The Joint Role of Resveratrol and Curcumin Against Nephrotoxicity and Hepatotoxicity of Narghile Smoking in Mice: Microscopic and Biochemical Insights

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Original Article

ABSTRACT

Background: Narghile smoking is a variety of tobacco utilization that can influence the standard of life and urge oxidative stress. The bioactive role of curcumin and resveratrol may aid in thwarting stress responses of toxins.

Aim of the Work: To explore the joint role of resveratrol and curcumin against the cytotoxicity of narghile smoking on the kidney and liver of mice.

Materials and Methods: Five groups of BALB/c mice were designed. Group 1 was subjected to fresh air, group 2 (NRGL) was subjected to narghile smoking for 1 month, group 3 (NRGL+ curcumin) was subjected to narghile smoking and curcumin (40mg/kg/day), group 4 (NRGL+ resveratrol) was subjected to narghile smoking and resveratrol (25mg/kg/day), while group 5 (NRGL+ curcumin+ resveratrol) was subjected to narghile smoking, resveratrol (25mg/kg/day) and curcumin (40mg/kg/day). Curcumin and resveratrol were injected intraperitoneally. A smoking machine was utilized for 30 days, and serum samples were gathered to assess liver enzymes and kidney functions. The kidney and liver were cut off for microscopic tissue analysis.

Results: Narghile smoking raised liver enzymes, creatinine and urea serum standards in addition to remarkable histopathological deterioration in the liver and kidney. Lost hepatocytes and renal cortical architecture were remarkable microscopic findings. The groups that were administered curcumin and/or resveratrol and subjected to narghile smoking displayed improved standards of all investigated chemical biomarkers with restoration of the tissue microscopic design of liver and kidney.

Conclusion: Curcumin and/or resveratrol (alone or in combination) utilization could lessen the hurtful impacts of narghile smoking in mice. Both agents improved the morphology and functions of kidneys and liver.

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Key Words: Animal model, narghile smoking, biochemical insight, tissue analysis.

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BACKGROUND

Tobacco utilization can prompt assorted deadly illnesses, as cardiovascular and pulmonary disorders and cancers. All are regarded as crucial health issues worldwide[1-3]. In the last century, it is delineated that tobacco smoke created roughly one hundred million mortalities[4,5]. Over 400 chemicals are included in tobacco which are remarked as lethal and carcinogenic[6]. There is a view that waterpipe or cigarettes smoking exceeds addiction craving. Nicotine is metabolized by hepatocytes disrupting oxidants and antioxidants steady state. Nicotine provokes free radicals and reactive oxygen species (ROS) accumulation, disables the antioxidant defense processes and urges oxidative stress[7].

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Narghile smoking generate countless medical disorders, like cardiovascular and respiratory risks. It temporarily induces vasoconstriction raising the blood pressure and heart rate. It can also occlude an artery by formation of the blood clots. It can cause lung tissue damage, leading to breathing abnormalities[8]. The liver processes nicotine that is excreted by the kidneys. In due course, narghile smoking may have unfortunate impact on liver and kidneys. The precise connection between renal diseases and narghile smoking is yet uncertain. Those who utilize nicotine seem to have a heightened hazard for proteinuria and edema due to renal impairment. Nephrosclerosis and glomerulonephritis may be a result of narghile smoking and may propagate to chronic failure. As well, narghile smoking may provoke or aggravate diabetic nephropathy[9-11].

Alongside influencing the renal system, narghile smoking also alters hepatic structures[12-14]. It could elicit its degeneration with significant rise in the hepatic enzymes in blood. As well, former reports disclosed raised lipid peroxidation and ROS with low glutathione antioxidant standards in hepatic tissues. So, it provokes hepatic oxidative stress, DNA harm, inflammation and hepatocyte apoptosis. Accumulating information announced procreation of liver diseases due to chemicals of tobacco smoke. The cytotoxic consequences of these chemicals could provoke actuation of hepatic stellate cells and fibrosis[15-19].

