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Water-pipe Tobacco Components and their Association with Oxidative Stress

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Abstract

Oxidative stress (OS) results from an imbalance between the formation and detoxification of reactive species. Although reactive species at low or moderate levels play numerous physiological roles, high concentrations can lead to disturbances in signaling and metabolic pathways and cause different metabolic, chronic, and age-related disorders. Several endogenous and exogenous processes may lead to the formation of reactive species. The severity of OS can be reduced with the help of antioxidants. Tobacco is one of the most important environmental factors contributing to reactive species production. After cigarette smoking, water-pipe tobacco (WPT) smoking is ranked as the second most popular tobacco product. Its popularity is proliferating due to flavored products, social acceptability, etc. However, studies have shown that WPT smoking is associated with an increased risk of arterial stiffness, ischemic heart disease, and several cancer types. In this study, we aimed to review the most recent evidence on WPT smoking constituents and their association with OS.

Keywords: Water-pipe tobacco, Tobacco, Oxidative stress, Cigarette, Tobacco product

Introduction

Oxidative stress, which results from several endogenous and exogenous processes, is characterized by an imbalance between the formation and removal of reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfur species (RSS) (1, 2).Free radicals have critical roles in various biological processes at low or moderate levels, including the synthesis of cellular structures, the host defense system, and signaling pathways. For instance, nitric oxide (NO) serves as a well-known cell-to-cell messenger. This signaling molecule is responsible for modulating proper blood flow, normal neural activity, smooth muscle contractility, bioenergetics regulation, platelet aggregation, immunity regulation, and cell death (3-5). Excessive oxidants can lead to a wide range of metabolic, chronic, and age-related disorders (6, 7). OS can contribute to disease through two mechanisms: First, macromolecule oxidation, cell dysfunction, and death; second, aberrant redox signaling (8). Regarding the first mechanism, modifications in proteins, lipids, and DNA have been reported due to high levels of reactive species (4, 9, 10).

On the other hand, several oxidants can act as second messengers and in excess concentration, they can disrupt signaling pathways (11, 12). Antioxidants can help reduce the severity of OS (13).

As mentioned before, several processes lead to OS. The mitochondrial electron transport chain, endoplasmic reticulum, peroxisomes, nicotinamide adenine dinucleotide phosphate (NADPH)

oxidase (NOX), and dual oxidases are the primary endogenous sources of ROS (14). In addition, exposure to ultraviolet (UV) radiation, cigarette smoke, pesticides, heavy metal ions, ozone, drugs, toxins, allergens, and pollutants are major environmental factors responsible for cellular ROS production (15).

As the second leading cause of death, it is estimated that tobacco will result in 4 million deaths annually, projected to rise to 10 million by 2030 (16). Approximately 1.1 billion people consume tobacco products worldwide. The four emerging tobacco products are snuff, water-pipe, dissolvable tobacco products, and electronic nicotine delivery systems. After cigarette smoking, water-pipe tobacco (WPT) smoking is ranked as the second most popular tobacco product among college students in the United States (17).

This review focuses on the association between WPT smoking, its constituents, and OS.

2. Water-pipes

It is assumed that WPT smoking was introduced in Persia and the Middle East in the 1600s. National and local surveys in certain Arab countries show that 22–43% of people smoke the water-pipe. Additionally, in many parts of the world, particularly in the Eastern Mediterranean (7.25%), the Middle East (6% to 34%), and the United States (3.8%), WPT smoking is increasing among the youth (18). Its popularity is attributed to several reasons, including misleading marketing strategies, social acceptability, and a lack of policies and regulations (19, 20).

