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Toxicological impact of waterpipe smoking and flavorings in the oral cavity and respiratory system

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Abstract

Waterpipe smoking (WS), an emerging trend has major health concerns. It is prevalent worldwide as a recreational activity both indoors and outdoors. The aim of this review was to assess the impact of waterpipe smoke on the oral and respiratory system (oral cavity and pulmonary tissues). A number of studies have shown that periodontal health status is compromised in waterpipe smokers compared with non-smokers. Some studies have associated WS with oral premalignant and malignant lesions; however, due to the poor quality of these studies, the presented outcomes should be interpreted with caution. Although cigarette smoking has been considered as a potential risk factor for dental caries; there are no studies in indexed literature that have shown an association to exist between dental caries and WS. Inhaled waterpipe smoke imposes oxidative

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stress and inflammatory responses, and compromises the ventilatory capacity of the lungs and may lead to an increased risk of decline in lung function. WS may cause oral and pulmonary diseases, such as periodontal disease and chronic obstructive airway disease, respectively. The association between WS and development of dental caries and oral pre-cancer and their relationships with chronic airways disease requires investigations. This review discusses the current evidence of waterpipe smoke effects on the oral health and respiratory system based on basic and clinical science, and provides future directions for research and regulatory science on how WS can affect the oral cavity and the respiratory/pulmonary system.

Keywords

Dental; Hookah; Narghile; Oral; Periodontal; Pulmonary; Smoking Waterpipe; Cancer; COPD

INTRODUCTION

Waterpipe, also known as hookah, narghile or narghila, shisha or sheesha, and hubbly-bubbly, is a tobacco-smoking device. In this form of tobacco smoking, charcoal-heated air is passed through a perforated aluminium foil and across flavored tobacco to become smoke that bubbles through water before being inhaled. Nearly 100 million people use waterpipe on a daily basis (Wolfram et al., 2003); and this form of smoking causes approximately 5 million deaths per annum (Neergaard et al., 2007). WS is a cultural custom in many Middle-Eastern countries including Bahrain, Egypt, Jordan, Qatar, Saudi Arabia, Syria, Turkey, Lebanon, and the United Arab Emirates (Natto, 2005, Moh'd Al-Mulla et al., 2008, Maziak et al., 2009, Borgan et al., 2014, Jaghbir et al., 2014, Almutairi, 2015, Maziak et al., 2015a, Javed et al., 2016a); However, this form of tobacco smoking has gained popularity in many other countries including Canada, Denmark, Greece, India, Pakistan, Malaysia, Sweden, United Kingdom and the United States (U.S.) (Jensen et al., 2010, Kassim et al., 2014, Ramji et al., 2015, Hammal et al., 2016, Sidani et al., 2016). In the U.S., the Tobacco Products and Risk Perceptions Surveys of 2014 and 2015 found a prevalence of 15.8% of ever smoking waterpipe among adults (Majeed et al., 2017).

Waterpipe smoke contains toxins, such as carbon monoxide (CO), carcinogenic polycyclic aromatic volatile aldehydes and hydrocarbons, which are similar to the toxins found in cigarettes (Eissenberg & Shihadeh, 2009, Cobb et al., 2010, Cobb et al., 2011); however, waterpipe smoking (WS) is associated with nearly a 4-fold greater CO exposure and 56-fold greater inhaled smoke volume (Cobb et al., 2011). It has also been reported that levels of plasma nicotine concentration among individuals smoking waterpipe once daily are comparable to cigarette smokers who smoke up to 10 cigarettes a day (Maziak et al., 2004, Rastam et al., 2011). Moreover, waterpipe and cigarette smoking have been associated with the same health hazards, such as nicotine addiction and increased risk for a variety of oral and systemic diseases including periodontal disease and pulmonary disorders, respectively (Joseph et al., 2012, Radwan et al., 2013, Layoun et al., 2014, Javed et al., 2016a). In a retrospective study, Javed et al. (2016a) compared the clinical and radiographic periodontal status among habitual waterpipe smokers (WSS), cigarette smokers and never smokers (individuals who reported to have never consumed any form of tobacco product). The results

