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ORIGINAL ARTICLE

Protective effect of some plant oils on diazinon induced hepatorenal toxicity in male rats

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Abstract Environmental pollution and exposure to environmental pollutants are still some of the major global health issues. Pesticides have been linked to a wide range of health hazards. The toxicity of pesticides depends on several factors such as its chemical properties, doses, exposure period, exposure methods, gender, genetics, age, nutritional status and physiological case of exposed individuals. Medicinal plants, natural products and nutrition continue to play a central role in the healthcare system of large proportions of the world's population. Alternative medicine plays an important role in health services around the world. The aim of this study was to investigate the effect of olive, sesame and black seed oils on hepatorenal toxicity induced by diazinon (DZN) in male rats. The experimental animals were divided into nine groups. The first group served as control. The second group was exposed to DZN. The third group was treated with olive oil and DZN. Rats of the fourth group were subjected to sesame oil and DZN. Rats of the fifth group were exposed to black seed oil and DZN. The sixth, seventh and eighth groups were supplemented with olive, sesame and black seed oils respectively. Rats of the ninth group were treated with corn oil. Levels of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, creatinine, blood urea nitrogen and malondialdehyde were significantly increased in rats exposed to DZN. Moreover, levels of serum glutathione and superoxide dismutase were significantly decreased. Several histopathological changes were observed in the structures of liver and kidney due to DZN exposure. This study showed that these oils attenuated the physiological disturbances and histopathological alterations induced by DZN intoxication. Moreover, the antioxidant properties of these oils support the bioactive roles of its protective effects on DZN toxicity. This study therefore suggests that these oils could be used as preventive factors against the toxicity of DZN due to its antioxidant properties.

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1. Introduction

Environmental pollution is tangled with unsustainable anthropogenic activities, resulting in substantial public health problems. The significance of environmental factors to the health and well-being of human populations' is increasingly apparent

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(Rosenstock, 2003; WHO, 2010). The occurrence of harmful chemicals in the environment has become an issue of great debate in recent decades (Bao et al., 2015). Environmental pollution caused by pesticide residues is a major concern due to their extensive use in agriculture and in public health programs (Waliszevski et al., 1996). Organophosphorus compounds are one of the most common types of organic pollutants found in the environment (Tang et al., 2009). Toxicities of organophosphorous insecticides cause adverse effects on many organs (Gupta, 2006). Systems that could be affected by organophosphorous insecticides are the nervous system, immune system, liver, muscles, urinary system, reproductive system and hematological system (Benjamin et al., 2006; Al-Attar, 2009, 2010, 2015; Al-Attar and Al-Taisan, 2010; Al-Attar and Abu Zeid, 2013; Holy et al., 2015; Tian et al., 2015; Abdel-Daim, 2016; Judge et al., 2016; Li et al., 2016; Mehri et al., 2016). Diazinon (DZN), $C_{12}H_{21}N_2O_3PS$, is an organophosphorous insecticide which is widely and effectively used throughout the world with applications in agriculture and horticulture for controlling insects in crops, ornamentals, lawns, fruit, vegetables and other food products (Grafitt et al., 2002; Tang et al., 2009; Sarabia et al., 2009). The main mechanism of action of DZN is acetyl-cholinesterase enzyme inhibition (Kamanyire and Karalliedde, 2004). Moreover, several investigations have showed that DZN was capable of inducing histopathological, biochemical and physiological alterations (Al-Attar, 2009, 2015; Al-Attar and Al-Taisan, 2010; Al-Attar and Abu Zeid, 2013; Abdel-Daim, 2016).

In recent years, interest has increased in using natural products for pharmacological purposes, as a form of complementary or replacement therapy. Herbal medicine is increasingly gaining acceptance from the public and medical professionals due to advances in the understanding of the mechanisms by which herbs positively influence health and quality of life (Panda and Naik, 2009). The use of herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for treatment of various health challenges in different national healthcare settings (WHO, 2004).

