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Original article

Effect of *Nigella sativa* and *Foeniculum vulgare* seeds extracts on male mice exposed to carbendazim

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ABSTRACT

The increasing prevalence of environmental pollutants such as pesticides is a major global problem that affects living organisms. Exposure to environmental pollutants remains a major source of health risk throughout the world. The potential health benefits of various medicinal plants and natural products in relation to protect various diseases are currently receiving considerable attention. A current approach is to develop a new biological compound from natural products that inhibits pain. Ethnopharmacological surveys have been found to be one of the most reliable tools for the discovery of the natural and semi-synthetic drug. The present study was performed to investigate the hematological and biochemical changes induced by carbendazim (CBZ) and the potential protective effect of seeds extracts of Nigella sativa (NSSE) and *Foeniculum vulgare* (FVSE) against CBZ toxicity in male mice. Mice were distributed into 6 groups. Mice of group 1 were served as control. Group 2 was exposed to CBZ. Group 3 was supplemented with NSSE and exposed to CBZ. Group 4 was treated with FVSE and CBZ. Normal mice of group 5 and 6 were subjected to NSSE and FVSE respectively. Body weight gain was significantly decreased in mice of group 2. In mice of group 2, significant declines of RBC, HB, Hct, WBC, total protein, FSH, LH, testosterone, T4, T3, CAT and SOD were observed. Moreover, the levels of ALT, AST, ALP, total bilirubin, creatinine, BUN, uric acid, glucose, cholesterol, CK, LDH, MDA and GSH were significantly enhanced. Treatment with NSSE and FVSE showed attenuation effects against CBZ induced hematological and biochemical changes. The results suggest that the attenuation effects of NSSE and FVSE attributed to their antioxidant properties.

1. Introduction

Exposures to environmental pollution remain a major source of health risk throughout the world, though risks are generally higher in developing countries, where poverty, lack of investment in modern technology and weak environmental legislation combine to cause high pollution levels. Pollutants take many forms. They include chemicals, organisms and biological materials (Lindley et al., 1996). The number of potential pollutants is therefore essentially countless. Over the past three decades, there has been an increasing global concern over the public health impacts attributed to environmental pollution, in particular, the global burden of disease. Numerous studies have found an association between pollution and several adverse health effects in the general population. These effects range from subclinical effects to premature death (Briggs, 2003; Dragone et al., 2017; CDC, 2018). The World Health Organization estimated that about a quarter of the diseases facing mankind today occur due to prolonged exposure to environmental pollution (WHO, 2016; Appannagari, 2017; Rice, 2018). Pesticides in the environment have potential for unintended impacts to wildlife and humans. Pesticides disrupt essential biological processes, for example through affecting nerve transmission or mimicking hormones. Thus, human health concerns related to exposure via water, food, or close proximity to spraying have been raised (RCEP, 2005; DEFRA 2006). Due to their intrinsic properties, pesticides can also be harmful to organisms in the wider environment (Csillik et al., 2000). Mixtures of pesticides are common both in

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the human food supply (Hayes et al., 2006; Laetz et al., 2009). Though assessment of mixture toxicity has been a challenge, a single-chemical approach is likely to underestimate ecological risk. Carbendazim (CBZ), $C_9H_9N_3O_2$, is a member of the class of benzimidazoles that is 2-aminobenzimidazole in which the primary amino group is substituted by a methoxycarbonyl group. CBZ is a commonly used industrial fungicide with broad spectrum antifungal property and is used in the control of fungal pathogen in cereal and fruit crops (Mahob et al., 2014). It is well absorbed (80–85%) after oral exposure and is subsequently metabolized into many compounds within the organism (Zari and Al-Attar, 2011). The main metabolites are 5-hydroxy-2-benzimidazole carbamate and 5,6-HOBC-N-oxides. CBZ and the metabolites, are poorly catabolized but are retained in tissues such as gonads, liver, adrenals, adipose, skin and other organs (Barlas et al., 2002; Zari and Al-Attar, 2011; Lutz, 2012; Abolaji et al., 2017).

Historically, the use of medicinal plants dates back to the earliest times of humanity. Human societies have been in close contact with their environments since the beginning of their formation and used the ingredients of the environment to obtain food and medicine. The foundations of typical traditional systems of medicine for thousands of years that have been in existence have formed from plants. The plants remain to offer mankind with new medicines. Some of the beneficial properties ascribed to plants have recognized to be flawed and medicinal plant treatment is based on the experimental findings of hundreds to thousands of years**.** Medicinal plants have undoubtedly been considered by human beings since ancient times. Herbals especially medicinal herbs have constantly acted as an overall indicator of ecosystem health. Although many people nowadays use herbal medicines as a constituent of primary health care, there are still many concerns about the safety and efficacy of using plants (Singh, 2002; Singh, 2015; Dar et al., 2017; Jamshidi-Kia et al., 2018). The use of extractions and natural products from plants is an important resource for treatment, cure and prevention of different diseases and is often guided by the accumulated body of knowledge arising from the direct relationship between humans and the environment. Ethnobotany is the science responsible for the investigation of the relationship between products of medicinal plants and human (Araújo et al., 2012). Nigella sativa (Family: Ranunculaceae) is a widely used medicinal plant throughout the world. The seeds of N. sativa have been widely used in the treatment of different diseases and ailments. In Islamic literature, it is considered as one of the greatest forms of healing medicine. It has been recommended for using on regular basis in Tibb-e-Nabwi (Prophetic Medicine) (Al-Bukhari, 1976). The seeds of *N. sativa* are widely used in the treatment of various diseases like bronchitis, asthma, diarrhea and skin disorders. It is also used as liver tonic, digestive, anti-diarrheal, appetite stimulant, to fight parasitic infections, and to support immune system (Abdel-Sater, 2009; Abel-Salam, 2012). Many active compounds have been isolated in different varieties of black seeds. The most important active compounds are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), sesquiterpene longifolene (1%-8%) α-pinene and thymol etc (Nickavar et al., 2003; Cheikh-Rouhou et al., 2008). *Foeniculum vulgare* Mill. (Family: Apiaceae or Umbelliferaceae) commonly known as fennel and it is a well know and important medicinal and aromatic plant widely used as carminative, digestive, galactagogue and diuretic. Different pharmacological experiments in a number of in vitro and in vivo models have convincingly demonstrated the ability of *F. vulgare* to exhibit antifungal, antibacterial, antioxidant, antithrombotic and hepatoprotective activities, lend-ing support to the rationale behind several of its therapeutic uses (EMA, 2007; Badgujar et al., 2014). *F. vulgare* has been reported to contain 6.3% of moisture,9.5% protein, 10% fat, 13.4% minerals, 18.5% fibre and42.3% carbohydrates. The minerals and vitamins present in *F. vulgare* are calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin, niacin and vitamin C (Mishra et al., 2016; Mihats et al., 2017). Recently, there is no any experimental investigation about the potential protection of N. sativa and *F. vulgare* seeds extracts against carbendazim toxicity. Therefore the aim of present study is to evaluate the effect of CBZ toxicity on male mice and examine the possible protective effect of N. sativa and *F. vulgare* seeds extracts on CBZ -induced hematological and biochemical alterations.

