Efficacy of topical flax paint for the treatment of recurrent aphthous stomatitis

Tagreed Altaei, M.Sc., Ph.D. (1)
Shaheen A. Ahmed, M.Sc. (2)
Ahmed A. Haider, F.D.S. (3)

ABSTRACT

Background: Recurrent aphthous stomatitis is commonly observed and is mediated by the immune system. Lesions appear as painful, tiny, discrete vesicles. Flax (*Linum usitatissimum*) has antiseptic, anti-inflammatory properties. The present study was a randomized, double-blinded, placebo controlled conducted to assess the efficacy of Flax paint in this disease.

Methods: Dermal irritation study; was performed by primary irritation to the skin and measured by a patch-test technique on the intact skin of the albino rabbit. Clinical study; 64 RAS patients, randomized to receive Flax paint or placebo topically (three times a day, for five days). The efficacy of the treatment was estimated (healing time, ulcer size reduction, pain score, change in condition), β-2 microglobulin (β-2M), α-1Antitrypsin (α-1AT), CRP & ESR, Safety, tolerance, side effects were assessed.

Results: Dermal irritation test *in vivo* showed no sign of irritation in Flax paint. Clinical study; four days after treatment, 95% of Flax group were completely healed from aphthous ulcers, compared with placebo group ($p < 0.0001$). Flax paint group showed significant pain reduction after the 1st or 2nd dose application compared to baseline and placebo. Serum β-2M, α-1AT, CRP, & ESR values showed significant reduction in Flax paint treated group compared to baseline and placebo. No sign of adverse effects or tolerance.

Conclusion: This is the first time reporting that Flax paint reduced the time to repair mucosal tissue (ulcer healing), and pain persistence, it has anti-inflammatory, and analgesic effect. There was no evidence of any adverse effects.

Keyword: Flax, recurrent aphthous stomatitis. (J Bagh Coll Dentistry 2011; 23(sp. issue):100-107).

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking.(1)

A prodrome of localized burning or pain for 24 to 48 hours can precede the ulcers. The lesions are painful, clearly defined, shallow, round or oval, with a shallow necrotic center covered with a yellow-grayish pseudomembrane and surrounded by raised margins and erythematous haloes. The pain lasts for three to four days, at which point early epithelialization can occur.(2)

Most patients have only one to three ulcers, and some have recurrences only two to four times each year (simple aphthosis). Others may have almost continuous disease activity with new lesions developing as older lesions heal, or may have ulcers associated with systemic diseases (complex aphthosis).(3) Lesions heal in 1 to 2 weeks but may recur monthly or several times a year. This chronic inflammatory disease shows evidence of inappropriate immune response and studies confirm involvement of the innate immune system in its pathogenesis.(4)

(1)Assistant professor. College of Dentistry/ Hawler Medical University
(2)Assistant Lecturer. College of Dentistry/ Hawler Medical University
(3)Assistant professor. College of Dentistry/ Hawler Medical University

Depending on the severity and the size of ulcer, different treatments have been reported: Antibiotics, anti inflammatory, immunological mediators, topical anesthetic, and alternative.(5)

Flax (*Linum usitatissimum*. Linn, Linaceae) is derived from the flax plant. Flaxseed oil are rich in alpha-linolenic acid (ALA), an essential fatty acid that appears to be beneficial for heart disease, inflammatory bowel disease, arthritis, and a variety of other health problems. Several studies reported that ALA has anti-inflammatory effects.(6) The expressed oil contains vitamins A, B, D and E minerals and amino acids, leading to its recommendation as a general nutritional supplement. Lignans can be used as natural antioxidants.(7) A dosage of up to 50 g of the flaxseed, which is nearly equal to 20 g flaxseed oil taken a day, is known to be safe and also palatable for most patients.(8)

This study evaluates the Flax paint safety and effectiveness for ulcer healing, and pain relief from aphthous stomatitis.

