Prevention of post-surgical adhesion bands by local administration of frankincense n-hexane extract

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ABSTRACT

Background: and purpose: The formation of postoperative intra-abdominal adhesion band formation may lead to severe complications. This study aimed to evaluate the preventive effect of local administration of frankincense n-hexane extract (FHE) on the formation of postsurgical adhesion bands.

Materials and methods: FHE was extracted from the resin of a Boswellia sacra tree and its components were identified by gas chromatography-mass spectrometry (GC-MS). In an animal model, the expression levels of TNF-α and TGF-β1 cytokines after application of FHE were assessed to check the inflammatory and fibrotic cues, respectively.

Results: Following FHE compound analysis, in vivo experiments demonstrated that intraoperative local administration of FHE resulted in the prevention of adhesion band formation. The adhesion grades in the FHE-treated group were significantly lower than those in the negative control (NC) and the positive control (Interceed). The infiltration of inflammatory cells observed by histopathology revealed a significant anti-inflammatory potential of FHE. Furthermore, the gene expression results proved that significant suppression of TNF-α and TGF-β1 was responsible for its antiadhesion properties.

Conclusions: The study reported the potential of FHE as an ointment for the prevention of adhesion bands.

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1. Introduction

One of the common postoperative complications following abdominal surgeries is the formation of adhesion bands.1 These bands may lead to several clinical side effects such as female infertility, bowel obstruction, and chronic abdominal-pelvic pain.2 Different approaches and strategies have been applied to prevent adhesion band formation with the fewest side effects.3,4 Removing adhesion bands by surgical techniques such as mechanical separation might be associated with side effects, as they required an additional surgical intervention. However, using physical barriers against tissues coming into direct contact postoperatively, such as fluids, solids, and different types of gels, could prevent the problem.4,5 Additionally, these barriers can be made of anti-adhesive

Abbreviations: FHE, Frankincense n-Hexane extract; GC-MS, gas chromatography-mass spectrometry; NC, negative control; PC, positive control.

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agents such as anticoagulants, anti-inflammatory agents, antibiotics and anti-fibroinolytic agents. Among these physical barriers, Surgicel, Seprafilm, Interceed, and ePTFE have been approved by the FDA, and they have moderate effectiveness in the prevention of adhesion bands but their use is associated with some technical problems. Interceed is a degradable oxidized cellulose membrane that is clinically approved to act as a barrier for the prevention of adhesion band formation between adjoining surfaces.

To find an appropriate preventive agent for adhesion band formation, the mechanism underlying their induction needs to be fully understood. The etiopathogenesis of adhesion bands is a complicated process involving oxidative stress, ischemia, infection, and inflammation. The lack of equilibrium between the fibrinolytic system and coagulation leads to inappropriate healing of the damaged tissue. This process handles the formation of adhesions within the abdominopelvic cavity. Adhesion band is formed from cellular components including macrophages, red blood cells, mast cells, eosinophils, tissue debris, and fibroblasts accompanied with the extracellular matrix. Following adhesion development, the cells are modified from polymorphonuclear leukocyte cells into predominated fibroblasts. There are some factors which can mediate inflammatory and immune responses, tissue remodeling, angiogenesis involving in the adhesion band development.

Pro-inflammatory and fibrotic factors play a critical role in the initiation of intra-abdominal adhesion band formation. An increase in the secretion of inflammatory cytokines such as tumor necrosis factor α (TNF-α) is responsible for the migration of inflammatory and fibroblast cells, forming adhesion bands. Additionally, profibrotic transforming growth factor β (TGF-β) plays a critical role in the formation of adhesion bands. This growth factor is released from activated fibroblasts and mesothelial cells in the peritoneal cavity. The expression of fibrotic genes caused by activation of the TGF-β1/Smad signaling pathway is responsible for the improper healing of damaged tissue. Therefore, TGF-β1 has been demonstrated to play a substantial role in fibrogenesis, resulting in adhesion band formation.

Several preventive agents with anti-inflammatory and anti-fibrotic properties have been used to reduce postsurgical intra-abdomen adhesion formation. Natural products have shown excellent bioactivities to prevent adhesion band. Sahbaz et al. found that pycnogenol, an extract from the bark of the French maritime pine is effective for the prevention of inflammation and fibroblast cells, forming adhesion bands.