The olive tree (*Olea europaea* L.), family: Oleaceae, has been widely accepted as one of the species with the highest antioxidant activity via its oil, fruits, and leaves. It is well known that the activity of the olive tree by product extracts in medicine and food industry is due to the presence of some important antioxidant and phenolic components to prevent oxidative degradations. There is growing evidence that olive oil may have great health benefits including the reduction in coronary heart disease risk, the prevention of some cancers and the modification of immune and inflammatory responses (Keys, 1995; Stark and Mader, 2002; Visioli and Galli, 2002). Sesame (*Sesamum indicum*) is one year old seed and belongs to the Pedaliaceae family (Zavareh et al., 2008). Sesame is one of the richest dietary sources of lignan, phytoestrogiens which exist in it were known to humans from the beginning of civilization and they are mixed with human food because of having many benefits for health (Thompson et al., 1991). Moreover, the seeds of sesame are used as a demulcent in respiratory affections, infantile cholera, diarrhea, dysentery and other bowel infections and bladder diseases. The seed powder is useful in amenorrhea, dysmenorrhea, ulcers and bleeding piles. Unsaponifiable matter (sterols), fibers as well as lignan-type compounds such as sesamin, sesamolin, sesamol and sesaminol are recognized to be potent therapeutic agents (Namiki, 2007). *Nigella sativa* (commonly known as black seed and black cumin), is a dicotyledon of Ranunculaceae family. The oil and seed constituents have shown potential medicinal properties in traditional medicine (Salem, 2005). The seeds of *N. sativa* have long been used in the middle and far east as a traditional medicine for a wide range of illnesses including bronchial asthma, headache, dysentery, infections, obesity, back pain, hypertension and gastrointestinal problems (Schleicher and Saleh, 1998; Al-Rowais, 2002). Thymoquinone is the most potent and pharmacologically active constituent in the volatile oil of seeds of *N. sativa*. It has been reported to have various therapeutic effects such as antiinflammatory, antibacterial, antifungal, antiparasitic, antiasthmatic, antidiabetic, anticancer and antioxidant (Houghton et al., 1995; Worthen et al., 1998; Galaly et al., 2014; Saravanan et al., 2014; El-Sheikh et al., 2015; Erboga et al., 2016). The present study is aimed to investigate the effect of olive, sesame and black seed oils on hepatorenal injury induced by DZN intoxication in male rats.

2. Materials and methods

2.1. Animals model

Male albino rats of the Wistar strain (*Rattus norvegicus*), weighing 92.8–133.3 g were utilized in the present study. The experimental animals were obtained from the Experimental Animal Unit of King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia. Rats were acclimatized to the laboratory conditions for one week prior to the initiation of experimental treatments. The experimental animals were housed in standard plastic cages and maintained under controlled laboratory conditions of humidity (65%), temperature (20 ± 1 °C) and 12:12 h light: dark cycle. Rats were fed *ad libitum* on normal commercial chow and had free access to water. The experimental treatments were conducted in accordance with ethical guidelines of the Animal Care and Use Committee of King Abdulaziz University.

2.2. Experimental design

A total of ninety rats were randomly divided into nine experimental groups, ten of rats each. The experimental groups were treated as follows:

1. Rats of group 1 were untreated and served as controls.
2. Rats of group 2 were orally administrated with 50 mg/kg body weight of DZN in corn oil, daily for 6 weeks.
3. Rats of group 3 were orally supplemented with olive oil at a dose of 600 mg/kg body weight and after 4 h exposed to DZN at the same dose given to group 2, daily for 6 weeks.
4. Rats of group 4 were orally supplemented with sesame oil at a dose of 600 mg/kg body weight and after 4 h subjected to DZN at the same dose given to group 2, daily for 6 weeks.
5. Rats of group 5 were orally supplemented with black seed oil at a dose of 600 mg/kg body weight and after 4 h treated with DZN at the same dose given to group 2, daily for 6 weeks.

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6. Rats of group 6 were orally supplemented with olive oil at the same dose given to group 3, daily for 6 weeks.
7. Rats of group 7 were orally supplemented with sesame oil at the same dose given to group 4, daily for 6 weeks.
8. Rats of group 8 were orally supplemented with black seed oil at the same dose given to group 5, daily for 6 weeks.
9. Rats of group 9 were orally supplemented with corn oil at the same dose given to group 2, daily for 6 weeks.

2.3. Blood serum analyses

After six weeks, the experimental animals were fasted for 12 h, water was not restricted, and then anaesthetized with diethyl ether. Blood samples were collected from orbital venous plexus in non-heparinized tubes, centrifuged at 2500 rpm for 15 min and blood sera were then collected and stored at −80 °C. Serum samples were used to determine levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin, creatinine, blood urea nitrogen (BUN), glutathione (GSH), superoxide dismutase (SOD) and malondialdehyde (MDA). Serum levels of ALT and AST were evaluated using the method of Reitman and Frankel (1957). The method of (MacComb and Bowers (1972) was used to determine the level of serum ALP. The method of Szasz (1969) was used to measure the level of serum GGT. Serum level of total bilirubin was estimated using the method of Doumas et al. (1973). The level of serum creatinine was estimated using the method of Larsen (1971). The level of serum BUN was measured according to the method of Patton and Crouch (1977). Serum levels of GSH, SOD and MAD were determined using the methods of Beutler et al. (1963), Nishikimi et al. (1972) and Ohkawa et al. (1979) respectively.