METHOD

Formulation of paints

Flax oil paint is composed of a standard Flax oil in glycerine (glycerol). Both constituents are authorised in the EU for oral use (European Pharmacopoeia V). Placebo free from active constituents. The product was presented in white

plastic 10mL bottle containing approximately 9mL of paint.[9]

Study of Flax paint on rabbit dermal irritation

Animals:

Six healthy Albino rabbits (weight: 1500 ± 500 g each), were individually housed in suspended cages with temperature of 25 ± 2 °C, for 1 week before the experiment. The experimental protocol has been approved by the ethics committee of Faculty of Dentistry, Baghdad University, before the experiment.

Experimental protocol:

Primary irritation to the skin is measured by a patch-test technique on the intact skin of the albino rabbit in accordance with the guidelines of the Consumer Product Safety Commission, Title 16, Chapter II, Part 1500[10]. Briefly, the backs of the rabbits were clipped free of fur with an electric clipper at least 4 h before application of the sample. Introduction under a square patch of surgical gauze measuring 1 inch by 1 inch and two single layers thick, the test paint and placebo were applied on the back of the animals. The animals are immobilized with patches secured in place by adhesive tape. Made the first evaluation after 1 h, then the entire trunk of the animal is wrapped with a rubberized cloth, for the 24 h period of exposure. After 24 h of exposure, the patches are removed and the resulting reactions are evaluated on the basis of the designated values for erythema and edema with the Draize scoring criteria.[11] Readings are again made at the end of 48, and 72 h.

The Primary Irritation Index (P.I.I.) was calculated following test completion. Material producing a P.I.I. score of greater than or equal to 5.00 would be considered positive; the material would be considered a primary irritant to the skin.

Clinical study: This study was done in the College of Dentistry, Hawler Medical University, the protocol was reviewed by the appropriate institutional review board. At the baseline appointment candidates received full written and verbal information about the study and possible side effects of treatment. Those meeting the inclusion criteria signed a detailed informed consent form.

The patients were divided randomly into 2 groups: Flax paint treated group and a Placebo group.

The Dentists and the participants were blinded to the group assignment until the study ended.

The patients received instructions about daily treatment: they followed up daily for ulcer reduction, healing time, pain reduction, and tolerance, the patient was asked about condition and side effects.

At the beginning of the study, each patient was shown an Analogical Visual Scale [12, 13] and asked the level of pain sensation experienced before using the product (time 1). The patient was then directed how to use the paint, in the presence of the investigator; lightly apply the paint with cotton swab on the oral ulceration. The effect of the treatment was immediate and the pain evaluation was repeated 5 (time 2), 10 (time 3), 15 (time 4), and 20 (time 5) minutes after the application of the product, and monitored till the end of the trial period. Additional clinical and epidemiological data were collected in a questionnaire.

β-2 M assay; Serum was collected and stored at -20°C. It was assayed by ELISA (Phoenix pharmaceuticals).

The serum concentration of ***α-1AT*** were measured by the single radial immunodiffusion technique (Kent laboratories, USA), and were expressed in mg/dL.

Serum ***CRP*** levels were measured using fluorescence immunoassay (*i*-CHROMA^{TM} CRP).

Safety assessments consisted of routine oral examinations, an evaluation of reported adverse events, laboratory determinations, vital signs, and body weight throughout the study.

Statistics

All values are expressed as mean. Statistical significance of the difference was assessed by Student's *t*-test. Values of $p<0.05$ were considered as significant.

RESULTS

Effect of Flax paint on rabbit dermal irritation

Dermal application test of flax paint caused no serious signs of erythema and edema on the intact sites. Individual results of dermal scoring appear in Table (1). Some of rabbits had very slight erythema after 24 h and 48 h, while there was no erythema in all animals. P.I.I. is calculated, based on the sum of the scored reactions divided 24 (two scoring intervals multiplied by two test parameters multiplied six rabbits. P.I.I. of Flax paint of 1, 24, 48, and 72 h was 0.333, and 0.666 for placebo group; Irritation barely perceptible was observed on the skin of the rabbits of both groups.