2.1. Sample collection and preparation of FHE

Royal Hougari White (RHW) frankincense (Boswellia sacra) was collected from Hougari Mountain, Salalah in 2012 and authenticated by a taxonomist, Natural and Medical Sciences Research Center, University of Nizwa. The voucher specimen (RHW-02/2012) of the resin was deposited in the herbarium of the Natural & Medical Sciences Research Center, University of Nizwa, Oman. The air dried gum resin of frankincense (10 g) was ground to a fine powder and used for the extraction of FHE through a Soxhlet apparatus. The FHE was exhaustively extracted with 100% analytical grade n-hexane (250 mL) at 70 °C (with continuous and vigorous shaking) for 6 h and the n-hexane was evaporated under reduced pressure to yield a yellow semisolid residue (1.5 g).

2.2. Gas-chromatography-mass spectrometry (GC-MS) analysis

Gas chromatography-mass spectrometry (GC-MS) analysis was performed on a PerkinElmer Clarus 600 GC System fitted with an Rtx-5MS capillary column (30 mm × 0.25 mm I.D. 0.25 μm film thickness; maximum temperature of 350 °C) and coupled to a PerkinElmer Clarus 600 mass spectrometer. Ultrahigh purity helium (99.9999%) was applied as the carrier gas at a constant flow rate of 1.0 mL/min. The injection, transfer line, and ion source temperatures were adjusted to 250, 260 and 260 °C, respectively. The ionizing energy was 70 eV. Electron multiplier (EM) voltage was attained from autotuning. All data were acquired by obtaining full-scan of mass spectra within the scan range 40–550 a.m.u. A 1 μL sample was injected with a split ratio of 10:1. The oven temperature program was 60 °C (held for 1 min) at a rate of 4 °C/min–260 °C (held for 4 min). The total run time was 50 min. The identification of unknown compounds was performed by matching the spectra with mass spectrum libraries (NIST 2011 v2.3 and Wiley, 9th edition).

2.3. Animal study

Twenty-one male CD-1 mice with weight between 25 and 30 g were housed in standard condition (12 h light, 12 h dark, temperature 20–25 °C, and humidity 55 ±10%). The mice were hosted with a maximum of seven mice per cage and allowed to acclimate for one week before starting the procedure. Water and food were available ad libitum.

2.4. Experimental design

In the present work, the surgical procedures were authorized by the Animal Ethics Committee, University of Nizwa. Twenty-one male CD-1 mice were randomly divided into three groups (7 mice per group) as follows: negative control (NC), surgical abrasion without any treatment (n = 7); positive control (PC), surgical

Frankincense n-hexane extract (FHE) and have been demonstrated to have antifibrotic and anti-inflammatory activities. In addition to its antifibrotic and anti-inflammatory properties, FHE can also act as a physical barrier.

In the present study, the antiadhesive properties of FHE were compared with those of Interceed as a positive control in a mouse model. To the best of our knowledge, no reports have previously described the anti-adhesive effects of FHE as a result of its anti-inflammatory and antifibrotic activities. The aim of this study was to evaluate the adhesion bands prevention properties of FHE in comparison with the conventional treatment.

Several compounds such as Incensole, Incensole acetate, 1-pinene, and linalool have been isolated from frankincense n-hexane extract (FHE) and have been demonstrated to have antifibrotic and anti-inflammatory activities. In addition to its antifibrotic and anti-inflammatory properties, FHE can also act as a physical barrier.

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abdominal cavity was incised and assessed morphologically (Fig. 1). Before suturing the abdominal wall, a 1.5 × 1.5 cm piece of Interced or 60 μL FHE/mice were applied between the abdominal wall and peritoneum in the PC and FHE groups, respectively. After 1 week, the animals were euthanized using an overdose of anesthesia, and the peritoneum in the PC and FHE groups, respectively. After 1 week, the animals were euthanized using an overdose of anesthesia, and their abdominal cavities were reopened. Post-surgical adhesion band formation was evaluated using two scoring systems presented by Zühlke et al. (1997) and Duran et al. (2003) (Table 1).24,25

2.6. Histologic evaluation

The adhesion bands and the peritoneal tissues around them were isolated from the other tissues and then fixed with 10% formalin and immersed in paraffin. Several sections were prepared using a rotary microtome followed by staining with hematoxylin and eosin. The inflammation degree was obtained using a semi-quantitative scoring system, as shown in Table 1.26

2.7. Quantitation of cytokine gene expression by real-time PCR

Total RNA was isolated from adhesion tissues by means of RNaseq-Plus Solution (Sinacron, Iran); cDNA was synthesized with the aid of M-MuLV reverse transcriptase and random hexamer, according to the manufacturer’s protocols (Thermo Fisher Scientific, USA). The expression levels of tumor necrosis factor α (TNF-α) and transforming growth factor β1 (TGF-β1) were quantified by the real-time PCR. PCR amplification was performed using Maxima™ SYBR Green/Fluorescein qPCR Master Mix (Thermo Fisher Scientific), and B2M (Beta2-microglobulin) transcripts served as endogenous controls. All reactions were performed in triplicates. The results are described as the relative expression of the genes normalized to the mRNA transcript expression. The primer sequences are listed in Table 2.

