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Research Article
Protective Effect of Olive Leaves Extract in Male Rats after the Administration of Cimetidine

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Abstract

Background and Objective: Cimetidine is a drug used in the treatment of ulcers in a wide range put have highly harms the male reproductive system. This study was undertaken to determine the protective effects of the administration of olive leaves extract (OLE) on male rats after the administration of cimetidine. **Materials and Methods:** In this investigation, 30 male rats were randomly classified into three groups, the control group (G1): Receiving normal saline, the cimetidine group (G2): Receiving 100 mg kg^{-1} b.wt., of cimetidine and the third group (G3) contain cimetidine (100 mg kg^{-1} b.wt.)+olive leaves extract (500 mg kg^{-1} b.wt.) orally for 38 days from 20 November, 2022 to 28 December, 2022. After completing the study, the animal was slaughtered and the testis was analyzed histologically. **Results:** The cimetidine group showed a significant decrease in body weight and testicular weight compared to the control group a significant decrease in semen parameters and also a significant decrease in sex hormones and antioxidant markers. However after treatment with the cimetidine+OLE group detected a significant increase in body and testicular weight, semen parameters, sex hormones and antioxidant markers compared to the cimetidine group. **Conclusion:** The OLE has a significant protective effect from cimetidine toxicity on the male reproductive system.

Key words: Olive leaves pharmacology, cimetidine toxicity

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The medicine cimetidine has been authorized for the treatment of stomach acid secretion by the Food and Drug Administration (USA). It is used to alleviate the symptoms of peptic ulcers and hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas and erosive gastroesophageal reflux[1]. Cimetidine have ability to reduces the production of acid from stomach that triggered by food, histamine, pentagastrin, caffeine and insulin. Cimetidine antagonist for H2 receptor, it competes with DHT receptors in brain, pituitary gland and organs that used DHT. On the other hand, DHT, a sterol that is produced when testosterone (T) is converted, fulfils the function of the 'true male hormone' in accessory glands like the prostate and seminal vesicle gland. It is referred to be a "weak nonsteroidal anti-androgen"[2]. For people living in the mediterranean area, the olive (*Olea europaea*, Oleaceae) plant is a commercially and culturally significant long-viable tree that contains phytoestrogen. Numerous flavonoid and polyphenolic compounds with anti-inflammatory, anti-cancer, anti-diabetic, gastroprotective and wound-healing properties are present in this plant's leaves[3,4]. According to Bouaziz *et al.*[5] the olive tree has the highest antioxidant activity through its fruits, oil and leaves. According to Allouche *et al.*[6] olive leaves have antioxidant properties due to the presence of oleuropein. It is widely known that the presence of a few significant antioxidant and phenolic components to prevent oxidative degradations is what has sparked interest in olive tree byproduct extracts in the food and pharmaceutical sectors. Oleuropein, hydroxytyrosol and extracts of *Olea europaea* leaves (including 1.8% flavonoid glycosides, 3,4-dihydroxy-phenyl and 19% oleuropein esters) were shown to be more powerful antioxidants than diet E or any other mounted antioxidant, according to Oliveras-López *et al.*[7] research. With 2 g of oleuropein per kilogram of olive leaves, olive leaves are the highest source of this significant polyphenol when compared to other olive tree parts[8], relates to the ability of olive leaves to decrease blood cholesterol levels, according to prior study by Barbaro *et al.*[9]. Cholesterol is recognized as a precursor for testosterone synthesis due to its presence in the body and its impact on the leydig cells since it is required for the production of sexual hormones, primarily testosterone[10,11].

The aim of the current study was to explore the possible therapeutic impact of olive leaf extract on some physiological and biochemical parameters in male rats.

MATERIALS AND METHODS

Study area: This study was conducted in the period from 20 December, 2021 to 28 January, 2022. Where this study was conducted in the Animals House, College of Veterinary Medicine, Tikrit University.

Chemicals and materials: The chemicals and materials used in this study are cimetidine powder pure 100% (Iraq), olive leaves (Iraq), formalin buffer 10% (England), nigrosin-eosin stain (Sweden), soxhlet electrothermal (USA), light microscope (Japan) and refrigerators (China).

Study design: Thirty male rats were used in this study, male adult rats in good health were obtained from the Tikrit University, College of Veterinary Medicine, Animal House. Age ranges from 8-10 weeks and weight from 200-280 g. These animals were maintained in an air-conditioned room with a temperature range of 20-25°C and a 12 hrs daily light cycle. The animals were kept in (46×28×13) cm plastic cage enclosures. Food was provided in the form of freshly made ration pellets. Care was made to avoid any extra stress. Once every week, the cages were cleaned. The pets were housed for at least 2 weeks before being (adaptation period).