Clinical study

Patient characteristics as showed in table (2) females (54.6%) more than male (45.3%), no significant differences were seen between positive and negative family history, they are not smokers. The ulcer duration were 2 to 5 days, and the recurrence between 1 and 6 months in patients entering this study.

The majority type of RAS was minor 81.25%, followed by major aphthous 15.125%, and herpitiform 3.125% as showed in table (3), the major site of ulcer in all groups was cheek followed by lip and buccal.

Treatments with Flax paint showed significant reduction of ulcer size within 4 days compared to baseline (0 time) and placebo group p (<0.0001) as showed in fig. (1 & 2).

The pain score; VAS showed significant reduction in pain after the 1st dose of Flax paint & disappear after 15-20 min. of paint application compared to baseline & placebo group p(<0.0001), fig.(3).

The mean serum β-2M concentration was diminished significantly after using Flax paint, while placebo group showed no difference p (<0.001), Fig. (4).

Serum α-1AT concentration was raised in RAS patients (baseline & placebo), after treatment with Flax paint for 5 days, the values were decreased significantly compared to baseline & placebo group p (<0.001), fig. (5).

CRP was decreased significantly p (<0.01) in Flax treated group (90% of the sample studied), compared to baseline & placebo group, fig. (6). ESR also decreased significantly in Flax treated group p (<0.01), fig. (7).

Safety study: The studied medication was well tolerated, no adverse effects, and no change in weight were identified.

Table 1: Primary skin irritation test from six rabbits observed at1, 24, 48, and 72 hours.

Animal #	Flax Paint								Placebo							
	Erythema				Edema				Erythema				Edema			
	1 h	24 h	48h	72h	1h	24h	48 h	72 h	1 h	24 h	48 h	72 h	1h	24h	48h	72h
1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	0
3	0	1	1	0	0	0	0	0	0	2	1	1	0	0	0	0
4	0	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0
5	0	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0
6	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
Total	0	5	3	0	0	0	0	0	0	8	5	3	0	0	0	0
PII	0.333								0.666							

For erythema: 0 = No erythema, 1 = Very slight erythema (barely perceptible), 2 = Well-defined erythema, 3 = Moderate to severe erythema,
4 = Severe erythema (beet redness) to slight eschar formations (injuries in depth).

For edema: 0 = No edema, 1 = Very slight edema (barely perceptible), 2 = Slight edema (edges of area well defined by definite raising), 3 = Moderate edema (raised approximately 1 millimeter), 4 = Severe edema (raised more than 1 millimeter and extending beyond the area of exposure).

Evaluation of primary irritation index (PII): 0.00 No irritation, 0.04 – 0.99 Irritation barely perceptible, 1.00 – 1.99 Slight irritation, 2.00 – 2.99 Mild irritation, 3.00 – 5.99 Moderate irritation, 6.00 – 8.00 Severe irritation.

Table 2: Patients' characteristics

No. of patients	**64**
Sex **Female** **Male**	 35 (54.69 %) 29 (45.31 %)
Age (yr) **Mean**	32
Weight (Kg)	71
RAS Family history + ve **- ve**	22 (34.375 %) 42 (65.625 %)
Smoking	No
Flax paint group	34 (53.125 %)
Placebo group	30 (46.875 %)
Ulcer **Duration (days)** **Recurrence (month)**	 2-5 1-6

Table 3: The site of aphthous ulcers in relation to types:

Sites of ulcer	Types of aphthous ulcer			Total
	Minor	Major	Herpitiform	
lip	16	2	2	20
Cheek	18	5	0	23
Buccal	10	3	0	13
Tongue	5	0	0	5
Palate	3	0	0	3
Total	52	10	2	64
%	81.25	15.625	3.125	100

