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AMELIORATIONS OF OLEA FERRUGINEA FRUIT PULP EXTRACT IN CCL4 INDUCED TESTICULAR PATHOLOGY IN MICE

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ABSTRACT

In present study the testicular histo-ameliorations of wild olive (*Olea ferruginea*) fruit pulp extract (OFPE) against intra-gastric CCl_4 exposure in mice was investigated. Thirty male albino mice were allocated into three groups of ten each: 1) Vehicle control (Vc); 2) CCl_4 (C); and 3) CCl_4+ *Olea ferruginea* (COf). All groups, except the Vc, were administered CCl_4 (0.1mL of a 0.2mLkg^{-1} solution) in corn oil. Over the subsequent five days, the COf group received 0.1mL of *Olea ferruginea* plant extract (OFPE) daily, while the Vc and CCl_4 groups were provided water in place of OFPE. Testes were recovered at day 7. Within the CCl4 group, there was significant misalignment of spermatogenic cells, such as spermatogonia, spermatocytes, spermatids, and tailless sperm heads, observed in the seminiferous tubules, along with a concomitant depletion of interstitial tissue. Partial recovery of the interstitial and spermatogonial density and realignment of spermatogenic cells were seen in COf group. Nevertheless, aggregates of dislocated spermatogenic cells were present in the middle of the seminiferous tubules. Micrometric analysis showed significant decrease ($P < 0.05$) in cross-sectional area (CSA) of the seminiferous tubules in COf than the Vc and C groups. Contrary to the sperm tail length the CSA's of spermatogenic cell were significantly higher in C than the Vc and COf groups. So results show that OFPE can rescue the ruined testicular parameters of CCl_4 exposure.

Keywords: Testicular histopathology, CCl_4, *Olea ferruginea*

INTRODUCTION

Carbon tetrachloride intoxication has been found to cause liver, kidney, and testicular damage in experimentally exposed animals due to oxidative stress (Hashem et al., 2021). Mice treated with CCl_4 have shown massive germ cell death (Noroozi et al., 2024; Nadia et al., 2022), decreased sperm count, and reduced levels of endogenous testicular antioxidant enzymes in rats (Elsawy et al., 2019).

It has been investigated that the ethanol extracts of the allantoin plants *show* antioxidant properties (Selamoglu et al., 2017; Mustafa et al., 2020). Cyclocybe cylindracea detected in mushroom could be consumed as a good antioxidant due to presence of gallic acid, hesperidin, catechin, syringic acid and hydroxybenzoic acid (Sevindik et al., 2018). Plants of the Genus *Lavandula* possess wide spectra of biological activities such as antispasmodic, carminative, analgesic, sedative, hypotensive, antiseptic, antimicrobial, antifungal, antidiuretic and general tonic action (Salehi et al., 2018; Salehi et al., 2020; Saba et al., 2021). The fruit extract of *Ficus carica*, *Basella alba*, *Grewia asiatica* showed rehabilitative properties against CCl_4 exposure-relatedmodifications in testicular histopathologies (Nadia et al., 2022).

Wild olive plants (*Olea ferruginea*) are commonly found in Afghanistan,

Pakistan, and Kashmir. Unlike *Olea europaea*, the primary source of olive fruit and oil, *Olea ferruginea* has largely been neglected in phytochemical and medicinal research, except for its use in traditional folklore for treating cough, cold, flu, and skin infections (Shah et al., 2022). The ripe fruit of wild olive are small ovoid drupes (8mm long and 5mm wide) containing active medicinal ingredients such as phenols, flavonoids, tannins, glycosides, saponins, and alkaloids (Irakli et al., 2024).

However, a related species, *Olea europaea*, has been found to contain various phytochemicals in its fruit pulp, including flavonoids, phenolics, glucosides, secoiridoids, cornoside, salidroside, halleridone, galactolipids, diacylglycerol, triacylglycerols, and fatty acids (Tunc et al., 2024). These diverse phytochemical ingredients are responsible for *Olea europaea's* ethno-medicinal properties, such as antioxidant, anti-inflammatory, anti-carcinogenic anti-microbial, anti-hypertensive, laxative, and cardio-protective effects (Elhrech et al., 2024). Olive leaf extract has been found to protect the testis from various toxicological damages (Sarbishegi et al., 2017). Additionally, olive oil has been shown to improve lipid profiles (Isaakidis et al., 2023). Despite the extensive research on *Olea europaea*, there is limited information on the potential applications of COf for testicular pathology, and most reported medicinal applications are restricted to *Olea europaea*. The present study reports, the histo-ameliorative capacity of the *Olea ferruginea* fruit pulp extract against testicular histopathology of acute CCl_4 exposure.