Curcumin or diferuloylmethane polyphenols (a prime ingredient of turmeric curcuma longa), possesses anti-inflammatory and antioxidant capability against toxin-produced stress responses. They promote cytoprotective proteins expression for tissue preservation[20,21]. Curcumin counteracts nitric oxide, advocating the antioxidant enzymes and suppressing lipid peroxidation. Nicotine is able to do oxidative harm to organs; however, curcumin is able to protect against such injury. Curcumin has been applied in folk medicine as a food supplement. It is renowned for its antibacterial potentials. Curcumin co-acts with resveratrol against cytotoxicity. Prior reports advocated its defensive and curative capacity in diverse health issues such as neurodegenerative disorders and tumors[22]. In *vivo* models and clinical trials, curcumin has been proven to suppress cell growth, adenomas and carcinogenesis of colon[23,24].

Resveratrol (an antioxidant polyphenol) is an active element of red grapes and certain berries. Resveratrol has been investigated for its projected impacts on aging and cardiac health. It protects the body against liver and heart problems and tumors[25-28]. Resveratrol may be an impressive element for prevention of colorectal cancer. In *vivo*, it suppresses the development of the intestinal preneoplastic lesions and adenomas. This growth inhibitory impact of resveratrol is attributed to apoptosis[29,30].

In this work, we determined the impact of narghile (waterpipe) smoking on the functions and tissue morphology of the kidney and liver of albino mice. As well, we evaluated the achievable defensive impacts of curcumin and/or resveratrol (alone or in combinations) against kidney and liver injury caused by narghile smoking by the aid of some histological and biochemical approaches.

MATERIALS AND METHOD

Ethical approval:

The procedures were conforming to the National Institutes of health (NIH) recommendations for animal experiments which is approved by the Research Scientific Committee, University of Jordan[31].

Chemicals:

Honeyed-Maassal was from a local market in Jordan (Two Apples Flavored Molasses #6253345300081). Both Curcumin and resveratrol were in high-purity forms (Diferuloylmethane, C1386, Sigma-Aldrich, China) and (trans-1,2-(3,4',5-Trihydroxydiphenyl) ethylene, R0071, TCI Co., Japan).

Study design:

Fifty male albino BALB/c mice (aged 8-9 weeks and weighed 21-25 grams) were prepared for the study. All were subjected to typical living conditions with 14 days acclimatization prior to the procedures. They received the standard laboratory chew and water. Five groups of these mice were arbitralily designed (*n*= 10/group):

Group 1(control): was subjected to fresh air.

Group 2 (NRGL): was subjected to narghile smoking.

Group 3 (NRGL + Curcumin): was subjected to narghile smoking and curcumin (40mg/kg/day, intraperitoneal injection)[20].

Group 4 (NRGL + Resveratrol): was subjected to narghile smoking and resveratrol (25mg/kg/day, intraperitoneal injection)[25].

Group 5 (NRGL+ Curcumin + Resveratrol): was subjected to narghile smoking and resveratrol and curcumin using the same doses and routes of groups 3 and 4.

Narghile smoking, curcumin and/or resveratrol administration was repeated daily for 30 days. Resveratrol and/or curcumin solution was given to mice one hour before subjection to narghile smoking.

Tobacco honeyed-maassal and narghile preparation:

Honeyed-Maassal elements are tobacco, molasses, flavors, glycerin and 0.05% nicotine. Shraideh *et al*., 's digital smoking device was utilized as a source of narghile smoke. Five grams of maassal were utilized in this procedure. To burn tobacco, a fast-lighting disk of 40mm charcoal was placed upon a perforated aluminum foil on the narghile head[32].

Preparation of Resveratrol:

Dissolving 50 mg of resveratrol in 1 ml of absolute ethanol was to prepare a stock solution. The working solution was diluted by phosphate-buffered saline (0.01M, pH 7.4).

Preparation of Curcumin:

A stock solution of curcumin was prepared by dissolving 10mg of curcumin in 1mL of absolute ethanol. The solution was diluted using phosphate-buffered saline (0.01M, pH 7.4). The solutions were contained within 1ml disposable insulin syringes.