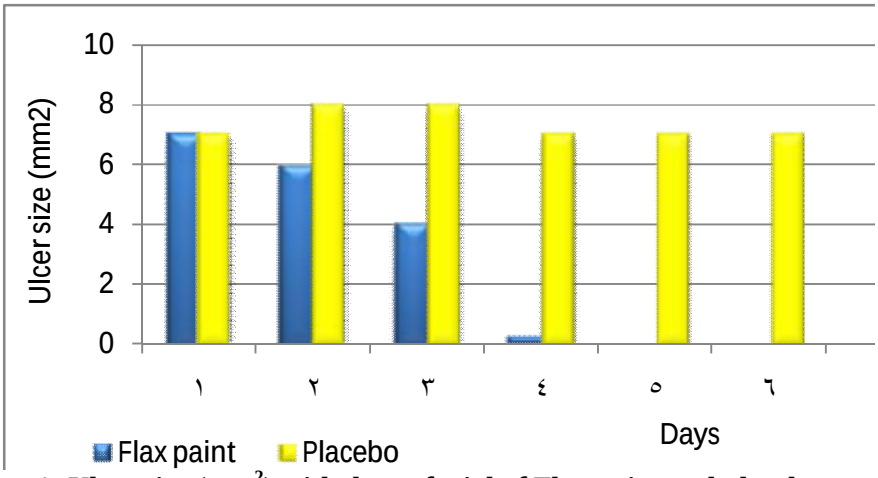

Figure 1: Ulcer size (mm^2) with days of trial of Flax paint and placebo groups.

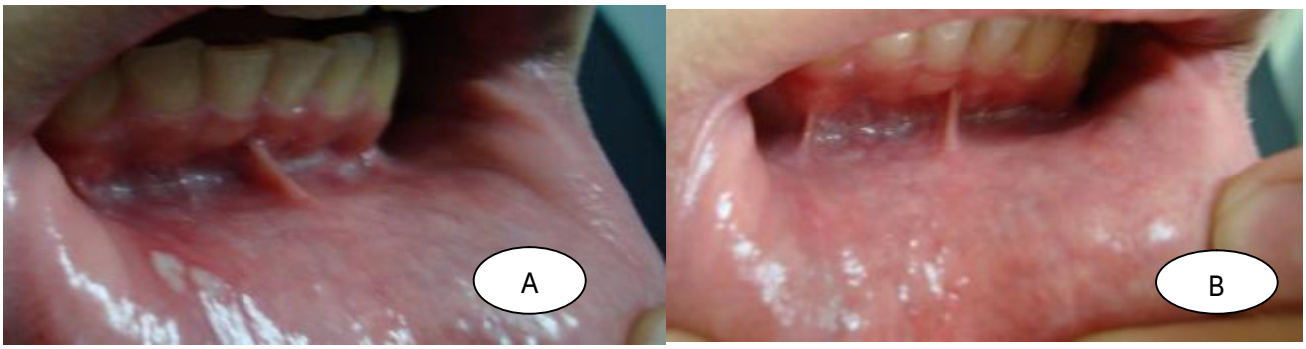

Figure 2: RAS patient. A- Before treatment, B- Healed ulcer after treatment with Flax paint.

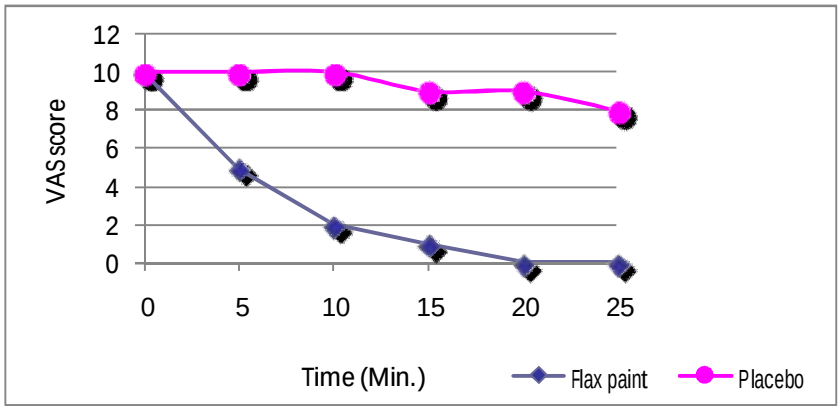

Figure 3: Pain score after topical treatment of Flax paint compared to placebo over time.