2.4. Histopathological examination

After blood sampling, liver and kidney tissues were quickly isolated from each group, fixed in 10% buffered formalin. Fixed tissues were routinely processed, then embedded in paraffin, and cut into 4 μm thick sections; they were mounted on slides for hematoxylin and eosin staining. All liver and kidney sections were examined and photographed using binocular digital microscope (SCO Tech GmbH, Germany).

2.5. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS for windows, version 22.0). Each value is expressed as mean ± standard deviation (S.D.) and values were analyzed using a one-way analysis of variance (ANOVA) to determine differences between the mean values of experimental groups. *P*-values of less than 0.05 were considered as significant.

3. Results

Levels of serum ALT, AST, ALP, GGT, total bilirubin, creatinine, BUN, GSH, SOD and MDA in control, DZN, olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil treated rats are shown in Fig. 1(A–J). Statistically increases in the level of serum ALT were observed in rats exposes to DZN (47.9%) and sesame oil plus DZN (39.4) compared with control rats (Fig. 1A). Remarkable increases in the level of serum AST were observed in DZN (49.0%) and sesame oil plus DZN (19.8) treated rats as compared with control rats (Fig. 1B). Levels of serum ALP were statistically elevated in rats treated with DZN (59.6%) and sesame oil plus DZN (30.9%) compared with control rats (Fig. 1C). Serum GGT level was statistically enhanced in rats exposed to DZN (178.4%) and sesame oil plus DZN (35.6%) compared with control rats (Fig. 1D). There were significant increases in the level of serum total bilirubin in rats subjected to DZN (69.3%) and sesame oil plus DZN (77.2%) compared with control rats (Fig. 1E). Insignificant changes in the level of ALT, AST, ALP, GGT, total bilirubin were observed in rats treated with olive oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil (Fig. 1A–E). In comparison with control rats, levels of serum creatinine (36.1%) and BUN (16.5%) were markedly elevated in DZN treated rats (Fig. 1F and G). Levels of serum creatinine and BUN were statistically unchanged in rats treated with olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil compared with control rats (Fig. 1F and G). Levels of serum GSH were statistically decreased in rats treated with DZN (43.7%) and sesame oil plus DZN (24.2%) compared with control rats (Fig. 1H). In comparison with control data, the level of serum SOD (Fig. 1I) was significantly declined in rats administrated with DZN (31.1%) and sesame oil plus DZN (9.7%). Levels of serum MDA were statistically enhanced in rats exposed to DZN (39.4%) and sesame oil plus DZN (21.1%) as compared with control rats (Fig. 1J). In comparison with control rats, there were no significant alterations in levels of serum GSH, SDO and MDA observed in rats treated with olive oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil (Fig. 1H–J).

Liver histopathological results depicted in Figs. 2A–J showed the normal structure in control, olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil treated rats respectively. The liver sections of control, olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil treated rats showed normal liver cells or hepatocytes with preserved cytoplasm, prominent nucleus and nucleolus, and well brought out central vein. These cells are cuboidal epithelial cells arranged in anastomosing plates and cords. In classical lobules, the plates radiate from the central vein and cords alternate with sinusoids. After six weeks of DZN treatment (group 2), the treated rats revealed an abnormal morphology characterized by a damage of liver structure along with disarrangement of hepatic strands and rupture in hepatocytes. Several cells also show histological features of necrosis. Moreover, an enlargement of the sinusoids and vacuole formations in hepatocytes, dilation and congestion of blood vessels with hemorrhage, dense lymphocytic infiltration round the central vein and dark stained hepatocytic nuclei indicating cell pycnosis were noted (Fig. 2B and C).

Histopathological examination of kidney or renal sections of control, DZN, olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil treated rats are represented in Fig. 3A–J. Control