Sample collection:

At the end of the experiment, blood samples from each group was drawn to determine kidney functions and liver enzymes (biochemical analysis). A capillary tube was inserted into the venous orbital plexus to withdraw blood under anesthesia by injecting sodium pentobarbital (50mg/kg, intraperitoneally)[33]. The serum was obtained under dark conditions at the room temperature (clotting time 60 minutes and then centrifugation at 3800rpm/10 minutes). Tissue specimens were taken from the kidneys and liver of each group after overnight recovery from the last smoke exposure to ensure adequate fixation. The structural features of both organs were assessed after exposure to narghile smoking, and to analyze the impact of curcumin and/or resveratrol.

Light microscopy protocol:

Pieces of kidney and liver tissues were washed with normal saline (0.9% NaCl), and then preserved for at least 24 hours in 10% formal saline. The tissues were handled in SHANDON citadel 1000 tissue processor. Dehydration was achieved through a graded series of alcohol (70%, 80%, 95%, 100%, and 100%). After two sets of xylene, infiltration and embedding in pure paraffin wax were done. Utilizing a Leica RM2125 RTS manual microtome, thin 5 µm sections were attained, and colored with hematoxylin and eosin (HandE) stains[34]. The images were attained by LEICA DM 750 Microscope with ICC50E Camera Module (Leica Microsystems (Schweiz) AG) at Ibn Sina University for Medical Sciences, Amman, Jordan.

Biochemical analysis:

Liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)), and kidney function tests (creatinine and urea) were evaluated according to kits manuals instructions (Teco Diagnostics, Anaheim, CA, USA). A UV/VIS single-beam spectrophotometer was utilized to do these tests (EMC-11D-V; EMCLAB equipment, Duisburg, Germany)[35].

Statistical Analysis:

The biochemical findings were analyzed by statistical software (GraphPad Prism Version 8.0.2, IBM, USA), to attain the means and standard deviation, which were computed using ordinary two-way ANOVA followed by Tukey post hoc, with individual variance measured for each comparison, and with P value <0.05 as a significant difference[36].

RESULTS

Histopathological results:

Group 1 examination detected typical architecture of the renal cortex; Malpighian corpuscles with regular, continuous Bowman's capsules, and proximal and distal convoluted tubules with typical epithelium (Figure 1A). Compared to group 1, group 2 (NRGL) examination explored focal deterioration of the cortical tissue architecture. There was a widening in the capsular space, vascular congestion, glomerulus condensation, and nucleus condensation (deeply stained nuclei). Some proximal and distal convoluted tubules showed degeneration of their epithelium, identified by vacuolization and pyknotic nuclei. As well, there was marked mononuclear cells accumulation (Figure 1B). Group 3 (NRGL+ curcumin) manifested mild regression of the above lesions. Some glomeruli were vacuolated and congested. Some proximal and distal convoluted tubules showed vacuolated cytoplasm, and pyknotic nuclei of their epithelium were seen. There was minimal mononuclear cells accumulation (Figure 1C). Group 4 (NRGL+ resveratrol) exhibited minimal protection of the renal cortical tissue. Some tubular epithelial vacuolization, and a few pyknotic nuclei (less nuclear condensation) were found. In addition, mononuclear cells accumulation was observed (Figure 1D). Regarding group 5 (NRGL+ curcumin+ resveratrol), the examination detected marked protection of the tissues with nearly typical microscopic appearance similar to the control group. The sections revealed normal glomeruli and capsular spaces in addition to typical tubular epithelium with no vacuoles. The mononuclear cells accumulation was rare in sections (Figure 1E).

Histological examination of the liver illustrated that group 1 (control) displayed typical structural features of the parenchyma. Branching hepatocyte cords radiated from a central vein were separated by blood sinusoids that had endothelial lining with Kupffer cells. The hepatocytes were identified by their polyhedral shape, granular acidophilic cytoplasm, and large, rounded, vesicular nuclei that had prominent nucleoli. Some of these cells were binucleated (Figure 2A). Group 2 (NRGL) exhibited severe hepatic structural changes. Markedly dilated and congested central veins as well as blood sinusoids detected in most sections. Several hepatocytes were irregular and shrunken with deeply stained nuclei. Heavy mononuclear cells accumulation was remarked near the dilated central vein and blood sinusoids (Figure 2B). Group 3 (NRGL+ curcumin) manifested partial amelioration of these lesions. Many normal hepatocyte structures were detected. Less dilated and congested central veins and blood sinusoids were remarked with less mononuclear cells accumulation

