Volatile compounds and antioxidant activity of the aromatic herb Anethum graveolens

Background/Aim
Anethum graveolens L. (dill) (Apiaceae) is one of the most popular culinary herbs in the world. Dill has been cultivated since ancient times, and the use of this plant for medicinal and consumption purposes has been recorded dating back to the Greek and Egyptian civilizations. Dill is widely used to give flavor to food. The aim of this work was to assess the chemical composition of the volatile compounds in dill as well as their hepatoprotective and nephroprotective activity against free radicals generated by paracetamol.

Materials and methods
The chemical composition of the volatile compounds of dill was assessed by gas chromatography and gas chromatography-mass spectrometry. Four groups of rats were used (the normal control group, the A. graveolens-supplemented group, the paracetamol-intoxicated group, and the A. graveolens-protected group) for studying the effect of plant infusion on panadol (paracetamol)-induced free radicals and hepatotoxicity. Plasma total antioxidant capacity, plasma catalase, cellular glutathione peroxidase, plasma total protein, albumin, alanine amino transferase, aspartate amino transferase, alkaline phosphate, γ-glutamyl transferase, total bilirubin, and direct bilirubin levels were determined. In addition, kidney functions (plasma urea and creatinine) and histopathological and histochemical changes in the liver were investigated.

Results
The phytochemical results identified volatile components 7-α-hydroxy manool (24.43%), l-carvone (14.28%), limonene (13.9%), epi-α-bisabolol (6.81%), α-terpinene (5.44%), and α-phellandrene (4.63%) as the main constituents. p-Cymene (2.13%), sabine (1.98), and α-pinene (1.43%) were determined as the minor constituents. The biochemical results showed that a mega dose of paracetamol induced the production of free radicals, which caused damage to hepatocytes and nephrocytes in rats. The aqueous extract of dill revealed high antioxidant properties and acted as an extracellular neutralizer of free radicals. Histopathological and histochemical observations showed severe damage in the liver. Supplementation with dill in paracetamol-intoxicated rats attenuated the damage to the liver.

Conclusion
The present study revealed that A. graveolens has antihapatotoxic properties that could minimize the deleterious effects generated by hepatotoxin paracetamol, and therefore it can be used as a potent antihapatotoxic agent.

Keywords:
Anethum graveolens, antioxidants, hepatoprotective, nephroprotective, rats, volatile compounds

Introduction
Anethum graveolens is a short-lived perennial herb. The A. graveolens fruit is oval, compressed, winged, and about a tenth of an inch wide. The genus name Anethum is derived from a Greek word meaning strong smelling. The Anethum spp. fruit is used as a spice and the fresh and dried leaves of the plant called dill are used as a condiment and in tea. The use of this plant for medicinal and consumption purposes has been recorded dating back to the Greek and Egyptian civilizations. The Egyptians used dill in the production of cosmetics and perfume. This aromatic herb was commonly used for flavoring and seasoning of various foods such as pickles, salads, sauces, and soups [1,2]. Dill fruits have a strong aromatic smell and taste but they lose these properties on cooking because of the loss of essential oils. Dill oil is extracted from the seeds, leaves, and stems of the plant, and is an essential oil used as flavoring in the food industry [1,3]. Further, chewing the seeds improves bad breath. Anethum spp. stimulates milk flow in lactating mothers and cures urinary complaints, piles, and mental disorders [4]. It has been reported that the aqueous extract of A. graveolens has a broad-spectrum antibacterial activity. The essential oil and extract of dill have been reported to possess various degrees of antymicobacterial activity and to exhibit strong antifungal activity [5,6]. Antioxidants are compounds that can delay, inhibit, or prevent the oxidation of oxidizable matters by scavenging free radicals and diminishing oxidative stress [7].
Herbs contain a wide variety of antioxidant phytochemicals or bioactive molecules that can neutralize the free radicals and thus retard the progress of many chronic diseases associated with oxidative stress and reactive oxygen species [8,9]. *A. graveolens* has been reported to contain flavonoids, phenolic, and essential oil [5]. The increased consumption of vegetables and herbs containing high levels of phytochemicals has been recommended to prevent or reduce oxidative stress in the human body [8–10]. Endogenous antioxidant defense mechanisms may be insufficient and hence dietary intake of antioxidant compounds is essential [11]. The intake of natural antioxidants has been associated with reduced risk for cancer, cardiovascular disease, diabetes, and diseases associated with aging [12]. The liver is associated with many important life functions; it has great capacity to detoxicate toxic substances and synthesize useful principles [13]. The extract of *A. graveolens* could protect the liver against high-fat-diet-induced oxidative damage in rats [14].