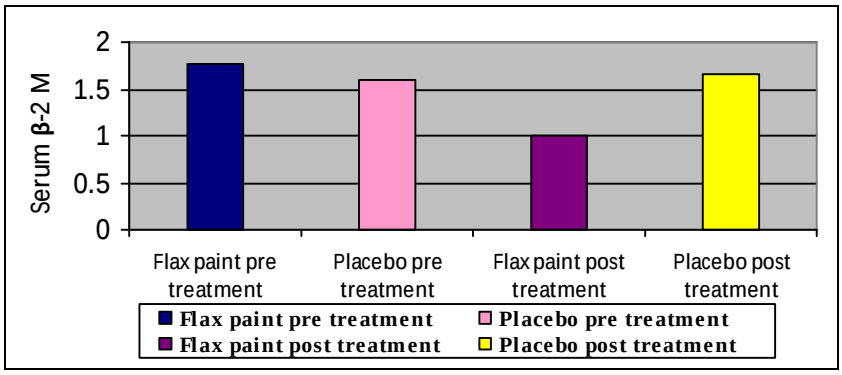

Figure 4: Mean Serum β-2 microglobulin (mg/L) concentration pre and post treatment by Flax paint and Placebo.

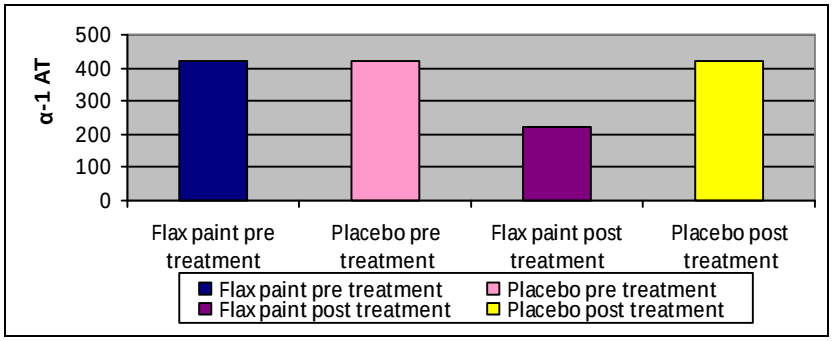

Figure 5: Mean Serum α-1 Antitrypsin (mg/dl) values of pre and post treatment by Flax paint and Placebo.

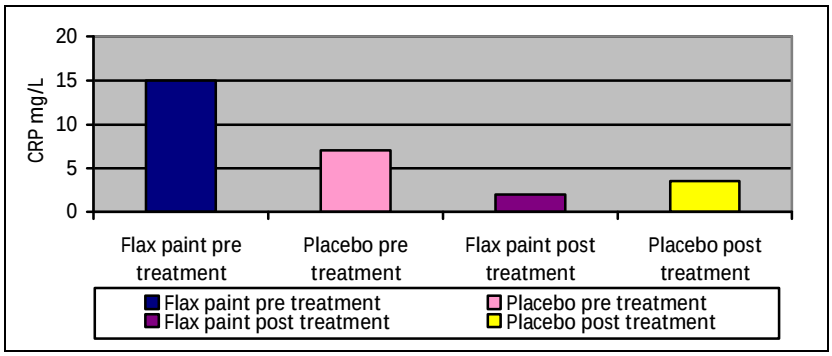

Figure 6: Mean CRP (mg/L) values of Flax paint and placebo groups pre and post treatment.

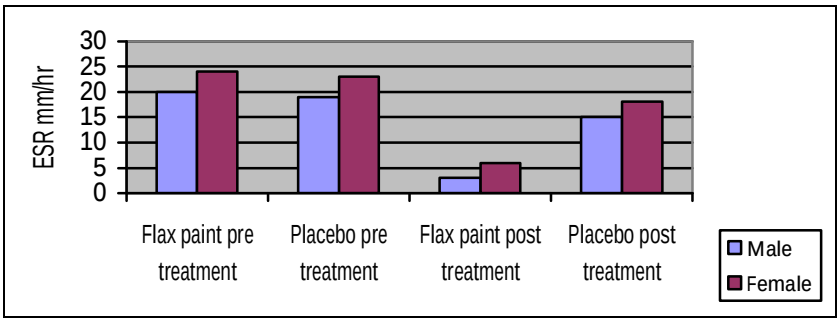

Figure 7: Mean ESR (mm/hr) values of Flax paint and placebo groups pre and post treatment.