The water-pipe device, also known as ghalyan, narghile, shisha, hookah, boory, goza, or hubble-bubble, is a multi-stemmed apparatus consisting of a head, a wooden or metal body, a base, a slender, and a flexible hose (Figure 1). The head, typically made of clay, metal, or ceramic, contains tobacco. The most common types of tobacco used in water-pipes are Ma'ssel (composed of 30% tobacco and 70% honey or molasses), Ajami or Tumbâk (a dark and pure tobacco paste), and Jurâk (of Indian origin). Ma'ssel is usually sweetened and flavored with options like double apple, orange, peach, cherry, grape, etc. (21, 22). Flavored water-pipe tobacco (WPT) has a high moisture content and cannot burn in a self-sustaining manner like tobacco in cigarettes, necessitating an external heat source (23). Consequently, the tobacco is either added directly to charcoal or a briquette or covered by perforated aluminum foil. The base bowel contains a liquid, such as water, milk, alcohol, etc. Inhaling through the hose creates a vacuum above the liquid, resulting in airflow throughout the body of the water-pipe. The air passes over the charcoal and ignites the coal, generating thermal energy. The vapors from tobacco combine with the heated air and combustion products. After cooling and condensing, these vapors form a white aerosol or water-pipe smoke. The user inhales the smoke through a

hose that terminates with a mouthpiece (18). In fact, this aerosol consists of components readily translocated from the raw material and chemically synthesized during smoking and constituents that are both translocated and synthesized in situ (24). Generally, a single WPT smoking session lasts for 0.5–1.5 hours. It is estimated that water-pipe smokers inhale the smoke that is 50–100 times the amount inhaled from a single cigarette (20).

Emerging evidence indicates that exposure to short-term and long-term water-pipe smoke is associated with various health consequences. Lung malignancy, respiratory illnesses, low birth weight, periodontal issues, and infectious diseases are associated with WPT smoking (25). Al-Belasy et al. examined the risk of developing a dry socket among cigarette smokers, shisha smokers, and nonsmokers. The results showed that the risk of developing a dry socket was 3 times greater in shisha smokers compared to nonsmokers (26). Tamim et al. demonstrated that the risk of low birth weight was 2.4 times higher in narghile smokers who smoked more than once per day compared to nonsmokers (27).

Researchers have found that exposure to WPT smoking enhances the production of ROS and increases inflammation. Acute exposure (one hour daily for 7 days) to water-pipe smoking was shown to increase white blood cells, proinflammatory markers, and OS markers in mouse lungs (28). Nemmar et al. have shown that exposure to water-pipe smoke for a month leads to elevated systolic blood pressure. This exposure also triggers inflammation and OS in the heart, promoting prothrombotic and hypercoagulable effects, both in vivo and in vitro (29). The same team of researchers evaluated the short-term (5-day) effects of exposure to water-pipe smoke on the cardiovascular system. Their findings revealed an increase in lipid peroxidation and elevated levels of catalase (CAT) and glutathione (GSH) in the heart tissue of mice (30). In a different investigation, individuals who smoked cigarettes and water-pipes exhibited higher plasma levels of the DNA damage marker 8-hydroxy-2'-deoxyguanosine (8-OHdG) compared to nonsmokers. Furthermore, the mRNA expression levels of DNA repair genes (OGG1 and XRCC1) were notably suppressed in both groups– cigarette and water-pipe smokers– by 30% and 60%, respectively. This suppression was correlated with a significant reduction (50%) in the expression of detoxifying genes (NQO1 and GSTA1), alongside an increase in mRNA expression of Cytochrome P450 1A (CYP1A1), a gene associated with promoting cancer (31). In Arazi et al.'s study to examine how the body's antioxidant response changes after intense exercise, the differences in peroxidase (POX) and 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) activities were evaluated between water-pipe tobacco WPT smokers and nonsmokers after a session of strenuous aerobic exercise. Nonsmokers displayed a significant increase in POX activity and a marked reduction in DPPH activity compared to WPT smokers. They

