INTRODUCTION

Smokeless tobacco (SLT) has been identified as one of the major risk factors associated with developing oral cancer and is consumed in a large number of variations based on geographical location. Its use in South-East Asian countries is usually in the form of betel quid and while in Western countries, snuff is well documented. A number of carcinogens including non-volatile alkaloid-derived tobacco-specific N-nitrosamine and N-nitrosamino acids have been reported to be present in SLT. While SLT use is also prevalent in other parts of the world including North African countries and Arabic Peninsula, very little research has been carried out to explore the associated risks.

Shammah is a traditional form of SMT, commonly used in Middle Eastern countries including Saudi Arabia, Algeria and Yemen (Figure 1). It is a mixture of powdered tobacco, slaked lime, ash, black pepper, oils and flavorings and is placed in the mouth as a quid till the affect and the flavor of the substance lasts. Shammah is obtainable in various forms, such as a powdered mixture, a compressed tablet, or a toothpick-like stick. The use of shammah has been linked to a higher risk of developing oral potentially malignant disorders (OPMD) and/or oral cancer.

Introduction: Shammah is a form of smokeless tobacco commonly used in the Arabian Peninsula. The data on the harmful effects of shammah on oral health, particularly oral malignancies, are scarce. The aim of this review was to explore the association between shammah use and development of oral potentially malignant disorders (OPMD) and/or oral cancer.

Materials and methods: PubMed, EMBASE, Scopus, Web of Science and grey literature from January 1990 up to and including April 2018 were searched. Two independent reviewers performed the study selection according to eligibility criteria.

Results: A total of 10 studies that met the eligibility criteria were included. The odds of developing OPMD and/or oral cancer in relation to shammah use varied, with one study reporting a 39 increased risk (95% CI: 14-105). The associated increased risk was relatively low among those that have stopped using shammah and ranged from threefold (3.65; 95% CI: 1.40-9.50) to 12-fold (12.6; 95% CI: 3.3-48.2).

Conclusion: Shammah use seems to increase the risk of development of OPMD and/or oral cancer.

KEYWORDS
oral malignancy, oral precancer, risk, shammah, tobacco
in various varieties, with two main forms—a greenish-yellow (so-called “white”) or brownish to black powder or paste. It is usually placed in the buccal mucosa or lower labial mucosa. Shammah is a moist form of tobacco with a strong aroma, highly addictive, and its use is widespread among males.

The association between different types of SLT products and their harmful effects on the oral health is evident and varies from symptoms of burning mucosa to the development of oral potentially malignant disorders (OPMD) and oral cancer. However, the associated risks of shammah use on oral health, particularly in relation to oral cancer, have not been extensively studied. The aim of this review was to systematically quantify the existing literature and assess the relationship between shammah use and the development of OPMD and oral cancer.

2 MATERIAL AND METHODS

2.1 Protocol and registration

International Prospective Register of Systematic Reviews (PROSPERO) databases were searched for any registered protocols on similar topic. In addition, the current systematic review was registered as a protocol with PROSPERO platform (ID: CRD42019122480). The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.2 Eligibility criteria

2.2.1 Inclusion criteria

PICOS framework (Population, Intervention, Comparison, Outcomes, Studies) was used to formulate the focused question of the review, of which (P) patients with diagnosis of OPMD and/or oral cancer; (I) shammah use; (C) patients with no history of OPMD and/or oral cancer; (O) associated risk of developing OPMD and/or oral cancer; (S) observational studies and/or clinical trials.

Observational studies (case-control, cross-sectional or population-based) and/or clinical trials (randomized controlled trial) that recruited patients with clinically and/or histologically confirmed diagnosis of OPMD and/or oral cancer and evaluated the associated risk of Shammah and OPMD/oral cancer were included. Articles published in English language only were included.

2.2.2 Exclusion criteria

The following exclusion criteria were applied: (a) studies that did not report shammah use; (b) case reports, reviews, experimental studies, short communications and personal opinions, letters to the editor and conference abstracts.

2.3 Focused question

The focus question was “Does shammah use increases the risk of OPMD and/or oral cancer?”.

2.4 Search strategy

Detailed automated literature searches were performed in PubMed, EMBASE, Scopus and Web of Science from January 1990 up to and including April 2018. An additional search of the grey literature was carried out on Google Scholar, ProQuest and OpenGrey. Reference lists of all included articles were manually searched to identify any potential relevant articles. EndNote software (EndNote X7, Thomson Reuters, Philadelphia, USA) was used to manage the references and remove any duplicate articles.