The crude extract of *A. graveolens* has been reported to have antihypercholesterolemia and antihyperlipidemic properties. The effect of *A. graveolens* extract on serum lipoproteins in hypercholesterolemic rats and the possible mechanism of action of a crude extract on liver enzymes activity have been studied [15]. The present study was designed to specifically investigate the antioxidant efficacy of the aqueous extract of *A. graveolens* against paracetamol drug-induced oxidative stress in albino rats.

### Materials and methods

#### Isolation and characterization of Anethum graveolens volatile compounds

Two hundred grams of dried fruit of *A. graveolens* were ground to a fine powder using an electric grinder. The essential oil was obtained by steam distillation in 3000 ml H$_2$O for 3 h using a Clevenger apparatus. The oil was dried over anhydrous sodium sulfate and filtered. Extraction was carried out in duplicate and the results were averaged. Analysis of the volatile compounds of the plant infusion was carried out using chromatographic techniques such as gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS).

#### Gas chromatography

The volatile oil of *A. graveolens* was thermally desorbed using a modified injector port directly on the front of a (DB5) (60 m × 0.32 mm internal diameter) fused-silica capillary column, in the oven of a Hewlett-Packard HP 5890 gas chromatograph, Agilent technologies company, USA and the temperature was increased from 45 to 240°C at a rate of 4°C/min. Kovat's indices were determined by coinjection of the sample with a solution containing homologous series of n-hydrocarbons (C$_6$–C$_{26}$) under the same conditions as described above. The separated components were identified by matching with NIST mass-spectral library data, and by comparison of Kovat's indices with those of authentic samples and with published data [16]. Quantitative determination was carried out on the basis of peak area integration. Retention indices of each compound were calculated from the standard alkane retention time and the peak retention time.

### Gas chromatography-mass spectrometry

Analyses were performed on an HP model 6890 GC, Thermoscientific company, USA interfaced to an HP 5791A mass selective detector (GC-MS), Thermoscientific company, USA which is used for mass spectral identification of GC components at (MS) an ionization voltage of 70 eV. A 30 m × 0.25 mm internal diameter (DF = 0.25 lm) DB-WAX bonded-phase fused-silica capillary column, Thermoscientific company, USA was used for GC. The linear velocity of the helium carrier gas was 30 cm/s. The injector and the detector temperatures were 250°C. The oven temperature was programmed from 40 to 240°C at 4°C/min and held for 50 min.

#### Preparation of plant infusion

Dry fruits of *A. graveolens* were purchased from Omdurman market in Khartoum State, Sudan. The dry fruits under study were ground separately and a quantity of 3 g was infused with 100 ml of freshly boiled water for 5 min, followed by filtration.

The infusion filtrate of *A. graveolens* was subjected to the following tests:

1. Quantitative determination of the total phenolic content (TPC) was performed using the Folin–Ciocalteu method [17].
2. Quantitative determination of antioxidant activity was performed according to the β-carotene bleaching method [18] and diphenyl picryl hydrazyl (DPPH) free radical scavenging assay [19].

