

## ORIGINAL INVESTIGATION

# Phenolic Compounds in Particles of Mainstream Waterpipe Smoke

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## ABSTRACT

**Introduction:** Waterpipe tobacco smoking has in recent years become a popular international phenomenon, particularly among youth. While it has been shown to deliver significant quantities of several carcinogenic and toxic substances, phenols, an important class of chemical compounds thought to promote DNA mutation and cardiovascular diseases, however, has not been studied. Due to the relatively low temperature characteristic of waterpipe tobacco during smoking (i.e., <450 °C), it was hypothesized that phenolic compounds, which form at approximately 300 °C, will be found in abundance in waterpipe smoke.

**Methods:** In this study, phenolic compounds in the particle phase of waterpipe mainstream smoke were quantified. Waterpipe and cigarette mainstream smoke generated using standard methods were collected on glass fiber pads and analyzed using gas chromatography/mass spectroscopy selected ion current profile chromatogram method for quantification.

**Results:** We found that relative to a single cigarette, a waterpipe delivers at least 3 times greater quantities of the 7 analyzed phenols (phenol, *o*-cresol, *m*-cresol, *p*-cresol, catechol, resorcinol, and hydroquinone). Moreover, phenol derivatives such as methylcatechol, and flavorings such as vanillin, ethyl vanillin, and benzyl alcohol were found in quantities up to 1,000 times greater than the amount measured in the smoke of a single cigarette.

**Conclusion:** The large quantities of phenols and phenol derivatives in waterpipe smoke add to the growing evidence that habitual waterpipe use may increase the risk of cancer and cardiovascular diseases.

## INTRODUCTION

Waterpipe tobacco smoking has in recent years become prevalent across the globe. A waterpipe consists of a head, body, water bowl, and corrugated hose. It is often smoked with a moist, sweetened, and flavored tobacco mixture known as ma'assel, with burning charcoal placed atop as a heat source. Thus, in addition to smoke constituents originating from the tobacco, waterpipe smoke also contains charcoal combustion emissions. While a common perception among users is that waterpipe is relatively safe, it has been shown to deliver to the user large quantities of polycyclic aromatic hydrocarbons, aldehydes, tar, nicotine, and carbon monoxide (Al Rashidi, Shihadeh, & Saliba, 2008; Sepetdjian, Shihadeh, & Saliba, 2008; Shihadeh & Saleh, 2005). Also, waterpipe smoke can be a major source of furans specially 5-(hydroxymethyl)-2-furaldehyde (Schubert, Bewersdorff, Luch, & Schulz, 2012).

Phenols are listed as priority pollutants by the U.S. Environmental Protection Agency due to their high toxicity

(Yan & Quan, 2009). In particular, polyphenolic compounds such as catechols and hydroquinones and their methyl derivatives that are present in tobacco smoke are important tumor promoters and provoke an increase in metastasis of lung cancer (Gopalakrishna, Chen, & Gundimeda, 1994; Hoffmann, Djordjevic, & Hoffmann, 1997). Other health impacts caused by phenolic compounds have been linked to genotoxic activities and cardiovascular effects (Fowles & Dybing, 2003; Harvey, Howe, Lynch, & Rees, 2005; Leanderson & Tagesson, 1990).

The generation of phenols in cigarette mainstream smoke is attributed to the distillation, depolymerization, and decomposition of tobacco components during pyrolysis. The precursors of catechol formation are the polyphenols such as quinic acid and quinic acid derivatives present in tobacco. Also, chlorogenic acid and lignin are considered precursors of hydroquinone formation at lower temperatures (<600 °C) (Czégény et al., 2009; Torikau, Uwano, Nakamori, Tarora, & Takahashi, 2005). McGrath, Brown, Meruva, and Chan (2009) showed that hydroquinone, catechol, and methyl derivatives of catechol are

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## Phenolic compounds

produced in highest amounts at tobacco pyrolysis temperatures  $\leq 350^\circ\text{C}$  due to their limited thermal stability at higher temperatures. Formation of other phenols such as cresols, phenol, and resorcinol is favored between 350 and  $600^\circ\text{C}$ . Hence, temperature is considered an essential factor for the formation and the decomposition of many toxins like phenolic compounds in the smoke. The temperature at which the tobacco is heated inside the head of the waterpipe reaches up to  $450^\circ\text{C}$  (Shihadeh 2003; Shihadeh & Saleh, 2005), whereas the burning temperatures of cigarette tobacco can reach up to  $950^\circ\text{C}$  (Czégény et al., 2009). Therefore, high levels of phenols and their derivatives are expected in the waterpipe smoke because the smoke is generated at optimal temperatures for phenols production.

