameter of ulcers was significant in each episode (Repeated-measures test, $p<0.0001$). But between-episode comparative analysis did not show significant differences. There were no significant differences in the diameters of ulcers in each day of three episodes (one-way ANOVA test) (Table 2).

Comparison of the diameter of inflammatory zone, in different episodes of RAU: The evaluation of the trend of diameter of inflammatory zone was significant in each episode (Repeated-measures test, $p<0.0001$). But between-episode comparative analysis did not show significant differences. One-way ANOVA test did not show any significant differences in each day of episodes (Table 3).

Comparison of healing time, in different episodes of RAU: The means of the healing time of episodes were as follows: 15.2±8.5 in no-treatment episode, 13.3±2.02 in placebo mouthwash episode and 11.8±2.00 in hypericum mouthwash episode ($p = 0.052$).

DISCUSSION

RAS is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking. Since the etiology of RAS remains unknown and the cyclic nature of the disease makes it difficult to conduct well-designed prospective double-blind controlled clinical studies, there is no definitive treatment. Misclassification bias may explain the inconsistency of results found in the vast literature on treatment outcomes. The best treatment is that which will control ulcers for the longest period with minimal adverse side effects. The treatment approach should be determined by disease severity (pain), the patient's medical history, the frequency of flare-ups and the patient's ability to tolerate the medication. In all patients with RAS, it is important to rule out predisposing factors and treat any such factors, where possible, before introducing more specific therapy. Perhaps surprisingly, few randomized controlled clinical trials have been conducted to determine the best treatments for RAS (Scully *et al*., 2003).

In recent years there has been a little information in the medical literature about management of RAU with herbal remedies. Paulofilho reported the effect of Eupatorium Laevigatum extract in form of a paste to management of RAU (Paulo Filho *et al*., 2000).

Hypericum perforatum has been used as an old medical remedy in Iran. This is now used for treatment of depression and migraine headaches (Harrer *et al*., 1999; Schrader, 2000; Szegedi *et al*., 2005; Wheatley, 1997; Woelk, 2001). Kirakosyan *et al*. (2004) demonstrated it has neurological effects through inhibition of MAOI enzymes. Rabanal *et al*. (2005) investigated the analgesic and topical anti-inflammatory activities of the infusion, methanol extract and fractions of the aerial part in blossom of two species of Hypericum family. The results of that study indicated that Hypericum species have analgesic and topical anti-inflammatory effects in mice. Abdel-Salam (2005) demonstrated anti-inflammatory, anti-nociceptive and anti-edaematogenic effects for this plant. Herold *et al*. (2003) in a study with the aim of assessment of the anti-oxidant and anti-inflammatory effect of hydroalcoholic extract of some plants represented that Hypericum extract had a clear anti-oxidant and anti-inflammatory activity; so they recommended it in the management of disorders with inflammatory and allergic origins. Öztürk *et al*. (2007) demonstrated the effect of *Hypericum perforatum* on wound healing.

The topical effect of hypericum mouthwash on pain relief was clearly shown in this study which is compatible with the literature. *Hypericum perforatum* could reduce slightly the healing time of ulcers ($p = 0.052$). But it had no effect on reduction of inflammatory zone and size of ulcer which was not compatible with the effects of hypericum that was proven in other studies. These effects can be clarified in future controlled studies with more samples, although there are inevitable variations in characteristics of RAU in each episode which can affect the results of such studies. Some patients have mild outbreaks, whereas others have severe and longer episodes. Some present with a few small ulcers, while others present with larger ulcers or a combination of small and large (Ship, 1996). In some patients, the severity and frequency of outbreaks ease with the passing of years; in others, severity and frequency worsen. Finally the results of this study showed *Hypericum perforatum* can reduce the pain of RAU, but other effects need to be investigated in further studies.

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