### Biochemical study

#### Experimental animals

Adult male Swiss albino rats with initial weights ranging from 120 to 150 g were used as experimental animals for biochemical and histological studies. All animals were from the Breeding Unit of the National Research Centre (Cairo, Egypt). The animals were housed individually in stainless steel wire mesh cages and acclimatized for 1 week. Commercial standard pellets and tap water were supplied *ad libitum*.
Experimental design
Twenty-eight adult male albino rats were used for studying the effect of plant infusion on panadol (paracetamol)-induced free radicals and hepatotoxicity [20]. The rats were divided equally into four groups (seven rats in each group): group 1 (the normal control group) rats received tap water. Group 2 (the A. graveolens group) rats were given a supplement of freshly prepared aqueous extract of A. graveolens (3 g/100 ml water) for 30 days to examine the beneficial effects of the plant. Group 3 (the paracetamol group) rats received a single dose of paracetamol orally (2 g/kg of rat body weight) after 4 weeks (28 days) [20]. Group 4 (the protected group) rats received a supplement of freshly prepared A. graveolens (3 g/100 ml) for 28 days, and then received paracetamol (2 g/kg of rat body weight). The experiment duration was continued for 30 days. The rats were killed 2 days after the single oral dose of paracetamol (panadol).

Histological study
To examine the extent of cellular damage caused by paracetamol, the liver samples of experimental and control rats were fixed in 10% formalin saline for 24 h. Following a rinse with water, the tissues were dehydrated in graded series of alcohol, cleaned in xylol, and embedded in paraffin wax (58–60°C). Using a rotary microtome, 6-µm-thick sections were obtained. The sections were deparaffinized in xylene and hydrated in graded series of alcohol ranging from 100 to 90, 70, 50, and 30% and then in distilled water. Thereafter, the sections were stained with hematoxylin and counterstained with aqueous eosin for microscopic investigations [32]. The stained sections were mounted in DPX.

Histochemical study
Total proteins
The mercury bromophenol blue method was used for the histochemical demonstration of total proteins [33].

The polysaccharide inclusions
The periodic acid Schiff (PAS) method was applied for visualization of polysaccharide materials [34].

Statistical study
The data presented in the study were statistically evaluated as mean ± SE for each group. Statistical evaluation of the difference between the group mean values was carried out by analysis of variance (ANOVA) analysis. P values less than 0.05 were considered significant [35].

Results
Phytochemical analysis
Composition of the essential oil
Composition of the essential oil of A. graveolens fruits was established by GC and GC-MS. Figure 1 and Table 1 showed 40 identified compounds and their percentages were obtained by GC-MS as well as by the retention time listed in order of their elution from the capillary column used. Chemical identification of the volatile oil constituents was made on the basis of their retention indices and mass spectral data and authentic samples. According to GC-MS data, monoterpenes were the main constituents of the essential oil. The main volatile components were 7-α-hydroxy manool (24.43%), l-carvone (14.28%), limonene (13.9%), epi-α-bisabolol (6.81%), α-terpinene (5.44%), and α-phellandrene (4.63%). p-Cymene (2.13%), sabine (1.98), and α-pinene (1.43%) were the minor constituents.
Total phenolic content and antioxidant activity

The TPC in the *Anethum graveolens* aqueous extract was determined by Folin–Ciocalteu reagent and compared with the standard solutions of gallic acid equivalents (GAE); the result is presented as mg GAE/l. The TPC value of the dill aqueous extract was 2040 ± 14.7 mg/l (Table 2). The radical scavenging activity of the dill aqueous extract on β-carotene/linoleic acid and DPPH free radicals increased with increasing concentration of aqueous extract from 50 to 400 µg/ml. Table 2 also illustrates the percentage inhibition of β-carotene-linoleate and DPPH free radicals exhibited by the dill aqueous extract. The dill extract showed excellent radical scavenging activity, with percentage inhibition at the highest concentration of 400 µg/ml being 87.5 ± 2.7 and 89.7 ± 2.4% according to the β-carotene-linoleate method and DPPH free radicals method, respectively.