Many analytic techniques were developed to determine phenols in cigarette smoke (Moldoveanu & Kiser, 2007). The most common techniques are high-performance liquid chromatography (HPLC) with ultra violet or fluorescence detection and capillary gas chromatography with mass spectrometry (GC-MS) (Moldoveanu & Kiser, 2007). In this study, the identification and quantification of phenolic compounds and their derivatives in the particle phase of the mainstream waterpipe smoke was realized using GC-MS selected ion current profile (GC-MS-SICP) chromatogram method after sample derivatization.

## EXPERIMENTAL

### Chemicals

A standard mixture of seven phenols (phenol, *o*-cresol, *m*-cresol, *p*-cresol, catechol, resorcinol, and hydroquinone) and a mixture of two deuterated phenols (phenol-d6 and 4-methylphenol-d8) at  $1000\ \mu\text{g/ml}$  each were purchased from Absolute Standards. Polystyrene divinylbenzene (PS-DVB) SPE cartridges (CHROMABOND®; EASY 200mg, 3 ml) were purchased from Sorbent Technology. The derivatizing reagent, bis(trimethylsilyl)-trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS) and HPLC-grade solvents of methanol, dichloromethane, and ethylacetate were purchased from Sigma-Aldrich.

### Smoke Generation and Collection

Mainstream waterpipe smoke was generated and collected in accordance with the Beirut method (Katurji, Daher, Sheheitli, Saleh, & Shihadeh, 2010; Shihadeh & Saleh, 2005) using Nakhla Double Apple (Egypt) waterpipe tobacco preparation and Three Kings (Holland) charcoal. During each machine smoking session, the smoke exiting the waterpipe mouthpiece was split into four parallel branches and each stream drawn through a 47-mm glass fiber filter pad (47 mm, Pall Gelman Type A/E). As in Shihadeh et al. (2012), filters were changed during a smoking session whenever the filter assembly flow friction coefficient exceeded a predetermined threshold; the threshold indicated a mass loading approaching 150 mg, the maximum allowed by smoking machine testing standard ISO 4387:1991. Three to four filter sets (i.e., 12–16 filters in total) were required during a smoking session. Additional details of the waterpipe smoking session and smoke sampling procedures can be found in Shihadeh et al. (2012). For each smoking session, all of the filters from one of the four parallel branches were analyzed for phenol content. The mass of consumed tobacco and charcoal was determined gravimetrically by comparing the

weight of each prior to and at the end of the smoking session. The waterpipe hoses used in this study were of leather construction and exhibited infiltration rates of 0.93–1.8 standard liters per minute (slpm) at a nominal waterpipe flow rate of 12.2 slpm as determined using the method described by Saleh and Shihadeh (2008).

Cigarette smoke was generated using the Federal Trade Commission protocol and trapped on glass fiber filters (47 mm, Pall Gelman Type A/E). Smoke from three cigarettes (Marlboro-KG) was drawn through each analyzed filter. The puff regimens and resulting tobacco, charcoal consumption, total particulate matter, and carbon monoxide amounts generated for waterpipe and cigarette smoke are provided in Table 1.

### Sample Preparation

Glass fiber filter pads of cigarette and waterpipe smoke were spiked with  $100\ \mu\text{g/ml}$  deuterated internal standards and extracted through mechanical shaking (IKA Vortex Genius 3) for 2 hr at room temperature with 20 ml of acidified water (0.1 M HCl with 0.1% ascorbic acid). Ascorbic acid was added to prevent any potential oxidation of phenols. Two and five milliliters of the respective cigarette and waterpipe resulting solutions were loaded on separate PS-DVB cartridges preconditioned with 10 ml of each: dichloromethane, methanol, and HCl (0.05 M). PS-DVB cartridges with polymeric materials are mainly used to concentrate phenols from water samples, have been shown to be more stable when compared to silica base sorbents in high acidic media (Rodríguez, Lompart, & Cela, 2000). After loading the samples, the cartridges were washed 3 times with 3 ml 1% acetic acid in order to eliminate interferences while retaining the phenolic compounds. Next, the cartridges were left to dry for 2 hr under vacuum. Phenol samples were eluted with 12 ml ethylacetate and the collected volume was reduced to approximately 150  $\mu\text{l}$  under a flow of nitrogen. The 100  $\mu\text{l}$  of the derivatizing agent BSTFA with 1% TMCS was added to the samples (Moldoveanu & Kiser, 2007). The vials were capped and heated at  $80^\circ\text{C}$  for 30 min to obtain the trimethylsilyl derivatives of phenols analyzed by GC-MS-SICP. The derivatization step was recommended by Mußmann, Levsen, and Radeck (1994) to avoid the broadening and tailing of chromatographic peaks otherwise

