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Review article

Waterpipe (shisha, hookah) smoking, oxidative stress and hidden disease potential

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ABSTRACT

Due to the abundant research on the harmful effects of cigarette smoking and the strict regulations enacted by many health authorities, many smokers are seeking for safer and more acceptable tobacco forms. Waterpipe (also known as shisha or hookah) use has increased dramatically during the past decade, mostly due to its improved taste, lack of regulations and social acceptability as a safer option than cigarettes. However, recent clinical and experimental studies indicate that waterpipe use is as, or even more, harmful than cigarettes. Although they differ in the method of consumption, waterpipe tobacco has similar deleterious constituents found in cigarettes but are generated at greater amounts. These constituents are known to induce oxidative stress and inflammation, the major underlying mechanisms of a wide array of chronic pathological conditions. We review the relationship between waterpipe tobacco use and oxidative stress and the disease potential of waterpipe use.

1. Introduction

It is estimated that 1.1 billion people use tobacco products worldwide, with cigarettes being the most favored product (82%) [1]. The World Health Organization (WHO) estimates that nearly 6 million people die from tobacco-related incidents yearly and predicts that more than 1 billion will die if current trends in use persist [1]. Several studies report that cigarette smoking is related to an array of illnesses including cardiovascular disease and cancer, the top two leading causes for premature death globally [2]. The American Heart Association (AHA) have set many tobacco control interventions and policies to mitigate the use of cigarettes and e-cigarettes [3]. However, the increasing trend of waterpipe tobacco smoking is yet to be addressed. Although ambiguous in origin, waterpipe (hookah, shisha) used to be traded by India and China throughout Asia and Africa in the sixteenth century [4]. The waterpipe was intended to reduce the harm of conventional tobacco smoking (since the smoke initially passes through a receptacle of water), a belief that is still rampant amongst waterpipe users today [5]. The waterpipe apparatus includes a tobacco head, body, water bowl, hose and a mouthpiece. Briefly, smoke passes through holes in the aluminum foil covering the tobacco head that has burning coal on top; the smoke then passes through the central conduit submerged in the water bowl before reaching the mouthpiece from where it gets inhaled.

The growing epidemic of waterpipe smoking, especially in the Eastern Mediterranean region, is attributable to several factors including: i) misleading marketing strategies promoting flavored waterpipe tobacco smoking as a palatable and safer alternative to cigarettes and claims of having less nicotine and tar, ii) social acceptability in households, coffee shops and restaurants, iii) influence of social media, and iv) lack of waterpipe-specific policy and regulations [5]. Regular and occasional use by adults reached 7.25% in the Eastern Mediterranean and 3.8% in the Americas, while recent use (past 30 days) by youths is estimated at 10.6% in Europe, 10.3% in the Eastern Mediterranean and 6.8% in the Americas [6]. According to the Global Youth Tobacco Survey, the use of tobacco products other than cigarettes by 13–15 years old children increased in 34 of 100 sites surveyed. This increase is mainly attributed to increased waterpipe use [7]. Importantly, waterpipe smoking can also increase the rate of cigarette smoking [8].

The increased prevalence of waterpipe smoking prompted more research to examine its association with chronic conditions and end organ damage. It is crucial to address the underlying mechanisms of disease caused by waterpipe smoke, such as oxidative stress. In this minireview, we focus on the strong association between waterpipe tobacco and its constituents and oxidative stress.

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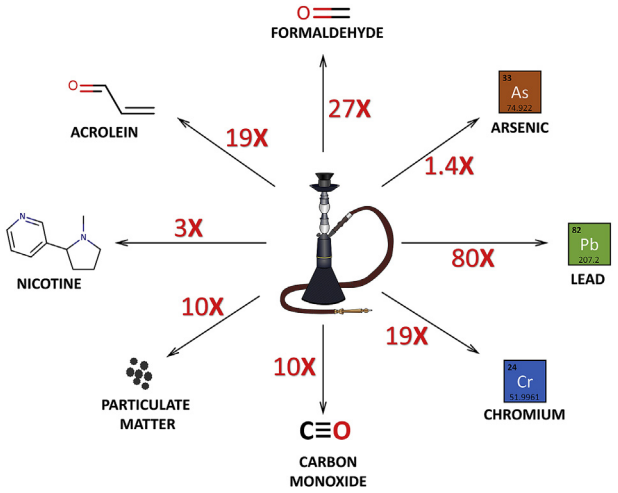

Fig. 1. Relative amounts of harmful substances in one session of waterpipe tobacco smoke (8–12 g) versus smoking a single cigarette (1 g of tobacco).