2.8. Statistical analysis

All variables are represented as the mean ± SD. Differences between the adhesion and inflammation scores were evaluated by Kuskal-Wallis test and the significant difference (p < 0.05) between specific mean ranks was determined using one-way analysis of variance (ANOVA).

3. Results

3.1. Component analysis using gas chromatography-mass spectrometry (GC-MS)

Several compounds were identified by the comparison of fragmentation patterns in the GC/MS spectra with the literature.30,31 These compounds, along with their retention time, peak area, and RI, are presented in Table 3. As the peak area represents the amount of each compound, it could be concluded that FHE contains a high proportion of β-amyrin (23.49%), retinoic acid, methyl ester (8.54%), trans-verbenol (8.10%), α-farnesene (5.69%), and betulin (3.42%).

3.2. In vivo morphological and histological assessment

Among the FHE treated mice, no infection, mortality, or changes in behavior were detected through the end of the experimental period, suggesting the biocompatibility of FHE. To evaluate the impact of treatment on the prevention of adhesion bands, the abdominal cavity was incised and assessed morphologically (Fig. 1). The intra-abdomen adhesion bands were scored according to the Zühlke and Duran approaches (Fig. 2).

As stated in Fig. 2, the FHE treated group revealed fewer adhesion bands than the NC and PC groups. To quantify the adhesion band grades, scores were given by two surgeons blinded to the treatment group according to the Zühlke and Duran methods. The adhesion Zühlke score of the FHE group was significantly lower than that of the negative and positive controls, indicating decreased adhesion band formation in the FHE-treated mouse abdomen compared to the other groups. Regarding the Duran score, the FHE-treated mouse abdomen revealed a smaller adhesion band area, resulting in a remarkably lower score than that of the negative and positive controls.

As inflammation plays a vital role in the formation of adhesion bands, the infiltration of inflammatory cells was assessed and scored by two expert pathologists. As shown in Figs. 3 and 4, the infiltration of inflammatory cells around the peritoneal surface was observed in the NC group. Even though there were fewer inflammatory cells in the PO-treated group compared to NC group, the difference between their inflammation scores was not significant (P > 0.05). As shown in Fig. 3, there was less infiltration of inflammatory cells in the FHE-treated group than in the NC and PC.

| Grade | Criteria Adhesion bands morphology | Histopathology |
|-------|-------------------------------------|----------------|
| 0     | Zühlke et al. No adhesion           | Inflammation Nil |
| 1     | Filmy adhesions: gentle, blunt dissection required to free adhesions ≤25% of area | Giant cells, occasional scattered lymphocytes, and plasma cells |
| 2     | Mild adhesions: aggressive blunt dissection required to free adhesions 25-50% of area | Giant cells with increased numbers of admixed lymphocytes, plasma cells, eosinophils, neutrophils |
| 3     | Moderate adhesions: sharp dissection required to free adhesions 50-100% of area | Many admixed inflammatory cells, micro abscesses present |
| 4     | Severe adhesions: not dissectible without damaging organs | |
groups. Accordingly, the inflammation score assessment in Fig. 4 demonstrated a significant anti-inflammatory effect of FHE in comparison with NC and PC.

3.3. Quantitative gene expression by real-time PCR

The expression of candidate cytokine genes (TNF-α and TGF-β1) was evaluated in the FHE and PC groups compared to the NC group. The results showed that the expression levels of TNF-α and TGF-β were downregulated in the FHE group (0.044 and 0.334 times, respectively) and upregulated in the PC group (2.639 and 6.543 times, respectively) compared to the NC group, significantly. As illustrated in Fig. 5, FHE caused a statistically significant decrease in TNF-α and TGF-β1 mRNA levels (p < 0.05) compared to the positive control group.

4. Discussion

In this study, the effect of FHE on the prevention of intra-abdominal adhesion band has been assessed using an in vivo mouse model. We reported here that FHE significantly decreased the infiltration of inflammatory cells and inhibited the formation of postoperative adhesion bands. This is possibly resulted from the anti-inflammatory and anti-fibrotic properties of the active compounds.