**Table 1.** Puff Parameters for Cigarette and Waterpipe Smoke Generation

Topography	Cigarette	Waterpipe
Tobacco product	Marlboro-KG Lebanon	Nakhla Double Apple
Number of puffs	8.86 ± 0.5	171
Total volume (L)	0.31 ± 0.01	90.30 ± 0.15
Flow rate (L/min)	1.01	12.19 ± 0.02
Puff duration (s)	2	2.6
Interpuff interval (s)	58	17
Tobacco consumed (g/session)	–	4.9 ± 0.3
Charcoal consumed (g/session)	–	7.4 ± 0.2
TPM (mg)	11 ± 2	1586.2 ± 202
Carbon monoxide (mg)	4.85 ± 0.8	186 ± 20.8

characteristic of phenols due to their high polarity. The GC-MS-SICP method ensures high selectivity even though standards of phenolic derivatives are not available.

### Detection and Calibration

Detection and quantification of the samples were done using derivatized standard mixtures injected on GC-MS in the full scan mode. Calibration curves were prepared using seven concentration ratios of phenol standards/deuterated phenol standards. Phenol standard concentrations ranging from 0.5 to 20 µg/ml were mixed with 2 µg/ml of deuterated phenol standard. The  $R^2$  ranged between 0.998 and 0.999. Blank filters were analyzed in parallel to assess the background level of phenols during sample preparation.

### Recovery and Limit of Detection

Percent recovery of phenols and deuterated standards were calculated by spiking glass fiber filters with 100 µl of phenols standard mixture at concentrations ranging from 0.5 to 20 µg/ml and 2 µg/ml for deuterated phenol standards. Standards were extracted and analyzed using the same procedure used for analyzing the cigarette and waterpipe samples. High recoveries

(81%–89%) for all tested concentrations were obtained for phenol, *o*-cresol, *m*-cresol, and *p*-cresol. Due to the unavailability of their respective deuterated compounds, lower recoveries (17%–43%) were found for catechol, resorcinol, and hydroquinone (Vaughan, Stanfill, Polzin, Ashley, & Watson, 2008). This could be attributed to the loss of these compounds during drying and evaporation steps. The limits of detection ranged between 0.23 and 0.30 µg and were calculated as 3 times the standard deviations of their lowest detected concentrations by GC-MS.

## RESULTS

As shown in Table 2, the yields of the seven phenols determined for cigarette mainstream smoke fall within the reported values (Baker, Massey, & Smith, 2004; Moldoveanu & Kiser, 2007; Vaughan et al., 2008), indicating the basic reliability of the method used in this study.

Derivatives of phenol and cresols such as dimethylphenols and ethylphenols ( $m/z = 194$ ) showed similar amounts in cigarette and waterpipe samples (Table 3; Figure 1a). However, three methylated-dihydroxybenzene compounds ( $m/z = 268$ )

**Table 2.** Mass (µg) of Phenols in Cigarette and Waterpipe Mainstream Smoke

Compound	Cigarette (current study)		Cigarette (previous studies)			Waterpipe (current study)	
	Average ( $n = 6$ ), µg/ cigarette	% RSD	Vaughan et al. (2008) <sup>a</sup> , µg/cigarette	Moldoveanu and Kiser (2007) <sup>b</sup> , µg/cigarette	Baker et al. (2004) <sup>c</sup> , µg/cigarette	Average ( $n = 12$ ), µg/ waterpipe	% RSD
Phenol	22.3	22	16.3	4.86–16.07	10.0–19.6	58.03	44
<i>o</i> -Cresol	5.79	21	4.9	1.23–3.70	2.81–4.75	4.409	61
<i>m</i> -Cresol	4.33	20	3.5	0.93–2.95	8.48–13.7 <sup>d</sup>	4.655	56
<i>p</i> -Cresol	10.1	21	9.1	2.12–6.97		5.375	55
Catechol	40.7	18	49.5	20–62.35	44.2–54.5	316.1	42
Resorcinol	0.79	15	1.7	0.72–1.81	<1.1	1.689	28
Hydroquinone	34.6	19	44.0	19.78–56.44	44.7–51.2	110.7	39

Note. RSD = Relative Standard Deviation.