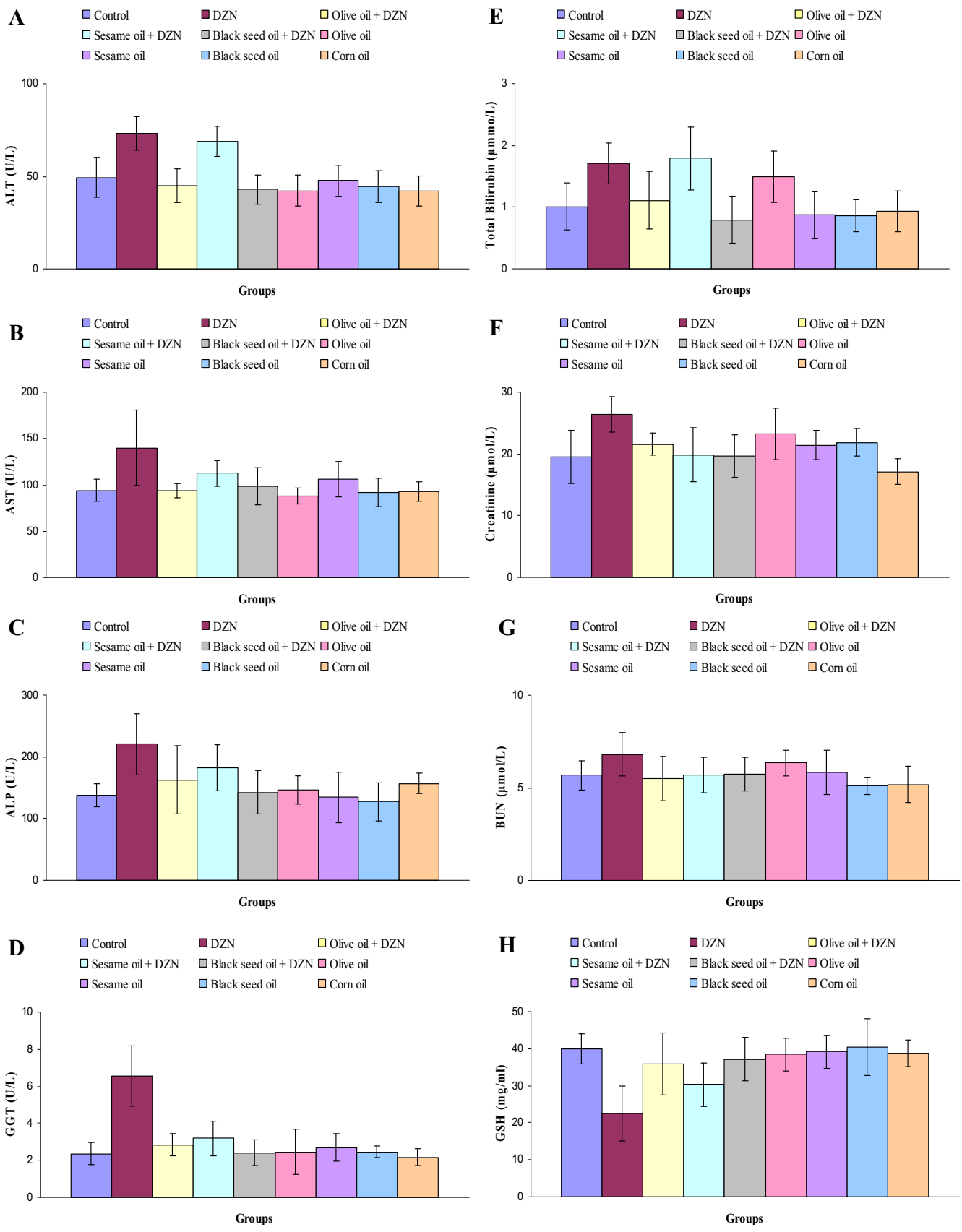

Figure 1 (A–J) Levels of ALT (A), AST (B), ALP (C), GGT (D), total bilirubin (E), creatinine (F), BUN (G), GSH (H), SOD (I) and MDA (J) in serum from control, DZN, olive oil plus DZN, sesame oil plus DZN, black seed oil plus DZN, olive oil, sesame oil, black seed oil and corn oil treated rats.