Rats were classified into 3 groups 10 rats each:

- **G1 (Control group):** This group contains 10 adult male rats each rat received normal saline daily for 38 days
- **G2 (Cimetidine group (100 mg kg^{-1} b.wt.)):** This group contains 10 adult male rats each rat received cimetidine 100 mg kg^{-1} b.wt., daily for 38 days
- **G3 (Cimetidine group (100 mg kg^{-1} b.wt.)+olive leaves extract (500 mg kg^{-1} b.wt.)):** This group contains 10 adult male rats each rat received cimetidine 100 mg kg^{-1} b.wt. and olive leaves extract (500 mg kg^{-1} b.wt.) daily for 38 days

Preparation of a crude (70% alcohol) olive leaf extract: The Soxhlet apparatus, which consists of an electric heater with a thermostat regulator on top of which a round-bottomed glass flask is placed, was used to create the alcoholic extract from the olive leaf in accordance with the method of Zheng *et al.*[12] olive leaves were collected fresh from trees in the Alzwea Village in Salah-Adden and left to dry at room temperature before being crushed by a grinder. The extraction device itself contains the flask that is connected to it and holds the solvent and the cellulose. This thimble has the plant material in

powdered form. A distiller unit is connected to the extraction to condense the vaporized solvent 25 g of olive leaf powder from the plant and 250 mL of 70% ethanol alcoholic ethanol were added to the thimble. After 4-5 hrs of extraction at a solvent temperature of 40°C, a transparent and colorless solvent appeared in the extracting unit. The extract was then kept at room temperature in order to concentrate it. The completed dry extract was kept frozen at a temperature of -20°C. The extract was used to make the different concentrations of solutions that would be used in this experiment.

The removed testis was promptly fixed in 10% formalin and prepared for paraffin embedding in accordance with protocol. The testis was sliced into five-micron-thick serial slices and stained with Hematoxylin and Eosin (H&E). Using a light microscope (Japan), two examiners who were uninformed of the specifics of the experiment independently identified the testicular histomorphological alterations[13-16].

Ethical clearance: This procedure was completed in the Physiology, Department of Pharmacology and Biochemistry, College of Veterinary Medicine, Tikrit University, under Supervisor Assist. Prof. Dr. Omar Salim Ibrahim, Department of Pharmacology, College of Medicine, Al-Anbar University and Assist. Prof. Dr. Dakheel Hussen Hadri, Physiology, Department of Pharmacology and Biochemistry, College of Veterinary Medicine, Tikrit University and found authorization by an official letter from the college regarding ethical clearance.

Statistical analysis: The one-way ANOVA study of variance was used in the statistical study. According to Duncan's Multiple Ranges, the significant differences were found at a significant level ($p \leq 0.05$)[17].

RESULTS

Estimation of body and testicular weight: This study showed a significant decrease ($p>0.05$) in body and testicular weight in group 2 given cimetidine 100 mg kg^{-1} after 38 days from treatment compared with the control group but a significantly graduated increase ($p<0.05$) in cimetidine+olive leave extract treated group (Table 1).

Estimation of semen analysis: The sperm motility, sperm morphology sperm count and in the cimetidine group showed a significant decrease ($p>0.05$) in the number of sperm compared with the control group (Table 2), while a significant increase ($p<0.05$) in cimetidine+olive leave extract treated group as shown in Table 3.

Estimation of sex hormones: Table 4 showed a significant decrease ($p>0.05$) in testosterone and FSH and increasing in LH in group 2 receiving cimetidine 100 mg kg^{-1} after 38 days from treatment compared with the control group but a significantly graduated increase ($p<0.05$) in cimetidine+olive leave extract treated group and decrease in LH after treated.

Estimation antioxidant markers: Table 5 showed a significant increase ($p \leq 0.05$) in MDA in group 2 receiving cimetidine 100 mg kg^{-1}) after 38 days from treatment compared with a control group and an increase in GSH, but significantly graduated decreased ($p \geq 0.05$) in MDA in cimetidine+olive leaf extract treated group and decrease in GSH, but CAT does not significantly change in all group.

Histology of testis tissue examination: The result of histological examination for testicular tissue, after 38 days from treatment daily for control, cimetidine, cimetidine+olive leave extract.

Control group: The results of the histological examination for testicular tissue in the control group Fig. 1.

Cimetidine group: The results of the histological examination for testicular tissue in the cimetidine group Fig. 2.