(Figure 2C). Group 4 (NRGL+ resveratrol) displayed a certain type of liver protection in the form of many typical hepatocytes, less dilated and congested central veins and blood sinusoids with less mononuclear cells accumulation than group 2 (Figure 2D). Examination of group 5 (NRGL+ curcumin+ resveratrol) demonstrated marked protection of the liver parenchymal structures with apparently typical features analogous to the control group. Even so, mild dilatation of a few central veins and blood sinusoids was remarked in a few areas. No mononuclear cells accumulation was witnessed (Figure2E).

Biochemical findings:

The standards of ALT, AST, and LDH displayed a significant rise in mice subjected to narghile smoking (CTRL) in contrast to the control (NRGL). On the contrary, treatment with curcumin and/or resveratrol, accompanied with subjection to narghile smoking (NRGL + CUM, NRGL + RSV, NRGL + CUM + RSV), did not exhibit any significant differences compared to the control (CTRL) group. As well, the mean creatinine and urea levels displayed substantial rise in the NRGL compared to the CTRL group. Besides, the antioxidant-treated groups, in parallel to narghile exposure, demonstrated non-significant alteration compared to the CTRL group (Figure 3).

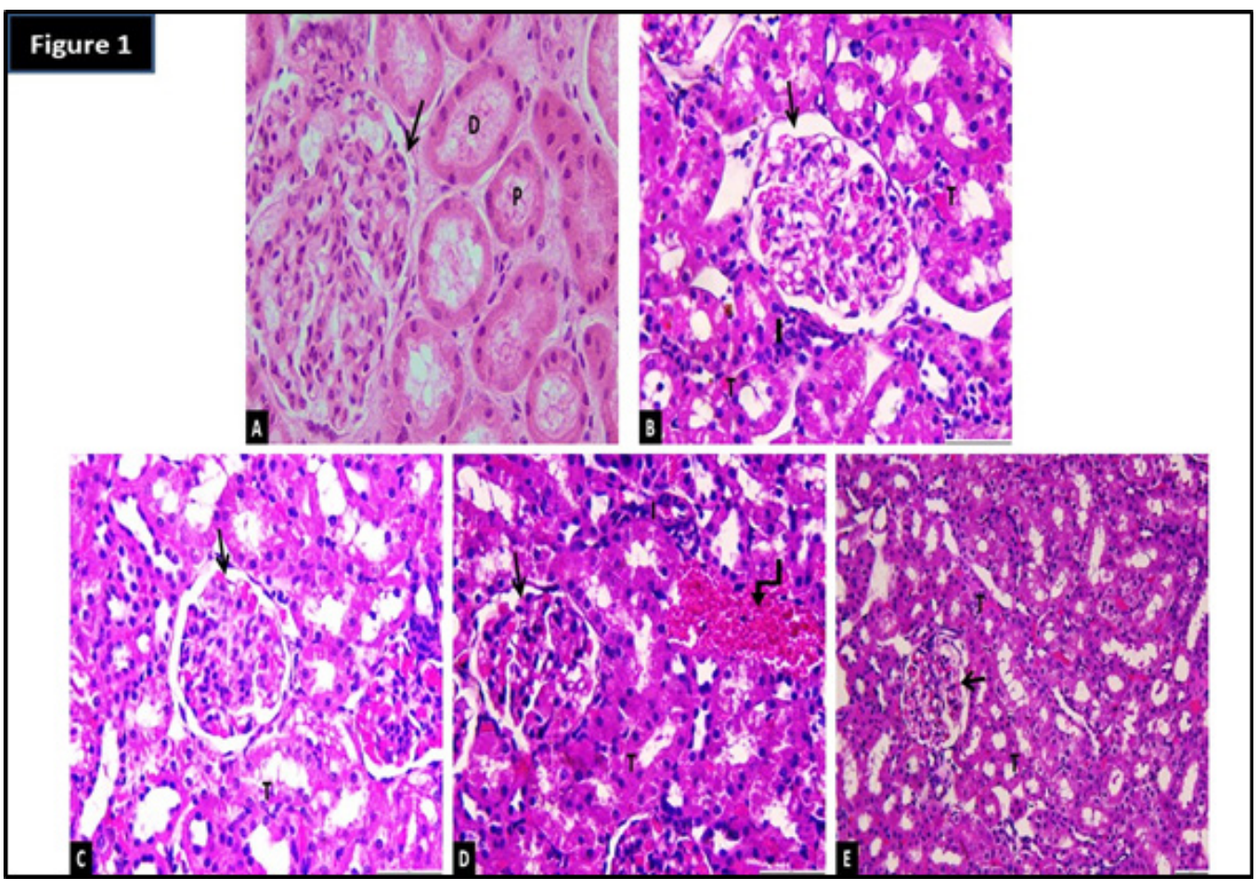

Fig. 1: Photomicrographs of renal cortical sections from all investigated groups (X400). [A] The control group shows typical Malpighian corpuscles with regular continuous Bowman's capsules (arrow), proximal (P) and distal (D) convoluted tubules with typical epithelium [B] Group 2 exhibits wide capsular space, glomerulus condensation, vascular congestion (arrow), tubular epithelium (T) with vacuolization and pyknotic nuclei. Note marked mononuclear cells accumulation (I) [C] Group 3 exhibits some vacuolated and congested glomeruli (arrow), some disorganized tubules (T) with vacuolated cytoplasm and a few pyknotic nuclei of their epithelium. [D] Group 4 reveals typical glomeruli (arrow), tubular epithelial vacuolization, and a few pyknotic nuclei (T) in addition to mononuclear cells accumulation (I) and extravasated red blood corpuscles (curved arrow). [E] Group 5 displays apparently typical glomeruli (arrow) in addition to typical tubular epithelium (T) with no vacuoles analogous to the control group.

