ORIGINAL ARTICLE

The effectiveness of olibanum orally disintegrating tablet in the treatment of oral aphthous ulcers: A randomized, double-blind, placebo-controlled clinical trial

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Background: *Boswellia serrata* oleo-gum-resin (frankincense; olibanum) has anti-inflammatory, analgesic, and antimicrobial effects. This study aimed to evaluate the clinical effectiveness of frankincense extract in the treatment of oral aphthous ulcers. **Materials and Methods:** In a randomized, double-blind, placebo-controlled clinical trial, patients with aphthous ulcers were randomly assigned to either experimental (Frankincense extract) or placebo groups to use orally disintegrating tablets (ODT) of frankincense and placebo, respectively, four times a day for 3 days. The size of aphthous ulcers and the pain severity by visual analogue scale were recorded at days 0, 2, and 4 and compared between the groups. **Results:** Twenty-five patients in each group completed the study. Olibanum extract ODT significantly reduced the ulcer size on the second ($P < 0.001$) and fourth ($P < 0.001$) days as well as the pain score on the second ($P = 0.002$) and fourth ($P < 0.001$) days of the intervention compared to placebo. Furthermore, at the end of the intervention, the number of patients with complete ulcer healing and pain relief in the experimental group was significantly more than the placebo group (5 vs. 0, $P = 0.02$; and 11 vs. 0, $P < 0.001$, respectively). **Conclusion:** Taking olibanum extract ODTs reduces the ulcer size and pain severity and accelerates the healing process in the oral aphthous lesions.

Key words: *Boswellia serrata,* clinical trial, Frankincense, olibanum, oral aphthous ulcer

How to cite this article: Soltani R, Saberi Z, Ghanadian SM, Taheri A, Entezarhojjat A. The effectiveness of olibanum orally disintegrating tablet in the treatment of oral aphthous ulcers: A randomized, double-blind, placebo-controlled clinical trial. J Res Med Sci 2022;27:8.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal lesion that is present first in childhood or adolescence. Aphthous ulcers, commonly known as "aphthae," are usually round or elliptical with yellowish-gray color and have erythematous margins which is the inflamed mucosa.[1,2] They are usually seen on the nonkeratinized oral mucosa such as lips, buccal mucosa, ventral surface of the tongue, and the oral cavity, whereas they are less common in areas of oral keratinization such as hard palate, gum, and dorsal surface.[3] The etiology of recurrent aphthous stomatitis (RAS) lesions is unknown, but several etiological factors including local trauma (e.g., smoking), systemic diseases (e.g., Behcet's disease, Crohn's disease, and ulcerative colitis), immunologic/allergic factors (e.g., food sensitivity), genetic factors, viral and bacterial infections, and nutritional deficiencies (e.g., iron, folic acid, and zinc deficiencies) have been mentioned as the cause of frequent oral ulcerations. However, in some patients, no etiology can be identified and a diagnosis of

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.jrms_247_21

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Submitted: 20-Mar-2021; **Revised:** 13-May-2021; **Accepted:** 26-Jul-2021; **Published:** 29-Jan-2022

exclusion must be made.[4] The etiology of RAS seems to be different in each individual. Some studies indicate the involvement of imbalances in the production of free radicals and antioxidant defenses in the onset and progression of aphthous lesions.[5,6] Mucosal destruction appears to induce a T cell-dependent immune response, which subsequently produces tumor necrosis factor-alpha. This factor is an important inflammatory cytokine leading to the destruction of superficial epithelium by cytotoxic T cells (CD8+). It has been shown that the presence of this factor in the saliva of people with RAS is 2–5 times higher than healthy ones.[7] It is also reported that there are changes in the levels of salivary defense enzymes such as superoxidase dismutase in RAS outbreak.[8]

Due to the relatively unknown etiology and the recurrent nature of RAS, there is no definite cure for this disorder and treatment is usually symptomatic. In the treatment of RAS, the goal is to control the pain, reduce the daily dysfunction (e.g. difficulty in eating and drinking), decrease the incidence of RAS, and prevention of the new ulcers.