Cimetidine and olive leaves extract: The results of the histological examination for testicular tissue in the cimetidine+olive leaves extract group Fig. 3.

Table 1: Effect of treatments on the body and testicular weights of the animals before and after 38 days

	Parameter			
Group	Before experiment (body weight)	After experiment (body weight)	Right testis	Left testis
G1 (Control)	210.0 ± 2.0^{A}	250.0 ± 2.2^{A}	2.950 ± 0.0707^{A}	2.700 ± 0.000^{A}
G2 (Cimetidine 100 mg kg^{-1} b.wt.)	207.5 ± 1.5^{D}	195.0 ± 2.0^{C}	2.500 ± 0.141^{D}	2.350 ± 0.212^{C}
G3 (Cimetidine 100 mg kg^{-1} b.wt.+olive leave 500 mg kg^{-1} b.wt.)	210.0 ± 2.0^{A}	220.0 ± 2.4^{B}	2.700 ± 0.000^{C}	2.450 ± 0.0707^{B}

Mean±standard deviation (letter means significant difference), significant ($p \leq 0.05$) and No.: 10 animals

Table 2: Effect of treatments on sperm motility and morphology after 38 days

	Parameter			
Group	Motility (%)	Immotility (%)	Normal morphology (%)	Abnormal morphology (%)
G1 (Control)	89.0000000±1.7320508^{A}	11.0000000±1.7320508^{D}	89.0000000±1.7320508^{A}	11.0000000±1.7320508^{D}
G2 (Cimetidine 100 mg kg^{-1} b.wt.)	58.000000±2.00000000^{D}	42.0000000±2.0000000^{A}	43.3333333±2.8867513^{E}	56,6666667±2.8867513^{A}
G3 (Cimetidine 100 mg kg^{-1} b.wt.+ olive leave 500 mg kg^{-1} b.wt.)	69.3333333±1.1547005^{C}	30.6666667±1.1547005^{B}	63.3333333±2.8867513^{C}	36.6666667±2.8867513^{C}

Mean±standard deviation (letter means significant difference), significantly ($p<0.05$) and No.: 10 animals

Table 3: Effect of treatments on sperm counts after 38 days

	Parameter
Group	Sperm count (%)
G1 (Control)	8.2666667±0.3605551^{A}
G2 (Cimetidine 100 mg kg^{-1} b.wt.)	5.9000000±0.3605551^{D}
G3 (Cimetidine 100 mg kg^{-1} b.wt.+olive leave 500 mg kg^{-1} b.wt.)	6.4333333±0.1154701^{C}

Mean±standard deviation (letter means significant difference), significant ($p\leq0.05$) and No.: 10 animals

Table 4: Effect of treatments on sex hormones after 38 days

	Parameter		
Group	Testosterone (ng mL^{-1})	FSH (IU mL^{-1})	LH (IU mL^{-1})
G1 (Control)	4.650±0.572^{A}	42.07±3.79^{A}	24.92±0.320^{D}
G2 (Cimetidine 100 mg kg^{-1} b.wt.)	2.160±1.80^{C}	25.61±4.76^{C}	69.53±0.363^{A}
G3 (Cimetidine 100 mg kg^{-1} b.wt.+olive leave 500 mg kg^{-1} b.wt.)	3.453±0.463^{B}	34.72±3.84^{B}	33.16±3.96^{C}

Mean±standard deviation (letter means significant difference), significant ($p\leq0.05$) and No.: 10 animals

Table 5: Effect of treatments on antioxidant markers after 38 days

	Parameter		
Group	MDA (μmol L^{-1})	GSH (μmol L^{-1})	CAT (μmol L^{-1})
G1 (Control)	8.17±3.85^{BC}	0.3263±0.0040^{A}	51.786±0.888^{A}
G2 (Cimetidine 100 mg kg^{-1} b.wt.)	10.81±5.53^{A}	0.2797±0.0700^{B}	51.140±0.992^{A}
G3 (Cimetidine 100 mg kg^{-1} b.wt.+olive leave 500 mg kg^{-1} b.wt.)	9.92±2.54^{AB}	0.2720±0.0711^{B}	50.267±1.507^{A}

Mean±standard deviation (letter means significant difference), significant ($p\leq0.05$) and No.: 10 animals