2. Materials and methods

2.1. Animals

Healthy male albino mice with a body weight of 19–21 g were utilized in the present study. Mice were allocated 10 per standard cage and allowed to acclimatize for one week before starting the experimentations. Animals were fed *ad libitum* on normal commercial chow and had free access to water. Mean daily animal room temperature ranged from 20 °C to 21 °C and mean daily relative humidity ranged from 60% to 65% during the study. Light timers were set to provide a 12-hour light/12-hour dark photoperiod. The principles of laboratory animal care were followed through out the duration of experiment and instruction given by King Abdulaziz University ethical committee was followed regarding experimental procedure.

2.2. Extraction of N. Sativa and F. Vulgare seeds

Fine quality of N. sativa and *F. vulgare* seeds were purchased from a local market. The seeds were botanically authenticated and its identification was confirmed by a specialist of plant taxonomy. The seeds were cleaned, dried and powdered in an electrical grinder and stored at 5 °C until further use. Every seeds powder was extracted with a sufficient volume of 90% ethanol using Soxhlet extraction apparatus. Ethanol was evaporated at 40–50 °C under reduced pressure. The yield of extract was stored in a refrigerator for subsequent experimentations.

2.3. Experimental protocol

The mice were distributed into six groups (10 mice per group). Mice of group 1 were untreated and served as normal control group. Group 2 of the experimental animals was orally exposed to CBZ at a dose of 150 mg/kg body weight/ daily for 5 weeks. Mice of group 3 were orally supplemented with N. sativa seed extraction (NSSE) at a dose of 400 mg/kg body weight and after 3 h were exposed to CBZ at the same dose given to group 2/ daily for 5 weeks. Group 4 was orally supplemented with *F. vulgare* seed extraction (FVSE) at a dose of 400 mg/kg body weight and after 3 h was treated with CBZ at the same dose given to group 2/ daily for 5 weeks. Mice of group 5 and 6 were subjected to NSSE and FVSE at the same doses given to groups 3 and 4 respectively/ daily for 5 weeks.

2.4. Hematological and biochemical measurements

After five weeks, mice were fasted for 8 h, water was not restricted, and then blood samples were drawn from diethyl ether anaesthetized rats via orbital venous plexus. Blood specimens were collected into heparinized and non-heparinized tubes. The blood in heparinized tubes were immediately used for hematological measurements including red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (Hct) value and white blood cell (WBC)

count using automated hematology analyzers (BC-2800 vet.). For serum biochemical measurements, blood in non-heparinized tubes were centrifuged at 2000 rpm for 15 min and blood sera were then collected and stored at −80 °C till the determination time of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatinine, blood urea nitrogen (BUN), uric acid, glucose, total protein, cholesterol, creatine kinase (CK) and lactate dehydrogenase (LDH). All of these biochemical parameters were analyzed using an automatic analyzer (Dimension Vista® 1500 System, USA). The levels of serum follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, thyroid stimulating hormone (TSH), thyroxine (T4) and triiodothyronine (T3) were measured by the enzyme linked immunosorbent assay kits and radioimmunoassay kits according to the manufacturers' protocol. The methods of Aebi (1984), Nishikimi et al. (1972), Ohkawa et al. (1979) and Beutler et al. (1963) were used to evaluate the levels of serum catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) and glutathione (GSH) respectively.

2.5. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS for windows, version 22.0). All values were expressed as mean with their standard deviation and the values were statistically analyzed by one way analysis of variance to estimate differences between the mean values. $P \leq 0.05$ was considered significant.

3. Results

The body weight changes after five weeks of all experimental groups are represented in Fig. 1. Significant increases of body weight gain were noted in normal control group (+54.9%) and mice treated with NSSE plus CBZ (+53.2%), FVSE plus CBZ (+50.5%), NSSE (+55.1%) and FVSE (53.3%). The minimum increase of body weight gain was observed in mice exposed to only CBZ (+34.8%).

The values of RBC, Hb, Hct and WBC are shown in Fig. 2A-D. Statistically decreases in the value of RBC were observed in CBZ ($P \leq 0.000$), NSSE plus CBZ ($P \leq 0.05$) and FVSE plus CBZ ($P \leq 0.01$) treated mice. Similar decreases in the value of Hb were noted in rats of groups 2 ($P \leq 0.000$), 3 ($P < 0.05$) and 4 ($P \leq 0.02$). In animals treated with CBZ ($P \leq 0.000$), NSSE plus CBZ ($P \leq 0.05$) and FVSE plus CBZ ($P \leq 0.01$), Hct values were significantly decreased compared with control mice of group 1. CBZ caused significant decrease in WBC value of group 2 ($P \leq 0.000$). The values of WBC were not significantly different in mice treated with NSSE plus CBZ and FVSE plus CBZ compared with control rats of group 1.

The serum ALT, AST, ALP and total biltrubin exhibited significant increases in mice of group 2 ($P < 0.000$). Also, these results were observed in mice treated with NSSE plus CBZ ($P \leq 0.05$) and FVSE plus CBZ ($P \leq 0.02$) (Fig. 3A-D). Fig. 4A-D illustrates the levels of serum creatinine, BUN, uric acid and total protein in all experimental groups. The levels of serum creatinine, BUN and uric acid were significantly higher ($P \leq 0.000$) in CBZ-treated mice (group 2) than that of normal control mice. The levels of serum creatinine ($P \leq 0.02$), BUN ($P \leq 0.02$) and uric acid ($P \leq 0.03$) were statistically enhanced in NSSE plus CBZ treated mice. Moreover, FVSE plus CBZ -treated mice showed significant increases in the levels of serum creatinine ($P \leq 0.003$), BUN ($P \leq 0.002$) and uric acid ($P \leq 0.004$) compared with normal control group. The level of total protein was statistically decreased in animals of group 2 ($P \leq 0.05$), while this parameters was unchanged in mice of group 3 and 4.