In the traditional medicine, different herbal extracts or essential oils have been suggested for the control of RAS including *Echinacea purpurea*,[9] *Zataria multiflora* essence,[10] curcumin gel,[11] *and Rosa damascena* mouthwash.[12]

The frankincense or olibanum, known as "Kondor" in Iran, is an aromatic oleo-gum-resin derived from several species of the plants in the genus *Boswellia* including *Boswellia serrata, Boswellia carterii, Boswellia papyrifera, and Boswellia frereana*. Recently, frankincense has attracted much attention due to its prominent anti-inflammatory and antibacterial properties.[13-16] Four active isoforms of boswellic acid (a series of ursane type pentacyclic triterpenes) are the main constituents of the resin, from which 3-acetyl-11-keto-beta-boswellic acid (AKBA) has the most anti-inflammatory effect.[13] To the best of our knowledge, there is no report of the effect frankincense in the treatment of aphthous ulcers. Therefore, considering the inflammatory mechanism of aphthous ulcers and the possible role of microbial antigens as a causative factor in its occurrence as well as the annoying pain of these lesions, the present study aimed to evaluate the effectiveness of olibanum orally disintegrating tablet (ODT) in the treatment of oral aphthous ulcers in a clinical trial.

MATERIALS AND METHODS

Ethical considerations

The study protocol was approved by the ethical committee of Isfahan University of Medical Sciences (IUMS) with the ethics code of IR.MUI.REC.1396.3.572.

Preparation of oral disintegrating tablets of frankincense and placebo

The *B. serrata* oleo-gum-resin was purchased from the Isfahan plant local market. It was identified by Department of Pharmacognosy, IUMS. The resin was extracted by acetone, filtered, and concentrated in a rotary evaporator (Heidolph, Germany) connected to the vacuum pump. The concentrated extract was freeze-dried (Christ, Germany) to remove the remaining solvent and form a lyophilized dry powder.

To make ODTs of boswellia extract and placebo, the quantities of each of the ingredients were carefully weighed, and after crossing the sieve with a mesh of 60 separately for each component, complete mixing of the powders was performed. The tablets were then prepared by single punch tablet press (Kilian, Germany) with Matrix No. 10 and 8 mm diameter. The values of the ingredients of the tablet formulations are given in Table 1.

Gas chromatography-mass standardization of the Frankincense oral disintegrating tablet

Standardization was performed using Agilent 7890A gas chromatography (GC) coupled with Agilent 5975C mass detector with triple quadruple mass analyzer and electron ionization (EI) (Agilent, USA) based on AKBA as its main constituent. To prepare the sample, 10 tablets were completely powdered and mixed. Then a quantity equivalent to the weight of one tablet was weighed and dissolved in chloroform: Hexane (1:1; Merck, Germany) for 1 h in sonicator bath (QSONICA, USA) to extract the sample. Then it was filtered, dried by liquid nitrogen, and dissolved in a solution of aprotic ethyl acetate (1 mL). To produce silyl derivatives, N, O-bis (Trimethylsilyl) acetamide, and TMCS (chlorotrimethylsilane) (Sigma-Aldrich, USA) each 0.5 mL were added. Reaction mixture was shaken under nitrogen for 1 h at 40°C. When silylation reaction was completed, the solution was completely dried under nitrogen, dissolved in hexane, and injected to the gas chromatograph equipped with an HP-5 GC column (30 m × 0.25 mm; film thickness of 0.25 μm). The oven temperature was started from 50°C for 2 min, raised by 8°C/min up to 250°C, and by 3°C/min up to 330 ºC. The total analysis time was 58 min.[17]

Table 1. Formulation ingredients of oral disintegrating tablets of Boswellia extract and placebo

Formulation ingredient	Boswellia ODT (mg)	Placebo ODT (mg)
Boswellia extract	200	-
Mannitol	593	793
Avicel	296.5	296.5
Cross povidone	124	124
Aspartam	12.5	12.5
Magnesium stearate	12.5	12.5
Total weight	1238.5	1238.5

Clinical study

This was a randomized, double-blind, placebo-controlled clinical trial. The study was registered in the Iranian Registry of Clinical Trials (IRCT) with the code of IRCT20150721023282N10. Patients were selected through a recall from those who were referred to the dental clinic of IUMS. Inclusion criteria were: (1) over 18 years of age; (2) having 0 to 5 oral aphthous ulcers; (3) no more than 48 h of aphthae occurrence; (4) assessable ulcer; (6) not receiving any anti-inflammatory or immunosuppressive drug within the past 2 weeks; (7) not receiving any systemic antibiotic within the past 2 weeks; (8) nonpregnant; and (9) nonlactating. Patients with any underlying aphthous ulcer-inducing disease, including Behcet's disease, inflammatory bowel disease, and acquired immune deficiency syndrome were excluded from the enrollment.