Biochemical results

Table 3 shows the effect of the aqueous extract of *Anethum graveolens* fruits on some antioxidant biomarkers (plasma TAC, plasma CAT activity, and erythrocyte GPx) in paracetamol-intoxicated rats. ANOVA analysis indicated that rats supplemented with the aqueous extract had a significant increase in all tested antioxidant biomarkers compared with control. Administration of paracetamol only recorded a significant decrease in TAC, CAT, and GPx compared with normal control rats. Rats treated with the aqueous extract before paracetamol administration showed a significant increase in all tested antioxidant biomarkers compared with paracetamol-intoxicated rats. In contrast, compared with normal control, the values of the aqueous extract-protected group returned to be comparable with control values.

Table 4 illustrates the effect of the aqueous extract of *Anethum graveolens* fruits on liver and kidneys functions in paranol-intoxicated rats. Plasma activities of ALT, AST, ALP, and GGT, and plasma levels of total proteins, albumin, total bilirubin, direct bilirubin, and indirect bilirubin of all studied groups were evaluated. The results of liver function tests revealed that activities of AST, ALT, ALP, and GGT as well as levels of plasma...
Table 3 Effect of paracetamol and Anethum graveolens extract on plasma total antioxidant capacity, plasma catalase, and cellular glutathione peroxidase in rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Biomarkers</th>
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<tr>
<td></td>
<td>TAC (mmol/l)</td>
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<tr>
<td>Control</td>
<td>1.15 ± 0.13^a 386.17 ± 28.02^a 0.16 ± 0.03^a</td>
</tr>
<tr>
<td>Extract</td>
<td>1.52 ± 0.18^b 398.38 ± 46.33^b 0.19 ± 0.2^b</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>0.92 ± 0.06^c 198.91 ± 19.54^c 0.12 ± 0.02^c</td>
</tr>
<tr>
<td>Paracetamol+extract</td>
<td>0.99 ± 0.10^c 364.76 ± 27.84^c 0.16 ± 0.02^c</td>
</tr>
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</table>

Data are presented as mean ± SD; CAT, catalase; GPx, glutathione peroxidase; TAC, total antioxidant capacity; Values in the same column with the same superscripts are not significant at p < 0.05.

Liver polysaccharides

Examination of thin sections of the liver of control rats showed the proteic inclusions in the hepatocytes as grayish blue irregular particles of various sizes against weakly to moderately stained ground cytoplasm. The nuclear chromatin and nucleoli were densely stained, indicating their rich content of proteic constituents (Fig. 3a). In Kupffer cells, the proteic inclusions are mainly localized at the periphery of the cytoplasm. The nuclei of these cells are moderately stained. In case of treatment with paracetamol, protein inclusions became smaller in size compared with those of control rats (Fig. 3b). Oral administration of A. graveolens plant extract showed normal distribution of the protein inclusions in the hepatocytes (Fig. 3c). In contrast, administration of A. graveolens plant extract before panadol displayed diffuse staining. A few hepatocytes displayed dense staining compared with others (Fig. 3d). The above results revealed that paracetamol causes a reduction in the content of protein materials in the liver of treated rats and the volume of this reduction is decreased with the treatment of the plant extract.

Table 4 Effect of paracetamol and Anethum graveolens extract on liver and kidney functions in rats

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Liver function tests</th>
<th>Kidney function tests</th>
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<tr>
<td></td>
<td>AST (U/l)</td>
<td>ALT (U/l)</td>
</tr>
<tr>
<td>Control</td>
<td>61.57±4.28</td>
<td>16.43±1.54</td>
</tr>
<tr>
<td>Extract</td>
<td>59.00±3.22</td>
<td>14.50±2.81</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>85.00±5.48</td>
<td>29.57±2.64</td>
</tr>
<tr>
<td>Paracetamol +extract</td>
<td>74.57±3.51</td>
<td>30.17±3.10</td>
</tr>
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</table>

All data are presented as mean ± SE; ALP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; GGT, γ-glutamyl transferase; All values in the same column with the same superscripts are not significant at p < 0.05.
Oral administration of *A. graveolens* plant extract resulted in normal distribution of the polysaccharide inclusions in the hepatocytes (Fig. 4c).