showed that numbers of missing teeth, plaque index (PI), clinical attachment loss (CAL), probing depth (PD) ≥ 4 mm, and marginal bone loss (MBL) around teeth were statistically significantly higher among WSS and cigarette smokers compared with non-smokers. Interestingly, the results showed no statistically significant difference in these periodontal inflammatory parameters among WSS and cigarette smokers (Javed et al., 2016a). Similar results were reported by Khemiss et al. (2016) on periodontal inflammatory parameters among WSS and cigarette smokers. Results of an experimental study by Walters et al. (2017) showed that light waterpipe usage is associated with epigenetic changes and related transcriptional modifications in the investigated the effect of WS on DNA methylation of the small airway epithelium; a pathologic characteristic also manifested in cigarette smokers (Buro-Auriemma et al., 2013). To date, 300 chemical compounds have been identified in inhaled waterpipe tobacco and smoke out of which, 82 chemicals have been labelled as "toxicants" (Shihadeh and Saleh, 2005, Shihadeh et al., 2015). Examples of toxicants identified in waterpipe smoke include polyaromatic hydrocarbons (such as acenaphtylene, naphthalene and pyrene), heterocyclic compounds, carbonylic compounds (such as formaldehyde and aldehyde) and volatile organic compounds (including benzene, isoprene and styrene) (Shihadeh et al., 2015). Aside from high concentrations of tar, nicotine, carbon monoxide, other chemicals include carbonylic compounds in micrograms, such as formaldehyde, acetaldehyde, priopionaldehyde, butyraldehyde, nitosamines (N-nitrosanatabine, N′-nitrosonornicotine, N-nitrosoanabasine, polyaromatic hydrocarbons (naphthalene, acenaphtylene, fluoranthene, pyrene, heavy metals (arsenic, beryllium, lead, copper, zinc, lead, cobalt, beryllium, chromium), metal nanoparticles, phenolic compounds (catechol, resorcinol, hydroquinone, and flavoring chemicals (base propylene glycol, glycerol, vanillin, cinnamaldehyde), and free radicals which induce oral and pulmonary toxicity (Shihadeh et al., 2012). Most of these toxicants are present in cigarette smoke and have been proven to cause oral and systemic diseases, including periodontal diseases and pulmonary disorders. Since one session of waterpipe tobacco smoke inhalation is equivalent to smoking up to 10 cigarettes (Maziak et al., 2004, Rastam et al., 2011); and that WS jeopardizes oral and pulmonary health in a manner similar to conventional cigarette smoking (Buro-Auriemma et al., 2013, Javed et al., 2016a, Walters et al., 2017), it is thus hypothesized that the oral and pulmonary health statuses are compromised in WSS compared with non-smokers. Further, several studies are available on the magnitude of association between cigarette smoking and oral diseases; however, only a limited number of studies have assessed the relationship between oral inflammatory conditions (such as periodontal disease and oral cancer) among WSS. To our knowledge from indexed literature, there are no studies that have assessed the dental caries status among WSS and non-smokers. In the present study, we postulated that WSS are more susceptible to dental caries compared with non-smokers. Certainly, this hypothesis is based on the premise that smokers are prone for oral and pulmonary diseases, and we envisage similar damaging effects by WS. Overall, the aim of the present literature review was to assess the impact of waterpipe (narghile) smoking and its flavorings on oral and pulmonary tissues (oral respiratory systems).