Individuals who met the inclusion criteria were enrolled in the study if they signed the written consent form and were randomly assigned to either experimental (Frankincense) or placebo groups. For randomization, block randomization method was used, in which blocks of four were used. The participants in experimental and placebo groups were instructed to use frankincense and placebo ODTs, respectively, four times daily for three days and to avoid eating and drinking for at least 30 min after using the tablets. For blinding, the frankincense and placebo ODTs were made with similar shape, weight, size, and color. The prescribing dentist, data collector, and data analyst were blind to the type of intervention. The severity of pain and size of the ulcer before the intervention (day 0) and at the beginning of the second and fourth days (end of treatment) were recorded for each patient. The pain severity was assessed using visual analogue scale (VAS), whereby the severity was scored from 0 (no pain) to 10 (the worst pain) by the patient. The size of ulcer was recorded as the largest diameter of the white area of aphthous ulcer in millimeters measured with a dental caliper (ASA Dental, Italy).

Statistical analysis was performed using 24th edition of SPSS software (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to determine the distribution pattern of quantitative data (normal or non-normal). Chi-square and independent samples *t*-test were used to compare sex distribution and mean age between the two groups, respectively.

Because of non-normal distribution of results, Wilcoxon signed-rank test was selected to compare the mean values at the different times with baseline in each group, whereas Mann-Whitney U test was used to compare the values between the two groups at each time point. Kaplan-Meier analysis was used for the comparison of the number of patients with complete ulcer healing and pain relief at the end of intervention between the groups. P <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Gas chromatography-mass standardization of oral disintegrating tablets of frankincense extract

Based on GC-Mass spectra and total ion current chromatogram of oral disintegrating tablets of *Frankincense extract*, it was standardized on 5.90% (w/w) of AKBA at retention time of 46.4 as depicted in Figure 1.

Clinical study

During the study, a total of 97 patients were evaluated that 82 of whom met the inclusion criteria. Eighty-one patients participated, of whom 31 patients were excluded because of either distance issues or discontinuation of the intervention due to various reasons including the feeling of early improvement or worsening of the ulcers and regret participating in the study. Finally, 50 patients, including 25 in each group, completed the study [Figure 2].

Twelve patients in experimental group (48%) and 10 patients in placebo group (40%) were male (P = 0.776). The mean (± standard deviation) age of patients in the

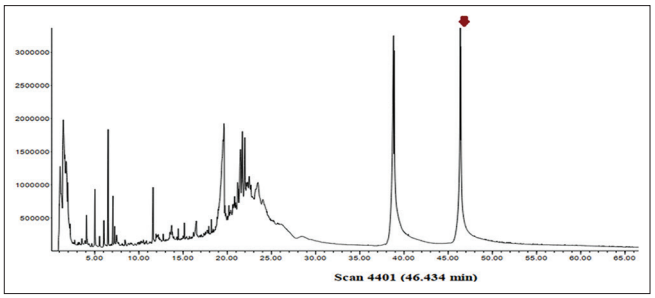

Figure 1: Gas chromatography-mass spectrum of frankincense orally disintegration tablet. The sample is silylated prior to injection. For silylation N, O-bis (Trimethylsilyl) acetamide, and TMCS (chlorotrimethylsilane) each 0.5 mL were added for 1 h at 40°C. The gas chromatograph equipped with an HP-5 gas chromatography column, 30 m × 0.25 mm (film thickness of 0.25 μm). Helium was used as carrier gas (flow = 2 mL/min), and the oven temperature was started from 50°C for 2 min, raised by 8°C/min up to 250 ºC, and by 3°C/min up to 330°C. The total analysis time was 58 min

Table 2: Kolmogorov-Smirnov test for data distribution pattern

Parameter	Time (days)	*P*	
		Experimental group	Placebo group
Ulcer size	0	0.051	0.008
	2	0.001	0.024
	4	0.030	0.012
Pain score (VAS)	0	0.008	0.018
	2	0.044	0.037
	4	*P*<0.001	0.002