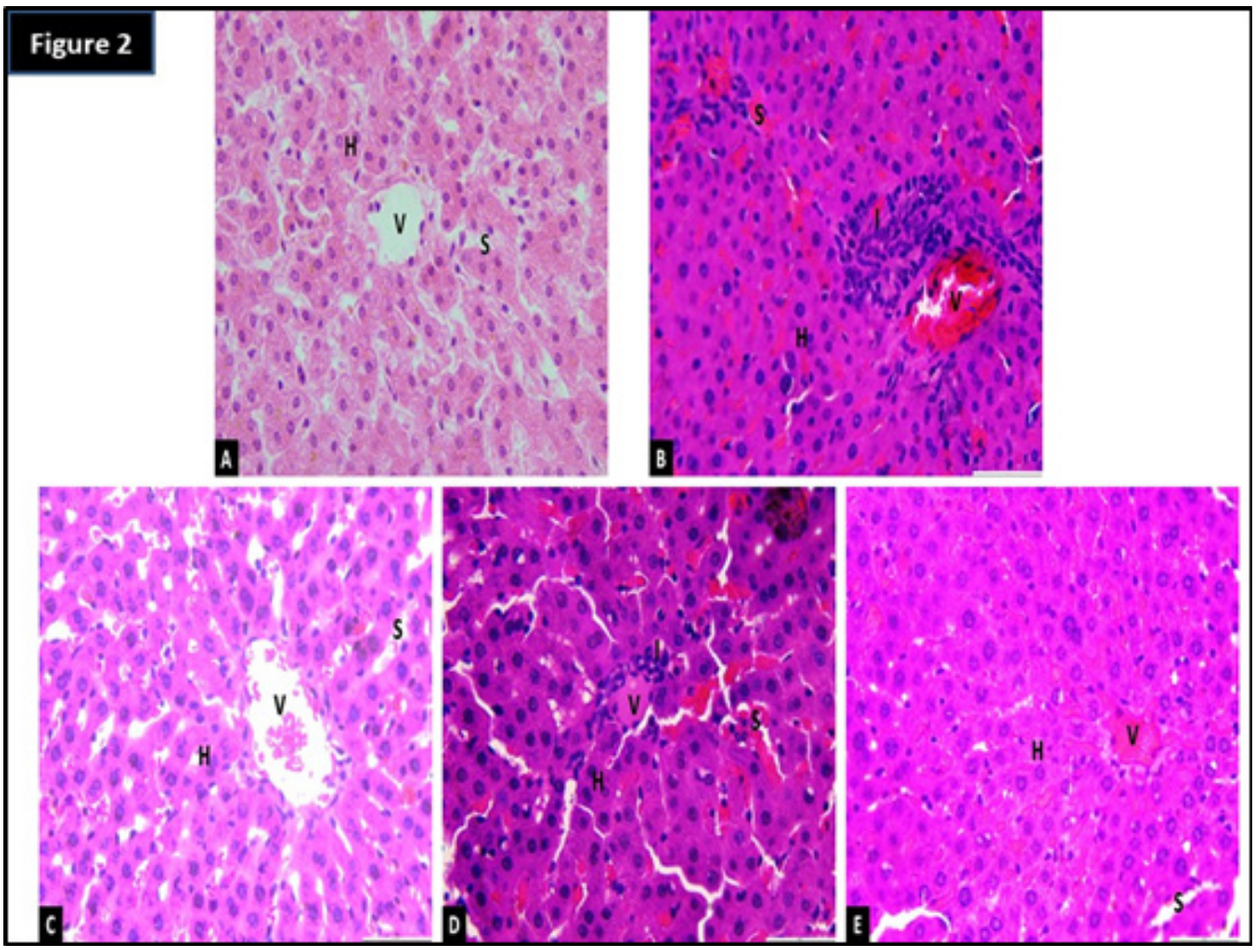

Fig. 2: Photomicrographs of liver sections from all investigated groups (X400). [A] The control group displays typical parenchyma with branching hepatocyte cords (H) radiated from a central vein (V). The cords were separated by blood sinusoids (S) that had endothelial lining with Kupffer cells. Note the granular acidophilic cytoplasm and large rounded vesicular nuclei of the hepatocytes. [B] Group 2 displays markedly dilated and congested central veins (V) as well as sinusoids (S), shrunken hepatocytes with deeply stained nuclei (H). Note heavy mononuclear cells accumulation (I) [C] Group 