The levels of serum glucose, cholesterol, CK and LDH are presented in Fig. 5A-D. CBZ exposure (group 2) induced significant increases in the levels of serum glucose ($P \leq 0.001$), cholesterol ($P \leq 0.000$), CK ($P \leq 0.000$) and LDH ($P \leq 0.000$) in comparison to untreated animals of group 1. The levels of serum glucose ($P \leq 0.05$), CK ($P \leq 0.03$) and LDH ($P \leq 0.01$) were evoked in mice of group 3. Significant increases in the levels of serum glucose ($P \leq 0.01$), cholesterol ($P \leq 0.05$), CK ($P \leq 0.01$) and LDH ($P \leq 0.01$) were detected in mice of group 4 compared with normal mice of group 1.

Fig. 6A-F shows the levels of serum FSH, LH, testosterone, TSH, T4 and T3. Significant declines were observed in the levels of serum FSH ($P \leq 0.02$), LH ($P \leq 0.01$), testosterone ($P \leq 0.01$), T4 ($P \leq 0.001$) and T3 ($P \leq 0.001$), while the level of TSH ($P \leq 0.000$) was increased in mice of group 2. No statistically significant differences of FSH, LH and testosterone levels were observed in mice of group 3, while the level of serum TSH ($P \leq 0.05$) was increased, and the levels of T4 ($P < 0.02$) and T3 ($P \leq 0.03$) were decreased. In mice treated with FVSE plus CBZ (group 4), the levels of serum FSH ($P \leq 0.03$), LH ($P \leq 0.03$), testosterone ($P \leq 0.05$), T4 ($P \leq 0.02$) and T3 ($P \leq 0.02$) were inhibited, while the level of TSH ($P \leq 0.02$) was evoked when compared with normal control mice.

The levels of serum CAT ($P \leq 0.000$) and SOD ($P \leq 0.001$) were decreased, while elevated MDA ($P \leq 0.000$) and GSH ($P \leq 0.000$) levels were observed in mice of group 2. In the animals subjected to NSSE plus CBZ, the level of serum CAT ($P \leq 0.05$) was decreased

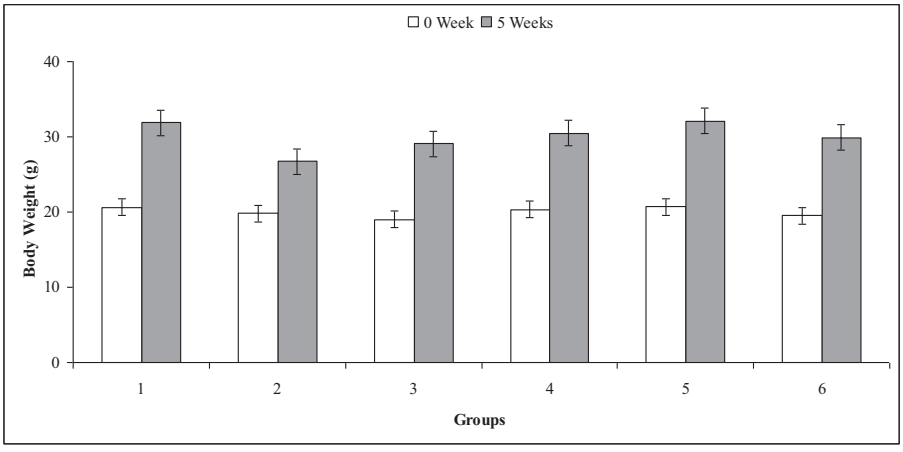

Fig. 1. Changes of body weight after five weeks in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice.

