Clinical Efficacy of Topical *Avena sativa* Versus Betamethasone in Chronic Pruritus due to Sulfur Mustard Exposure

Shohrati M (Pharm.D.)[1]*, Davoud M (M.D.)[2], Rezazadeh Sh (Ph.D.)[3], Najafian B (M.D.)[4]

1- Research Center of Chemical Injuries, Baqiatallah University of Medical Sciences, Tehran, Iran
2- Department of Dermatology, Baqiatallah University of Medical Sciences, Tehran, Iran
3- Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran
4- Department of Pediatrics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, IR Iran
* Corresponding author: Research Center of Chemical Injuries, Baqiatallah University of Medical Sciences, Tehran, Iran
Tel: +98-912-3839236
E-mail: shohratimajid@yahoo.com

Received: 20 Apr. 2016 **Accepted:** 12 Aug. 2017

Abstract

Background: ***Avena sativa,*** **a well-known herbal medicine; has been used in various skin diseases such as eczema, burn and pruritus.**

Objective: **The objective of this study was to evaluate the effect of this herbal medicine for treatment of chronic pruritus in Sulfur Mustard (SM) exposed patients.**

Methods: **Veterans who referred to Baghiat-Allah dermatologic clinic for itching problems were examined by a dermatologist and randomly assigned in three different groups. Group A received ointment derived from *Avena sativa* plant, group B, placebo and group C, betamethasone 0.1% cream twice a day for 4 weeks. Twenty five patients were included in each group. A visual analogue scale were used for assessment of severity of pruritus and 2 questionnaire for quality of life and quality of sleep were filled for each patient.**

Results: **Pruritus severity after the study by VAS method was significantly decreased in all the groups, but betamethasone group showed the largest decrease (-2.4, P<0.001). The average quality of life based on DLQI criteria and quality of sleep based on PSQI after the treatment showed the most significant difference in betamethasone group (3.52, P<0.001 and 0.96, P=0.001 respectively). Although *Avena sativa* showed significant effect on these criteria but it was only superior to placebo and not as effective as betamethasone.**

Conclusion: **The result demonstrated that *Avena sativa* ointment reduced chronic pruritus, increased quality of life and quality of sleep in patients exposed to SM but betamethasone was superior in all aspects.**

Keywords: ***Avena sativa,*** **Chronic pruritus, Sulfur mustard**

Introduction

Sulfur Mustard (bis (2-chloroethyl) sulfide) (SM) is a blister-forming agent that was widely used during the World War I and in the Iran–Iraq war between 1983 and 1988 [1]. SM is highly lipophilic and penetrates mucosal surfaces easily, and the organs most commonly affected are the skin, eyes, respiratory tract and sometimes the gastrointestinal tract [2, 3]. SM promote severe inflammatory effect as erythema, itching and vesicles in acute phase as a result of damage to hydrolipid barrier of the skin [4] and production of inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor alpha (TNF α) [5].

Skin is one of the organs with most exposure to SM gas and as a result suffers the most damage [6]. Xerosis, itching, rash and hypo-hyper pigmentation occurred in chronic phase [7]. Changes in trans-epidermal water loss (TEWL) which has been reported in patients exposed to SM is one of the main factors in development of xerosis followed by pruritus [8]. Also hyperpigmentation with increase in the skin melanin level is another symptom of chronic phase [9].

In the chronic phase, treatment is mainly symptomatic including antihistamines, moisturizers and topical corticosteroids [10]. Although betamethasone, a topical corticosteroids has been used in these patients but chronic application may results in adverse effects such as striae, atrophy of the skin and acne routinely [11, 12]. Various studies indicated effective topical products for the treatment of itching skin lesions in SM exposed veterans [13, 14].

Avena sativa (L. Geraminae) (oat) is one of the popular traditional medicinal herbs and has been generally found in different part of the world. In Iran, *Avena sativa* green herb commonly known as "Jow-dosar" in Iran and used in traditional medicine to treat nervous exhaustion, insomnia and also as a bath for eczema. *Avena sativa* seed contains high amount of soluble silica, minerals, steroidal compounds [15], and oats polyphenols (avenanthramides) are potent anti-inflammatory agents with anti-irritant effects [16, 17]. However its efficacy in chronic skin complication of SM exposed patients has not been assessed in other studies.