<sup>a</sup>Microgram per cigarette phenols Marlboro brand, 35-ml puff volume, 2-s puff duration, 60-s puff interval.

<sup>b</sup>Microgram per cigarette phenols range in three common commercial cigarettes.

<sup>c</sup>Microgram per cigarette phenols range in cigarettes after adding a range of ingredients to the tobacco ( $n = 5$ ).

<sup>d</sup>Values of *m*- + *p*-cresols.

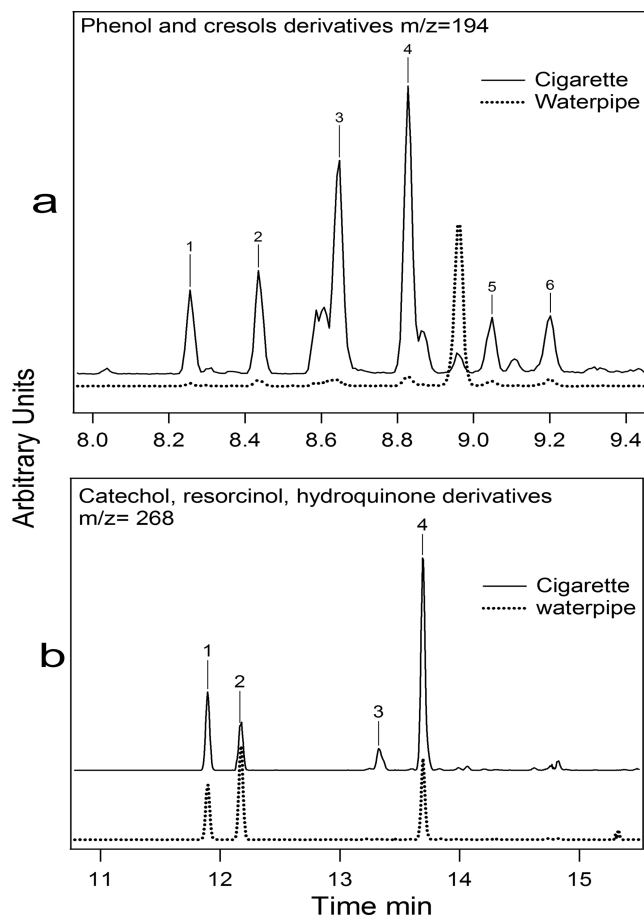
**Table 3.** List of Phenols Derivatives Identified in the Cigarette and Waterpipe Samples

Compound	Total amount of possible isomers, µg/cigarette ( $n = 6$ )			Total amount of possible isomers, µg/waterpipe ( $n = 12$ )		
	Average	SD	% RSD	Average	SD	% RSD
Derivatives of phenol and cresol <sup>a</sup> ( $m/z = 194$ )	7.6	1.4	18	6.000	3.686	61
Derivatives of catechol, resorcinol, and hydroquinone <sup>b</sup> ( $m/z = 268$ )	30	5.3	18	259.8	92.62	36
Vanillin ( $m/z = 194$ )	2.2	1.2	57	3192	1242	39
Ethyl vanillin ( $m/z = 194$ )	0.5	0.5	102	616.0	271.6	44
Benzyl alcohol ( $m/z = 165$ )	0.9	0.2	20	232.4	74.54	32

Note. RSD = Relative Standard Deviation.

<sup>a</sup>Possible isomers: 2-ethylphenol, 4-ethylphenol, 2,5-dimethylphenol, 3,5-dimethylphenol, 2,6-dimethylphenol, 2,3-dimethylphenol, 3,4-dimethylphenol.

<sup>b</sup>Possible isomers: 4-methylcatechol, 3-methylcatechol, 3-methylresorcinol, 2-methylresorcinol, methylhydroquinone.