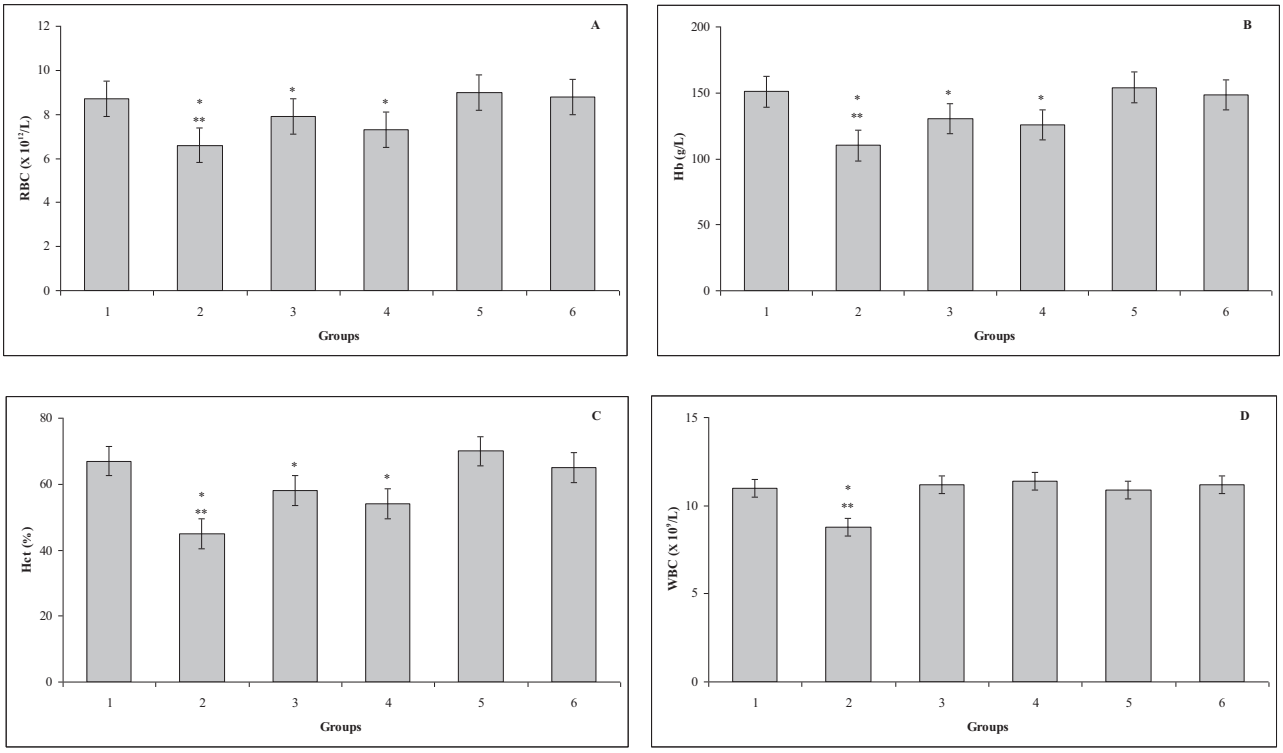

Fig. 2. (A-D) The values of RBC (A), Hb (B), Hct (C) and WBC (D) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

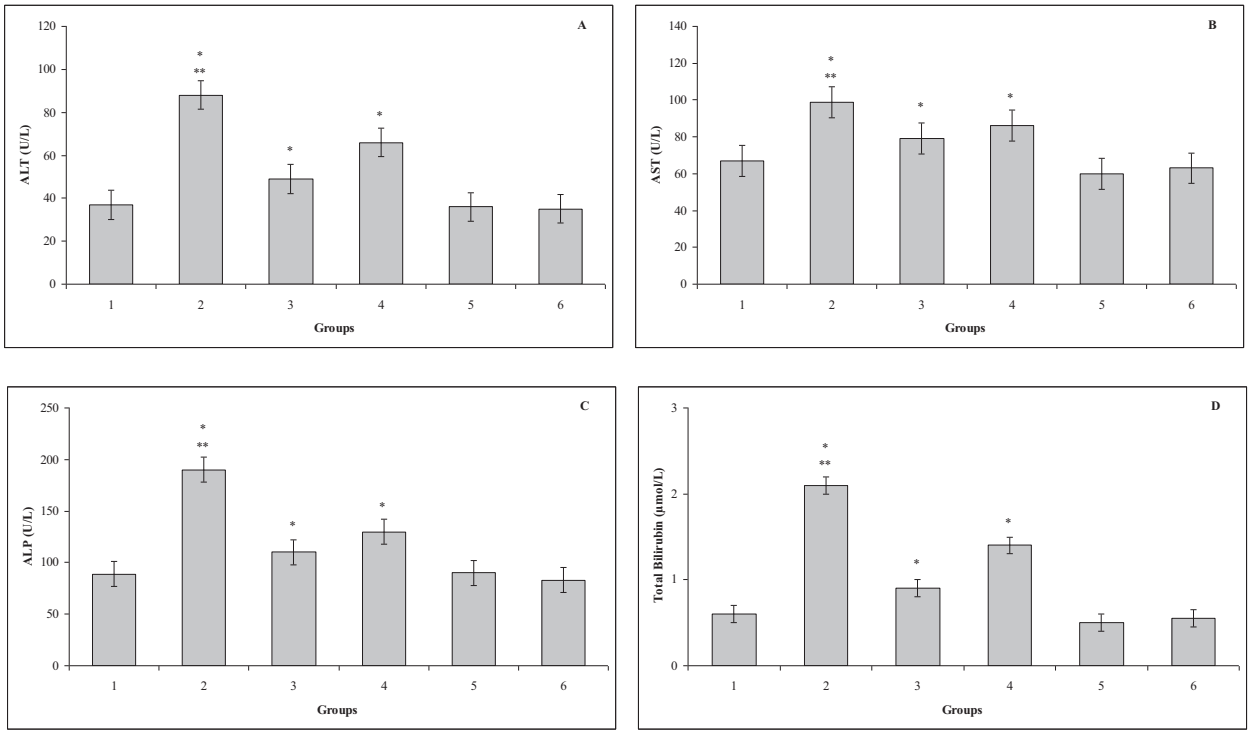

Fig. 3. (A-D) The levels of serum ALT (A), AST (B), ALP (C) and total bilirubin (D) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