The aim of this study is to evaluate clinical efficacy of topical *Avena sativa* extract in the treatment of inflammatory skin lesions and pruritus in comparison to betamethasone in veterans with chronic SM exposure.

Materials and Methods

This double-blind clinical trial was conducted on chemical veterans suffering from skin lesions due to sulfur Mustard, such as xerosis and pruritus, in dermatology clinic of Baqiyat-Allah hospital from February 2012 to February 2013 (1 year). The study was approved by ethic committee of Baghiat-Allah university. All the participants were informed about aspects of the study and signed a consent form. Patients with previous exposure to sulfur mustard suffering from chronic pruritus were included in this study. Previous exposure to SM was proven by the medical commission of foundation of martyrs and veterans affair's

records. Exclusion criteria of the study were primary pruritic skin disorders, medical conditions associated with pruritus and psychocutaneous syndromes. Also patients with a history of topical treatment within one month of the trial were excluded.

Patients were assigned in three different groups based on the computer-generated random number. Group A treated with the ointment derived from *Avena sativa* plant extract, group B received placebo (Eucerin) and group C treated with betamethasone 0.1% cream (Sina Darou pharmaceutical Co., Tehran, Iran). In this study each group used one finger tips of topical creams locally, two times a day for 4 weeks. For more precision in amount of drug which were applied by patients, we used Finger Tip Unit, amount of cream applied from the distal skin-crease to the tip of the index finger, which almost equals to 0.47 g [18]. Twenty five patients were included in each group. All patients were instructed about the correct amount of use in the first clinic visit.

The plant of *Avena sativa* (L. Geraminae) was collected in the beginning of summer in Iran and extraction was conducted by using a Ethanol 70% as solvent and the extracted fluid was filtered and concentrated in vacu. Then *Avena sativa* %5 w/w ointment was prepared with the base of Eucerin.

A visual analogue scale (VAS) was designed to evaluate the severity of pruritus. A 100 mm horizontal line, which zero meant no itch and 100 meant worst experienced itch [19, 20]. Also timing of pruritus during the day was recorded.

For quality of life assessment, Dermatology Life Quality Index (DLQI) was employed which validity and reliability of this questionnaire has been confirmed in Iranian population and also SM exposed patients with chronic skin lesions [21, 22]. DLQI questionnaire includes 10 questions (symptoms and feelings [2 question], daily activities [2 question], leisure [2 question], work and school [1 question], personal relationships [2 question], and treatment [1 question]). Each question has four options for answer 3 for "very much", 2 for "a lot", 1 for "a little", and zero for "not at all". By summing all the scores of questionnaire, score of 0– 30 can be obtained where the higher the scores the more severe impairments of life quality gets. Effects on patient's quality of life are categorized as below; DLQI scores of 0-1 (no), 2–5 (small), 6–10 (moderate), 11–20 (very large), and 21–31 (extremely large).

For sleep quality, Pittsburg Sleep Quality Index (PSQI) (23) was employed which validity and reliability of this questionnaire also has been confirmed in Iranian population and also in SM exposed patients with chronic skin lesions [24, 25]. The questions include difficulty of sleep due to pruritus, general quality of sleep (reversely scored) and usage of sleep medication. Total scores range from 0 to 9.

SM exposed veterans were examined by an expert dermatologist in the first visit in the clinic and at the end of study (4 weeks later). A check list consists of skin complications (Xerosis, erythema, scaling, lichenification and hypo-hyper pigmentation) and outcomes of the study including reduced severity of itch, frequency of itching, improvement in quality of life and quality of sleep were completed by the dermatologist. Patients and physician remained

blinded to treatment allocation during the study.

Statistical analysis

After the collection of data, IBM SPSS Statistics for windows, version 22.0 (Armonk, NY: IBM Corp) were used for analysis. The results of the study were shown as mean±SD or Number (%). The Chi-square test was used for categorical variables. The three-way ANOVA was used to determine the interaction between variables. $P<0.05$ was considered statistically significant.