Oral administration with paracetamol plus *A. graveolens* plant extract before panadol administration led to diffuse staining. A few hepatocytes displayed dense staining compared with others (Fig. 4d). Thus, it was seen that paracetamol causes a reduction in the amount of polysaccharide materials in the liver of treated rats. The degree of this reduction is decreased with the treatment of *A. graveolens* plant extract.

### Discussion

The present results indicated that there are 40 volatile compounds in *A. graveolens* (dill) fruits according to their elution order on the DB5 column, with 7-α-hydroxy manool (24.43%), 1-carvone (14.28%), limonene (13.9%), epi-α-bisabolol (6.81%), α-terpinene (5.44%), and α-phellandrene (4.63%).
being the main constituents and \( p \)-cymene (2.13%), sabinene (1.98), and \( \alpha \)-pinene (1.43%) being the minor constituents. Terpenes were the most abundant volatiles detected in \( A. \) graveolens. Dill oil contains carvone and \( d \)-limonene, which together represent a high percentage of the compounds identified by GC-MS [5]. The aroma compound of dried dill stems (\( \alpha \)-phellandrene) was identified. \( \alpha \)-Phellandrene, the main constituent of dill aroma, greatly contributes to the sensory impression of the dill herb. The content of dill ether in dried samples is significantly lower than that in fresh dill. Dried dill stems contain more of \( p \)-cymene than do fresh ones [36]. The hexane extract of \( A. \) graveolens contains volatile components such as \( \alpha \)-phellandrene, which has been detected as a major compound, as well as \( \beta \)-phellandrene, \( \alpha \)-pinene, and \( \beta \)-pinene. Cultivation conditions may have an effect on the bioactivity and phytochemical content of dill samples [37]. The chemical composition of dill volatile oil varies depending on the plant parts. Rădulescu et al. [38] reported that the main compound in the essential oil was carvone (75.21%), whereas the content of \( \alpha \)-phellandrene was only 0.12% and that of limonene was 21.56%. The essential oil from the dried leaves, flowers, and fruits of \( A. \) graveolens cultivated in Romania was isolated by hydrodistillation and analyzed with GC-MS. The main components in leaves were \( \alpha \)-phellandrene (62.71%), limonene (13.28%), and anethofuran (16.42%). The main components in flowers were \( \alpha \)-phellandrene (30.26%), limonene (33.22%), and anethofuran (22%). Carvone and limonene are the major constituents of fruit volatile oil. Monoterpenic hydrocarbons are predominant in fruit oil. Anethofuran (dill ether) is present in leaves and flowers at a proportion of 16.42 and 22%, respectively, but is missing in fruit oil [39]. These data agree with our results with some differences that were observed in dill phytochemical contents. It has been proved that the method of distillation could affect the chemical composition in essential oils. Chemical variations were observed in the essential oil of the same dill sample obtained by hydrodistillation and microdistillation. In addition to the method of distillation, the duration of distillation is another critical factor that may influence the essential oil composition [40]. One of the major classes of natural antioxidants found in the studied plant that could remove free radicals is polyphenol. The presence of phenolic compounds and essential oil in \( A. \) graveolens has been reported [5]. Polyphenols are able to neutralize free radicals, scavenge singlet and triplet oxygen, and break down peroxides. The TPC in dill aqueous extract was evaluated using the Folin–Ciocalteu method [17]. The extract showed a high level of TPC (2040 ± 14.7 mg/l). The method of determination of the level of total phenolics is not based on absolute measurements of the amount of phenolic compounds but on their chemical reducing capacity relative to gallic acid. It is very important to note that there is a positive relationship between the antioxidant activity potential and the amount of phenolic compounds in the extract. From the phenol antioxidant index a combined measure of the quality and quantity of antioxidants in herbs has been obtained [41]. The excellent antioxidant activity of the aqueous extract of dill showed 87.5 ± 2.7% scavenging activity against \( \beta \)-carotene-linoleate and 89.7 ± 2.4% scavenging activity against DPPH radical when compared with the synthetic antioxidant tert-butyl hydroquinone at the same concentration of 400 μg/ml (Table 1). Our result is compliant with many studies on dill extract of Thia and Turkish origin [5,40,42]. The excellent antioxidant activity of dill aqueous extract is attributed not only to the presence of a high content of polyphenols but also to that of volatile constituents that are present abundantly in dill fruits. These components could change free radicals such as DPPH to nonradical DPPH-H. Monoterpenes are the main chemical constituents of dill essential oil and are found as mixtures of odoriferous components that can be obtained by steam distillation or solvent extraction from a large variety of aromatic plants. Recent works have demonstrated that monoterpenes may present important pharmacological properties, including antioxidant activity. Monoterpenes with oxygen in their structure constitute a wide group of antioxidant molecules, largely because of their functional groups (alcohols) [43,44].