concluded that WPT negatively affected important plasma antioxidant systems and significantly reduced antioxidative response following strenuous exercise (32). Vitamin A serves as a potent antioxidant and is particularly effective at neutralizing singlet oxygen. Due to its affinity for lipids, it can easily traverse cell membranes to counteract ROS. Vitamin C, on the other hand, is a water-soluble compound that adeptly combats free radicals. Furthermore, it supports the restoration of active vitamin E (α-tocopherol) from α-tocopheroxyl radicals generated during neutralizing ROS. Researchers have noted specific findings regarding the impact of tobacco smoking on serum antioxidant vitamin levels. Ibrahim et al. documented a significant reduction in the serum concentrations of vitamins A, C, and E among shisha smokers than nonsmokers (33). Investigation of the effect of chronic exposure to water-pipe smoking on renal oxidative parameters in mouse kidneys demonstrated a notable reduction in superoxide dismutase (SOD), CAT, and glutathione peroxidase (GPx) activity (34). However, Al-Sawalha et al. found that, although chronic exposure to WPT smoking led to an increase in the number of airway inflammatory cells, OS markers, such as SOD and GPx, were not affected (35). Table 1 presents important results regarding the association between WPT smoking and OS.

3. Water-pipe Tobacco Smoking Components and Oxidative Stress Induction

Tobacco smoke contains numerous harmful and potentially harmful constituents (HPHCs). The most critical toxicants include nicotine, carbon monoxide, volatile organic chemicals, particulate matter (PM), heavy metals, acrolein, and various carcinogens. WPT smokers inhale an estimated 100 times or more the volume of cigarette smoke in a single session of smoking (consuming 8–12 g of tobacco). Table 2 shows the relative toxicant content in one water-pipe session versus smoking a single cigarette (1 g of tobacco) and its associated health effects (19, 20). Figure 2 displays the possible mechanism of inducing OS by some of the significant WPT smoking components.

Nicotine, the leading cause of tobacco dependence, is produced by the tobacco plant, constituting about 95% of the total alkaloid content. Approximately 80%-90% of inhaled nicotine and 60%-80% of nicotine from environmental smoke are absorbed, as demonstrated by studies using ^{14}C-labeled nicotine. Within 10 to 20 seconds after inhalation, this psychomotor stimulant activates nicotinic acetylcholine receptors. Dopaminergic neurons release dopamine following stimulation, increasing pleasurable sensations, mild euphoria, arousal, relaxation, and reduced fatigue (36-39). While nicotine itself is not a carcinogen, it facilitates exposure to many carcinogens in tobacco by driving smoking behavior (38, 39).

Several studies have explored the effects of nicotine on OS and its related mechanisms. Both Minna (40) and Cattaneo (41) demonstrated that nicotine, in its pharmacological concentrations, activated proliferation signals, such as protein kinase C (PKC) and kinase Raf-1, in various cell types and tissues. However, Barr et al. observed that concentrations as low as 1 μM of nicotine significantly increased ROS levels in rat mesencephalic cells, triggering the activation of nuclear factor kB (NF-κB) pathway (42). Hussain et al. investigated the effects of chronic nicotine administration on the antioxidant system of rat tissues. The results revealed GSH depletion in the liver and testes. Additionally, nicotine increased CAT activity in the kidneys and testes, contrary to its effect on the liver (43). Earlier, Marwick's group had concluded that cigarette smoke activated proinflammatory gene transcription controlled by NF-κB and AP-1, leading to a chronic cycle of inflammation (44). Furthermore, as previous research shows, nicotine activates the NLRP3-ASC inflammasome through ROS, resulting in pyroptosis in human aortic endothelial cells (45). The results of Aranyl et al.'s study investigating the effects of nicotine on renal function reveal elevated OS markers in the kidney, along with exacerbated ROS generation through NADPH oxidase and mitochondria. This cascade activates the activator protein (AP)-1 transcription factor through Jun N-terminal kinase (JNK) and subsequent renal injuries (46). Moreover, this group observed that nicotine was responsible for increasing p66shc expression through p53 and DNA hypomethylation, leading to p66shc Ser36-phosphorylation. Consequently, p66shc is translocated to the mitochondria and binds to cytochrome C, producing mitochondrial ROS (47). In an attempt to reduce potential damage, some non-tobacco products have been introduced to the market for use in water-pipes. However, studies have shown that these products contain other toxicants damaging human lung cells (24).