Results

In this prospective, randomized double blinded trial among SM exposed patients who referred to Baghiat-Allah dermatology clinic with chief complaint of pruritus, 82 patients were included from which 7 were dropped out of study due to various reasons and finally 25 patients were included in each group.

All of our patients were male. Average age of patients enrolled in the study in group A (*Avena sativa* ointment), group B (placebo) and group C (betamethasone) was 45.8±5.7, 44.7±3.8 and 43±5.8 years respectively and there was no significant difference between groups (P=0.17). All the patients were exposed to sulfur mustard 25 to 31 years ago and referred to dermatology clinic due to the chronic skin complications.

The region with most frequent itching was upper extremities. The pruritus was also reported in lower extremities, head and face, anterior trunk, posterior trunk, flexures, genitalia and as well as generalized pruritus. The frequency of itching in these areas is depicted in Table 1 and the timing of pruritus is shown Table 2.

The average (mean±SD) of pruritus severity before the study by VAS method in group A and B and C was 8.04±1.59, 7.44±1.23 and 7.48±1.12 respectively there was no significant difference ($P>0.05$). Pruritus severity after the study by VAS method in group A , B and C was 6.52±1.73, 6.20±1.06 and 5.08±1.08 respectively and there were a significant difference between group A and B compared to C (P=0.003) (Table 3).

There are a significant difference in quality of life between betamethasone and another two groups (P=0.001), based on DLQI criteria, The average quality of life before the treatment was 18.04±3.51, 17.12±1.98, 17.36±1.89 in group A, B and C respectively, with no significant difference ($P>0.05$) however after the treatment the most significant difference was observed in betamethasone group 18.52±1.98 (P=0.001) (Table 3).

In Table 4 Pittsburg Sleep Quality Index (PSQI) is depicted. The betamethasone group had the most significant improvement in quality of sleep.

Table 1- Frequency of pruritus in different anatomical regions of patients in each group

Location of lesion	Groups			P value
	A	B	C	
Head and neck	4 16%	4 16%	3 12%	0.89
Anterior Trunk	1 4%	3 12%	2 8%	0.58
Posterior Trunk	1 4%	1 4%	4 16%	0.19
Upper Extremities	8 32%	10 4%	6 24%	0.47
Lower Extremities	4 16%	8 32%	2 8%	0.08
Flexures	3 12%	1 4%	0 0%	0.15
Genitalia	5 20%	3 12%	5 20%	0.68
Generalized	4 16%	9 36%	8 32%	0.24

Table 2- Timing of pruritus in each group

Time of pruritus	Groups			P value
	A	B	C	
Morning	2 8%	2 8%	3 12%	0.85
Evening	5 20%	2 8%	3 12%	0.44
Night	11 44%	16 64%	17 68%	0.18
All the time	7 28%	5 20%	2 8%	0.18

Table 3- Compared efficacy of *Avena sativa*, betamethasone and placebo on severity of pruritus and quality of life

Variables	Groups	Before		After		diff	P value	P-value
		Mean	SD	Mean	SD			
Severity of pruritus	A (A. Sativa)	8.04	1.59	6.52	1.73	-1.52	<0.001	0.003
	B (Placebo)	7.44	1.23	6.20	1.06	-1.24	<0.001	
	C (Betamethasone)	7.48	1.12	5.08	1.08	-2.4	<0.001	
Quality of life	A (A. Sativa)	18.04	3.51	19.68	3.19	1.64	<0.001	0.001
	B (Placebo)	17.36	1.89	18.52	1.98	1.16	0.001	
	C (Betamethasone)	17.12	1.98	20.64	2.36	3.52	<0.001	

Table 4- Pittsburg Sleep Quality Index (PSQI) in each group before and after the treatment

Group		Before		After		Diff	P value	P-value
		Mean	SD	Mean	SD			
PSQI	Avena	4.9231	2.54438	4.4615	2.50169	-.4615	0.058	0.206
	Placebo	5.8696	2.30226	5.4348	2.25280	-.4348	0.060	
	Beta	6.3600	2.28910	5.4000	2.04124	-.9600	0.001	

Discussion

Most patients, who were exposed to mustard gas, are suffering from inflammatory skin lesions and itching problems, that are resistant to most of systemic or topical treatments [26]. Our trial on the effect of topical extract of *Avena sativa* in SM exposed patients showed that, although this herbal medicine decreased pruritus and improved quality of life and quality of sleep but topical betamethasone was more effective in all these areas after 4 weeks of study.