3 exhibits many typical hepatocytes (H), mild dilatation and congestion of the central vein (V) and sinusoids (S) [D] Group 4 displays many typical hepatocytes (H), mild dilatation and congestion of the central vein (V) and sinusoids (S) and a few mononuclear cells accumulation (I) [E] Group 5 displays apparent typical hepatocyte structure (H) analogous to the control group. Note mild dilatation of a few central veins (V) and sinusoids (S).

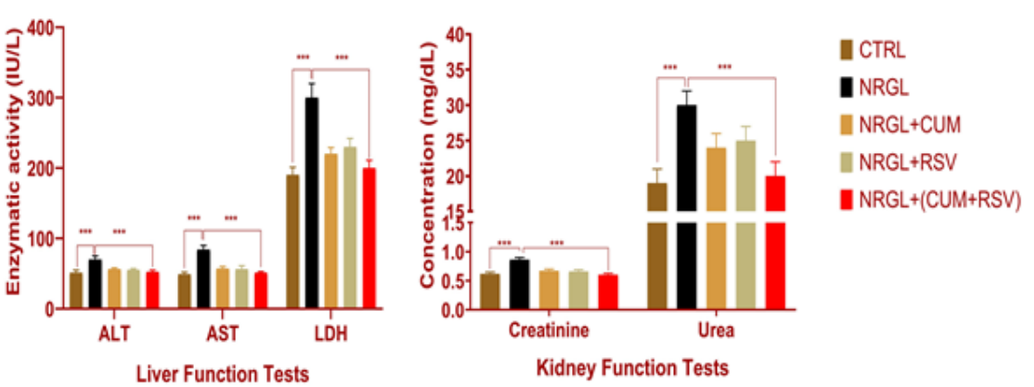

Fig. 3: Quantification of biomarkers of liver and kidney functions among the investigated groups. The data are remarked as mean ± standard deviation.