Flavored tobacco/molasses used in waterpipe

The introduction of flavorings in tobacco (such as candy, apple, strawberry, cinnamon, grape, melon, mint, cherry, chocolate, coconut, licorice, cappuccino, spices including herbal

compounds, watermelon and alcoholic beverages, such as pina colada) spurred the popularity of WS and also tempted never-smokers to start smoking (Schubert et al. 2013 Jawad and Millett, 2014, Corey et al. 2016, Cornacchione et al. 2016). There is growing evidence that flavored tobacco products have a unique appeal and may attract young users and serve as starter products to regular tobacco use (Salloum et al., 2017, Villanti et al., 2017). A systematic review of qualitative studies examining perceptions of and experiences with flavored non-menthol tobacco products found that participants believed flavored tobacco products to be less harmful than cigarettes (Kowitt et al., 2017). However, a study using gas-chromatography–mass spectrometry identified 79 volatile flavoring compounds present in waterpipe tobacco containing high amounts of the fragrance benzyl alcohol as well as considerable levels of limonene, linalool and eugenol, all of which are known as being allergenic in human skin (Schubert et al., 2013). The toxicity of these flavorings on oral and pulmonary health including obstructive lung and allergic airway diseases requires investigations. Further, there are no studies that assessed the association between oral health status and herbal fillings (herbal molasses) in waterpipe, or on flavored tobacco/molasses used in waterpipe. Certainly, this is an emerging area of research as the new products are being launched every day. The effects of flavoring chemicals used in molasses on dental/oral and pulmonary health require investigations.

Impact of waterpipe smoking on oral tissues

Oral pre-cancer and cancer—Abundant evidence has shown that pre-malignant and malignant oral lesions (such as leukoplakia and oral squamous cell carcinoma, respectively) are more often manifested in cigarette smokers compared with non-smokers (Llewellyn et al., 2004, Nayak et al., 2012, Chher et al., 2016, Ramoa et al., 2017). Similar effects of oxidative stress and inflammation are seen in plasma and lungs of smokers and patients with chronic obstructive pulmonary disease (COPD) (Rahman et al., 1996, Rahman et al., 2002). The possibility that WS is a potential risk factor for pre-malignant and malignant oral lesions cannot be disregarded since the aldehyde compounds found in waterpipe smoke are known to be carcinogenic and toxic (Al Rashidi et al., 2008). Moreover, according to Daher et al. (2010), amounts of carcinogenic volatile aldehydes and carbon monoxide emitted in the side-stream are approximately 4 and 30 times higher, respectively during a single session of WS compared with smoking one cigarette. Furthermore, concentrations of tar and its constituents are higher in waterpipe smoke compared with cigarette smoke (Shihadeh, 2003, Dar-Odeh & Abu-Hammad, 2009, Primack et al., 2016), which may undergo Fenton Chemical reactions to generate deleterious hydroxyl radicals with heavy metals (iron). Studies have shown that WS is a risk factor for malignancies of systemic organs including bladder cancer (Bedwani et al., 1997, Letasiova et al., 2012), lung cancer (Chaouachi & Sajid, 2010, Aoun et al., 2013), esophageal cancer (Gunaid et al., 1995; Shakeri et al. 2012) and pancreatic cancer (Lo et al., 2007); however, upon an exhaustive literature search, 8 studies (El-Hakim & Uthman, 1999, Nasrollahzadeh et al., 2008, Feng et al., 2009, Malik et al., 2010, Khan et al., 2011, Dangi et al., 2012, Dar et al., 2012, Khlifi et al., 2013) that investigated the association between WS and oral cancer were identified (Table 1). The evidence from these studies (El-Hakim & Uthman, 1999, Nasrollahzadeh et al., 2008, Feng et al., 2009, Malik et al., 2010, Khan et al., 2011, Dangi et al., 2012, Dar et al., 2012, Khlifi et al., 2013) has shown that WS is possibly associated with a number of harmful health

consequences including head and neck cancer. Though high-quality studies with a large sample size that have shown an association to exist between WS and oral cancer are to date unavailable; the likelihood that WS is a potential risk factor for pre-malignant and malignant oral lesions cannot be overruled. However, more research is needed in this regard.