MATERIAL AND METHOD

a) Animal groups care and maintenance

Young male albino laboratory mice were utilized for the study weighing 28-30 g, housed in the Animal House at the Department of Zoology, University of Sargodha, Pakistan. The animals were allocated into three distinct groups.

i. Vehicle control group (Vc): Administered 0.1mL of corn oil (single dose) by gavage on day one, followed by free access to normal drinking water on days 2-6.
ii. CCl_4 group (C): On day one, a single gavage dose of 0.1mL from a 0.2mL/kg CCl_4 solution in corn oil (delivering 0.006mL CCl4 for a 30g animal weight) was administered, followed by free access to normal drinking water on days 2-6.
iii. CCl_4+*Olea ferruginea* (COf) group: Initial dose treatment was the same as in the C group on day one, followed by 0.1mL of freshly prepared OFPE for days 2-6 every 12 hr.

On day 7^{th}, the animals were euthanized by cervical dislocation, and their testes were removed and immersed in Cornoy's fixative for 48hours. Post-fixation, the samples were subjected to wax embedding and subsequently sectioned with a microtome. All procedures of this study were approved by the ethical committee of the Department of of Zoology, University Sargodha, Sargodha, Pakistan (Code: SU/Zol/2665).

b) Preparation of Olive (Olea ferruginea) fruit-pulp extract

Ripe fruits of *Olea ferruginea* were collected from the Soon Valley near District Khushab, Pakistan (Figure 1). The small, blackish berries were thoroughly washed, and their seeds were separated from the pulp. The pulpy mass was ground into a fine paste, which was then vacuum-dried to remove its aqueous content. The resulting material was dissolved in menthol using a magnetic stirrer. This alcoholic solution was centrifuged at 1000 rpm for 15 minutes, after which the residue was

discarded and the supernatant was vacuum-dried to obtain the extract, following established lab protocols (Ahmad et al., 2016; Inayat et al., 2020; Ahmad et al., 2021). A freshly prepared saturated aqueous solution of this extract was then used for feeding the OFPE and COf group animals.

Figure 1: Olive (*Olea ferruginea*) purple-black fruit drupes (white arrow) on the leafy shoots

c) *CCl4 Solution Preparation*

The laboratory grade CCl4 was dissolved in corn oil (15:85 v/v respectively) to prepare the stock solution. This stock CCl4 solution was further diluted (6:94 v/v) to prepare the required strength of 0.006 mL CCl4/0.1 mL (single dose volume for each animal in the relevant experimental groups). To achieve the required 0.015mL CCl4 in 0.1mL of dilution, a solution was prepared with a CCl_4 to corn oil ratio of 15:85.

d) Testicular histology

Using a rotary microtome, 5µm histological sections were prepared and placed on albumen-coated glass slides for Hematoxylin & Eosin (H & E) staining. Digital images of these stained testicular sections were then taken at 400x and 1000x magnification to collect histometric data.

e) Histometery of the spermatogonia, spermatocytes and spermatozoa

Photographs of randomly selected spermatozoa, spermatogonia, and spermatocytes from each groups were captured at 400x and 1000x optical magnification using a 7.2-megapixel Sony digital camera mounted on a trinocular research microscope (Labomid CXR2) Sperm cell dimensions, such as head length, breadth, and tail length, were measured using CorelDRAW11 graphics software. Calibration was done with images of a stage micrometer taken using the same camera and microscope setup. The following formula was employed to calculate the cross-sectional area.

$$\mathbf{ACSA = (Length \times Width/4)\ \pi}$$

f) Statistical analysis

Group means ± SEM were calculated from the histometric and micrometric data, as presented in Table 1. Further analysis was performed using analysis of variance (ANOVA) and post-hoc comparisons of group means via Duncan's multiple range test.

RESULTS

a) Testicular Histology and Histopathology

In the vehicle control group, densely packed endocrine cells of the interstitial tissue (leydig cells) were observed distributed among the adjacent sections of the seminiferous tubules. In each seminiferous tubule section, spermatogonia were organized in two or more concentric layers along the inner margin of the basement membrane.