2. Waterpipe constituents

The types of Harmful and Potentially Harmful Constituents (HPHCs) in waterpipe tobacco are quite similar to those in cigarette tobacco, with some differences in the combustion mode, temperature at which the tobacco burns and smoke volume delivered [9]. In addition, the waterpipe is not readily accessible or easily carried and each waterpipe smoking session lasts longer. The main HPHCs are carbon monoxide (CO), nicotine, particulate matter (PM), volatile organic chemicals (VOCs), acrolein, arsenic and heavy metals. A comparison of the fold differences of some HPHCs in smoking one cigarette (1 g of tobacco) versus one session of waterpipe (8–12 g of tobacco) is shown in Fig. 1 [10–12]. The plasma levels of nicotine after one session of waterpipe smoking are estimated to be equivalent to smoking 2–3 cigarettes [13]. Although the size of PM delivered during waterpipe smoking is smaller than found in cigarettes (0.04–0.15 μm vs. 0.15–0.5 μm), the number of PM delivered in one waterpipe breath (1L) can reach up to 70×10^9 particles when compared to one breath (45 ml) of cigarette (9.2×10^9 particles) [10]. Evidently, a 1-h session of waterpipe smoking (around 100 puffs) can generate up to 10-times the amount of PM inhaled in comparison to smoking one cigarette (10 puffs) [14]. Waterpipe use also generates greater amounts of CO, mainly because of the use of charcoal; the CO emitted by waterpipes is reduced by 90% when charcoal is substituted with an electric heater [15]. The exhaled CO after a waterpipe session is estimated to be higher than the amount exhaled after smoking an entire pack of cigarettes [16]. Waterpipe use can also produce a large number of VOCs. Using a standardized smoking machine protocol, one session of waterpipe smoking generated increases in formaldehyde (27-fold), acrolein (19-fold), methacrolein (4-fold) and propionaldehyde (9-fold) [17]. The source of heavy metals such as lead (Pb) and chromium (Cr) is thought to be the charcoal used for waterpipe smoke [18].

3. Waterpipe constituents and oxidative stress

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity. Although ROS are crucial for signaling in many pathways, excessive amounts can oxidize proteins, lipids and DNA, events that are implicated in several pathological conditions [19]. Waterpipe tobacco constituents induce oxidative stress via different mechanisms as shown in Fig. 2.

Although the pathological effects of nicotine occur mostly through receptor activation and catecholamine release, several studies report that cellular damage to nicotine-dependent oxidative stress in various experimental models occurs either by enhancing ROS production or impairing antioxidant capacity. Treatment of human endothelial cells exposed to nicotine with *N*-acetyl-cysteine prevented endothelial cell inflammation and death [20]. Furthermore, nicotine treated mice have increased renal oxidative stress markers, increased expression of the pro-oxidant SHC-transforming protein (p66Shc), and decreased expression of the antioxidant SOD [21].

Waterpipe tobacco is a major source of PM, which promotes oxidative stress and inflammation. A 45-min waterpipe session can produce up to 802 mg of nicotine-free dry particulate matter (TAR) [8]. Moreover, a study of 50 waterpipe coffee shops showed a higher average dust particulate matter with a hazard quotient (HQ) > 1, which represents a very high risk for human health [22]. The increases in superoxide anion ($O_2^{\bullet -}$) production in rats exposed to $PM_{2.5}$ for 10 weeks was inhibited by apocynin, implicating NADPH oxidase as a major source of ROS [23]. Exposure to $PM_{2.5}$ also increases the expression of inducible nitric oxide synthase (iNOS), another important source of ROS [24]. A recent review discusses in detail the role of PM in inducing oxidative stress and causing cellular damage, and the relationship between ROS and inflammation and endoplasmic reticulum (ER) stress [25].