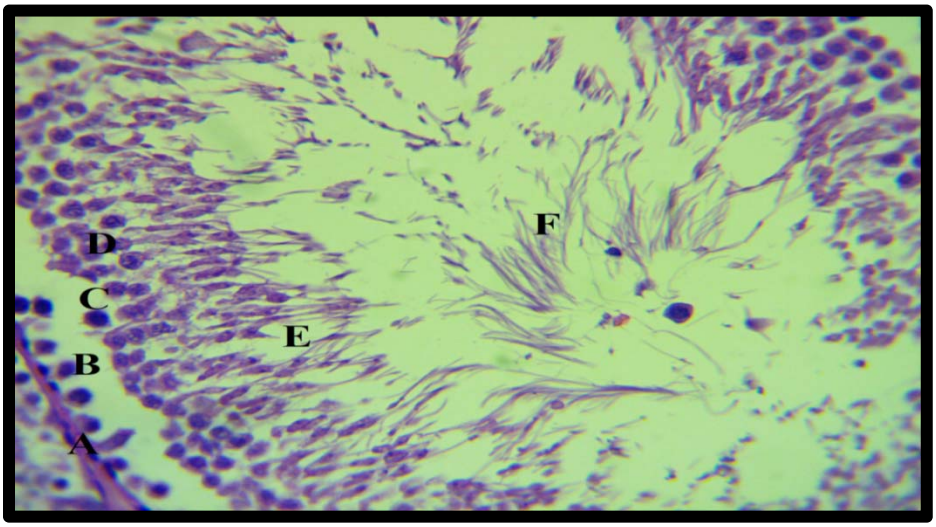

Fig. 1: Seminiferous tubule

(A) basement membrane, (B) Spermatogonia, (C) Primary spermatocyte, (D) Secondary spermatocyte, (E) Spermatids, (F) Spermatozoa and Hematoxylin and Eosin×40

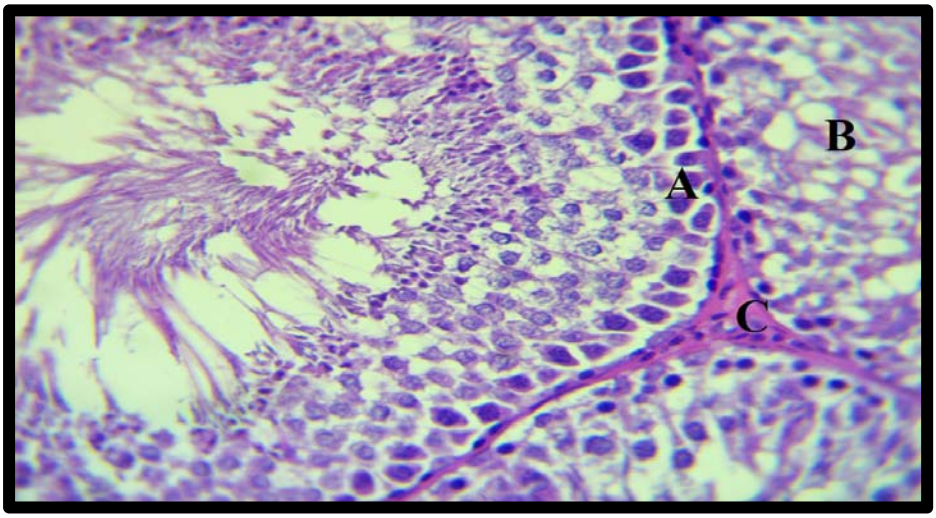

Fig. 2: Seminiferous tubules, pyknosis of nuclei
(A) Spermatogonia, (B) Hypertrophied degeneration of spermatogenic cells, (C) Thickness of basement membrane and Hematoxylin and Eosin ×40

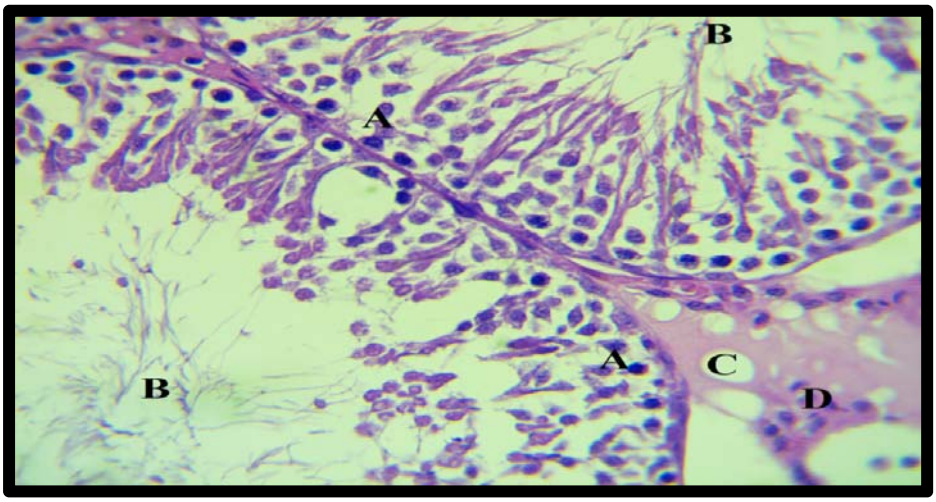

Fig. 3: Seminiferous tubule with different stages
(A) Spermatogenic development, (B) Spermatozoa, (C) Blood hemolysis in the interstitial C.T, (D) Fat droplets, leydig cells and Hematoxylin and Eosin ×40