VAS=Visual Analog Scale

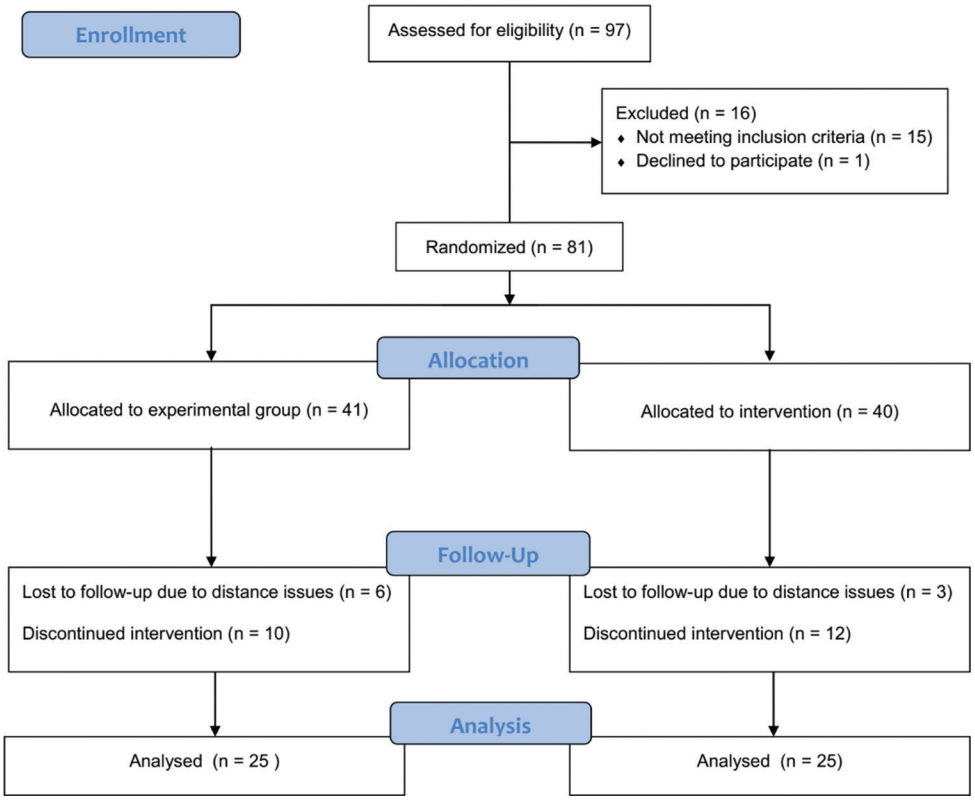

Figure 2: CONSORT flowchart of the study

experimental and placebo groups was 36.68 (±11.49) and 36.32 (±9.69) years, respectively ($P = 0.905$).

Table 2 shows the results of Kolmogorov-Smirnov test used for continuous quantitative variables to determine the normality pattern of the data distribution. As seen, except for the ulcer size in the experimental group at baseline ($P = 0.051$) which had normal distribution, the rest of the values had non-normal distribution. Therefore, nonparametric statistical tests were used to compare the values.

Table 3 shows the changes in ulcer size and pain score (VAS) within each group over the study days as well as the comparison of the values between the two groups at evaluated time points. As shown, there was no statistically significant difference between the groups regarding the baseline values. However, on the second and fourth day of the intervention, ulcer size and pain score significantly decreased in the experimental group compared to the placebo group ($P < 0.001$). Furthermore, in the experimental group, the ulcer size decreased significantly in the second ($P = 0.002$) and fourth ($P < 0.001$) days of intervention compared to the baseline (day 0), whereas in the placebo group, this parameter increased significantly in both times compared to the baseline. Furthermore, in the experimental group, pain score decreased significantly in the second and fourth days compared to the baseline ($P < 0.001$), whereas in the placebo group, there was no statistically significant difference in this parameter in the second and fourth days compared to the beginning of the study.

Table 3: The changes of parameters within each group and the comparison of the values between the two groups at evaluated time points

Parameter	Time (day)	Group		P^a
		Experimental (n=25)	Placebo (n=25)	
Ulcer size	0	3.44±1.53	4.04±1.74	0.277
	2	2.48±1.87	4.88±1.01	<0.001
	4	2.16±1.57	4.88±1.05	<0.001
	P^b	0.002	0.003	
	P^c	<0.001	0.015	
Pain score (VAS)	0	7.60±2.00	7.20±1.93	0.492
	2	4.44±3.52	7.52±1.93	0.002
	4	2.48±3.27	6.88±2.02	<0.001
	P^b	<0.001	0.442	
	P^c	<0.001	0.638	

The values represent mean±SD. [a]Comparison of the values between the two groups (Mann-Whitney U test); [b]Within-group comparison of the values between the days 2 and 0 (Wilcoxon signed ranked test); [c]Within-group comparison of the values between the days 4 and 0 (Wilcoxon signed ranked test). VAS=Visual Analog Scale; SD=Standard deviation

Kaplan-Meier survival test using log-rank test showed that there was a statistically significant difference between the two groups in terms of the complete healing of the aphthous lesions, as five patients in the experimental group had complete healing compared to no case in the placebo group ($P = 0.020$). The test also showed that there was a

statistically significant difference between the two groups regarding complete pain relief, so that in the experimental group, seven patients had complete pain relief on the second day of intervention and four patients at the end of the intervention (11 patients totally), whereas in the placebo group, no patient experienced complete pain relief ($P < 0.001$).