Chronic pruritus, one of the late complication of sulfur mustard gas exposure, is a common problem among chemical veterans [8]. Degraded epidermal barrier function follows by a variety of inflammatory cutaneous symptoms such as erythema and pruritus [27]. In order to suppress these symptoms, anti-inflammatory therapies are often suggested. Systemic and topical immunomodulators such as glucocorticoids, cyclosporine A, tacrolimus, pimecrolimus and ultraviolet light therapy continue to be the most effective antipruritic agents [28, 29]. Administration of topical or systemic corticosteroids, antihistamines or local anesthetics in long-term may lead to suppression of immune system and cause other difficulties, including fungal and bacterial infections [29]. For this reason some studies have evaluated other therapeutic options for chronic pruritus in SM exposed patients. In one study comparing topical doxepin 5% with betamethasone 1%, significant reduction of pruritus observed with topical doxepin which might be considered as an alternative to topical corticosteroids for treatment of pruritus [30]. In another study, immunotherapy with interferon-gama (IFN-γ) reduced DLQI and showed effectiveness in treatment of SM-induced chronic skin lesions [31].

Recently herbal medicine with lower profile of adverse effect has gained more attention in this field. In a study by Panahi et al, phytochemicals were used for treatment of pruritus which showed that phenol and menthol have significant therapeutic effects in chronic pruritus [32] and in another study revealed the impact of curcumin on serum inflammatory biomarker, interleukins 8 (IL-8) and antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase [33]. In chronic skin complication of SM, curcumin supplementation can reduce these factors and improve quality of life [34]. Capsaicin isolated from pepper plants (genus capsicum), when frequently used, prevents the release of substance P from C fiber and caused reduction of pain and itch [35] and one study showed its efficacy to reduce pruritus perceived

in chronic skin lesion from sulfur mustard exposure [36].

Leaves of oat plant contain silicon dioxide, polyphenols, flavonoids, monosaccharide and pectin with topical anti-inflammatory effect [37]. Colloidal Oatmeal is extracted from seeds of *Avena sativa*, contains essential fatty acids, flavonoids, phospholipids and sterols that exert a moisturizing and emollient activity associated with a protective action on the skin, maintaining the hydrolipidic property of the skin and reducing the transepidermal water loss, insoluble proteins contained in colloidal Oatmeal have buffering properties, maintaining cutaneouse PH at physiologic values [38]. In a study by Matheson et al. patients using the product made of colloidal oatmeal had significantly less itch than those using oil containing liquid paraffin [39]. Inflammatory cytokines such as interleukin-8 (IL-8) lead to pruritus and overexpression of these cytokines may result in pruritic skin disease [40]. A recent study on colloidal oatmeal demonstrated a decrease in IL-8 and NF-KB which is a nuclear receptor responsible in production of pro-inflammatory factors [40].

The result of our trial showed a significant effect in all groups, even the placebo group. The reason for this finding might be the use of lanolin, an emollient, in our placebo formulation. This reveals the influence of skin dryness on chronic pruritus and importance of skin hydration in the process of treatment.

Although oatmeal was inferior to betamethasone in this study but *Avena sativa* lotion includes anti-inflammatory and emollient properties and are able to increasing moisture in the skin, and as a result we may be able to administer it concomitant with corticosteroids and anti-histamines.

Conclusion

In conclusion *Avena sativa* ointment reduced chronic pruritus, increase quality of life and quality of sleep in patients exposed to sulfur mustard. However the effect was not as significant as betamethasone.

References

1. United Nations Security Council. Report of the mission dispatched by the Secretary General to investigate allegations of the use of chemical weapons in the conflict between the Islamic Republic of Iran and Iraq. 1988 S/19823.

2. Shohrati M, Peyman M, Peyman A, Davoudi M and Ghanei M. Cutaneous and ocular late complications of sulfur mustard in Iranian veterans. *Cutaneous and Ocular Toxicol*. 2007; 26 (2): 73-81.