Moving inward from the spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa were observed at various stages of differentiation, arranged in a sequential manner from the outer margin to the central region of the seminiferous tubules.

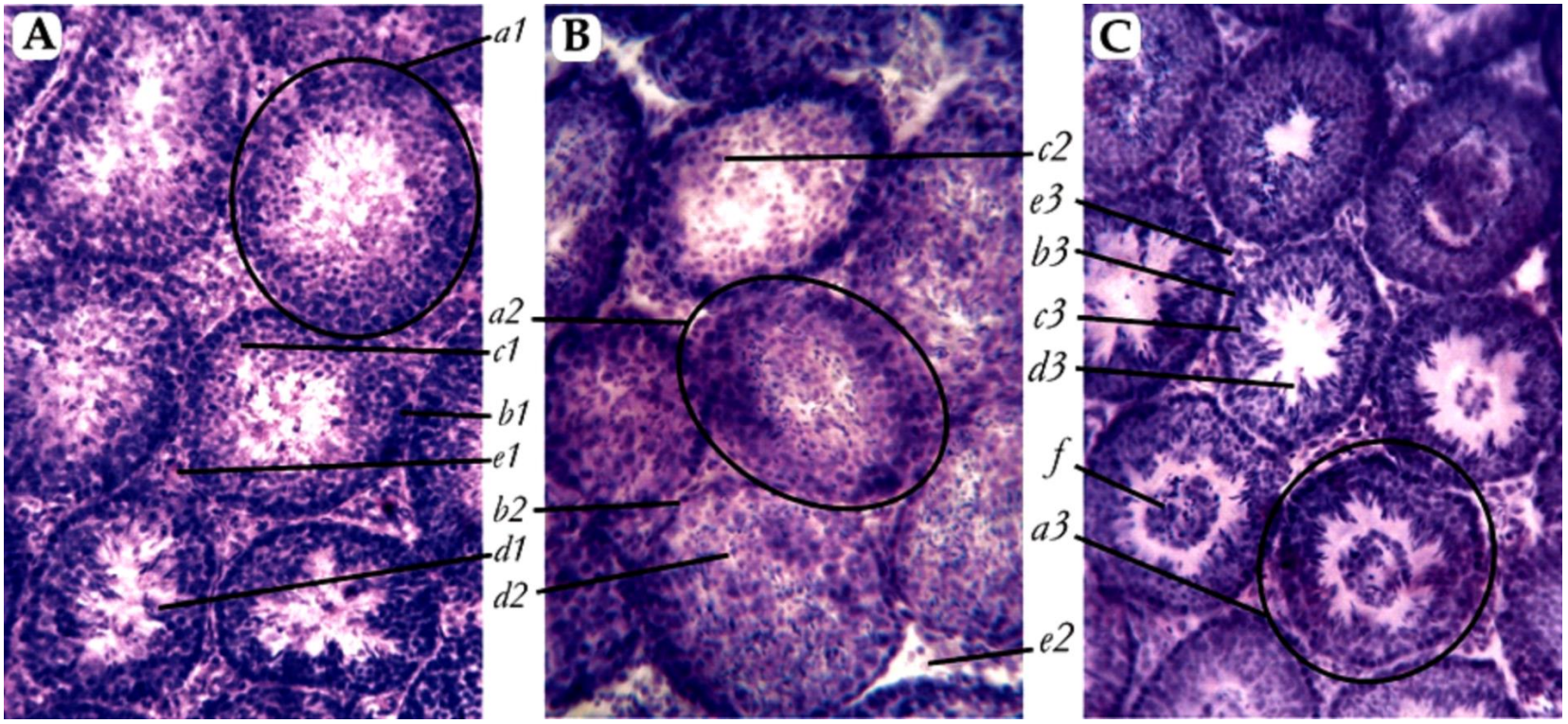

Figure 2: 2-A: section of Vehicle control group testis (400×) showing — a1: *TS of Seminiferous tubule reflecting typical pattern of arrangement of sperm producing cells;* b1: *spermatogonia arranges in more than one whirls (Probable A1 and A2 type);* c1: *Secondary spermatocyte;* d1: *differentiating spermatids in the process of formation of tails present imbedded in Sertoli cell with their heads;* e1: *normal interstitial tissue*