Carbon monoxide, a colorless, tasteless, odorless, and non-irritating gas, is another toxic product released during water-pipe smoking. Incomplete combustion of organic compounds leads to the release of carbon monoxide. In most cases, carbon monoxide in the blood remains below 5%, but heavy smokers may reach levels as high as 10%. Upon inhalation and absorption in the lungs, carbon monoxide quickly spreads across the alveolar membrane into the bloodstream, where it binds reversibly to divalent heme iron, forming carboxyhemoglobin (COHb). Its affinity to hemoglobin and myoglobin is 250 and 40 times greater than oxygen's, respectively. The consequences of central nervous system (CNS) hypoxia include ventilator stimulation, increased carbon monoxide uptake, elevated COHb levels, and respiratory alkalosis (48). One fundamental mechanism has been proposed to explain carbon monoxide toxicity. In this mechanism, COHb and myoglobin-carbon monoxide complex formation leads

to tissue hypoxia and reduced blood flow. This condition allows carbon monoxide to bind to cytochrome c oxidase in mitochondria, interfering with cellular respiration and ROS production. Additionally, CNS reoxygenation after tissue hypoxia facilitates ROS production. Carbon monoxide also binds to other sites, including the cytoplasmic family of mixed-function oxidases, monomeric globins, neuroglobins, and cytoglobin (49). Numerous studies have demonstrated a relationship between carbon monoxide inhalation and the formation of 4-hydroxy-2-nonenal (HNE), lipid peroxidation, and a decrease in the activity of glutathione reductase and GPx (50).

Heavy metals, such as arsenic, nickel, chromium, and lead, are additional factors in water-pipe smoke that play crucial roles in exacerbating OS. Carcinogenic metals alter normal signaling pathways by generating ROS. These pathways include MAPK signaling, calcium signaling, and the activation of transcription factors such as NF-kB, activator protein-1 (AP-1), nuclear factor of activated T-cells (NFAT), and hypoxia inducible factor-1 (HIF-1) (51). Numerous studies have investigated the role of heavy metals in ROS production. For example, Leonard et al. demonstrated that transition metals like chromium (VI), nickel (II), cobalt (II), and iron (II) were capable of interacting with H_2O_2 or $O_2^{\cdot-}$ and forming hydroxyl radicals through Fenton-like reactions (52). Macromolecules, such as proteins, become targets for hydroxyl radicals. Sulfhydryl-containing proteins, when targeted, result in thiol (protein-S•) radicals that can interact with GSH or form additional radicals. Increased superoxide production and inhibition of SOD have been observed in the presence of carcinogenic metals.

Two other carcinogenic metals, i.e., cadmium and lead, deplete the cellular resources of GSH and other sulfhydryls, interfering with the cell's reducing capabilities (53).

Particulate matter (PM) refers to suspended particles with sizes ranging from <0.1 to 10 µm (PM_{10}) in solid or liquid form in the air. These particles are composed of a carbonaceous core with salts, inorganic and organic substances, and aerobiological aggregates (54-56). Smaller PM particles can more effectively penetrate organs, resulting in more severe health effects, including cardiovascular and respiratory diseases (57). A study assessing PM levels inside hookah lounges revealed a high concentration of $PM_{2.5}$ (58). Numerous studies have demonstrated a connection between PM exposure and OS, DNA damage, and inflammation. Although the precise mechanism of PM's influence on oxidant generation remains unclear, the organic components and transition metals present in PM can directly contribute to ROS and RNS production (59). Consequently, OS leads to the activation of phagocytic cells and inflammation, which can then indirectly contribute to further OS (59-62).