Several compounds with anti-inflammatory activities have been found in FHE. α-Pinene has shown an interesting anti-inflammatory capacity by inhibiting COX-2. Additionally, β-eudesmol could decrease inflammation by regulating IL-6 levels. A remarkable regulation of inflammation has been observed in endotoxin-shocked mice treated with betulin. Additionally, α-santalol has been proven to be an anti-inflammatory agent that can diminish skin inflammation. In addition, the anti-inflammatory effects of retinoic acid on IFN-γ-treated astrocytes have been found to be mediated by suppression of the JAK/STAT pathway. Another study suggested an inflammation-regulatory effect of β-amyrin in a rat model of periodontitis. Likewise, eucalyptol, caraphyllene oxide, 1,6,10-dodecatrien-3-ol, 3,7,11-trimethyl-,(E)-, and retinol have anti-inflammatory activities that may improve chronic pain treatment.

It is worth mentioning that the FHE has greater

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**Table 2**
The primers and product lengths.

| Gene    | Forward primer | Reverse primer | Product length(bp) |
|---------|----------------|----------------|--------------------|
| TNF-α   | TCTTCTGATTCTGCTTCTG | ACTTGGTGTTTGGCTACG | 199                |
| TGF-β   | ATTCCTGGCTTACCTTGG | CCGTATCCGGTCTCTTGG | 117                |
| B2M     | GCTATCCAGAAAAACCCTC | CCCGTTCCTCAGAATTG | 132                |

**Table 3**
GC-MS analysis of the n-hexane extract of frankincense.

| Compounds                                | RT (min) | RI     | %     |
|------------------------------------------|----------|--------|-------|
| β-Amyrin                                 | 54.302   | 3337   | 23.49 |
| Retinoic acid, methyl ester              | 53.977   | 2528   | 8.54  |
| trans-Verbenol                           | 11.686   | 1162   | 8.10  |
| α-Farnesene                              | 10.115   | 1496   | 5.69  |
| Betulin                                  | 44.55    | 1752   | 3.42  |
| β-Elemenu                                | 18.274   | 1387   | 3.22  |
| 6-Isopropenyl-4,8a-dimethyl-3,5,6,7,8,8a-hexahydro-2(1H)-naphthalene | 34.83    | 1772   | 3.18  |
| trans-3(10)-Caren-2-ol                   | 10.386   | 1194   | 3.11  |
| γ-Gurjunene                              | 21.113   | 1469   | 3.05  |
| 1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl-,(E)- | 37.94    | 1555   | 2.65  |
| Caryophyllene oxide                      | 23.908   | 1575   | 1.89  |
| Berbenone                                | 12.64    | 1183   | 1.83  |
| (--)β-Bourbonone                         | 18.036   | 1386   | 0.93  |
| β-Eudesmol                               | 25.88    | 1644   | 0.91  |
| β-Myrcene                                | 5.781    | 979    | 0.83  |
| 5β,14β-Androstane-17β-carboxylic acid, 3β,14-dihydroxy | 47.898   | 2477   | 0.81  |
| Eucalyptol                               | 7.168    | 1020   | 0.78  |
| L-Pinocarveol                            | 10.863   | 1143   | 0.77  |
| α-Pinene                                 | 4.816    | 931    | 0.76  |
| Retinol                                  | 52.85    | 2453   | 0.71  |
| Bornyl acetate                           | 14.958   | 1269   | 0.63  |
| trans-Pinocarvyl acetate                 | 9.42     | 1281   | 0.62  |
| α-Bulnesene                              | 21.395   | 1508   | 0.59  |
| Limonene oxide, trans-                   | 8.717    | 1121   | 0.57  |
| Myrtenol                                 | 12.282   | 1174   | 0.54  |
| Isoborneol                               | 11.231   | 1146   | 0.49  |
| Murolan-3,9(11)-diene-10-peroxy          | 46.489   | 1729   | 0.49  |
| α-Santalol                               | 45.482   | 1669   | 0.48  |
| Cycloesacylitol acetate                  | 53.24    | 2900   | 0.39  |
| Bicyclo[2.2.1]heptane-3-methylene-2,2-dimethyl-5-ol acetate | 15.998   | 1271   | 0.32  |
| Aromandrenene                            | 20.831   | 1439   | 0.24  |
| Pregnan-20-one, 3β-hydroxy-              | 41.191   | 2254   | 0.24  |
| (--)Globulol                             | 22.066   | 1580   | 0.15  |
| cis-Z-α-Bisabolene epoxide               | 27.842   | 1704   | 0.13  |
| α-Terpinol acetate                      | 17.093   | 1322   | 0.12  |

RI = Retention indices; RT = Retention time (min); % = Percentage.
anti-inflammation properties than the water extract of frankincense. This is possibly due to the low efficiency of liposoluble component isolation in water-based methodologies.