The amount of CO inhaled in one session of waterpipe smoking is substantial. CO is readily absorbed in the lungs and can form a tight but reversible bond with hemoglobin to cause tissue hypoxia. The affinity of CO for hemoglobin and myoglobin is 250 and 40 times greater respectively than for oxygen [26]. Once CO is eliminated, tissue oxygen reperfusion occurs and produces a burst of ROS from many sources such as xanthine oxidase, NADPH oxidases and mitochondria [27]. Normal and pregnant rats exposed to high levels of CO had increased production of ROS such as hydroxyl anion ($^{\bullet}OH$) in the cortex, globus pallidus, cerebellum and Purkinje cells [28,29], while CO poisoning in rats increased xanthine oxidase activity and lipid peroxidation in brain microvasculature [30].

Waterpipe is also a source of heavy metals such as Pb and Cr. Pb accumulation inhibits the aminolevulinic acid dehydrase (ALAD) enzyme and thus leads to the accumulation of aminolevulinic acid (ALA), which then undergoes enolization at physiologic pH and autoxidizes to produce $O_2^{\bullet -}$ [31]. Pb also has high affinity for sulfhydryl (SH) groups that enables it to inhibit antioxidant enzymes such as SOD, catalase (CAT) and glutathione peroxidase (GPx) [32]. Moreover, arsenic can increase the production of peroxyl radicals, $O_2^{\bullet -}$, $^{\bullet}OH$ and hydrogen peroxide (H_2O_2) and induce oxidative stress by increasing the activity NAPDH oxidases while also decreasing the antioxidant capacity [33].

VOCs such as acrolein and formaldehyde are abundant during waterpipe smoking. Acrolein has been extensively studied as a toxic unsaturated aldehyde that can adduct proteins and DNA, and induce oxidative stress and inflammation. Acrolein decreases antioxidant enzyme levels and inhibits the translocation of Nrf2 *in vitro* and *in vivo*. Thus, it can promote ROS production, which in turn oxidizes lipids and so produces more acrolein [34]. Acrolein also triggers or suppresses immune response depending on exposure and dose. For instance, acute and high dose exposures to acrolein suppresses immune response while chronic exposure with low doses enhances inflammatory response [34], as is the case for repetitive waterpipe smoking.

Constituents in waterpipe tobacco induce oxidative stress and inflammation. Although scarce, experimental and clinical studies on waterpipe use provide evidence of increases in oxidative stress, and the main findings of some recent clinical studies are summarized in Table 1.

Mice exposed to waterpipe smoke for 30 min a day for 5 days have increases in cardiac levels of lipid peroxidation, interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α) [35]. Another study in rats exposed to waterpipe smoke 1 h a day for a month showed reduced hippocampal activity of SOD, GPx and CAT. Interestingly, maternal exposure to waterpipe smoke also induces oxidative stress in the offspring. In a series of studies, Al-Sawalha et al. reported that prenatal exposure to