Periodontal disease—There is a dearth of studies that have assessed the influence of WS on oral mucosal and periodontal tissues (Ramoa et al., 2017). It is often perceived that WS is less hazardous to health compared with cigarette smoking as the tobacco smoke in the former gets filtered through water, which absorbs a considerable amount of nicotine (Jacob et al., 2013, Jukema et al., 2014, Maziak et al., 2015b); however, results by Javed et al. (2016a) showed that WS is as hazardous to periodontal health as traditional cigarette-smoking. In this study, the authors compared the clinical (PI, PD and CAL) and radiographic (MBL) parameters of periodontal inflammation among WSS, cigarette smokers, and non-smokers. Although the results showed that compared with non-smokers, the clinical and radiographic parameters of periodontal inflammation were poorer in WSS and cigarette smokers (Javed et al., 2016a); there was no statistically significant difference in these parameters among WSS and cigarette smokers (Javed et al., 2016a). Moreover, clinical results by Natto et al. (2005) showed that the prevalence of periodontal disease is significantly greater in WSS and cigarette smokers compared with non-smokers. This study (Natto et al., 2005) concluded that the impact of smoking waterpipe towards periodontal destruction was similar to that of cigarette smoking. Similar results have been reported by other studies (Baljoon et al., 2005, Natto, 2005) (Table 2).

Association with dental caries—Dental caries is a disease of the mineralized tissues of teeth (enamel, dentin and cementum) caused by the action of cariogenic bacteria (such as streptococci and lactobacilli species) on fermentable carbohydrates, which if left uncontrolled/untreated may lead to the demineralization of these tissues and disintegration of their organic matrix (Javed et al., 2016b). A number of studies have reported that tobacco smoking is a risk factor for dental caries (particularly root surface caries) (Sugihara et al., 2010, Bharateesh & Kokila, 2014, Christensen et al., 2015, Edman et al., 2016). One explanation is that since scores of PI, CAL and MBL around teeth are significantly higher in cigarette smokers than non-smokers, the exposed root surfaces are predisposed to caries (Javed et al., 2007, Javed et al., 2016a). To date, there are no studies in indexed literature that have assessed the dental caries status among WSS. A similar mechanism may be possible for WSS rendering susceptible to infections. However, since high scores of PI and CAL have been in WSS compared with non-smokers (Javed et al., 2016a); it is hypothesized that WSS are more susceptible to develop dental caries (most probably root caries) than non-smokers (see above sections). Further studies are required to test this hypothesis.

Impact of waterpipe smoking on pulmonary tissues

According to Strulovici-Barel et al. (2016), compared with non-smokers, WSS exhibit the following characteristics: (a) more often coughing with sputum expectoration; (b) lower lung diffusing capacity; (c) abnormal epithelial lining fluid metabolome profile; (d) reduced amounts of small airway epithelia ciliated and basal cells; and (e) raised levels of apoptotic endothelial cell microparticles. Nearly 3 decades ago, in a study from Saudi Arabia, Al-