Our data showed for the first time the antioxidant activity of dill aqueous extract on Swiss albino rats treated with a supratherapeutic dose of paracetamol. Rats supplemented with the aqueous extract (group 2) recorded a significant increase in all tested antioxidant biomarkers – TAC, CAT, and GPx – compared with normal control rats. This pointed to its effect as a powerful activator of antioxidant status in normal rats besides its effect as a free radical scavenger and strong antioxidant in vitro (Table 2). The major metabolic pathways of paracetamol are glucuronidation and sulfation. Under normal conditions, about 5% of paracetamol is metabolized through the cytochrome P450 system, leading to the formation of the highly reactive intermediate \( N \)-acetyl-benzoquinone imine (NAPQI) [45]. NAPQI is conjugated with glutathione and eliminated until glutathione and available liver sulfur stores become critically low. If NAPQI is not removed, it binds to critical intracellular molecules and eventually leads to toxicity and cell death. Glutathione, in its reduced (GSH) and oxidized (GSSG) forms, is the main intracellular thiol redox system in erythrocytes [46]. One of its major functions is the detoxification of reactive electrophiles and toxic
oxygen metabolites generated during the metabolism of endogenous and exogenous substances [47]. Intermediates such as hydrogen peroxide and hydroperoxides are reduced by GPx at the expense of GSH. Some studies showed that acute paracetamol overdose can deplete erythrocyte GPx [48]. Moreover, paracetamol overdosing in rats produced significant changes in glutathione, glutathione-dependent enzymes, and antioxidant status [49]. Drugs that lead to the depletion of GSH or influence the activity of any of these GSH-dependent enzymes may result in toxic responses. Glutathione makes a complex with NAPQI in the liver [50] and the depletion of the former increases the risk of hepatotoxicity [51]. CAT is an enzymatic antioxidant widely distributed in all animal tissues. The decreased activity of CAT may be due to these free radicals generated by paracetamol. Treatment with dill aqueous extract significantly (\( P < 0.05 \)) increases the activity of GPx and CAT. Thus, these finding suggest that the aqueous extract contains free radical scavenging activity and is rich in phenolics (2040 ± 14.7 mg GAE/l) besides volatile compounds, mainly monoterpenes hydrocarbones and oxygenated monoterpenes, which could exert a beneficial action against pathophysiological alterations caused by the highly reactive intermediate NAPQI free radicals, indicating the regeneration of damaged liver cells.