2-B: section of CCl_4 group testis (400×) showing — a2: *TS of Seminiferous tubule reflecting complete disruption of the pattern of arrangement of sperm producing cells;* b2: *Basal layer of spermatogonia (A1 type) showing ellipsoidal instead of normal round nuclei and various empty spaces left behind in result of focal necrosis;* c2: *free floating primary spermatocyte; d2: tailless spermatid heads floating free in the lumen if the seminiferous tubule;* e2: *loss of interstitial tissue*

2-C: section of CCl_4-Olive group (400×) showing — a3: *TS of Seminiferous tubule showing partial rehabilitation of characteristic pattern of arrangement of the sperm producing cells and a central aggregation of free floating spermatogenic cells detached prematurely from the Sertoli cells;* b3: *rehabilitated whirl of A1 spermatogonia (with rounded nuclei and no empty spaces in between);* c3: *normally placed secondary spermatocyte and* d3: *differentiating spermatid heads affixed in the Sertoli cells indicating rehabilitation of spermatogenesis;* e3: *regenerated interstitial tissue,* f: *central rejected mass of spermatic cells.*

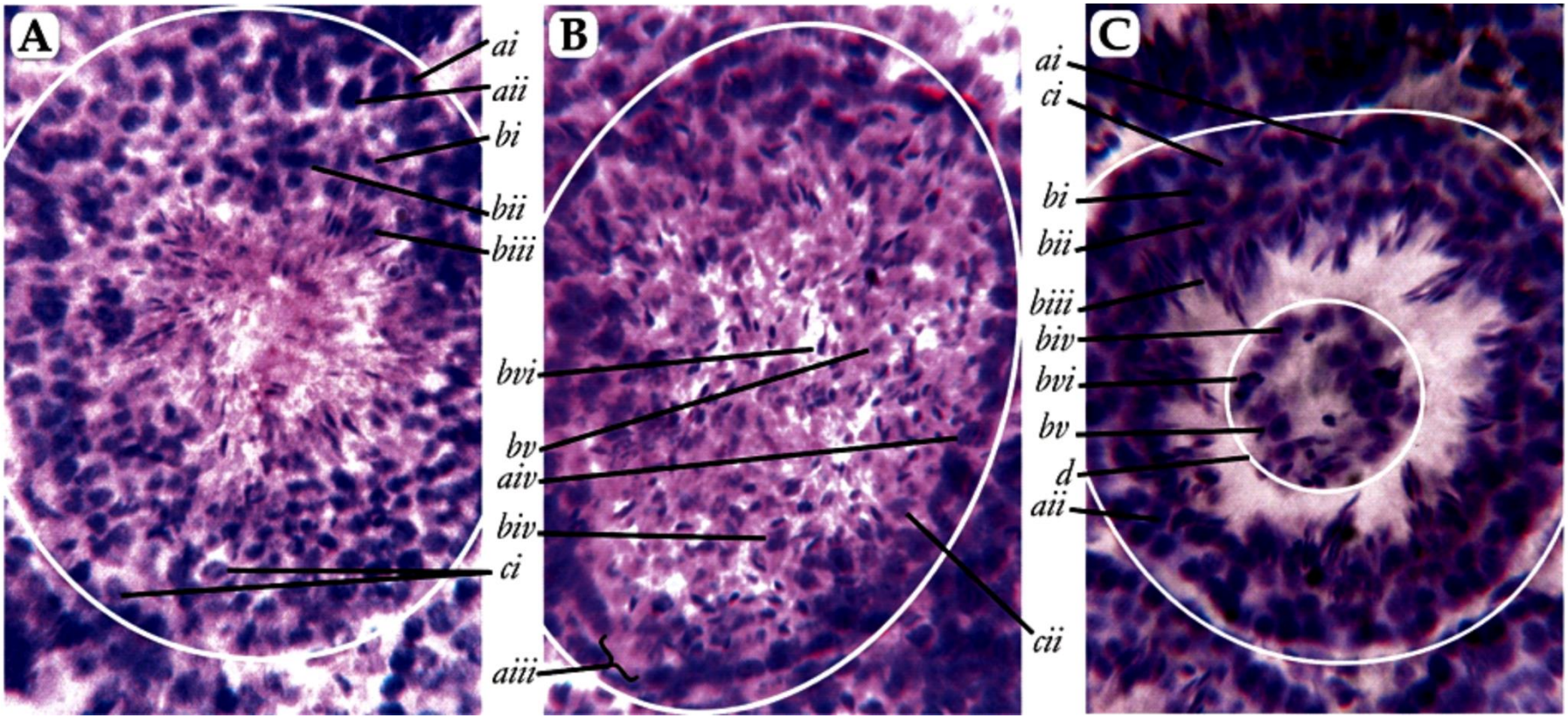

Figure: 3: 3-A: section of a seminiferous tubule from vehicle control group (1000×) showing — **ai:** *spermatogonium (A1 type);* **aii:** *spermatogonium (A2 type);* **bi:** *sister secondary spermatocytes after 1st meiotic division;* **bii:** *sister spermatids just after second meiotic division;* ***biii:*** *spermatid transforming into spermatozoa*

3-B: section of a seminiferous tubule from CCl_4 group (1000×) showing various pathological signs — **aiii:** *basement membrane without spermatogonia*; **biv:** *spermatogonium (A1 type) with ellipsoidal nucleus dislodged from the basement membrane;* **bv:** *apoptosing dislodges spermatid;* ***bvi:*** *dislodged sperm head*

3-C: section of seminiferous tubule from CCl_4+Olive group (1000×) showing obvious rejuvenating and rehabilitative effects of Olive extract on the CCl_4 induced histopathological disruptions **ci:** normal Sertoli cells; **cii:** *apoptosing Sertoli cell;* **d:** *central aggregation of the rejected spermatic cells mass prematurely dislodged from the harboring intoxicated Sertoli cells*