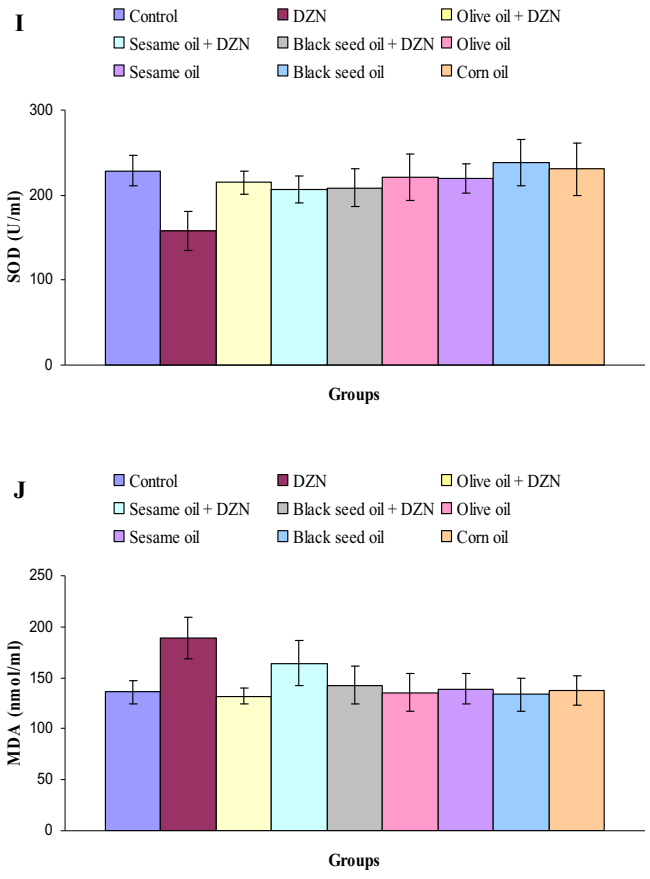

Fig. 1 (*continued*)

rats showed a normal structure of renal cortex and medulla. Fig. 3A showed the normal structure of renal (Malpighian) corpuscle. The normal renal corpuscle consists of a tuft of capillaries, the glomerulus, surrounded by a double-walled epithelial capsule called Bowman's capsule. Between the two layers of the capsule is the urinary or Bowman's space. Similar observations were noted in rats treated with olive oil plus DZN (Fig. 3D), sesame oil plus DZN (Fig. 3E), black seed oil plus DZN (Fig. 3F), olive oil (Fig. 3G), sesame oil (Fig. 3H), black seed oil (Fig. 3I) and corn oil (Fig. 3J). In rats treated with only DZN, there were several alterations in the structure of most renal corpuscles including a degeneration of glomeruli and Bowman's capsules (Fig. 3B and C).

4. Discussion

The present study was designed to evaluate whether pretreatment with olive, sesame and black seed oils would have protective influences on DZN induced hepatorenal injury in male rats. In the present study, levels of serum ALT, AST, ALP, GGT and total bilirubin were significantly higher in DZN treated rats, since necrosis or membrane damage releases these enzymes into circulation, which agrees with the previously reported results (Kew, 2000). Additionally, histopathological examination showed that DZN caused severe alterations. Similar physiological and histopathological observations were noted in experimental animals treated with DZN and other pesticides (Al-Attar, 2009, 2010, 2015; Al-Attar and Al-Taisan, 2010; Sarhan and Al-Sahhaf, 2011; Zari and Al-Attar, 2011; Padma et al., 2012; Al-Attar and Abu Zeid, 2013; El-Demerdash and Nasr, 2014; Farag et al., 2016; Mehri et al., 2016). Shakoori et al. (1990) reported that the increase of blood enzymatic activity is either due to (1) leakage of theses enzymes from hepatic cells and thus raising levels in blood, (2) increased synthesis and (3) enzyme induction of these enzymes. Moreover, ALT, AST, ALP, GGT and total bilirubin will leak into the serum resulting in elevating their serum concentrations. Serum levels of these parameters are very sensitive markers employees in diagnosis of liver diseases (de David et al., 2011).

In the present study, the kidney or renal function was evaluated by measuring levels of serum creatinine and BUN. Creatinine and BUN are waste products of protein metabolism that need to be excreted by the kidney, therefore a marked increase of these parameters, as observed in this study, confirms an indication of functional damage to the kidney (Panda, 1999). The present renal dysfunction was detected by significant increases of serum creatinine and BUN levels, and histopathological changes in rats exposed to DZN. However, the present increases of serum creatinine and BUN, and histopathological changes are generally in accordance with the findings of several studies showing increases of these parameters in experimental animals exposed to DZN and other pesticides (Attia and Nasr, 2009; Al-Attar, 2010, 2015; Al-Attar and Al-Taisan, 2010; Sarhan and Al-Sahhaf, 2011; Zari and Al-Attar, 2011; Padma et al., 2012; Al-Attar and Abu Zeid, 2013; Hou et al., 2014; Abdel-Daim, 2016; Farag et al., 2016; Li et al., 2016).

The present results showed that the administration of DZN caused statistically decreases in levels of serum GSH and SOD while the level of serum MDA was significantly increased. These findings are consistent with previous investigations which indicated that DZN and other pesticides caused oxidative damage which was confirmed by a significant decrease in levels of serum SOD and GSH, and increase in the level of serum MDA (Suke et al., 2008; Padma et al., 2011; Salehi et al., 2012; Abbassy et al., 2014; Mohamed and Ali, 2014; Beydilli et al., 2015; Eraslan et al., 2015).