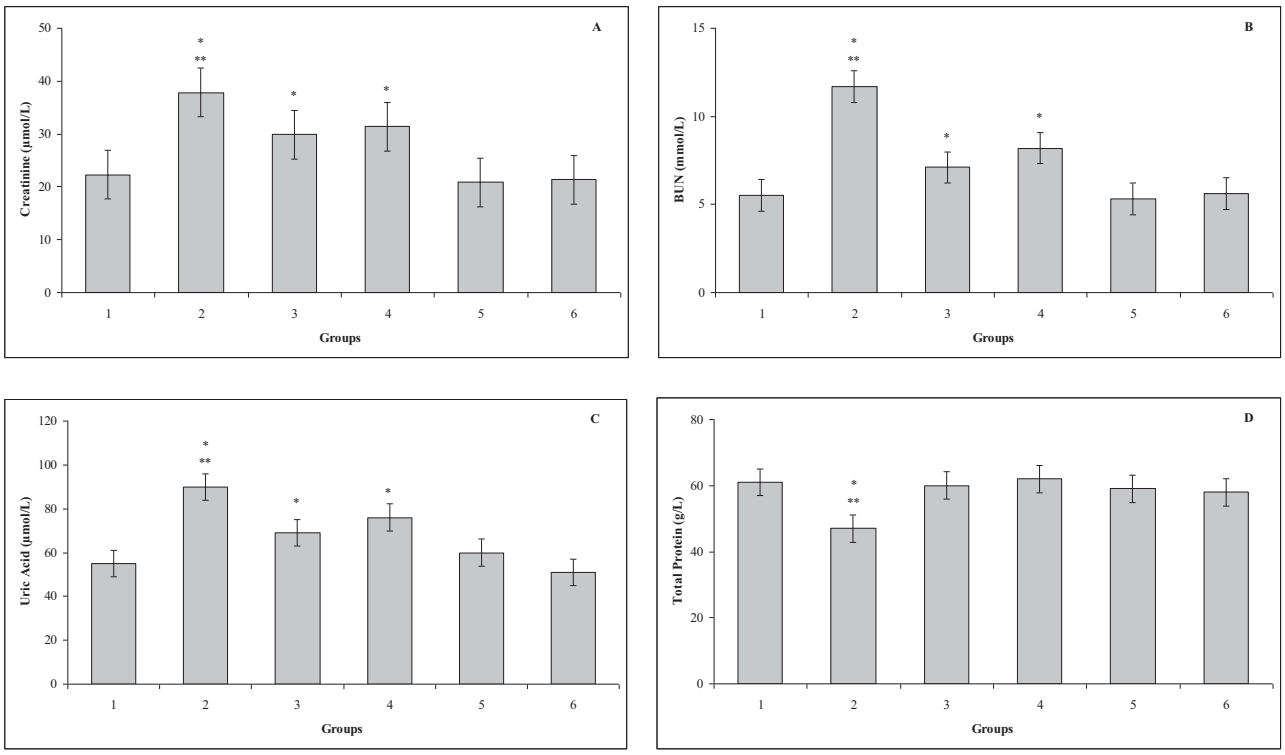

Fig. 4. (A-D) The levels of serum creatinine (A), BUN (B), uric acid (C) and total protein (D) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

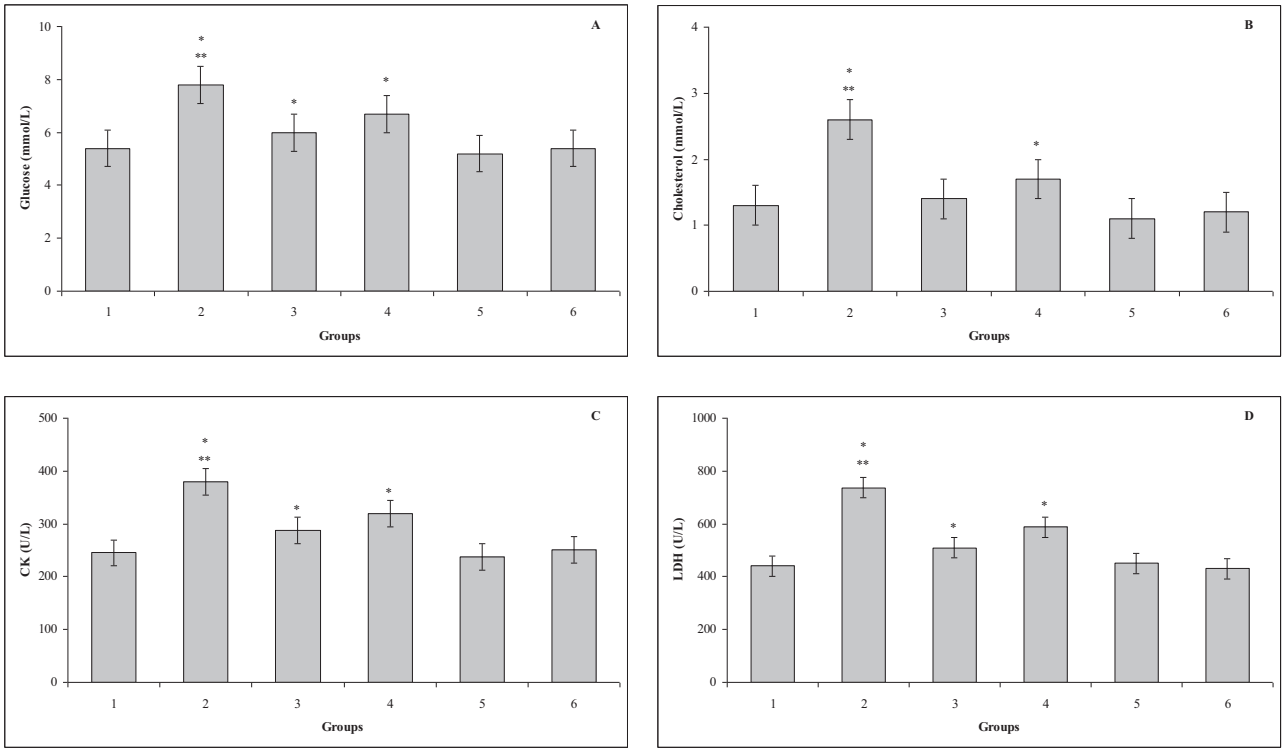

Fig. 5. (A-D) The levels of serum glucose (A), cholesterol (B), CK (C) and LDH (D) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