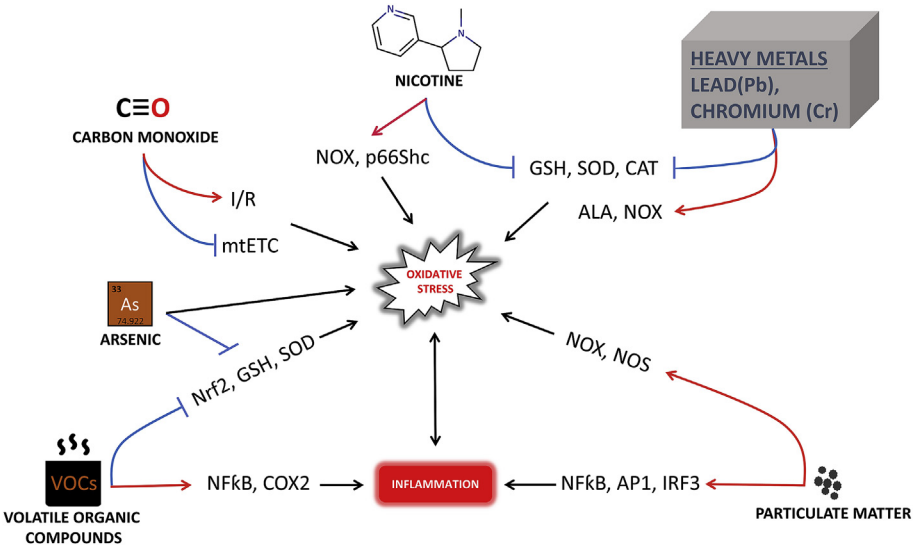

Fig. 2. Potential pathways involved in promoting oxidative stress and inflammation caused by waterpipe tobacco smoke constituents.
Abbreviations: ALA: aminolevulinic acid, AP1: activator protein 1, CAT: catalase, COX2: cyclooxygenase 2, GSH: glutathione, I/R: ischemia/reperfusion, IRF3: interferon regulatory factor 3, mtETC: mitochondrial electron transport chain, NFkB: nuclear factor kappa B, NOS: nitric oxide synthase, NOX: NADPH oxidase, Nrf2: Nuclear factor erythroid 2-related factor 2, p66Shc: SHC-transforming protein 1, SOD: superoxide dismutase.

Table 1
Evidence from clinical studies on the relationship between waterpipe tobacco smoking and oxidative stress.

Study	Exposure	Markers	Effect
Arazi et al., 2019 [39]	23 sedentary young women: i) 12 NS ii) 11 WPS	Salivary antioxidant status: 1) POX 2) DPPH	- Decrease in POX and DPPH activity in smokers after 1 h of exercise compared to non-smokers
Khan et al., 2019 [40]	Cohort I: 12 WPS and 25 NS Cohort II: 33 WPS and 22 NS	Oxidative stress: 8-isoprostane, myeloperoxidase, RAGE, MMP-9 Inflammation: IL-6, 8, 1B and TNF-α	- All markers were significantly higher in WPS from both cohorts
Alsaad et al., 2019 [41]	45 subjects: i) NS ii) CS iii) WPS	Oxidative stress: 8-OHdG DNA repair genes: OGG1 and XRCC1 Antioxidant genes: NQO1 and GSTA1	- Increased 8-OHdG levels - Decreased DNA repair and antioxidant gene expression in WPS
Yalcin et al., 2017 [42]	50 NS and 50 WPS	Total oxidative status Total antioxidant status Oxidative stress index	- All parameters were higher in WPS

Abbreviations: 8-OHdG: 8-hydroxy-2′-deoxyguanosine, CS: cigarette smokers, DPPH: 2,2-diphenyl-1-picrylhydrazyl, GSTA1: glutathione S-transferase A1, IL-6, 8 and 1B: interleukin-6, 8 and 1B, MMP-9: metalloproteinase 9, NQO1: NAD (P)H dehydrogenase [quinone] 1, NS: non-smokers, OGG1: oxoguanine glycosylase, POX: peroxidase, RAGE: receptor for advanced glycation end products, TNF- α: tumor necrosis factor- α, WPS: waterpipe smokers, XRCC1: x-ray repair cross-complementary protein 1.

waterpipe smoke increased plasma, renal and hippocampal levels of the lipid peroxidation marker thiobarbituric acid (TBARS) in adult offspring rats [36–38]. Clearly, the association between waterpipe smoke and oxidative stress is well established, strongly suggesting that waterpipe smoke causes irreversible chronic pathological conditions such as cardiovascular disease and cancer.