The present results demonstrated that the treatment of rats with olive oil, sesame oil and black seed oil improved the physiological and histopathological alterations induced by DZN intoxication. This indicated the effectiveness of these oils in prevention of DZN toxicity. DZN and other organophosphate pesticides with amino acid serine phosphorylation in the active site of acetylcholinesterase enzyme leads to the inhibition of the enzyme and accumulation of acetylcholine in cholinergic synapses and cholinergic crisis, seizures and in acute cases, brain injury and death (Abdollahi et al., 2004; Kappers et al., 2001). Being under acute and sub-acute exposure of some organophosphates inhibits cholinesterase and increases the production of free radicals and oxidative stress. The reaction of free radicals with lipids in cell membranes causes lipid peroxidation and destruction of membrane structure. Harmful effects of free radicals are controlled by the cellular antioxidant defense system including antioxidant enzymes such as SOD, catalase (CAT). In addition, GSH, as an antioxidant, increases the solubility and excretion of toxins through the kidneys. The imbalance between production of free radicals and antioxidant defense systems in the body is called oxidative stress, which causes many diseases (Sleven et al., 2006; Limon-Pacheco and Gonsebatt, 2009).

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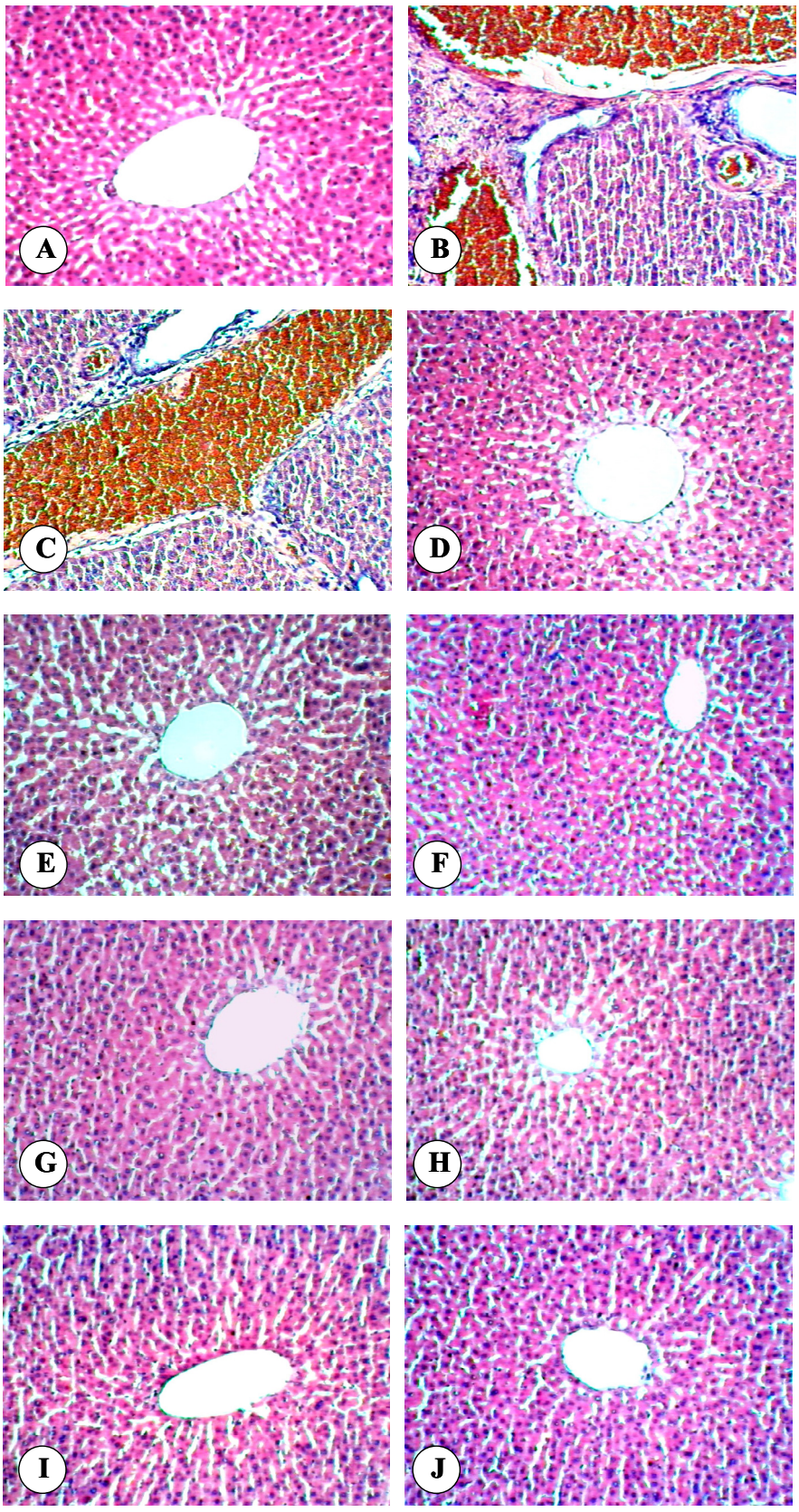

Figure 2 (A–J) Photomicrographs of liver sections of control (A), DZN (B and C), olive oil plus DZN (D), sesame oil plus DZN (E), black seed oil plus DZN (F), olive oil (G), sesame oil (H), black seed oil (I) and corn oil (J) treated rats. Original magnification ×200.