Fayez et al. (1988) reported that WS is associated with a suppressed pulmonary function, which may lead to an increased risk of COPD. The authors also emphasized that WS is as hazardous to health as cigarette smoking and jeopardizes the ventilatory capacity of the lungs in WSS (Al-Fayez et al., 1988). Similarly, tobacco smoking has been associated with oxidative stress and inflammatory responses in the pathogenesis of COPD (Rahman et al., 1996, Rahman et al., 2002). Walters et al. (2017) investigated the effect of WS on DNA methylation of small airway epithelium. The results showed that waterpipe usage at least 3 times a week is associated with epigenetic changes and related transcriptional modifications in small airway epithelial cells (Walters et al., 2017), a pathologic characteristic also manifested in cigarette smokers (Buro-Auriemma et al., 2013). Waterpipe smoke reduces the proliferation of alveolar epithelial cells, causes their cell cycle arrest and increases their doubling time (Shihadeh et al., 2014), which may be associated with increased oxidative stress. In a recent experimental study on mice, chronic exposure to waterpipe smoke was associated with a statistically significant increase in the number of airway inflammatory cells (Al-Sawalha et al., 2017). In another histological study on mice, Charab et al. (2016) assessed the association between waterpipe smoke exposure and oxidative stress in lungs. Mice in the test-group were exposed to waterpipe smoke 4 times every other day for within 8 successive days and in the control-group, the mice received no exposure. The results showed that lipid peroxidation markers malondialdehyde and nitric oxide levels were statistically significantly higher in the lungs and liver of mice in the test-group compared with mice in the control-group (Charab et al., 2016). The study concluded that waterpipe smoke induces oxidative stress in the lungs (Charab et al., 2016). Moreover, it has been shown *in-vitro* that waterpipe smoke (a) impairs endothelial vasodilatory function and repair mechanisms, (b) increases the transcriptional expression of matrix metalloproteinase (MMP)-2 and MMP-9 and an immune response regulator, Toll Like Receptor-4 and (c) contributes in the pathogenesis of COPD by inducing inflammation and impairing cellular growth (Rammah et al., 2012, Shihadeh et al., 2014). Waterpipe smoke inhalation has also been associated with elevation in the total white blood cell count, platelet activation, and increased expression of proinflammatory cytokines (such as interleukin-6 and tumor necrosis factor-alpha) in the bronchoalveolar lavage fluid (Khabour et al., 2012). Furthermore, from a clinical perspective, habitual WS has been associated with medical conditions such as tachycardia, hypertension, and compromised pulmonary function conditions and health consequences including COPD, bronchitis and oral and lung cancer (Haddad et al., 2016, Waziry et al., 2016, Montazeri et al., 2017). WS has also been associated with low birth weight, metabolic syndrome and mental illnesses including schizophrenia, major depressive disorder and bipolar affective disorder (Hamadeh et al., 2016).

Although WS has adverse effects on pulmonary function tests (such as vital capacity, submaximal aerobic capacity and total lung capacity) (Ben Saad et al., 2013, Ben Saad et al., 2014); these negative effects have been reported to be more intense in cigarette smoking than WS (Ben Saad et al., 2013). Nevertheless, based on this, it is imprudent to consider WS as a “non-injurious” form of smoking. It is pertinent to mention that children exposed to waterpipe smoke through the environment may also demonstrate variations in their normal pulmonary function. Interestingly, results from a study from Syria showed an increased prevalence of nocturnal coughing and wheezing among children exposed to waterpipe

smoke by their parents as compared to children not exposed to environmental tobacco smoke (Mohammad et al., 2014) (Table 3). Recent results from an experimental study on a mouse model showed an association between waterpipe tobacco smoke inhalation and airway inflammation (Al-Sawalha et al., 2017). WS may affect the respiratory system and the oral cavity increasing their susceptibility to infections by bacteria and viruses. Similarly, the biochemical and molecular mechanisms of waterpipe and its flavoring toxicity in users must be studied for biomarkers of toxicity (Table 4) (Rahman & Biswas, 2004), and progression of the disease so as to provide the mechanistic insights for therapeutic interventions. Further studies are required to assess the biomarkers of inflammation in the oral/periodontal tissues among WSS. The deleterious effects of WS on pulmonary health are summarized in Figure 1.

CONCLUSIONS AND FUTURE DIRECTIONS

There is sufficient evidence to confirm that WS compromises pulmonary tissues and chronic exposure to waterpipe smoke may expose its consumers to respiratory diseases. Although, there is a dearth of studies assessing the oral health status among WSS; there is a possibility that there is an increased prevalence of oral inflammatory conditions (including periodontal diseases and oral cancer) among WSS compared with non-smokers. Future studies will be directed to determine the prevalence of waterpipe (or Hookah) smoking use, and to assess the periodontal and pulmonary health status in a population by using a self-administered survey. Such cross-sectional and longitudinal studies will also help determine a possible relationship between periodontal – pulmonary diseases and waterpipe use in single or dual/poly-products (smokers and waterpipe users).

WS may cause oral and pulmonary diseases, such as periodontal disease and chronic obstructive airway disease, respectively. The association between WS and development of dental caries and oral pre-cancer and their relationships with chronic airways disease requires further investigations. Further research on WS and its flavoring detrimental effects on the oral cavity and the respiratory system based on basic and clinical science, will provide toxicological mechanisms of oral and pulmonary diseases which would be important for therapeutic targets/devising agents and tobacco regulatory science.