4. Pathological consequences of waterpipe use

Cardiovascular: The increasing trend in waterpipe smoking and use of e-cigarettes led to studies of their short- and long-term effects in animal models and in humans [43,44]. Similar to cigarette smoke, waterpipe smoke transiently increases heart rate and blood pressure immediately after exposure. However, long term use is associated with an increased risk of cardiovascular disease and mortality. Waterpipe users aged 40 years or older have a ~3-fold increase in the odds of having severe coronary artery stenosis [OR = 2.94; 95% CI 1.04–8.33] as well as coronary artery disease index (β = 7.835, p = 0.027) compared to non-smokers [45]. Heavy waterpipe smoking is associated heart disease prevalence in a study of 50, 045 residents of Golestan, Iran [OR = 3.75; 95% CI 1.52–9.22] [46]. Another study in Bangladesh reports that death due to ischemic heart disease was almost 2 fold higher in waterpipe smokers when compared to never users during a 7.6-year follow-up period [47].

Pulmonary: Waterpipe use also has detrimental effects on the pulmonary system. Chronic use significantly decreases functional parameters such forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), forced expiratory flow (FEF) and fractional exhaled nitric oxide (FeNO) [48]. The latter is mainly associated with decreased NO and its conversion to peroxynitrite (ONOO-) due to oxidative stress [49]. A systematic review indicates a positive association between waterpipe smoke and lung cancer [OR = 4.58; CI 95% 2.61–8.03] and esophageal cancer [OR = 3.63; 95% CI 1.39–9.44]. An extensive meta-analysis reports that waterpipe use is associated with chronic obstructive pulmonary disease [OR = 3.18; 95% CI 1.25–8.08], bronchitis [OR = 2.37; 95% CI 1.49–3.77], oral cancer [OR = 4.17; 95% CI 2.53–6.89], lung cancer [OR = 2.12; 95% CI 1.32–3.42], low birth weight [OR = 2.39; 95% CI 1.32–4.32], metabolic syndrome [OR = 1.95; 95% CI 1.25–2.45], cardiovascular disease [OR = 1.67; 95% CI 1.25–2.24], and mental health [OR = 2.4; 95% CI 1.2–2.8] [50].

Other: Waterpipe smoking has detrimental effects many biological systems. For example, waterpipe use can lead to cognitive deficits, as shown in a recent study where waterpipe use by school-aged youth (in 7th-10th grade) is associated with lower levels of brain-derived neurotrophic factor (BDNF), a protein that is important in the growth and differentiation of new neurons and survival of existing ones [51]. Several animal studies have shown protective effects of antioxidants use in lungs, heart, brain, kidney and liver against waterpipe smoke as summarized in Table 2. The use of antioxidants as a potential therapeutic intervention in waterpipe is hampered by their ineffectiveness of most anti-oxidants in human clinical trials [52,53].

Waterpipe smoke can also affect circadian molecular clock genes at a tissue level, which can lead to a circadian misalignment between central and peripheral oscillators and result in some pathological

Table 2
Antioxidant treatment outcomes in animals exposed to waterpipe tobacco smoke.

Study	Species	Exposure	Treatment	Parameters measured	Outcomes
Nemmar et al., 2019 [60]	C57BL/6 mice	WPS (30 min/d for 1 month	Gum arabica 15% w/v in drinking water	TNF-α 8-isoprostane DNA damage	In lungs: - Decreased all parameters - Inhibited Nf-ƙB translocation - Induced Nrf2 translocation
Nakhaee et la. 2019 [61]	Wistar rats	WPS for (30 min/day for 8 weeks)	Mild endurance swimming exercise (5 d/week, 20–60 min/day)	TNF-α Tissue lesions Heart contractility index SOD and GPx	In heart: - Decreased TNF-α levels - Improved cardiac contractility - Increased activity of SOD, GPX
Alzoubi et al., 2019 [62]	Wistar rats	WPS (1 h/day for 1 month)	Vitamin E (100 mg/kg/day for 1 month) oral gavage	Radial arms water maze CAT, GPx, GSH TBARS	In hippocampus: - Prevented memory impairment - Prevented decrease in CAT and GPx levels - no effect on TBARS
Alqudah et al., 2018 [63]	Wistar rats	WPS (1 h/day for 1 month)	Vitamin C (100 mg/kg/day for 1 month) oral gavage	Radial arms water maze GSH/GSSG GPX, CAT TBARS	In hippocampus: - Prevented memory impairment - Preserved the levels of GSH/GSSG, CAT, GPX - no effect on TBARS
Charab et al., 2018 [64]	Albino mice	WPS (15 min every other day within 8 days)	Selenium (0.59 or 1.78 μg/kg 15 min before WPS exposure	MDA GPx, CAT NO	In lung and liver: - Normalized CAT, GPx and NO levels - Decreased MDA levels