Various combinations of descriptors extracted from Medical Subject Headings (MeSH) and free terms were used; “Mouth Neoplasm” [MeSH] OR “Neoplasm, Mouth” [MeSH] OR “Neoplasms,

2.5 | Study selection and data extraction

The study selection process was completed in two stages. Firstly, titles and abstracts of all identified articles were screened by two independent reviewers (KHA and SP) using a standardized guide. This was followed by retrieval of full texts of studies that met the eligibility criteria and reviewed independently by the same two reviewers using a standardized and pilot-tested form. Any disagreements on study selection were mutually discussed, and a consensus was made before inclusion of the study.

The two reviewers (KHA and SP) independently collected the data on study characteristics (author, year of study and country), study design, sample population, OPMD/oral cancer site, exposure type and frequency of shammah use, statistical findings and conclusions.

2.6 | Risk of bias assessment

The risk of bias of included studies was assessed using a modified Newcastle-Ottawa scale (NOS). Two reviewers (KHA and SP) independently evaluated the quality of studies based on the following parameters: selection, comparability and outcome/exposure. A maximum of four stars was given in the selection domain, two stars in the comparability domain and four stars in outcome/exposure.
<table>
<thead>
<tr>
<th>Author et al (y), Country</th>
<th>Study design</th>
<th>Sample population</th>
<th>Lesion location</th>
<th>Exposure type</th>
<th>Duration/ frequency of shammah use</th>
<th>Odds ratio (95% CI)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem et al (12) , Saudi Arabia</td>
<td>Study type: Cohort study Setting &amp; period: Farassan Island, villages of Al-Ahmad and Samta districts, and Dental Department, King Fahd Central Hospital, Jazan, Saudi Arabia</td>
<td>671 individuals; Age ≥ 15 y 30 biopsy specimens of lesions from different anatomical locations from 30 different individuals</td>
<td>Tongue, Floor of mouth, Buccal mucosa, Labial mucosa</td>
<td>Shammah, Cigarettes</td>
<td>Not reported</td>
<td>Not reported</td>
<td>A causal relation exists between Shammah use and the development of oral lesions</td>
</tr>
<tr>
<td>Allard et al (13) , Saudi Arabia</td>
<td>Study type: Retrospective Setting &amp; period: Tumor Registry (TR) data from the King Faisal Specialist Hospital and Research Centre (KFSH&amp;RC), Riyadh, Saudi Arabia, 1976-1995</td>
<td>26 510 patients were referred for cancer treatment 794 oral cancer cases; age range 2-105 y; Mean age 59 y; 428 M, 366 F</td>
<td>Tongue, Floor of mouth, Buccal mucosa, Labial mucosa, Retromolar area</td>
<td>Shammah, Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>A relation exists between Shammah and oral cancer</td>
</tr>
<tr>
<td>Scheifele et al (14) , Germany</td>
<td>Study type: Case-control Setting &amp; period: 48 different villages and cities in Yemen; April-October 2004</td>
<td>Study group: 200 voluntary individuals; 199 M, 1 F; age range 11-82 y; Mean age 33.2 ± 13.3 y Cases: 116 cases (54 OL and 62 MB) Controls: 58 with no mucosal lesions</td>
<td>Tongue, Floor of mouth, Buccal mucosa, Gingiva, Labial mucosa</td>
<td>Shammah, Cigarettes, Qat</td>
<td>1-10 times per day 1-5 mins per serving</td>
<td>6.91 (2.66-17.95) for OL 4.90 (1.99-12.08) for daily use of &gt;10</td>
<td>Significant association between OL and Shammah use in a dose-dependent manner</td>
</tr>
<tr>
<td>Nasher et al (15) , Yemen</td>
<td>Study type: Case-control Setting &amp; period: Al-Thawra Modern General Hospital and Aljumhuri Teaching Hospital, Sana’a, Yemen; June 2009-February 2011</td>
<td>Cases: 60 patients with previously untreated OSCC; 32 M, 28 F Controls: 120 healthy individuals; gender-age matched; 64 M, 56 F</td>
<td>Tongue, Floor of mouth, Gingiva, Others</td>
<td>Shammah, Cigarettes, Qat, Alcohol</td>
<td>Not reported</td>
<td>39 (14-105) for current users 12.6 (3.3-48.2) for ex-users</td>
<td>Shammah use is a major risk factor for oral cancer</td>
</tr>
<tr>
<td>Al-Tayyar et al (16) , Malaysia</td>
<td>Study type: Cross-sectional Setting &amp; period: Al-Ebtesamah Dental Clinic in Dawan Valley, Yemen; June-November 2014</td>
<td>346 adult males; age range 18-68 y; Mean age 34.3 ± 12.29 y</td>
<td>Not reported</td>
<td>Shammah</td>
<td>9.6 (5.31) times per day 12.5 (8.60) mins per serving 10.5 (6.40) y</td>
<td>12.99 (6.34-26.59) for current users 3.65 (1.40-9.50) for ex-users</td>
<td>Shammah is a major factor in the development of oral leukoplakia-like lesions</td>
</tr>
<tr>
<td>Qaudri et al (17) , Saudi Arabia</td>
<td>Study type: Case-control Setting &amp; period: King Fahd Hospital, Jazan, Saudi Arabia</td>
<td>Cases: 48 oral cancer patients; Mean age 65.3 y Controls: 98 healthy individuals; age-gender and location matched</td>
<td>Shammah, Cigarettes, Qat, Pipe</td>
<td>Not reported</td>
<td>10-20 y</td>
<td>29.3 (10.3-83.1)</td>
<td>Shammah is associated with oral cancer in Jazan region</td>
</tr>
</tbody>
</table>