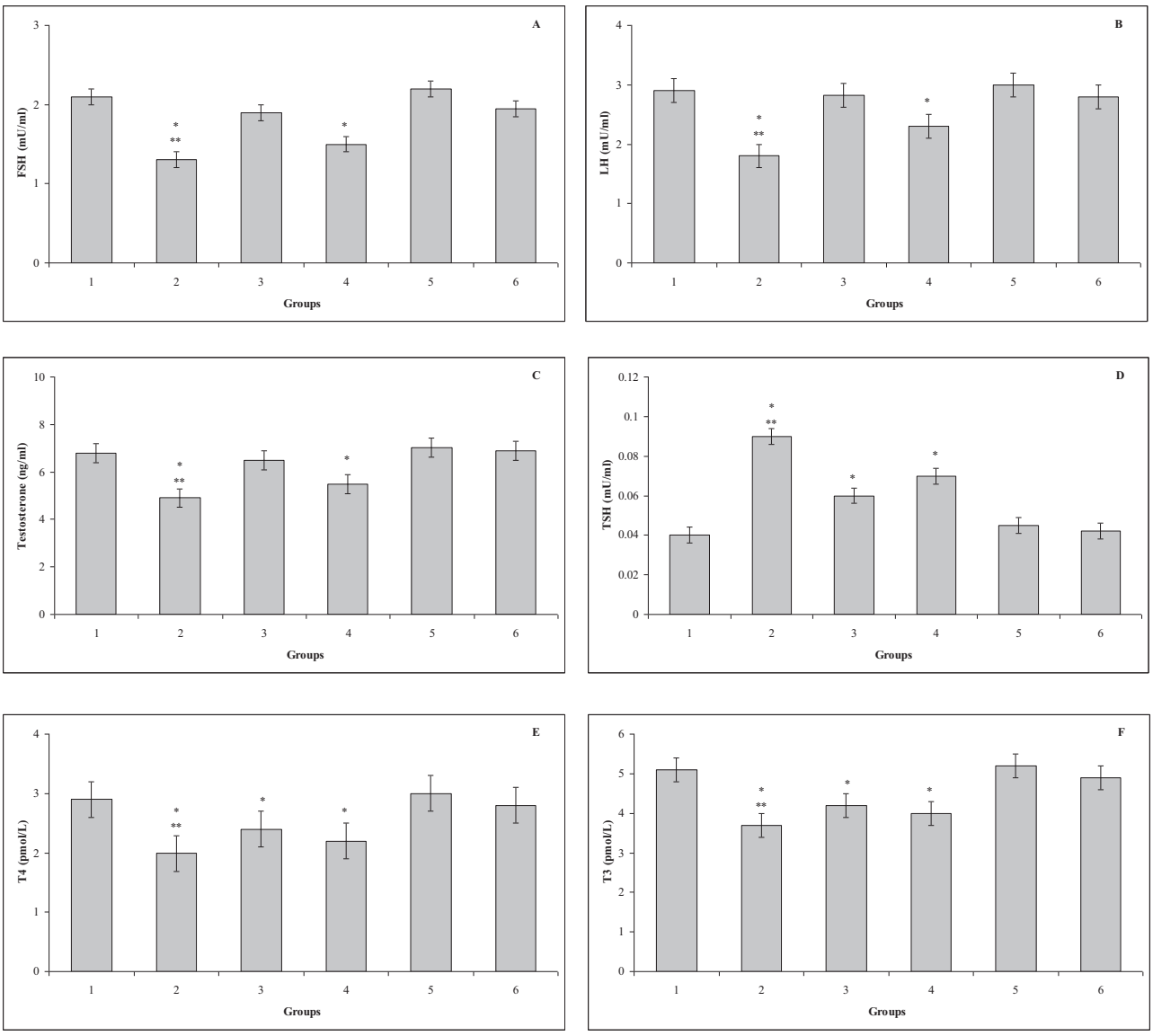

Fig. 6. (A-F) The levels of serum FSH (A), LH (B), testosterone (C), TSH (D), T4 (E) and T3 (F) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

and serum GSH was increased ($P \leq 0.02$), while the levels of serum SOD and MDA were significantly unchanged. The levels of serum CAT ($P \leq 0.01$) and SOD ($P \leq 0.05$) were declined in mice of group 4. Significant increases in the levels of serum MDA ($P \leq 0.01$) and GSH ($P \leq 0.01$) were observed in FVSE plus CBZ-treated mice when compared to normal control mice. Moreover, insignificant changes in the levels of all measured parameters were observed in normal mice supplemented with NSSE (group 5) and FVSE (group 5) (Fig. 7A-D).

4. Discussion

Environmental pollution is a worldwide problem and its potential to influence the health of human populations is great. Toxic chemicals are increasingly important causes of pollution worldwide (Fereidoun et al., 2007; Landrigan and Fuller, 2015). The diseases caused by pollution impose great economic costs on countries around the world—direct medical costs, opportunity costs reflecting the diminished productivity of populations damaged by pollution, and costs to health care systems (Landrigan and Fuller, 2015). Environmental contaminants especially pesticides are now responsible for the development of diseases both in wildlife and humans (Ye et al., 2013; Shin et al., 2017). Humans are exposed to these pesticides either directly as agricultural workers or indirectly through food consumption (Alam et al., 2019). Herbal medicines can be defined as raw or extracted products isolated from plants, and they are widely used for prevention and treatment of many chronic diseases because they have fewer side effects compared with pharmacological drugs (Park et al., 2011). Many plants are known to have medicinal and therapeutic properties because of their phytochemicals and have tremendous applications in pharmaceutical industry (Robles-Martínez et al., 2019).

In the present study, significant decrease in body weight gain recorded in mice administrated CBZ. Previous studies reported that the decrease in body weight might be due to the decrease in food consumption and/ or increase degradation of protein and lipids (Bailey et al., 2004; Mansour and Mossa, 2010; Nwozo et al., 2015). Administration of CBZ resulted in significant decrease of RBC, Hb, Hct and WBC values. The decrease of RBC, Hb and Hct val-