Polycyclic aromatic hydrocarbons (PAHs) are constituents of PM. Apart from polluting the environment and being carcinogenic to humans, some PAHs induce OS. As a result of the action of cytochrome P450 (CYP) enzymes and epoxide hydrolase on PAHs, trans-dihydrodiols are oxidized to reactive electrophiles, which serve as precursors to ROS. In one of the known pathways, aldo-keto reductases, in fact, oxidize the trans-dihydrodiols to o-quinones, which are capable of entering the redox cycle, and contribute to ROS formation (63). **Acrolein**, a volatile organic compound and reactive unsaturated aldehyde present in WPT smoking, is a very toxic chemical. This substance is endogenously generated during metabolism and lipid peroxidation, and it enters our body through inhalation, ingestion, and dermal exposure (64, 65). Because acrolein is totally soluble in water and alcohol, it spreads quickly by passive diffusion. Although acrolein mediates its toxicity directly through protein and DNA adduction, it can induce indirect mechanisms such as oxidative, mitochondrial, and endoplasmic reticulum stress. Acrolein can react with thiols, making GSH a potential target and leading to the depletion of GSH. Acrolein compromises the antioxidant defense system by interaction with GSH, GPx, glutathione S-transferases (GST), and SOD. In addition, it decreases the expression of glutamate-cysteine ligase (GCL) (GSH production regulator) and nuclear factor-e2-related factor 2 (Nrf2) level, an antioxidant response regulator, and increases heme oxygenase-1, a marker of OS. ROS production can lead to lipid oxidation and more acrolein synthesis (64). It is important to note that acrolein can generate reactive carbonyl species by carbonylating proteins. It also disrupts mitochondrial respiratory function through different mechanisms, such as increasing intracellular Ca^{2+}, carbonylation of mitochondrial proteins, and reducing oxygen consumption (66).

Conclusion and Perspectives

According to the evidence summarized in this review, an increase in OS is one of the most significant consequences of WPT smoking. WPT smoking may enhance OS through increased NADPH oxidase and heme oxygenase-1 activity, cellular GSH pool depletion, decreased antioxidant enzyme activity, and increased carbon monoxide production. As shown, WPT smoking is equally or even more unsafe than cigarette smoking. More research on the molecular mechanisms behind its action is necessary, as WPT smoking differs from cigarette smoking in modes of intake, duration, and type of tobacco. It is vital to develop strategies to decrease public interest in WPT smoking. Increasing public awareness of the dangers of WPT smoking and implementing strict rules on its consumption can be helpful.

Conflict of Interests

No conflict of interest.

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Table 1. Research on the association between waterpipe tobacco smoking and oxidative stress