Table 1: Showing the micrometry of the seminiferous tubules and spermatogenic cells

Micrometric Parameters	Groups		
	Vc	C	COf
CSA of seminiferous tubule (μm^2)* P < 0.001	†977.99±32[a]	953.9±22[a]	891.3±30[a]
CSA of the spermatogonia(μm^2)* P < 0.05	77.66±4.34[b]	148.8±12.9[b]	58.41±3.27[a]
CSA of the spermatocytes(μm^2)* P < 0.05	177.9±15.07[a]	275.52±18.1[b]	171.08±9.4[a]
Head size of spermatozoa(µm)** P < 0.05	15.99±1.63[a]	33.64±2.72[b]	23.52±1.91[c]
Tail Length of sperm(µm)** P < 0.05	88.35±5.89[a]	57.29±3.54[b]	65.90±2.58[c]

†: Group means ± SEMs "(Analyzed using one-way ANOVA), *: (P≤ 0.05), **: (P≤ 0.001), ***: (P≤ 0.0001)."Overall significant (p < 0.05) variation (ANOVA-two way) among the groups; a, b, c: any two groups mean values in a row not sharing the common lowercase letter differ significantly with each other (Post hoc comparative analysis conducted using Duncan's multiple range test).

The Sertoli cells were distinguishable due to their comparatively larger size, indistinct cell boundaries, and more prominent nuclei relative to the adjacent spermatogonia. These cells were situated either directly along or slightly away from the basement membrane (Figure 2-A and 3-A).

The tubular sections in CCl_4 group have shown disrupted order of arrangement of the various spermatogenic cells (spermatocytes, spermatids and spermatozoa). The scarce spermatogonia were distributed in a single basal concentric ring showing wide spaces in between (Figure 2-A and 2-B). The nuclei of these surviving spermatogonia were ellipsoidal instead of normal rounded shape. Adjacent to the basal spermatogonia, a heterogeneous collection of spermatogenic cells encompassing spermatogonia, spermatocytes along with spermatids, and tailless sperm heads was observed suspended within the lumen of the seminiferous tubules. Additionally, evidence of Sertoli cell necrosis was discernible (Figure 3-B). The loss in interstitial tissue has led to the appearance of small clumped masses of Leydig cells leaving behind wide empty spaces at the margins of the adjacent tubular sections (Figure 2-B).