Our study showed significant healing and pain-reducing effects of Boswellia oleo-gum-resin (frankincense) on oral aphthous ulcer. Although many studies have been conducted on the anti-inflammatory, analgesic, and wound healing effects of frankincense, at the best of our knowledge, this study is the first clinical study to issue the effect of frankincense extract on the treatment of oral aphthous lesions.

The cause of RAS is yet unclear; however, it seems that it is inflammatory in nature. Much research has been done on the anti-inflammatory properties of frankincense. In a study recently reported by Barbarisi *et al*., on the anti-inflammatory and anti-cancer effects of boswellic acid, this compound increased the anti-cancer effect of temozolomide and afatinib, attributed to its anti-inflammatory properties, reduction of nitric oxide and reactive oxygen species production as well as reduction of proinflammatory interleukins including leukotriene B4.[18] In another study conducted by Khosravi *et al*., the anti-inflammatory effect of frankincense on gingivitis caused by chronic oral plaques was investigated. According to the results, frankincense was significantly effective in the reduction of plaques and improvement of gingivitis.[19]

Consistent to our study showing pain-reducing effect of frankincense ODT in oral aphthous lesions, a recent study by Majeed *et al*. found that *B. serrata* extract significantly reduces joint pain and stiffness in patients with knee osteoarthritis compared with placebo.[20] Bannuru *et al*., in a meta-analysis study, showed significant pain reduction and improved function in knee osteoarthritis patients treated with frankincense.[21] The observed anti-inflammatory and analgesic effects of frankincense in recent studies were consistent with our results, and since nociceptive pain might be as a result of activation and sensitization of nociceptors by inflammatory mediators, the analgesic effect of frankincense may also be due to its anti-inflammatory effects.[22]

Other theories on the aphthous ulcer outbreak include the presence of microbial antigens that can play a role in both the development of the ulcer and the spread and involvement of the ulcer itself. Many studies have been conducted on the antibacterial effects of frankincense, especially of its terpene derivatives. A study by Raja *et al*. investigated the anti-staphylococcal and anti-biofilm formation effects of AKBA derived from *B. serrata*. The results of this study showed that this compound exhibits anti-staphylococcal effects by degradation of cell membrane and prevention of the formation of *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms.[16] In another study conducted by Ismail *et al*. on the antimicrobial effects of the resin of *B. serrata*, the results showed that this substance can act as a bacteriostatic agent.[23] Therefore, antimicrobial effects of frankincense may also justify the anti-aphthous effect of this resin in the present study.

The main limitations of our study were the small sample size, short duration of intervention, and lack of histological assessment of the ulcers. However, this is the first clinical study showing substantial positive effects of olibanum extract in a novel dosage form in the improvement of oral aphthae. Of note, more studies with larger sample sizes and longer durations are necessary to confirm these effects.

CONCLUSION

In our study, taking olibanum oral disintegrating tablets (ODT) reduced the ulcer size and pain severity and accelerated the healing process in oral aphthous lesions. Overall, given the high prevalence of RAS, its unknown etiology, and its lack of good response to the current therapies, due to the inflammatory and microbial nature of RAS as well as the pain that affects the quality of life in patients, it seems that the frankincense ODT could be applied in the oral cavity as a potential and effective treatment for aphthous ulcers.

Acknowledgments

This project was financially supported by the Vice-chancellery for Research and Technology of Isfahan University of Medical Sciences (IUMS). Authors would like to acknowledge the staff of Isfahan University of Medical Sciences dental clinic for their kind supports.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. J Int Oral Health 2015;7:74-80.
2. Woo SB, Sonis ST. Recurrent aphthous ulcers: A review of diagnosis and treatment. J Am Dent Assoc 1996;127:1202-13.
3. Fischman SL. Oral ulcerations. Semin Dermatol 1994;13:74-7.
4. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S.