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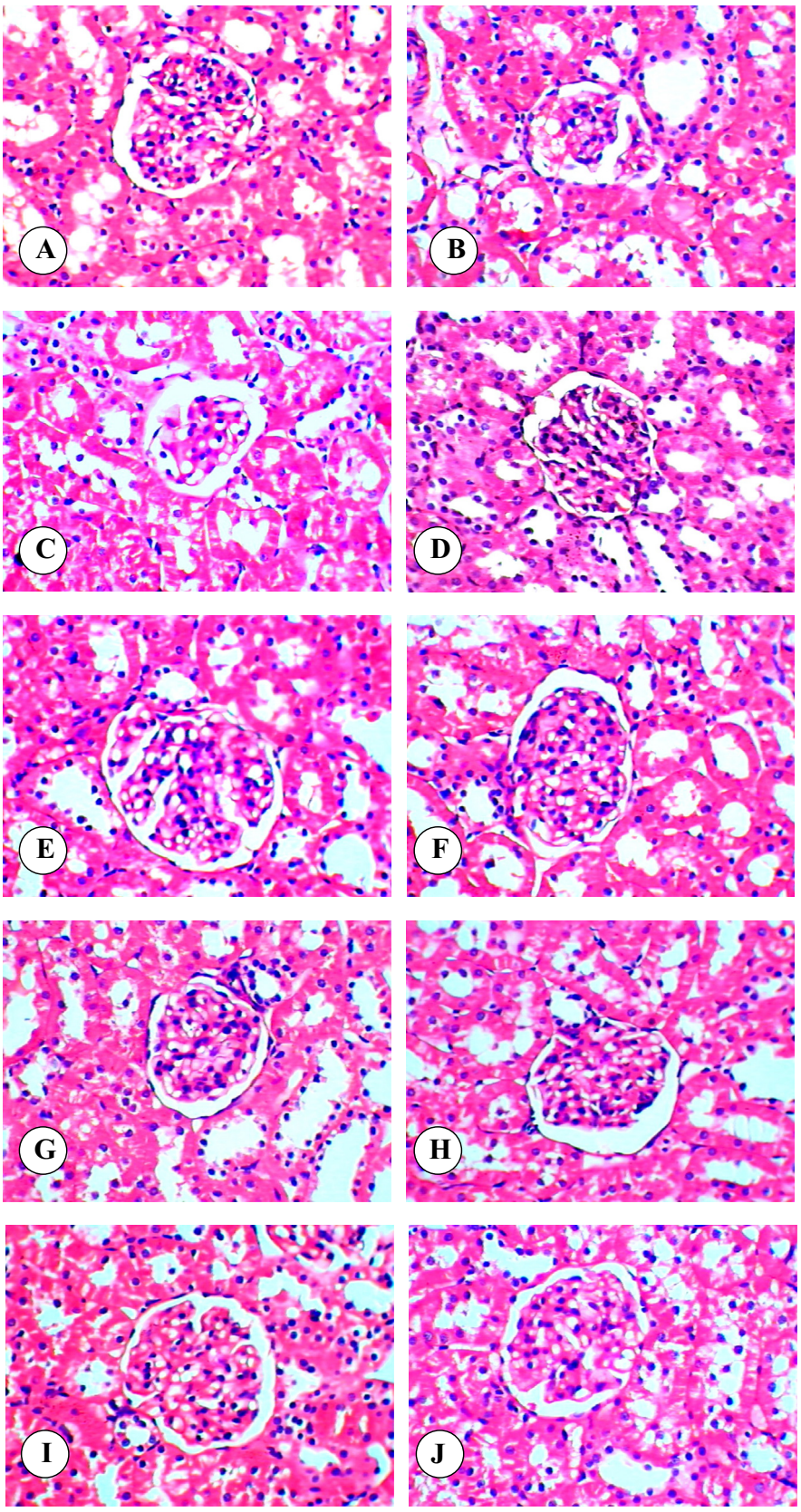

Figure 3 (A–J) Photomicrographs of renal corpuscles of control (A), DZN (B and C), olive oil plus DZN (D), sesame oil plus DZN (E), black seed oil plus DZN (F), olive oil (G), sesame oil (H), black seed oil (I) and corn oil (J) treated rats. Original magnification ×400.