DISCUSSION

The father of modern medicine, Hippocrates, discovered the anti-mucous and expectorant properties of Flax, and recommended it to soothe coughs. Flaxseed contains 30-40% fixed oil (including 36-50% linolenic acid and 23-24% linoleic acid), 6% mucilage, 25% protein, and small amounts of linamarin. Linamarin has a sedative effect on the respiratory system.[14]This may be explain the analgesic effect of Flax paint in reducing pain significantly ($p<0.0001$) from 1st to 2nd dose.

The dermal irritation test was performed to ensure the safety of human using these substances. Animals have been used to assess dermal irritation and changing range from erythema and edema to corrosion and ulceration. In this study, the treatment of Flax paint caused no serious signs of irritation, it produced barely irritation index (0.04-0.99), and this finding indicates that Flax paint can be categorized as a non-irritant.

Flax is the richest source of α-Linolenic acid (ALA) in the North American diet. It's converted to two major metabolites *in vivo*, the long-chain ω-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) after elongation and desaturation. The major metabolite of linoleic acid is arachidonic acid (20:4, ω-6). [15, 8]

In an experimental study on human monocytic THP-1 cells,[16] it was observed that polyunsaturated fatty acids have an inhibitory effect on LPS-stimulated inflammatory response, with alpha-linolenic acid (ALA) and docosahexaenoic acid (DHA) being more beneficial than linoleic acid (LA). Several cross sectional studies support the hypothesis that ω-3 fatty acid intake, especially in the form of eicosapentaenoic acid (EPA) and DHA, have anti-inflammatory properties.[17-19] effects.[20] The same authors show that the increase in the intake of ALA from flaxseed oil elicit anti inflammatory effects by inhibiting IL-6, IL-1β, and TNF-α production in peripheral blood mononuclear cells.[21] Flaxseed (oil and mucilage) have gastroprotective effect against ethanol-induced gastric ulcers.[22] ALA is a precursor of EPA and DHA, alters the fatty acid composition of cell membranes, inhibits the release of pro-inflammatory eicosanoids,[23] affects membrane fluidity and elasticity**,** Because ALA can interfere with the metabolism and biological actions of the ω-6 fatty acids, ALA may block the actions of platelet-activating factor (PAF), the formation of arachidonic acid and the formation of potent eicosanoids.[24, 25] This may occur as a result of decreased prostaglandin levels or decreased cytokine production.[26] Dietary flaxseed oil (14 g/d) has also shown 90% inhibition of pro-inflammatory cytokine production in patients with rheumatoid arthritis.[27] That's mean it acts as anti-inflammatory. Omega-3 fatty acids have been shown to suppress oxygen-free radicals from neutrophils and monocytes, as well as the production of interleukin-1, tumor necrosis factor, and leukotriene B4.[28] That's mean antioxidant effect of Flax have a role in treating RAS. These results from previous studies may explain the anti-inflammatory effect of Flax paint in reepethelization and ulcer healing.

Increased adherence of neutrophils may help perpetuate the ulceration,[29] and release of tumor necrosis factor has also been reported.[30] Elevated acute phase reactants such as C9 and C- reactive protein[31] and β-2 microglobulin [32] have been described in RAS patients. A low molecular weight protein, β-2M, which is released by lymphocytes.[33]The concentration of it in the serum is increased in various disorders especially those with an immunological basis.[34,35]Serum levels of β-2 microglobulin[32] have been reported to be raised in some patients, and may represent a non-specific acute phase response.[36]All patients entering this study had increased levels of β-2 M, Flax paint treated group showed significant reduction in serum β-2 M levels.