The present study indicated that dill aqueous extract is a good source of antioxidants and could be used to reduce biological oxidative stress and prevent cellular damage by scavenging free radical activity of the oxidative stress. As shown in Table 3, paracetamol overdose caused a significant increase (\( P<0.05 \)) in liver biomarkers (AST, ALT, ALP, GGT, total bilirubin, direct bilirubin, and indirect bilirubin), indicating significant liver damage. This finding suggested that mega doses of paracetamol induce the production of free radicals, which cause damage to the hepatocytes of rats. This result correlates with the finding of Yakubu et al. [11] who demonstrated that the toxicity of paracetamol occurs when it is taken in high amounts. The elevations of plasma liver enzymes indicated liver damage and this correlates with the report of Sai et al. [52]. Increased plasma bilirubin levels in paracetamol-intoxicated rats (group 3) could be looked upon as a compensatory/retaliatory phenomenon in response to cellular peroxidative changes, which cause damage to the biliary gland. This is because bilirubin functions in vivo as a powerful antioxidant, antimutagen, and an endogenous tissue protector [53]. The significant (\( P < 0.05 \)) reduction in total protein and albumin levels in paracetamol-intoxicated rats also indicated cellular damage. The damage produced might be due to the functional failure of endoplasmic reticulum, which leads to a decrease in protein synthesis [54]. In contrast, administering albino rats with dill aqueous extract caused a significant decrease (\( P \leq 0.05 \)) in all previous liver function enzymes, and they reached near control values (Table 3). These findings indicated the ability of the extract to protect hepatocytes from oxidative damage caused by paracetamol overdose. Reduction of bilirubin and elevation of total protein and albumin levels in protected rats (group 4) indicated stabilized biliary cell function and endoplasmic reticulum leading to bile acid and protein synthesis [55].

It was noted in the present study that the liver is not the only target organ of paracetamol; it causes free radical generation in other organs such as the kidneys as well. The significant increase in urea and creatinine in paracetamol-intoxicated rats revealed the toxic effect of paracetamol overdose on kidneys. Dill aqueous extract contains powerful antioxidant components that serve as an extracellular neutralizer of free radicals. Rich polyphenols and volatile compounds in dill possess antioxidant capacity and improve the normal renal function as shown in Table 4.

In the present study, the histopathological investigations supported the biochemical findings. The paracetamol-treated rats showed necrosis, vacuoles, space formation, and loss of cell boundaries in the liver. Oral administration of A. graveolens before paracetamol administration reverted the above-mentioned changes in the liver to near normal. Coen et al. [56] reported marked changes in the liver, such as vacuolated hepatocytes, necrosis, and congested sinusoids, in paracetamol-treated rats. Oliveira et al. [57] reported that administration of α-amyrin and β-amyrin to paracetamol-treated rats resulted in a normal histoarchitecture in the liver. Furthermore, Yanpallewar et al. [58] and Yadani et al. [59] reported that the administration of Azadirachta indica to paracetamol-treated rats gave a normal histoarchitectural pattern to the liver.

The present study showed a decrease in the carbohydrate and protein content in the liver of paracetamol-intoxicated rats, as reported by Chen et al. [60]. The authors stated that initiation of lipid peroxidation, necrosis, and subsequent impairment in cellular metabolism collectively altered the major cellular components, including protein and glycogen.

Reid and Li [61] found that reactive oxygen species may activate the ubiquitin proteasome pathway. Proteasomes are very large protein complexes located in the nucleus and cytoplasm in all eukaryotes [62]. The main function of the proteasome is to degrade un-needed or damaged proteins by proteolysis.
Proteasomes are part of a major mechanism by which cells regulate the concentration of particular proteins and degrade misfolded proteins.

The presence of phenolic compounds and essential oil in *A. graveolens* has been reported [5]. Polyphenols are able to neutralize free radicals, scavenge singlet and triplet oxygen, and break down peroxides.

**Conclusion**

The present study revealed that the *A. graveolens* extract has antihepatotoxic properties that may minimize the deleterious effects generated by hepatotoxin paracetamol. Thus, it could be used as a potent antihepatotox agent. Also, the extract should be encouraged in diets as it could be used as a functional food to prevent liver and kidneys damage because of its antioxidant properties. Moreover, dill could be recommended for clinical trial as hepatic support.

**Acknowledgements**

**Conflicts of interest**

None

**References**