Abbreviations: *CAT:* catalase, GPx: glutathione peroxidase, *GSH:* glutathione, *GSSG:* glutathione disulfide, *MDA:* malondialdehyde, *NO:* nitric oxide, *SOD:* superoxide dismutase, *TBARS:* thiobarbituric acid, *TNF- α*: tumor necrosis factor- α, *WPS:* waterpipe smoke.

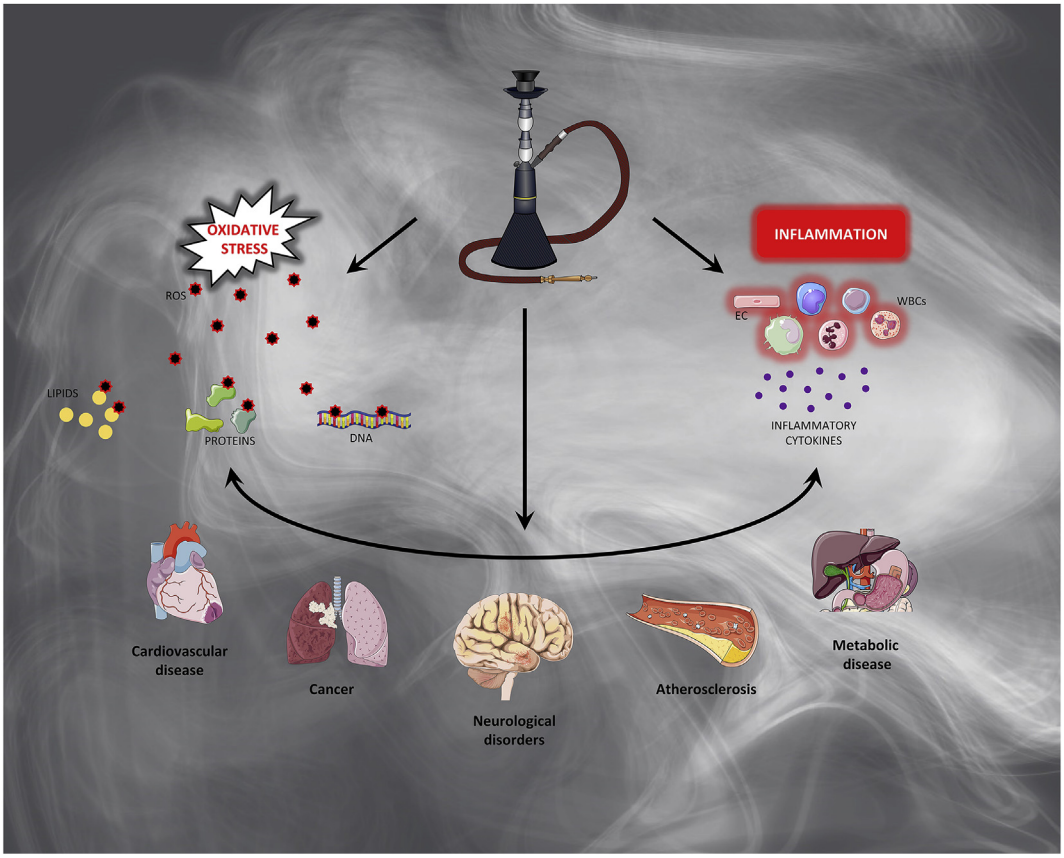

Fig. 3. Oxidative stress and inflammation resulting from waterpipe tobacco smoke may lead to a wide array of chronic conditions. EC: endothelial cells, ROS: reactive oxygen species, WBCs: white blood cells.