CRP is a plasma protein, its levels rise in response to inflammation.[37] CRP can affect some T-cell functions in that it binds selectively to human T lymphocytes and inhibits their ability to form spontaneous rosettes and the mixed lymphocyte reaction.[38] It is therefore postulated that during epithelial inflammation in recurrent oral ulcers some of the acute phase proteins (APP) are formed; such as CRP, α-1AT are increased and in some patients may modulate the immunological mechanism by their capacity to bind to T lymphocytes, to promote phagocytosis and to activate complement.[39] This study agrees with it, APP increased significantly, but after treatment with Flax paint, decreased significantly ($p< 0.001$). That's mean Flax may have the ability to enhance immunity.

Higher ESR values and decreased serum iron concentrations which might be an indirect index of loss of epithelium.[40] We agrees with this study in which ESR increases in RAS patients, but after treatment with Flax paint and healing of ulcers, it was decreased.

Authors conclude that Flax paint is a safe & good treatment for RAS, it need further studies on anti-inflammatory, analgesic, & antioxidant properties.

The authors declare that they have no conflict of interest.

REFERENCES

1. Miller MF, Ship II. A retrospective study of the prevalence and incidence of recurrent aphthous ulcers in a professional population, 1958-1971. Oral Surg Oral Med Oral Pathol 1977; 43(4): 532-7.
2. Crispian Scully, Meir Gorsky, Francina Lozada-Nur. The diagnosis and management of recurrent aphthous stomatitis. *J Am Dent Assoc* 2003; 134; 200-7.
3. Rogers RS 3rd. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. Semin Cutan Med Surg 1997; 16: 278-83.
4. Lewkowicz N, Lewkowicz P, Kurnatowska A, et al. Innate immune system is implicated in recurrent aphthous ulcer pathogenesis. J Oral Pathol Med 2003; 32(8):475-81.
5. Mcbride DR, Krause LS. Management of Aphthous ulcers. Am Family Physician 2000; 62: 149-54.
6. Toborek M, Lee YW, Garrido R, Kaiser S & Hennig B. Unsaturated fatty acids selectively induces an inflammatory environment in human endothelial cells. Am J Clin Nutr 2002; 75: 119–25.
7. Muir AD and ND Westcott. Flaxseed constituents and human health. In *Flax, The genus Linum*, (A.D. Muir and N.D. Westcott, Eds.), Taylor & Francis, London, 2003; 243-51.
8. Bhatty RS. Nutritional Composition of Whole Flaxseed and Flaxseed Meal. In *Flaxseed in Human Nutrition*, (S.C. Cunnane and L.U. Thompson, Eds.), AOCS Press, Champaigne, I l, 1995; 22-42.
9. Winfield AJ, Richards RME. Routes of administration and dosage forms. Churchill Livingstone, Elsevier. Pharmaceutical practice. 3rd ed. 2004; 179.
10. Bonnette KL, Rodabaugh DD, Wilson CW. Dermal irritation and sensitization. In: Derelanko MJ, Hollinger MA. eds. Handbook of Toxicology. 2nd ed. CRC Press LLC, 2001; 127-201.
11. Draize J. H. Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Association of Food and Drug Officials of the US, 1959; 49: 2-56.
12. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983; 17(1): 45-56.
13. Tesler MD, Savedra MC, Holzemer WL, Wilkie DJ, Ward JA, Paul SM. The word-graphic rating scale as a measure of children's and adolescents' pain intensity. Res Nurs Health 1991; 14(5): 361-71.
14. Oomah, BD and Mazza G. Health benefits of pytochemicals from selected Canadian crops. *Trends Food Sci Technol* 1999; 10: 193-8.
15. Vaisey-Genser M and D.H. Morris. Introduction: history of the cultivation and uses of flaxseed. In *Flax, The genus Linum*, (A.D. Muir and N.D.Westcott, Eds.), Taylor & Francis, London, 2003; 1-21.