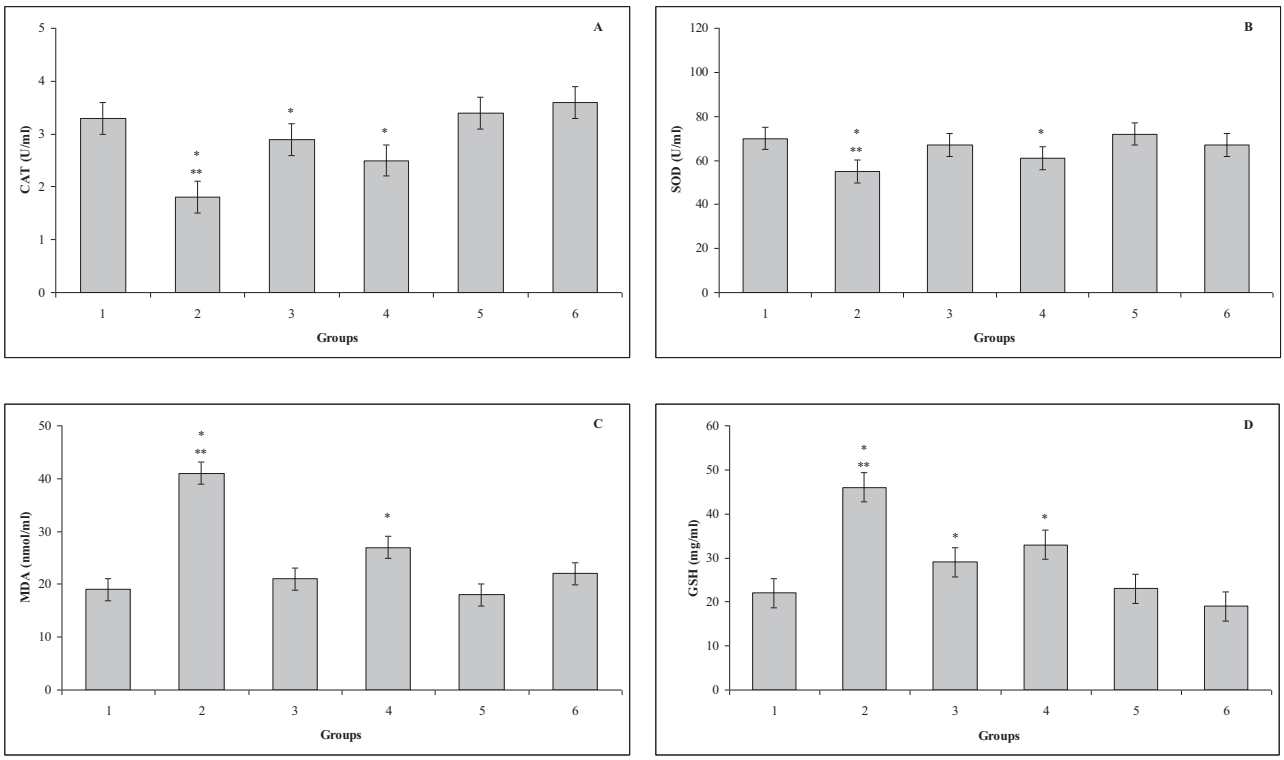

Fig. 7. (A-D) The levels of serum CAT (A), SOD (B), MDA (C) and GSH (D) in control (group 1), CBZ (group 2), NSSE plus CBZ (group 3), FVSE plus CBZ (group 4), NSSE (group 5) and FVSE (group 6) treated mice after five weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5 and 6.

ues can lead to anemia, coagulation disorders and other hemorrhagic disturbances. The reduction in RBC count (erythropenia) is considered due to the direct injurious action of the toxin on the animals. This reduction may be attributed to the injury of hematopoietic tissues and/ or the destructive effect on RBC membranes induced by CBZ. Decline of hemoglobin concentration may be due to increased rate of breakdown of RBC and/or reduction in the rate of RBC formation. WBC are involved in body defense against infection (Ganong, 1999). It has been suggested that the body's defense mechanism against infection is disturbed due to the disturbed WBC. The reduction of WBC count (leucopenia) might be due to direct toxic action of CBZ on leucopoiesis in lymphoid organs. Decrease in WBC count is directly related with either decreased production from germinal center of lymphoid organs or increased lysis process. Decreased WBC count might reflect immune system disorder. Considering the importance of the WBC in maintaining the integrity of the immune system, its reduction in the blood may cause a compromise in the immune defense system of mammals (Okonkwo et al., 2019).

The obtained results postulate that the damaging effect of CBZ on the liver is manifested by increases in serum ALT, AST, ALP and total bilirubin levels. The liver functional transaminases (AST and ALT) and ALP enzymes activity; and total bilirubin in serum are most frequently measured for diagnosis of liver diseases. Several studies showed that CBZ induced liver toxicity in experimental animals (Zari and Al-Attar, 2011; Ola-Davies et al., 2018; Patil et al., 2018). The kidney function parameters such as creatinine, BUN and uric acid are useful in early deduction of nephrotoxicity induced by exogenous compounds. These parameters are used as index of renal damage in living organisms (Coles, 1986). Nephrotoxicity induction by CBZ was established in several experimental investigation (Farag et al., 2011; Zari and Al-Attar, 2011; Nwozo et al., 2017; Patil et al., 2018).

The present decline in the level of serum total protein, and enhancement of glucose and cholesterol levels indicate disturbances in protein, carbohydrate and lipid metabolism due to CBZ toxicity. The progressive accumulation of plasma glucose revealed that rats exposed to CBZ became hyperglycemic (Zari and Al-Attar, 2011). Patil et al. (2018) reported that the administration of CBZ significantly increased the levels of blood cholesterol and triglyceride, while blood protein and globulin levels were decreased in mice. Addtionally, there are many studies showed that the exposure to pesticides are associated with increased levels of serum lipids which are a major risk factor for cardiovascular disease (Farag et al., 2011; Zari and Al-Attar, 2011; Al-Attar, 2015; Aroonvilairat et al., 2018; Uchendu et al., 2018). The present study revealed that the levels of serum CK and LDH were significantly increased in CBZ treated mice. The significant elevation of CK and LDH activity was indicating multi-organ damage such as cardiac, skeletal muscles and brain tissues. Cardiomyopathies often lead to myocarditis and myocardial infarction which might result in elevated levels of cardiac marker enzymes, importantly CK and LDH, and in the circulation, and thus serve as diagnostic markers in direct myocardial endothelial injury and damage to the myocardial cells (Ansari et al., 2006, Ansari et al., 2007). The increase of CK levels can indicate injury of muscular tissues including cardiac muscle. LDH is an enzyme with a ubiquitous expression. It is responsible for catalyzing the anaerobic, nicotinamide adenine dinucleotide phosphate-dependent conversion of pyruvate to lactate, which is important during times of high muscular activity (Wallimann et al., 1992; Spriet et al., 2000; Jacobson, 2008; Bosch et al., 2009; Jacobson, 2014).

In the current study, CBZ administration suppressed FSH, LH and testosterone levels. LH and FSH activities depend on both the quantity of these hormones and availability of their specific receptors in the testis. It was clarified that there is an adverse effect on

testicular function on exposure to environmental pollutants mediated by lowering LH secretion by pituitary and steroidogenesis by Leydig cells (Magnusson and Ljungvall, 2014; Geng et al., 2015). Reproduction is controlled by the hormones functional in the hypothalamic-pituitary–gonadal (HPG) axis. In the male they concern the maintenance of testicular testosterone production and spermatogenesis by FSH and LH. The testicular target cells of LH are the Leydig cells present in the interstitial space, and those of FSH are the Sertoli cells present in the seminiferous tubules. LH stimulates Leydig cells testosterone production, and FSH stimulates in Sertoli cells, in synergy with testosterone, the production of regulatory molecules and nutrients needed for the maintenance of spermatogenesis. Hence, both testosterone and FSH regulate spermatogenesis indirectly through Sertoli cells (Oduwole et al., 2018). At the level of the testis, FSH and LH mediate their actions via specific transmembrane receptors, FSH-R and LH-R, respectively. Predominantly, FSH-R is expressed in the Sertoli cells within the seminiferous cords/tubules whereas LH-R is expressed in the interstitial Leydig cells (Ramaswamy and Weinbauer, 2015). Zari and Al-Attar (2011) showed that treatment of male rats with CBZ resulted in severe damage and completely absences of spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids and spermatozoa and losses of the spermatogenesis process. Moreover, adverse reproductive effects attributed to pesticides, including their effect on fertility, have also been well established in various experimental studies (Hassan and Meligi, 2017; El-Demerdash et al., 2019; Ghorbani Taherdehi et al., 2019; Osama et al., 2019)