The histological sections in CCl_4+OFPE group have shown various rehabilitative signs of the testicular micro-architecture. These include regeneration of the interstitial tissue to repopulate the focal spaces seen in the CCl_4 group; the spermatogonia lining the basement membrane appeared tightly packed. Furthermore, the other spermatogenic cells, including spermatogonia, along with spermatocytes and spermatids with mature spermatozoa, were organized in their usual sequence, just like in the control group (Figure 2-C and 3-C). Nevertheless, aggregations of various dislocated (discarded) spermatogenic cells were found as clumped masses in the middle of the central tubular lumens (Figure 2-C and 3-C).

b) Micrometic Results

Analysis of the micrometric data has shown slight decline in the mean diameter of the seminiferous tubules in the CCl_4 (953.9±22) and significant (P < 0.05) decrease in COf group (891.3±30) than Vc group (977.99±32). Whereas the mean CSA of the spermatogonia and spermatocytes in CCl_4 (148.8±12.9 and 275.52±18.1 respectively) remained substantially (P < 0.05) above the Vc (77.66±4.34 and 177.9±15.07) and COf (58.41±3.27 and 171.08±9.4) groups. Although, the mean head size in COf group (23.52±1.91) remained statistically

(P < 0.05) higher than the Vc group (15.99±1.63), however its value statistically (P < 0.05) reduce than mean sperm head size in C group (33.64±6.72). Whereas the mean tail length of spermatozoa in COf group (65.90±2.58) remained statistically (P < 0.05) above than C (57.29±3.54) group yet it value reduce significantly (P < 0.05) that the Vc (88.35±5.89) group (Table 1).

DISCUSSION

The available literature showed that chronic intra-gastric exposure of CCl_4 has caused alterations in spermatogenesis, particularly through various degenerative changes in the seminiferous tubules in rat testis (Ahmad et al., 2016; Ahmad et al., 2022). These include disintegration of the germ line cells especially the more differentiated ones (like secondary spermatocytes and spermatids) while majority of the maturing sperms were deformed. In a similar study Al-Olayan et al., 2014 have shown that 2 mL/kg intraperitoneal CCl_4 weekly injections for 10 weeks has caused partial disappearance of the interstitial tissue and its simultaneous replacement with the inflammatory and fibroblastic cells, in rats, whereas these changes were convincingly addressed with concurrent treatment of pomegranate juice in drinking water. In present study we have seen disgrace both in the interstitial tissue and the spermatogenic cells in mice following only a single intra-gastric dose 0.2 mL/kg CCl_4 while these changes were rapidly reversed on post treatment of wild olive fruit pulp extract.

In general, the elevated reactive oxygen species has been reported to induce massive germ cell death by increasing apoptosis that may lead to infertility (Inayat et al., 2020) whereas CCl_4 treatment has been reported to induce oxidative deterioration of membranous lipids, antioxidant enzyme system and DNA in the testis (Elsawy et al., 2019;Nadia et al., 2022). Thus the resultant redox imbalance in animal body tissues and organs on intra-gastric CCl_4 exposure may be the most plausible cause of observed damage to the testicular histology and histometry in present study. *Olea ferruginea* fruit pulp is a rich natural source of dietary phenols (Hashmi et al., 2015; Elhrech et al., 2024) phenolics, flavanoids, tannins and saponins (Sharma et al., 2015).

The fruit pulp of a related species *Olea europaea* (the major source of edible olives and olive oil) in addition to the flavonoids, phenolics and various glucosides was found to contain secoiridoids (oleuropein), cornoside, salidroside, halleridone, hydroxytyrosol-elenolate, β-hydroxytyrosol ester of methyl malate, diacylglycerol (containing oleic and elenoic acid residues), triacylglycerols and fatty acids (Ghanbari et al., 2012; Liaqat et al., 2021). The intra-generic relationship of *Olea ferruginea* and *Olea europaea* indicates the probable presence of these unique phytochemicals in *Olea ferruginea* thus providing it the appreciable rescuing properties against CCl_4 exposure related testicular damage. In general, these findings indicate OFPE contain rehabilitative medicinal potentials against male reproductive toxicity of CCl_4, thus indicating further investigations on the phytochemistry and medicinal applications of *Olea ferruginea* fruit pulp and seed oil.

CONCLUSION

On the basis of above findings, we conclude that *Olea ferruginea* fruit pulp extract plays a significant role in the improvement of testicular damage of CCl_4 exposure in mice.

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required funds and facilities for this research work.

AUTHORS CONTRIBUTION

S.N.A. designed the experiment. T.I conducted the experiment. M.A.K provided all the instruments needed for the experiment. I.I helped in lab work. U.A. provided guidance. K.R.A. supervised the complete study and contributed to the scientific discussion and editing of manuscript. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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