16. Zhao G, Etherton TD, Martin KR, Vanden Heuvel JP, Gillies PJ, West SG, et al. Anti-inflammatory effects of polyunsaturated fatty acids in THP-1 cells. Biochem Biophys Res Commun 2005; 336: 909-17.
17. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation 2003; 108:155-60.
18. Zampelas A, Panagiotakos DB, Pitsavos C, Das UN, Chrysohoou C, Skoumas Y, et al. Fish consumption among healthy adults is associated with decreased levels of inflammatory markers related to cardiovascular disease: the ATTICA study. J Am Coll Cardiol 2005; 46:120-4.
19. Yoneyama S, Miura K, Sasaki S, Yoshita K, Morikawa Y, Ishizaki M, et al. Dietary intake of fatty acids and serum C-reactive protein in Japanese. J Epidemiol 2007; 17: 86-92.
20. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr 2004; 134: 2991-7.
21. Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr 2007; 85: 385-91.
22. Dugani A, Auzzi A, Naas F and Megwez S. Effects of the Oil and Mucilage from Flaxseed (Linum Usitatissimum) on Gastric Lesions Induced by Ethanol in Rats. L J Med AOP: 080612: 166-9.
23. Magrum, LJ and PV Johnston. Modulation of prostaglandin synthesis in rat peritoneal macrophages with omega-3 fatty acids. *Lipids* 1983; 18: 514-21.
24. Kettler DB. Flax Seed Oil Research. http://www.gaiaresearch.co.za/flaxseedoil.html.
25. Kettler DB. Can manipulation of the ratios of essential fatty acids slow the rapid rate of postmenopausal bone loss? *Altern Med Rev* 2001; 6: 61-77.
26. Blok WL, MB Katan, JW Van der Meer. Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. *J Nutr* 1996; 126: 1515-33.
27. James MJ, RA Gibson, LG Cleland. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000; 71: 343S-8S.
28. Prasad K. Dietary flax seed in prevention of hypercholesterolemic atherosclerosis. Atherosclerosis 1997; 132(1): 69-76.
29. Wray D, Charon J. Polymorphonuclear neutrophil function in recurrent aphthous stomatitis. J Oral Pathol Med 1991; 20(8): 392-4.
30. Taylor LJ, Bagg J, Walker DM, Peters TJ. Increased production of tumor necrosis factor by peripheral blood leukocytes in patients with recurrent oral aphthous ulceration. J Oral Pathol Med 1992; 21(1): 21-5.
31. Lehner T, Adinolfi M. Acute phase proteins, C9, factor B, and lysozyme in recurrent oral ulceration and Behcet's syndrome. J Clin Pathol 1980; 33: 269-75.
32. Scully C. Serum beta 2-microglobulin in recurrent aphthous stomatitis and Behcet's syndrome. Clin Exp Dermatol 1982 (b); 7: 61-4.
33. Bernier GM and Fanger MW. Synthesis of β -2-microglobulin by Stimulated Lymphocytes, J Immunol 1972; 109: 407-9.

34. Evrin PE and Wibell L. Serum Beta 2 Microglobulin in Various Disorders. Clin Chim Acta 1973; 43:183-7.
35. Shuster J, Gold P, Poulik MD. β-2-microglobulin Levels in Cancerous and Other Disease States. Clin Chim Acta 1976; 67: 307-13.
36. Rennie JS, Reade PC, Hay KD, Scully C. Recurrent aphthous stomatitis-review. Br Dent J 1985; 159: 361-7.
37. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. *Structure* 1999; **7** (2): 169–77.
38. Mortensen RF, Osmand AP & Gewurz H. Effects of C-reactive protein on the lymphoid system. I. Binding to thymus-dependent lymphocytes and alteration of their functions. J exp Med 1975; 141: 821.
39. Adinolfi M & Lehner T. Acute phase proteins and C9 in patients with Behcet's syndrome and aphthous ulcers. Clin exp Immunol 1976; 25, 36-9.
40. Challacombe SJ, Barkhan P & Lehner T. A clinical and haematological investigation of recurrent oral ulceration. Brit Dent J 1976.