DISCUSSION

Narghile smoking is a variety of tobacco utilization with hurtful elements. These hurtful elements could prompt oxidative stress and urge inflammation. So, more investigations were encouraged due to wide spread of narghile use and its relationship with countless pathological contexts and organs dysfunction[37]. Curcumin and resveratrol have influential cytoprotective capacity against oxidative stress. It has been documented that the concomitant therapy of both agents may display potent efficacy or lower harmfulness[38]. So, the current investigations aimed to determine impact of narghile (waterpipe) smoking on the kidneys and liver of albino mice. As well, the study evaluated the achievable defensive impacts of curcumin and/or resveratrol (alone or in combinations) against kidney and liver injury caused by narghile smoking.

Data of this study displayed that mice subjection to narghile smoking caused a significant rise in the mean values of liver enzymes besides impaired kidney functions. The histological analysis remarked the hurtful impacts of narghile smoking on kidney and liver. As well, the study displayed that administration of curcumin or resveratrol (each alone) to mice subjected to narghile smoke had a partial defensive potential on the kidney and liver functions and structure. However, the combination of curcumin and resveratrol induced a marked defensive impact on the kidney and liver functions and their structure, analogous to the normal standards.

These data were consistent with prior information, which illustrated that narghile smoking could promote kidney and liver injury influencing their morphology and functions. The mechanism participated in this injury may be by oxidative stress, mitochondrial deterioration, inflammation, DNA harm, and apoptosis. It has been reported that 5 days of narghile smoking could provoke pulmonary oxidative insult accompanied with marked inflammatory cells accumulation (neutrophils and lymphocytes) and raised standards of the proinflammatory cytokines TNFα, IL-6, and IL-1β[39-41].

Reactive oxygen specious accumulation and deteriorated antioxidant system (catalase and superoxide dismutase) in tissues are key elements of narghile smoking. This provokes injury to cytoplasmic structures, such as lipids, DNA and proteins, impairs its function and urge necrosis or apoptosis. These impacts are attributed to chemicals of tobacco smoking[37]. Oxidative stress and inflammation are strongly tied phenomena having a key role in various pathological issues. Our data were analogous to prior in *vivo* investigations on heart and lungs subjected to narghile smoking[42].

So, our microscopic findings (cytoplasmic vacuolation, vascular congestion and cell infiltration) were attributed to the increase in the proinflammatory cytokines TNFα, IL-6, and IL-1β in addition to reactive oxygen species. These inflammatory mediators react with the cell membrane lipids and proteins impairing the cellular morphology and functions. Moreover, narghile smoking may lead to increase in the cleaved caspase-3 and cytochrome C in hepatic and renal cells leading to apoptosis. Another explanation for our results was alteration of HIF-1α expression by narghile smoking. HIF-1α is a transcription factor that can upregulate the expression of various antioxidants as superoxide dismutase and catalase. So, altered HIF-1α expression may be associated with oxidative cellular damage in liver and kidney[13,43].

This study displayed that the administration of individual curcumin or resveratrol (each alone) to mice subjected to narghile smoking exhibited a partial defensive potential on the kidney and liver functions and structure. However, the combined administration of curcumin and resveratrol to mice subjected to narghile smoking demonstrated a marked defensive impact, analogous to a normal one. These agents have captured interest for their effective health advantages. They exhibit close identities in features due to their content of countless phenolic groups[44,45]. Individual curcumin or resveratrol administration has been reported to display a cell defensive potential by several processes. The two compounds may co-act against cytotoxicity of narghile smoking. Previous information demonstrated that the combination of curcumin and resveratrol made an effective capability against H_2O_2-produced oxidative stress through promotion of the nuclear factor erythroid-2-related factor 2 pathway and improvement of antioxidant enzymes[38]. They also co-act to diminish the proinflammatory cytokines, such as tumor necrosis factor-alpha, lessening tissue inflammation. As well, they significantly depress TNF-α-produced nuclear factor-kappa B inhibiting p65 nuclear protein expression[46].

Our data were analogous to prior investigations which proved the defensive potential of curcumin by scavenging ROS and promoting tissue survival. The cell defensive potentials of curcumin were due to its unique structure assisting its cell penetration. Even so, the cell defensive potential of resveratrol was due to the production of glutathione S-transferase and catalase, rising the tissue defense processes. As well, the common molecular process that contributes to the cell defensive potential of curcumin and resveratrol co-administration is the stimulation of the antioxidant Nrf2, lessening tissue inflammation[47,48]. The defensive potential of curcumin and resveratrol has been displayed in some disorders, such as ethanol-produced liver damage and acute liver injury[49,50].