Subjects	Goal	Main Findings	Ref.
Mice	The influence of acute exposure to WPT smoking on lung inflammation and OS	Elevation in GPx and CAT activity	(28)
BALB/c mice	The influence of short-term water-pipe smoke nose exposure on cardiac inflammation and OS	Elevation of lipid peroxidation, CAT, and GSH levels in heart tissue	(30)
Mice	Airway resistance, inflammation, and OS of nose-only exposure	Increase in lipid peroxidation, decrease in the activity of antioxidant enzymes	(67)
Human	The effects of long-term cigarette and WPT smoking on DNA damage and OS	Elevation in 8-OHdG and CYP1A1 mRNA expression, decrease in GST expression	(31)
Human	Evaluation of the differences between water-pipe smokers and nonsmokers regarding the salivary antioxidant status	Decrease in salivary POX activity and DPPH radical scavenging activity, low uric acid concentrations in waterpipe smokers than nonsmokers	(32)
Mice	The influence of selenium on OS induced by WPT smoking	Elevation in MDA and nitric oxide levels in the lungs and liver, decrease in SOD, GPx, and CAT activity	(68)
Mice	the impact of WPT smoking on kidney OS and functional parameters in acute and chronic exposure	Reduction in SOD activity in acute exposure, reduction in SOD, CAT, and GPx activity in chronic exposure	(34)
Human	The effect of water-pipe smoking on serum lipid profile and antioxidant vitamins	Reduction in serum antioxidant vitamins (A, C, and E) and increase in cholesterol, triglyceride, and LDL-C level	(33)
Human	Biomarkers of OS among young water-pipe smokers	An increase in 8-oxodG and 8-oxoGuo	(69)
Human	Assessing markers of inflammation, OS, and tissue damage and repair among WPT smokers, CS, and dual WPT smokers and CS	Higher levels of inflammatory mediators in WPT smokers, CS, and dual smokers, an increase in endothelial biomarkers in CS, An increase in 8-isoprostanes and MPO levels in urine samples of smokers	(70)
Rat	The effect of WPT smoking exposure during lactation on learning and memory of offspring rats and role of OS	Impairment in long-term memory, reduction in hippocampus brain-derived neurotrophic factor, and SOD and GPx activity.	(71)
Rat	The effect of WPT smoking exposure on reproductive hormones and OS	An increase in MDA level and CAT activity, reduction in GPx activity	(72)
Human	Relationship between toenail-bounded heavy metals and OS in waterpipe/cigarette cafés workers	An increase in 8-OHdG level	(73)
Mice	Evaluation of WPT smoking effect on lung toxicity in mice according to sex and strain (C57BL/6J vs BALB/cJ strain)	Increase in oxidized GSH and lipid peroxidation markers, including 15-isoprostane, MDA, and 4-hydroxy-2-nonenal in males and females, decreases in serum GSH levels in both strains, increase in 15-isoprostane in C57BL/6J strain, increase in 4-HNE in both strains. Increased in 4-HNE in males and decreased in females of both strains.	(74)

		Increase in MDA in females of both strains.	
Human	The effect of WPT smoking and cigarettes on OS profile in adolescents	Reduction in CAT and GPx activities	(75)
Mice	The effect of WPT smoking on airway inflammation in murine model of asthma	No effect	(35)

GST: Glutathione S-transferases, GPx: Glutathione peroxidase, GR: Glutathione reductase, GSH: Glutathione, SOD: Superoxide dismutase, 8-OHdG: 8-Hydroxyguanosine, CYP1A: Cytochrome P450 1A, POX: Peroxidase, DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate, CS: Cigarette smokers, WPT: Water-pipe tobacco, MPO: Myeloperoxidase, MDA: Malondialdehyde, 4-HNE: 4-hydroxy-2-nonenal, CAT: Catalase, OS: Oxidative stress, LDL: Low-density lipoprotein.

Table 2. Toxicant content in one session of water-pipe tobacco smoking relative to smoking a single cigarette

Compound	Toxicant Content Relative to Smoking a Single Cigarette	Health Effects
Nicotine	1.2 X	Tobacco dependence, cardiovascular, respiratory, gastrointestinal disorders, and immune response disruption (76)
Carbon monoxide	8X	Neurological dysfunction and myocardial toxicity (77)
Acrolein	4-15X	Cardiomyopathy and cardiac failure (78)
Polycyclic aromatic hydrocarbons	3-245X	Lung, larynx, and oral cavity cancer (20)
Heavy metals		Lung inflammation, chronic obstructive pulmonary disease (20) Cardiovascular, lung/larynx cancer (24)
Lead	80X	
Arsenic	1.4X	
Copper	-	
Zinc	-	
Chromium	20X	
Nickel	-	
Cobalt	925X	
Beryllium	-	
Boron	130X	
Particular Matter	10X	Cardiovascular disease, chronic obstructive pulmonary disease, lung cancer (20)