conditions. A recent study reported that 10 days of waterpipe smoke exposure altered the protein and gene expression of clock components (such as brain and muscle ARNT-Like 1 (BMAL1) and circadian locomotor output cycles protein kaput (CLOCK)) and clock-controlled output (period circadian regulator 2 (PER2) and nuclear receptor subfamily 1 group D member 1 (NR1D1 or REV-ERBα) in mouse lungs [54]. Changes in redox status (e.g. oxidative stress) attributed to environmental factors such as pollution, noise and mental stress can dysregulate circadian rhythm as recently reviewed [55]. Thus, an important consideration is that waterpipe smoking leads to oxidative stress which then circadian rhythms and possibly a cascade of associated events.

Emerging evidence indicates that exposure of human cells and cell cultures to waterpipe smoke can change the epigenetics, microbiome, transcriptome and secretome. Small airway epithelium extracted from 7 waterpipe smokers and 7 non-smokers for genome wide were compared for patterns of DNA methylation; there were 727 probe sets differentially methylated, which represented 673 unique genes in the two groups. Pathways associated with these epigenetic alterations were related to G-protein coupled receptor signaling, xenobiotic metabolism signalling and aryl hydrocarbon receptor signalling, all of which are related to smoking and lung disease [56]. The oral microbiome (overall structure and specific taxon abundances) were compared between smokers of different tobacco products (cigarettes, dokha and waterpipe) and non-smokers. Although the changes were not significant, waterpipe tobacco smoking caused alterations in the oral microbiome [57]. *In vitro*, whole-exome sequence analysis of cultured human oral keratinocytes treated with 0.5% of waterpipe tobacco extract for 8 months identified 521 somatic missense variants (corresponding to 389 genes) while RNA sequencing identified 247 differentially expresses genes when compared to parental cells. Pathway analysis revealed changes in interferon-signaling pathways and mitogen-activated protein kinase 1 (MAPK1) pathways which are also known to be associated with oral cancer [58]. Another study using the same exposure reported that a proteomic analysis of keratinocytes secrotome revealed that of the 1598 proteins identified, 218 proteins (such as aldo-keto reductase family 1-member C2 (AKR1C2), heat shock protein 105 kDa (HSPH1) and matrix metalloproteinase 9 (MMP9)) were differentially secreted in waterpipe tobacco extract treated cells [59]. These findings suggest that waterpipe smoking causes cellular changes at transcriptional, translational and epigenetic levels.

5. Conclusion and future directions

This review summarizes the evidence implicating oxidative stress as a key contributor to the pathology of waterpipe smoke (Fig. 3). Addiction and exposure to second-hand smoking are additional health and environmental hazards associated with waterpipe use. Importantly, environmental and lifestyle risk factors that result in oxidative stress can cause additional harms in smokers of waterpipe tobacco [65,66]. To that effect, carefully designed epidemiological studies (young vs old, male vs female, second-hand smoke, concurrent use of other addictive substances) are needed to assess the health risk of waterpipe use across all regions and cultures. Suggested strategies to mitigate the effects of waterpipe smoke include: i) developing culturally relevant cessation strategies, ii) spreading awareness through social media dispelling the fallacy that of waterpipe smoking is safer than cigarette smoking, iii) creating and implementing strict regulation policies on waterpipe tobacco in schools, public spaces, iv) more research focusing on elucidating underlying pathological mechanisms and intervention strategies.

A limitation of this review is the absence of studies examining specific molecular mechanisms underlying waterpipe tobacco smoking induced oxidative stress, even though much of the available studies focuses on oxidative stress markers and antioxidant treatment. Since the major constituents found in waterpipe tobacco are similar to cigarettes, it is tempting to suggest that t they share many mechanisms affecting the redox status of different biological systems [67,68], although there may be important differences related to modes of intake, disease pathologies etc.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2020.101455.

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