The possible mechanism of the studied olive, sesame and black seed oils as protective factors may be due to its antioxidant effects which impair the activation of DZN into the reactive form. Dietary intake of antioxidants can inhibit or delay the oxidation of susceptible cellular substrates so prevent oxidative stress. Phenolic compounds such as flavonoids, phenolic acids, diterpenes, saponins and tannins have received much attention for their high antioxidative activity (Rice-Evan et al., 1996). Therefore, it is important to enrich our diet with antioxidants to protect against many chronic diseases related to oxidative damage (Rubiolo et al., 2008). In addition, antioxidants play an important role in food quality preservation due to their ability to prevent oxidative deterioration of lipids (Erukainure et al., 2012). Several experimental studies evaluated the effect of olive oil on physiological, biochemical, histopathological and oxidative alterations induced by chemical toxicants such as cadmium, mercury, aluminum, chromium and acrylamide. These studied showed that olive oil attenuated the effects of these chemical toxicants and treatments of olive oil provide evidences that it may have a therapeutic role in free radical mediated the antioxidants defense mechanism against the toxicity of these chemical toxicants (Mohammed et al., 2014; Necib et al., 2014; Amamou et al., 2015; Ghorbel et al., 2015; Saber et al., 2015).

Hussien et al. (2013) studied the protective effect of sesame oil against cypermethrin-induced brain toxicity in rats. The results showed that cypermethrin increased thiobarbituric acid-reactive substances (TBARS), and GSH and the activities of the antioxidant enzymes. Brain injury was confirmed by histopathological changes and DNA damage. Also, the reduction in the activities of acetylcholinesterase (AChE) and monoamine oxidase (MAO), total protein, albumin and body weight, and the induction in triacylglycerol and cholesterol have been observed due to cypermethrin toxicity. In addition, sesame oil protected the brain histological changes and fragmentation of genomic DNA in animals treated with cypermethrin. They showed a protective effect of sesame oil against the cypermethrin induced brain toxicity and this could be associated mainly with the attenuation of the oxidative stress and the preservation in antioxidant enzymes. Soliman et al. (2015) examined the protective effects of sesame oil on the genetic alterations induced by cypermethrin in the liver and kidney of Wistar male rats. Cypermethrin administration decreased both the activity and mRNA expression of the examined antioxidants. Sesame oil co-administration recovered cypermethrin, downregulating the expression of glutathione-S-transferase (GST), CAT, and SOD. Cypermethrin induced degenerative changes in the kidney and liver histology which are ameliorated by sesame oil. They concluded that sesame oil has a protective effect against alterations and pathological changes induced by cypermethrin in the liver and kidney at genetic and histological levels.

Attia and Nasr (2009) investigated the effect of dimethoate on oxidative stress, biochemical parameters and enzyme activities in rat males as well as possible role of black seed oil in attenuation of dimethoate-induced changes. The results showed that black seed oil may neutralize dimethoate-induced changes in biochemical parameters, lipid peroxidation by activation of the antioxidant defense system in rats. Erboga et al. (2016) examined the nephroprotective, antioxidant, and antiapoptotic effect of the thymoquinone, the primary bioactive component of black seed, against cadmium-induced nephrotoxicity. The histopathological studies in the kidney of rats also showed that thymoquinone markedly reduced the toxicity of cadmium and preserved the normal histological architecture of the renal tissue. Immunohistochemical analysis revealed that thymoquinone significantly decreased the cadmium-induced over expression of nuclear factor-κB in renal tissue. Furthermore, thymoquinone treatment resulted in a decrease in the number of apoptotic cells. Thymoquinone significantly suppressed lipid peroxidation, compensated deficits in the antioxidant defenses in renal tissue that resulted from cadmium administration. They suggested that the nephroprotective potential of thymoquinone in cadmium toxicity might be due to its antioxidant and antiapoptotic properties, which could be useful for achieving optimum effects in cadmium-induced nephrotoxicity.

Based on the present study, it can be concluded that this study shows for the first time that olive, sesame and black seed oils improve the hepatorenal alterations induced by DZN intoxication. Moreover, the most protective effects were observed in rats treated with olive oil and black seed oil followed by sesame oil. Additionally, the antioxidant properties of these oils support the bioactive roles of its protective effects on DZN toxicity. To strengthen these findings, further experimental studies are needed to evaluate the effect of different doses of these oils as therapeutic factors against the toxicity of DZN and other toxicants.

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