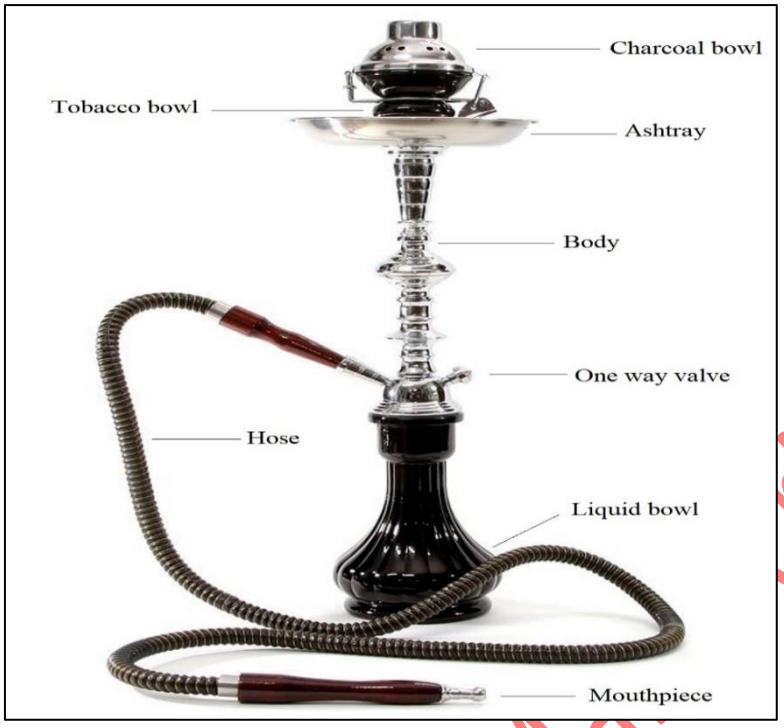

Figure 1. Different parts of water-pipe smoking device

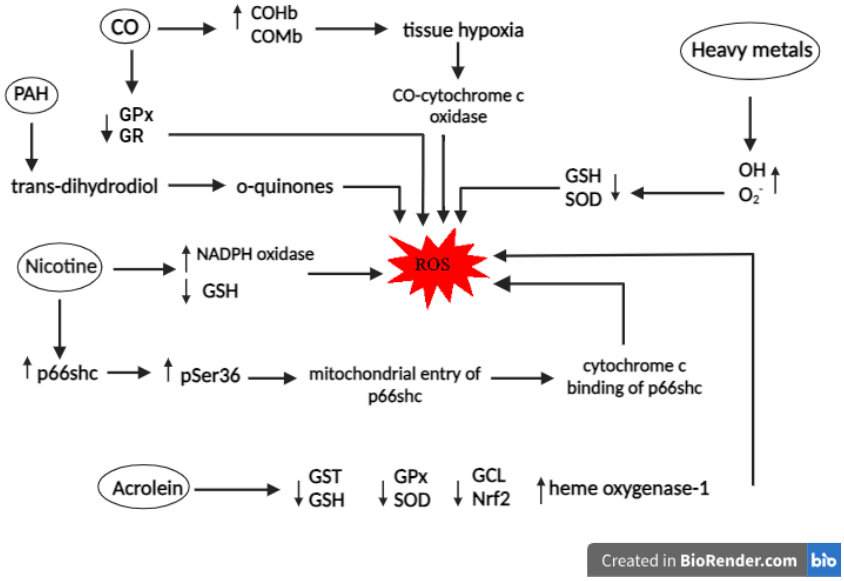

Figure 2. Possible mechanisms of inducing oxidative stress by the major constituents of water-pipe tobacco smoke. (The circled compounds are the main components of water-pipe tobacco smoke).

Abbreviations: Nrf2: Nuclear factor erythroid 2-related factor 2, p66Shc: SHC-transforming protein 1, GCL: Glutamate-cysteine ligase, GST: Glutathione S-transferases, GPx: Glutathione peroxidase, GR: Glutathione

reductase, PAH: Polycyclic aromatic hydrocarbons, GSH: Glutathione, SOD: Superoxide dismutase, COHb: Carboxyhemoglobin, COMb: Carboxy-myoglobin,