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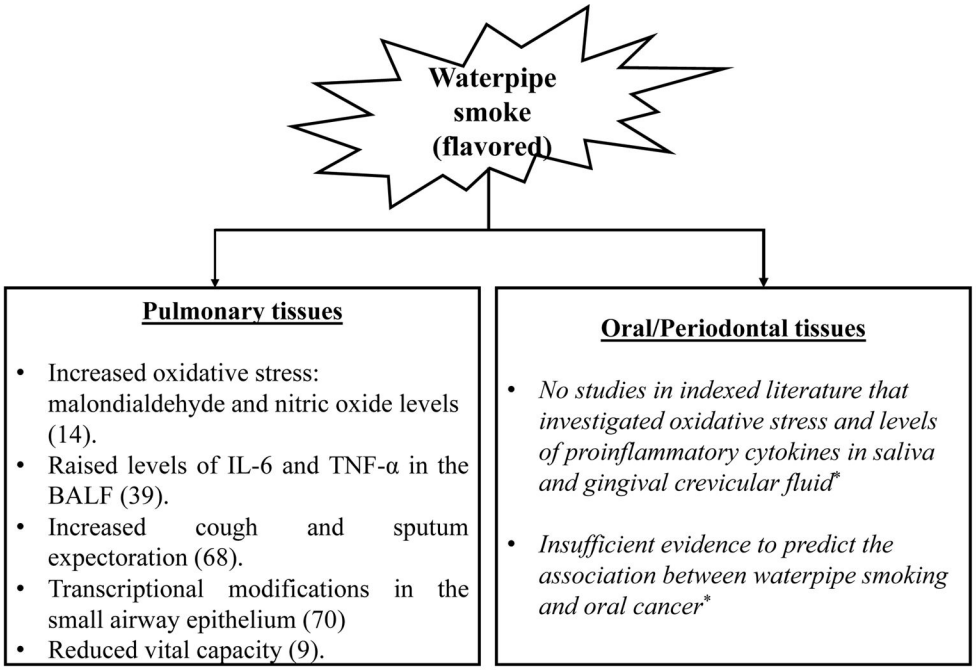

Figure 1. Summary of the impact of waterpipe smoke inhalation of pulmonary and oral tissues

Figure showing various markers of oxidative stress and inflammation by waterpipe smoking in human biological fluids including bronchalveolar lavage fluid (BALF) as well as pathophysiological responses. IL: Interleukin; TNF-α: Tumor necrosis factor alpha

*Further studies are needed to assess the biomarkers of inflammation in the oral/periodontal tissues among waterpipe smokers

Table 1

Studies assessing the association between waterpipe smoking and oral cancer

Authors	Study design	Number of subjects/patients	Duration of WS	Health outcome	Results
El-Hakim and Uthman (1999)	Case-report	3	Case-1: 4 years Case 2: 5 years Case 3: 20 years	Carcinoma of the oral mucosa or lip	There might be an association between WS and oral SCC.
Nasrollahzadeh et al. (2008)	Case-control/Questionnaire	WSS: 20 individuals NS: 23 individuals	≤ 19 years: 15 individuals >19 years: 5 individuals	esophageal SSC	WS was associated with an increased risk of esophageal SSC.
Khan et al. (2011)	Case-control/Survey	100 esophageal SSC patients 100 healthy controls	NA	esophageal SSC	WS was associated with an increased risk of esophageal SSC.
Dangi et al. (2012)	Case-control/Survey	761 patients with oral SSC	NA	Oral SSC	WS was associated with an increased risk of oral cancer.
Feng et al. (2009)	Case-control	636 nasopharyngeal carcinoma patients 615 healthy controls	NA	Nasopharyngeal carcinoma	WS was not associated with an increased risk of oral cancer.
Khlifi et al. (2013)	Case-control	159 head and neck cancer patients 351 healthy controls	Over 1 year	Blood Chromium and Nickel content	Blood Chromium and Nickel concentrations were significantly higher in smokers than non-smokers.
Dar et al. (2012)	Case-control	702 patients with esophageal SSC 1,663 healthy controls	Up to 33 years=318 individuals 34–45 years=423 individuals Over 46 years=376 individuals	esophageal SSC	WS was associated with an increased risk of esophageal SSC.
Malik et al. (2010)	Case-control	135 patients with esophageal SSC 195 healthy controls	NA	esophageal SSC	WS was associated with an increased risk of esophageal SSC.