3. Khaheshi I KS, Imani Fooladi AA, Ebrahimi M, Yazdani S, Panahi Y, Shohrati M and Nourani MR. Loss of expression of TGF-βs and their receptors in chronic skin lesions induced by sulfur mustard as compared with chronic contact dermatitis patients. *BMC Dermatol*. 2011; 14: 2-11.

4. Davoudi SM, Sadr B, Hayatbakhsh MR, Keshavarz S, Shohrati M, Naghizadeh MM and et al. Comparative study of skin sebum and elasticity level in patients with sulfur

mustard-induced dermatitis and healthy controls. *Skin research and technology: official Journal of International Society for Bioengineering and the Skin* 2010; 16 (2): 237-42.

5. Arroyo CM, Schafer RJ, Kurt EM, Broomfield CA and Carmichael AJ. Response of normal human keratinocytes to sulfur mustard: cytokine release. *JAT.* 2000; 20 Suppl 1: S63-72.

6. Balali-Mood M HM. The clinical toxicology of sulfur mustard. *Arch. Iranian Med.* 2005; 8: 162 - 79.

7. Shohrati NS M, Babaei F, Amini Harandi A, Mohsenifar A, Aslani J and Ghanei M. Evaluation of activity and phenotype of α1-antitrypsin in a civil population with respiratory complications following exposure to sulfur mustard 20 years ago. Biomarkers: *Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals* 2009; 15 (1): 1-5.

8. Balali-Mood M, Hefazi M, Mahmoudi M, Jalali E, Attaran D, Maleki M and et al. Long-term complications of sulphur mustard poisoning in severely intoxicated Iranian veterans. *Fundamental & Clinical Pharmacol*. 2005; 19 (6): 713-21.

9. Davoudi SM KS, Sadr B, Shohrati M, Naghizadeh MM, Farsinejad K, Rashighi-Firouzabadi M, Zartab H and Firooz A. Comparison of skin erythema and melanin level in sulfur mustard induced chronic skin lesion with normal skin. *Iran. J. Dermatol.* 2009; 11 (151-154).

10. Rice P. Sulphur mustard injuries of the skin. Pathophysiology and management. *Toxicological Reviews* 2003; 22 (2): 111-8.

11. Hengge UR, Ruzicka T, Schwartz RA and Cork MJ. Adverse effects of topical glucocorticosteroids. *Journal of the American Academy of Dermatol*. 2006; 54 (1): 1-15; quiz 6-8.

12. Schoepe S, Schacke H, May E and Asadullah K. Glucocorticoid therapy-induced skin atrophy. *Experimental Dermatol*. 2006; 15 (6): 406-20.

13. Vie K, Cours-Darne S, Vienne MP, Boyer F, Fabre B and Dupuy P. Modulating effects of oatmeal extracts in the sodium lauryl sulfate skin irritancy model. *Skin Pharmacology and Applied Skin Physiol*. 2002; 15 (2): 120-4.

14. Reunala T, Collin P, Holm K, Pikkarainen P, Miettinen A, Vuolteenaho N and et al. Tolerance to oats in dermatitis herpetiformis. *Gut* 1998; 43 (4): 490-3.

15. R W. The oat crop: production and utilization. London: Chapman and Hall Ltd; 1995.

16. Cerio R, Dohil M, Jeanine D, Magina S, Mahe E and Stratigos AJ. Mechanism of action and clinical benefits of colloidal oatmeal for dermatologic practice. *JDD*. 2010; 9 (9): 1116-20.

17. Sur R, Nigam A, Grote D, Liebel F and Southall MD. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. *Archives of Dermatological Res*. 2008; 300 (10): 569-74.

18. Long CC and Finlay AY. The finger-tip unit--a new practical measure. *Clinical and Experimental Dermatol*. 1991; 16 (6): 444-7.

19. Stander S, Augustin M, Reich A, Blome C, Ebata T, Phan NQ and et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of

Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. *Acta Dermato-venereologica*. 2013; 93 (5): 509-14.

20. Chrostowska-Plak D, Salomon J, Reich A, Szepietowski JC. Clinical aspects of itch in adult atopic dermatitis patients. *Acta dermato-venereologica* 2009; 89 (4): 379-83.