In this study, co-therapy with curcumin and resveratrol improved all investigated biochemical parameters (ALT, AST, LDH, Urea, and creatinine), denoting better kidney

and liver functions. Our data was in line with a prior investigation that displayed curcumin and/or resveratrol co-operative impact on fibronil-produced tissue injury[51].

The defensive potential of curcumin against cigarette smoking toxicity was illustrated in the different organs. These protective potentials of curcumin were through its antioxidant, anti-inflammatory, anti-apoptotic, and anti-carcinogenic capacities[52]. Moreover, previous studies also displayed a co-interaction of curcumin and resveratrol against carcinogenesis in lungs[53].

So, curcumin and resveratrol co-interacted against narghile smoking-produced kidney and liver damage, restoring their structure and functions.

CONCLUSION

Curcumin and resveratrol appear to complement each other, potentially aiding in suppressing narghile smoking-produced cytotoxicity on the kidney and liver of albino mice. However, further studies are recommended to understand the key mechanisms of their combined impact.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

الدور المشترك للريسفيراترول والكركمين في مكافحة سمية تدخين النارجيلة على الكلى والكبد لدى الجرذان: رؤى مجهرية وكيميائية حيوية

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مقدمة: يُعدّ تدخين النارجيلة أحد أشكال استهلاك التبغ التي قد تؤثر على جودة الحياة وتُسبب الإجهاد التأكسدي. قد يُساهم الدور الحيوي للكركمين والريسفيراترول في كبح استجابات الإجهاد الناتجة عن السموم.
الهدف من البحث: استكشاف الدور المشترك للريسفيراترول والكركمين في مواجهة السمية الخلوية لتدخين النارجيلة على كلى وكبد الفئران.
مواد وطرق البحث: تم تصميم خمس مجموعات من فئران BALB/c. تعرضت المجموعة الأولى للهواء النقي، وتعرضت المجموعة الثانية (NRGL) لتدخين النارجيلة لمدة شهر واحد، وتعرضت المجموعة الثالثة (NRGL + الكركمين) لتدخين النارجيلة وتناول الكركمين (٤٠ ملغم/كغم/يوم)، وتعرضت المجموعة الرابعة (NRGL + ريسفيراترول) لتدخين النارجيلة وتناول الريسفيراترول (٢٥ ملغم/كغم/يوم)، بينما تعرضت المجموعة الخامسة (NRGL + الكركمين + الريسفيراترول) لتدخين النارجيلة وتناول الريسفيراترول (٢٥ ملغم/كغم/يوم) والكركمين (٤٠ ملغم/كغم/يوم). تم حقن الكركمين والريسفيراترول داخل الصفاق. تم استخدام جهاز التدخين لمدة ٣٠ يومًا، وتم جمع عينات من مصل الدم لتقييم إنزيمات الكبد ووظائف الكلى. تم استئصال الكلى والكبد لتحليل الأنسجة مجهريًا.
النتائج: أدى تدخين النارجيلة إلى ارتفاع مستويات إنزيمات الكبد والكرياتينين واليوريا في الدم، بالإضافة إلى تدهور نسيجي مرضي ملحوظ في الكبد والكلى. وكان فقدان خلايا الكبد وتدهور بنية قشرة الكلى من أبرز النتائج المجهرية. أظهرت المجموعات التي تناولت الكركمين و/أو الريسفيراترول وتعرضت لتدخين النارجيلة تحسنًا في مستويات جميع المؤشرات الحيوية الكيميائية المدروسة، مع استعادة البنية النسيجية المجهرية للكبد والكلى.
خلاصة البحث: قد يساهم استخدام الكركمين و/أو الريسفيراترول (بمفردهما أو مجتمعين) في تخفيف الآثار الضارة لتدخين النارجيلة على الفئران. وقد حسّن كلا العاملين من مورفولوجيا ووظائف الكلى والكبد.