In addition to the anti-inflammatory activities, antifibrotic effects could be beneficial for the prevention of intra-abdominal adhesion bands. The antifibrotic properties of caryophyllene oxide have been demonstrated by Eltahir et al. (2020) and Amiel et al. (2012). Moreover, betulin could significantly inhibit the transcription signaling of TGF-β and NFκB/κB, which are key players in adhesion band formation. Likewise, the retinoic acid and β-amyrin available in FHE have exhibited strong antifibrotic activities.

Due to the mentioned cues in the initiation of adhesion band formation, the recognized anti-inflammatory and antifibrotic compounds in FHE may be responsible for its intraabdominal adhesion preventive properties. According to the result, TNF-α and TGF-β1 modulation involved in the intra-abdomen adhesion preventive properties of FHE. Kaidi et al. verified that the administration of anti-inflammatory drugs such as TNF-α blockers successfully reduced the rate of postoperative adhesion formation. Moreover, among many cytokines, transforming growth factor-β1 (TGF-β1) has been documented to be associated with intraperitoneal adhesion development. TGF-β1 may be the most important cytokine in adhesion band formation. Both TGF-β1 and its receptor are increased in the peritoneal tissue and fluid after peritoneal surgery. The suppression of TGF-β1 expression causes peristin inhibition, resulting in the prevention of adhesion band formation.

In line with our finding, breviscapine, a crude extract of Erigeron brevisscapus, was reported to prevent the formation of post-surgical adhesion bands via the fibrotic and inflammatory pathways. It has been revealed by Zhang et al. that breviscapine exerts antifibrotic and anti-inflammatory properties via the modulation of TNF-α, IL-18, and IL-6 in serum and TGF-β1, PAI-1, and connective tissue growth factor in the peritoneal fluid. In the presented study, FHE could significantly reduce TNF-α, and TGF-β1 cytokines expression in tissue homogenates showing its anti-inflammatory and antifibrotic effects. On the other hand, in PC group, the expression levels of TNF-α, and TGF-β1 cytokines were highly expressed in comparison with the NC. This was in agreement with the reported result by Zhang et al. Arora et al. have also revealed that Interceed induces an inflammatory response with foreign body giant cells, macrophages and eosinophils. In summary, the presented results suggest that the anti-adhesive properties of FHE may occur through the regulation of TNF-α and TGF-β1. These findings support the preventive potency of FHE in the inhibition of postsurgical adhesion formation.
5. Conclusion

This study concluded that FHE could prevent postsurgical adhesion formation. The results show that this effect may be mediated through its anti-inflammatory and antifibrotic activities. Further studies are warranted to assess other regulatory and inflammatory cytokines such as IL-1, IL-6, IL-10, and IL-17. Moreover, other factors such as oxidative stress, ischemia, and infection need to be addressed. Such studies might be helpful to identify the underlying pathways for the anti-adhesive properties of FHE and to develop a preventive agent for clinical applications.
Data statement

We declare here that all data belonging to the represented research are reproducible and clear. All the raw data are available for sharing upon request.

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Research involving animals

The animal experiments were performed according to the guidelines of the National Committee of Bioethics and the institutional Animal Ethics Committee (Approval ID: VCGSR, AREC/04/2020, Approval date: January 03, 2020). The animals were kept under standard laboratory conditions for housing, feeding, and breeding.

Author contributions

Fatemeh Jamshidi-adegan: Conceptualization, Methodology, Investigation, Writing-Original Draft, Saeid Vakilian: Methodology, Investigation, Writing-Review 
 Editing. Juhania Al-kindi: Methodology, Investigation, Writing-Review & Editing. Laila Alkalbani: Investigation, Writing - Review & Editing, Mohammed Al-Broumi: Investigation, Nasar Al-Wahabi: Methodology. Asem Shalaby: Investigation. Jamal Al-Sabahi: Investigation. Ahmed Al-Harrasi: Supervision, Funding acquisition, Writing - Review & Editing, Sulaiman Al-Hashmi: Conceptualization, Project administration, Writing-Original Draft, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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