DISCUSSION

The result of this study refers to improving the effect by using olive leaf extract after using cimetidine that leading to toxic effect. The findings of this study corroborated those of Støa-Birketvedt *et al.*[18] who found that cimetidine decreases appetite and body weight. The results of this investigation demonstrated that cimetidine considerably lowered body and testis weight. According to Shono *et al.*[19] cimetidine produces a decrease in animal health as well as weight loss in the testicles and body. However, the body and the testicular weight started to rise significantly in the groups that received olive leaf extract (OLE), according to Ibrahim *et al.*[20]. This study demonstrated a decrease in motile sperm and an increase in immotile sperm in the cimetidine-treated group compared to the control group. It is possible that this is because cimetidine inhibits cyclic adenosine monophosphate (cAMP), which in turn causes the adenylyl cyclase cAMP-dependent protein kinase-C reduces the amplitude of flagellar waves and the frequency of flagellum beats by reducing the number of phosphorylated proteins (Dynein and tubulin)[21], this result was also agreed with Al-Janabi *et al.*[22] and in groups treated with OLE, the motility of sperm started with a rise and a drop in immotile sperm[23]. The results showed a significant increase

in abnormal sperm morphology in the cimetidine-treated group when compared to the control group, when compared to the control group, this result is consistent with the findings of Al-Janabi *et al.*[22]. Cimetidine may cause flagellar lesions by impairing meiotic division, according to Oko and Hrudka[24]. According to Younan *et al.*[23], the group treated with OLE exhibited a substantial rise in normal sperm morphology and a decrease in aberrant sperm morphology. According to Franca *et al.*[25] this study's findings on the quantity of sperm in the group treated with cimetidine compared to the control group are in accord. Due to the presence of oleuropein, which increases sperm parameters, sperm counts in groups treated with OLE will be higher than in groups receiving cimetidine[26], this conclusion was also supported by Rostamzadeh *et al.*[27]. In line with Peden *et al.*[28] findings that cimetidine treatment increases GnRH levels due to LH negative feedback mechanism impairment in the response of LH to luteinizing releasing hormone (LH-RH), this study demonstrated a decrease in testosterone and FSH levels. Additionally, the impairment of the LH negative feedback mechanism causes an increase in LH secretion, which changes the amount of LH testosterone secreted[29,30]. But this study also showed a graduated significant increase in testosterone and FSH levels and a decrease in LH levels in groups treated with OLE, this result was similar to Molly[21]. Cimetidine treatment in this study resulted in higher levels of MDA and lower levels of GSH when compared to the control group, these findings were similar to those of Adikwu and Bokolo[31]. In contrast, olive leaf extract treatment resulted in significantly lower levels of MDA and higher levels of GSH, these findings were similar to those of Motawea *et al.*[32], but this result had no discernible impact on CAT. The biochemical results were supported by a histological examination of testis tissues. Current results, however, were in agreement with those of Ibrahim *et al.*[20] following the administration of an OLE result marker low severity, an improvement in histological structure and a noticeable restoration of spermatogenesis.

The future recommendation is to assess of cimetidine on other organs such as the liver and kidney. The study the effect mix of OLE and zinc on the male reproductive system and do not give any of the supplements with any antacid drugs.

CONCLUSION

The cimetidine has a toxic effect on the male reproductive hormones and seminal analysis if used daily for 38 days but olive leaf extract has a significant protective effect from cimetidine toxicity on the male reproductive hormones. The histological study showed severe damage and destruction in the testes due to the use of cimetidine.

SIGNIFICANCE STATEMENT

The study exhibited the harmful effect of cimetidine on the male reproductive system by decreasing the number of motile sperm as well as it elevating the number of abnormal sperm morphology. The harmful effects of cimetidine on the body and testicular weight which led to a decrease in their weight more over it also. Decreased the level of testosterone and FSH with negative feedback while the level of LH increased. The results of the present study indicated that OLE has a protective effect against male reproductive system abnormalities through its enhanced body and testicular weight and has a protective effect by the regulation of hormones testosterone, FSH and LH.

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