**Figure 1.** Selected ion current profile chromatograms of phenol derivatives in cigarette and waterpipe smoke. According to the National Institute of Standards and Technology library, the numbers are assigned to (a) phenol and cresol derivatives, namely, **1**: 2-ethylphenol, **2**: 4-ethylphenol, **3**: 2,5-dimethylphenol, **4**: 3,5-dimethylphenol, **5**: 2,6-dimethylphenol, and **6**: 2,3-dimethylphenol and (b) catechol, resorcinol, and hydroquinone derivatives, namely, **1**: 4-methylcatechol, **2**: 3-methylcatechol, **3**: 2-methylresorcinol, and **4**: 2-methylhydroquinone.

were identified in waterpipe smoke compared to four such compounds in cigarette smoke (Figure 1b). The quantity of the methylated-dihydroxybenzene compounds identified in the waterpipe smoke was at least 8 times greater than that determined for cigarette smoke (Table 3). Dihydroxybenzene derivatives were quantified using the catechol calibration curve in absence of methylated-dihydroxybenzene standards.

In addition to phenols' derivatives, additives such as vanillin, ethyl vanillin, and benzyl alcohol show mass exceedance in waterpipe mainstream smoke that reached up to 1,000 times the amount calculated for the cigarette mainstream smoke (Table 3).

## DISCUSSION

In comparison to cigarette smoke, the total yield of phenolic compounds quantified for the first time in the waterpipe smoke was at least 3 times higher than that in mainstream cigarette smoke. Variations in phenols amount between different waterpipe smoking sessions ( $28 < \% \text{ Relative Standard Deviation} < 61$ ; Table 2) are attributed to differences in smoke production that result from natural variations in charcoal briquette

burning rates, and hand-packing of the tobacco mixture in the waterpipe head. These variations are also apparent in the amounts of total particulate matter produced per session (Table 1). Furthermore, knowing that more additives and flavors are added to the ma'assel tobacco in waterpipe than cigarettes, it is expected that additives such as sugars, cellulose, and polysaccharides present at such high quantities can lead to an increase in the toxicity of the waterpipe smoke. Toxicity could be ascribed to increase in the total particulate matter concentrations as well as the formation of more additive-related pyrolysis or combustion harmful products (i.e., formaldehyde) (Baker et al., 2004; Wertz, Kyriss, Paranjape, & Glantz, 2011; Xiaomin et al., 2012).

It is also noteworthy that though phenols are highly polar and soluble in water (high Henry's constants) (Feigenbrugel, Le Calvé, Mirabel, & Louis, 2004), and susceptible to be trapped in the water bubbler, they are apparently present in high enough quantities that there is still a lot left in the smoke reaching the mouthpiece. Therefore, the reported yields of phenols and their derivatives represent the lower limits of their actual values in the waterpipe smoke.

If reported phenol emissions are normalized by the volume of smoke inhaled or Total Particulate Matter (TPM) produced,



cigarette smoke appears more toxic than waterpipe smoke. In terms of physiological/clinical relevance vis-à-vis the human body's toxicant clearance mechanisms, however, an equally important measure could be the intake of phenols per hour of smoking, in which case the waterpipe smoking involves higher hourly phenol intake than cigarette smoking. After considering the various parameters that could be reported, phenol emissions per unit smoked would be the most relevant to the community. Those in need of toxicant concentrations per milliliter smoke or per milligram TPM can derive such values from the presented data.

## CONCLUSION

When heated or burned, tobacco ingredients such as cellulose, polyphenols, chlorogenic acid, and quercetin dehydrate generate phenols and their derivatives. In waterpipe smoking, the relatively low temperature of the burning tobacco mixture favors production and survival of phenol compounds; in this study we observed high yields of hydroquinone, catechol, and methyl derivatives of catechol. In particular, we found that the yields of the seven standard phenol compounds in mainstream waterpipe smoke were at least 3 times higher than in mainstream cigarette smoke, and that derivatives and flavorings such as methylated-dihydroxybenzenes, vanillin, ethyl vanillin, and benzyl alcohol were up to 1,000 times more abundant in waterpipe mainstream smoke than they were in cigarette mainstream smoke. This study adds to the growing evidence that waterpipe smoking presents significant health risks.

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## DECLARATION OF INTERESTS

None declared.

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