NA: Not available; SSC: Squamous cell carcinoma; WS: Waterpipe smoking; WSS: Waterpipe smokers

Table 2

Studies assessing the impact of waterpipe smoking on periodontal tissues

Authors et al.	Study design	Participants	Parameters assessed	Conclusion
Javed et al. (2016a)	Cross-sectional	WS and NS	PI, CAL, PD, MT and MBL	WS is associated with a poorer periodontal health status.
Natto SB (2005)	Cross-sectional	WS and NS	PI, GI, MBL and PD	WS is associated with a poorer periodontal health status.
Khemiss et al. (2016)	Cross-sectional	WS and NS	MBL	WS is associated with a poorer periodontal health status.
Natto et al. (2005)	Cross-sectional	WS and NS	PI, GI and PD	WS is associated with a poorer periodontal health status.
Baljoon et al. (2005)	Cross-sectional	WS and NS	MBL	WS is associated with a poorer periodontal health status.

CAL: Clinical attachment loss; GI: Gingival index; PD: Probing depth; PI: Plaque index; MBL: Marginal bone loss; MT: Missing teeth; NS Never smokers; WS: Waterpipe smoking; WSS: Waterpipe Smokers

Table 3

Studies assessing the impact of waterpipe smoking (WS) on pulmonary tissues

Authors et al.	Study design	Participants/Subjects	Parameters assessed	Conclusion
Walters et al. (2017)	Experimental	Waterpipe smokers and non-smokers	Small airway epithelial cell DNA methylation	WS induces epigenetic changes and related transcriptional modifications.
Aoun et al. (2013)	Case-control	Lung cancer patients Healthy individuals	Health questionnaire	WS significantly correlated with lung cancer.
Strulovici-Barel et al (2016)	Case-control	Waterpipe smokers Non-smokers	Cough and sputum scores, lung function, small airway epithelial cells, plasma apoptotic endothelial cell microparticles	WS increases cough and sputum scores, lung function, small airway epithelium, plasma apoptotic endothelial cell microparticles.
Al-Sawalha et al. (2017)	Experimental	Mice exposed to waterpipe smoke Control mice (no exposure)	Bronchoalveolar lavage fluid	WS augments airway inflammation by increasing the number of eosinophils, neutrophils, macrophages and lymphocytes in the bronchoalveolar lavage fluid.
Ben Saad et al. (2013)	Case-control	Waterpipe smokers Cigarette smokers	Pulmonary function tests	Forced expiratory volume and forced vital capacity are compromised to a significantly greater extent in cigarette smokers than waterpipe smokers.

Table 4

Biomarkers and targets for periodontal and lung diseases by waterpipe smoke

Biomarkers	**Targets**
Oxidative stress	Lipid peroxidation products 4-hydroxy-2-nonenal, malondialdehyde, F_2-isoprostanes
Inflammatory responses (cytokines and prostaglandins)	NF-kappa B, Toll like receptors, NLRP3 inflammasome IL-6, IL-8, TNF-alpha
Exosomes/Microparticles	Distinct micro-vesicles
Innate host defense	RAGE receptors (S100A8 and S100A9) Advanced glycation end products Histone deacetylases (HDACs)
DNA methylation/epigenetic modifications	Differential
Proteases	Matrix metalloproteases (MMP-2, MMP-9)
Growth factors and proliferation of cells	VEGF, FGF, fibroblast growth factor (FGF), PDGF, TGF-β
Clinical parameters	PI, PD and CAL Pulmonary function (FEV1, FVC, and ratio)