The present results showed that the exposure to CBZ increased the levels of serum TSH, and reduced T4 and T3 levels. Thyroid hormone plays critical roles in growth, differentiation, development, and maintenance of metabolic homeostasis (Skeaff, 2011). Thyroid endocrine system is a major target of the so called EDCs. T4 is synthesized in the follicular cell and is propagated by TSH secreted by the pituitary gland. TSH synthesis is propagated by TRH. TSH stimulates thyroid gland to produce T4 and T3 which is responsible for the metabolism of virtually all tissues in the body. When there is low level of thyroid hormone in the blood, high thyroid-releasing hormone (TRH) is released by the hypothalamus, so high TSH is secreted by the pituitary to produce thyroid hormones (Wenzel, 1981; Maiti et al., 1995, Kovacic and Edwards, 2010). All the serum T4 originates from the thyroid gland, while more than 80% of T3 is produced by deiodination of T4 in other tissues (Torlak et al., 2007). Alteration of endocrine function is tightly associated with increase of reactive oxygen species (ROS) and free radicals in central nervous (McCann et al., 2005). However, CBZ-induced decreases in the serum T4 are probably caused by direct damage to the thyroid gland structure and function.

Results obtained in the current study showed that the exposure to CBZ caused significant decline of CAT and SOD, and enhancement of MDA and GSH levels. These findings indicate that CBZ induced oxidative stress in mice. The oxidative stress is an imbalance between the amount of free radicals production and the presence of antioxidants. The antioxidant defense system contains molecular antioxidants, antioxidant enzymes and metallic chemical agents (Sanja et al., 2009). ROS are constantly produced during the metabolic processes of all living species (Sakr, 2007). Under normal physiological conditions, cellular ROS generation is counterbalanced by the action of antioxidant enzymes and other redox molecules. Oxidative stress is potentially harmful to cells, and ROS are produced as a reaction to pesticide toxicity (El-Demerdash et al., 2019). SOD and CAT are important antioxidant enzymes in organisms, which can remove superoxide free radicals and prevent the production of hydroxyl free radical. MDA is a lipid peroxidation biomarker with cytotoxicity, which can indirectly reflect the degree of cell injury. GSH is the most abundant antioxidant in all aerobic cells, presenting with high-concentrations in body fluids and tissue. GSH which is synthesized from L-glutamate, L-cysteine and L-glycine is critical for protecting the tissue from oxidative stress, acting as a free radical scavenger and inhibitor of lipid peroxidation (Owen and Butterfield 2010; Liu et al., 2011; Zhao et al., 2019). Furthermore, various investigations showed that CBZ and other pesticides induced oxidative stress in experimental animals (Jiang et al., 2015; Dar et al., 2019; Gupta et al., 2019; Naderi et al., 2019).

The present study revealed that NSSE and FVSE attenuated the hematological and biochemical alterations induced by CBZ toxicity. This attenuation effect was more pronounced in mice treated with NSSE than FVSE. Thymoquinone is a potent natural antioxidant phytochemical constituent present in N. sativa seeds that acts mainly by scavenging ROS and prevents cellular damage due to different prooxidants (Kassab and El-Hennamy, 2017). Previous studies showed that the thymoquinone inhibited hematotoxicity, genotoxicity, immunotoxicity, cardia ctoxicity, reproductive toxicity, hormonal alterations and oxidative damage induced by pesticides intoxications in experimental animals and these studies suggested that the protective roles of thymoquinone attributed to its antioxidant effects (Mosbah et al., 2016; Danaei and Karami, 2017; Danaei et al., 2018; Mosbah et al., 2018). Mansour et al. (2011) investigated chlorpyrifos (insecticide) hepatotoxicity and assessed the hepatoprotective effect of *F. vulgare* oil on male rats. They suggested that the antihepatotoxic activity of *F. vulgare* oil may be due to its antioxidant activity, ability to scavenge free radical generated by chlorpyrifos and inhibition of cytochrome P450 and oxon formation. Koppula and Kumar (2013) investigated the properties of *F. vulgare* extract in stress reduction and memory enhancement in rats. They showed that *F. vulgare* has several functions such as anti-stress proceeding, increase in memory and antioxidant effects may reduce stress and stress-related disorders. El-Sheikh and Galal (2015) evaluated the toxic effects of emamectin benzoate (insecticide) on male rats and the possible ameliorative role of *F. vulgare* oil. They concluded that *F. vulgare* oil pretreatment mitigated hemotoxicity, immunotoxicity and hepatotoxicity induced by sub-chronic treatment of emamectin benzoate in male rats. This may be attributed to antioxidant, anti-inflammatory and hepatoprotective activity of *F. vulgare* oil. Abdel-Wahhab et al. (2016) evaluated the effect of FVSE on tienilic acid treated rats. The administration of FVSE to tienilic acid-treated animals significantly protected the liver against the injurious effects of tienilic acid. They concluded that the protective effect may be attributed to the high content of antioxidant compounds in FVSE. Al-Amoudi (2017) investigated the possible effect of *F. vulgare* oil against the toxicity of sodium-valproic in albino rats. The investigator concluded that *F. vulgare* oil has various pharmacological properties including antioxidant, anti-cancer activity, anti-inflammatory. These valuable effects might be due to the presence of aromatic compounds trans-anethole. These useful properties of *F. vulgare* could be due to its antioxidant activity that prevents the toxicity of sodium-valproic. In conclusion, this study showed that NSSE and FVSE have a powerful protective effect against CBZ toxicity. The results indicate that the protective activity of NSSE and FVSE is proposed to their chemical components. These chemical components act as antioxidant agents, and improved the hematological and biochemical alterations and oxidative stress response in mice exposed to CBZ. Further hematological and biochemical investigations will be required to study the influences of different doses of NSSE and FVSE against the toxicity of CBZ and other chemical pollutants.

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