(Continues)
The included studies were qualified as "Good," "Fair" and "Poor" quality based on the total NOS score they achieved. Studies with a NOS score ≥7 were considered good-quality studies.

### 2.7 Statistical analysis

Cohen's kappa statistic was used to calculate the agreement between the two reviewers (KHA and SP). Descriptive statistics for all included studies were populated and reviewed. NOS scores based on the assessment of quality of each study were also reported.

### 3 RESULTS

#### 3.1 Study selection

Of 33 full texts assessed, 24 articles were excluded. Therefore, nine articles that met the eligibility criteria were included (Figure 2). The inter-examiner agreement (Kappa) was 1.0 in the first stage (title and abstract screening stage) and 0.99 in the second stage (full-text reading stage).

#### 3.2 Studies characteristics

Of the nine included studies,12-20 six were from Saudi Arabia,12,13,17-20 and one each from Germany,14 Yemen15 and Malaysia.16 Four studies had case-control study design,14,15,17,20 three were retrospective,13,18,19 and one was cross-sectional in design.16 Also, one study had a cohort-based study design.12

The majority of studies reported OPMD and/or oral cancer sites,12-15 and buccal-alveolar mucosa, tongue, floor of mouth were the most common sites affected. In addition to shammah, studies also evaluated other tobacco-associated products including cigarettes, Qat and pipe. Table 1 provides the detailed characteristics of the included studies.

#### 3.3 Risk of bias assessment

The NOS score for the quality of the included studies ranged from 4 to 7 (Table 2). Only three studies15,17,20 had a NOS score of 7 to be considered a good-quality study. Four studies12,14,18,19 recorded a NOS score of “5,” while the remaining two studies13,16 had a NOS score of “4.” The majority of studies scored high in the selection domain, and comparability domain was the least scored domain. The majority of studies also scored high in the outcome/exposure domain.

#### 3.4 Associated risk of shammah and OPMD/oral cancer

Five studies reported an associated risk of shammah use and OPMD/oral cancer.14-16 The odds of having OPMD/oral cancer in relation to shammah use ranged from three to 39 times. One study reported that the odds of developing OPMD/oral cancer...
among current shammah users are 39-fold (95% CI: 14-105),15 while another study reported a 13-fold increased risk among current shammah users (12.99; 95% CI: 6.34-26.59).16 The associated risk was relatively low among those that have quit shammah use and ranged from threefold (3.65; 95% CI: 1.40-9.50) to 12-fold (12.6; 95% CI: 3.3-48.2).

3.5 | Gender disparities

Two studies found an associated risk of shammah in regard to gender difference.19,20 Both found a higher prevalence of shammah-associated lesions among females. While one study only found oral precancer/epithelial dysplasia (8.6%) was more common in females with a shammah habit,19 the other reported that Shammah-associated OSCC and epithelial dysplasia are twice as common in females as males.20

3.6 | Frequency and duration of use

Only two studies14,16 reported the frequency of shammah use per day which ranged from 1 to 10 times. Increased odds ratio of OL was reported with increased frequency of shammah use and ranged from 1.17 (95% CI: 1.02-1.36) to 4.90 (95% CI: 1.99-12.08).