Recurrent aphthous stomatitis: A review. J Oral Pathol Med 2012;41:577-83.
5. Gurel A, Altinyazar H, Unalacak M, Armutcu F, Koca RJ. Purine catabolic enzymes and nitric oxide in patients with recurrent aphthous ulceration. Oral Dis 2007;13:570-4.
6. Battino M, Ferreiro M, Gallardo I, Newman H, Bullon P. The antioxidant capacity of saliva. J Clin Periodontol 2002;29:189-94.
7. Eguia-del Valle A, Martinez-Conde-Llamosas R, López-Vicente J, Uribarri-Etxebarria A, Aguirre-Urizar JM. Salivary levels of Tumour Necrosis Factor-alpha in patients with recurrent aphthous stomatitis. Med Oral Patol Oral Cir Bucal 2011;16:e33-6.
8. Momen-Beitollahi J, Mansourian A, Momen-Heravi F, Amanlou M, Obradov S, Sahebjamee M. Assessment of salivary and serum antioxidant status in patients with recurrent aphthous stomatitis. Med Oral Patol Oral Cir Bucal 2010;15:e557-61.
9. Khozeimeh F, Saberi Z, Tavangar A, Badi FF. Effect of herbal *Echinacea* on recurrent minor oral aphthous ulcer. Open Dent J 2018;12:567-71.
10. Babaee N, Baradaran M, Mohamadi H, Nooribayat S. Therapeutic effects of *Zataria multiflora* essential oil on recurrent oral aphthous lesion Dent Res J (Isfahan) 2015;12:456-60.
11. Manifar S, Obwaller A, Gharehgozloo A, Boorboor Shirazi Kordi H, Akhondzadeh SJ. Curcumin gel in the treatment of minor aphthous ulcer: A randomized, placebo-controlled trial. J Med Plants 2012;1:40-5.
12. Hoseinpour H, Peel SA, Rakhshandeh H, Forouzanfar A, Taheri M, Rajabi O, *et al*. Evaluation of *Rosa damascena* mouthwash in the treatment of recurrent aphthous stomatitis: A randomized, double-blinded, placebo-controlled clinical trial. Quintessence Int 2011;42:483-91.
13. Raja AF, Ali F, Khan IA, Shawl AS, Arora DS. Acetyl-11-keto-β-boswellicacid (AKBA); targeting oral cavity pathogens. BMC Res Notes 2011;4:406.
14. Ammon HP, Mack T, Singh GB, Safayhi H. Inhibition of leukotriene B4 formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin exudate of *Boswellia serrata*. Planta Med 1991;57:203-7.
15. Schweizer S, von Brocke AF, Boden SE, Bayer E, Ammon HP, Safayhi H. Workup-dependent formation of 5-lipoxygenase inhibitory boswellic acid analogues. J Nat Prod 2000;63:1058-61.
16. Raja AF, Ali F, Khan IA, Shawl AS, Arora DS, Shah BA, *et al*. Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-β-boswellic acid from *Boswellia serrata*. BMC Microbiol 2011;11:54.
17. Mathe C, Culioli G, Archier P, Vieillescazes C. Characterization of archaeological frankincense by gas chromatography–mass spectrometry. J Chromatogr A 2004;1023:277-85.
18. Barbarisi M, Barbarisi A, De Sena G, Armenia E, Aurilio C, Libutti M, *et al*. Boswellic acid has anti-inflammatory effects and enhances the anticancer activities of temozolomide and afatinib, an irreversible ErbB family blocker, in human glioblastoma cells. Phytother Res 2019;33:1670-82.
19. Khosravi Samani M, Mahmoodian H, Moghadamnia A, Poorsattar Bejeh Mir A, Chitsazan M. The effect of Frankincense in the treatment of moderate plaque-induced gingivitis: A double blinded randomized clinical trial. Daru 2011;19:288-94.
20. Majeed M, Majeed S, Narayanan NK, Nagabhushanam K. A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel *Boswellia serrata* extract in the management of osteoarthritis of the knee. Phytother Res 2019;33:1457-68.
21. Bannuru RR, Osani MC, Al-Eid F, Wang C. Efficacy of curcumin and *Boswellia* for knee osteoarthritis: Systematic review and meta-analysis. Semin Arthritis Rheum 2018;48:416-29.
22. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice AS, *et al*. Do we need a third mechanistic descriptor for chronic pain states? Pain 2016;157:1382-86.
23. Ismail SM, Aluru S, Sambasivarao K, Matcha B. Antimicrobial activity of frankincense of *Boswellia serrata*. Int J Curr Microbiol Appl Sci 2014;3:1095-101.