21. Panahi Y, Davoudi SM, Sadr SB, Naghizadeh MM and Mohammadi-Mofrad M. Impact of pruritus on quality of life in sulfur mustard-exposed Iranian veterans. *International Journal of Dermatol.* 2008; 47 (6): 557-61.

22. Aghaei S, Sodaifi M, Jafari P, Mazharinia N and Finlay AY. DLQI scores in vitiligo: reliability and validity of the Persian version. *BMC Dermatol*. 2004; 4: 8.

23. Buysse DJ RC, Monk TH, Berman SR, Kupfer DJ. The Pittsburg Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry-Research* 1989; 28: 193 - 213.

24. Farrahi Moghaddam J, Nakhaee N, Sheibani V, Garrusi B and Amirkafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). *Sleep & breathing = Schlaf & Atmung* 2012; 16 (1): 79-82.

25. Roshan R, Rahnama P, Ghazanfari Z, Montazeri A, Soroush MR, Naghizadeh MM and et al. Long-term effects of sulfur mustard on civilians' mental health 20 years after exposure (The Sardasht-Iran Cohort Study). *Health and Quality of Life Outcomes* 2013; 11: 69.

26. Namazi S, Niknahad H and Razmkhah H. Long-term complications of sulphur mustard poisoning in intoxicated Iranian veterans. *Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicol*. 2009; 5 (4): 191-5.

27. Thawer-Esmail F. Skin Barrier function and atopic Eczema. *Current Allergy & Clinical Immunol*. 2011; 24 (4): 193-7.

28. Wahlgren CF, Scheynius A and Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Dermato-Venereologica* 1990; 70 (4): 323-9.

29. Luger T, Van Leent EJ, Graeber M, Hedgecock S, Thurston M, Kandra A and et al. an emerging safe and effective treatment for atopic dermatitis. *The British Journal of Dermatol*. 2001; 144 (4): 788-94.

30. Panahi Y, Davoudi SM, Beiraghdar F and Amiri M. Doxepin cream vs betamethasone cream for treatment of chronic skin lesions due to sulfur mustard. *Skinmed* 2011; 9 (3): 152-8.

31. Panahi Y, Sahebkar A, Davoudi SM, Amiri M and Beiraghdar F. Efficacy and safety of immunotherapy with interferon-gamma in the management of chronic sulfur mustard-induced cutaneous complications: comparison with topical betamethasone 1%. *The Scientific World Journal* 2012; 2012: 285274.

32. Panahi Y, Davoodi SM, Khalili H, Dashti-Khavidaki S and Bigdeli M. Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Medical Journal* 2007; 48 (5): 392-5.

33. Panahi Y, Sahebkar A, Parvin S and Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. *Annals of Clinical Biochem*. 2012; 49 (Pt 6): 580-8.

34. Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseininejad SL and et al.

Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *The British Journal of Nutrition* 2012; 108 (7): 1272-9.

35. Lynn B. Capsaicin: actions on C fibre afferents that may be involved in itch. Skin pharmacology: *The Official Journal of the Skin Pharmacology Society* 1992; 5 (1): 9-13.

36. Panahi Y, Davoudi SM, Moharamzad Y, Beiraghdar F and Naghizadeh MM. Comparison of topical capsaicin and betamethasone in the treatment of chronic skin lesions due to sulfur mustard exposure. *Cutaneous and Ocular Toxicol.* 2008; 27 (3): 203-11.

37. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K and van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. *The American Journal of Clinical Nutrition* 2001; 74 (4): 418-25.

38. Mills SY. The A-Z of modern herbalism. London: Diamonds Books. 1993.

39. Matheson JD, Clayton J and Muller MJ. The reduction of itch during burn wound healing. *The Journal of Burn Care & Rehabilitation* 2001; 22 (1): 76-81; discussion 75.

40. Reynertson KA, Garay M, Nebus J, Chon S, Kaur S, Mahmood K and et al. Anti-inflammatory activities of colloidal oatmeal (*Avena sativa*) contribute to the effectiveness of oats in treatment of itch associated with dry, irritated skin. *JDD.* 2015; 14 (1): 43-8.