Four studies reported the duration of shammah use among the study groups14,16,17 and ranged from 10 to 45 years and 1 to 12.5 minutes per serving. The reported odds ratio was 6.91 (95% CI: 2.66-17.95) for an average duration of shammah use of >5 minutes and 1.07 (95% CI: 0.98-1.17) for the duration of being a shammah user of more than 1 year.

4 | DISCUSSION

In our review, we found a strong causal relationship between shammah use and development of OPMD and/or oral cancer. The risk for shammah users to develop these lesions was 39 times (95% CI: 14-105) higher than non-users. It was also noted that the associated risk of OPMD and/or oral cancer was higher among the current shammah users for current users (39; 95% CI: 14-105 and 12.99; 95% CI: 6.34-26.59) compared to those that have quit (12.6; 95% CI: 3.3-48.2 and 3.65; 95% CI: 1.40-9.50).15,16

The majority of studies were carried out in Saudi Arabia.12,13,17,18 Oral cancer is the 3rd most common cancer in Saudi Arabia, representing approximately 26% of all head and neck cancers.22,23 Unfortunately, the majority of cancer cases present in an advanced staged and require palliative care. This high incidence of oral cancer is mostly confined to the south-western region of the Saudi Arabia, predominantly in the Jazan province and areas close to the Yemen border.24,25 Shammah use is a common practice in these regions, among both men and women. There are some 4500 villages in the Jazan province, and there is a variation in the type and brands of shammah used from one user to the next and from one region to the other.26,27 Since shammah is illegal in Saudi Arabia,28 actual prevalence rates of shammah use may be even higher due to social stigma and reluctance in admitting its use.29

The most common sites affected by shammah use were buccal and labial mucosa, a finding consistent with reports on other SMT use and due to its placement at these sites.3,9,30 The tongue was also found to be common site for developing OPMD/oral cancer among shammah users. Shammah was used by patients as young as 10-13 years old,3 and its use in infants to relieve pain caused by erupting teeth is well documented.31

We reviewed the available scientific data and present validated scientific conclusions regarding the association of shammah use and OPMD/oral cancer. International Agency for Research on Cancer (IARC) recognizes all SMT products as being generally harmful to humans and some being carcinogenic as well.21 Shammah is one such product which has been associated with increased risk of OPMD and oral cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/exposure</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem et al12</td>
<td>● o ● o o o o o ● 5</td>
<td></td>
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<tr>
<td>Allard et al13</td>
<td>● ● o o o o o o ● 4</td>
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<tr>
<td>Scheifele et al14</td>
<td>● o o ● o o o ● 5</td>
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<tr>
<td>Nasher et al15</td>
<td>● ● o o o o o o ● 7</td>
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</tr>
<tr>
<td>Al-Tayyar et al16</td>
<td>○ ● o o o o o o ● 4</td>
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<tr>
<td>Quadri et al17</td>
<td>● o o ● o o o o ● 7</td>
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<tr>
<td>Idris et al18</td>
<td>● ● o o o o o o ● 5</td>
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<tr>
<td>Saleh et al19</td>
<td>● ● o o o o o o ● 5</td>
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<tr>
<td>Al-Harbi et al20</td>
<td>● o o ● o o o o ● 7</td>
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</tbody>
</table>

**TABLE 2** Assessment of the quality of included studies using Newcastle-Ottawa scale (NOS) (12)
reported cancer cases that were confirmed either through histological analysis or hospital records and adjusted their risk estimates for other confounding factors including smoking. In addition, controls were age, gender, location and referral route matched and had the same method of exposure assessment as the cases. On the contrary, studies that scored low on NOS did not provide cases and controls matching, adjustment for confounders, and did not report any histological and/or hospital records.

There are a few limitations to this review. Firstly, the majority of studies included had a hospital-based sample which may have resulted in selection bias. In addition, as the studies were hospital-based, the findings may not be representative of the general population. There was also a possibility of recall bias that is pertinent to any case-control study. Information about frequency, duration and quantity of shammah use was not explored, hence missing an opportunity to evaluate their possible effect on strength of association. Finally, histopathological information on shammah-associated lesions is sparse, and it may be difficult to delineate the average amount of precancerous alterations in those lesions.

5 | CONCLUSION

This review shows a strong causal relation between shammah use and development of OPMD and/or oral cancer. The associated risk increases with increase in frequency and duration of shammah and is highest among current users compared to ex-users. Considering these findings, further well-designed large-scale studies with detailed investigations and vigorous follow-up are needed. The general public and healthcare professionals should be educated to recognize the potential dangers of shammah use.

ETHICAL APPROVAL

Not required.

CONFLICT OF INTEREST

None declared.

REFERENCES


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