

Research Progress of Cadmium Toxicity on Male Reproduction Health

Sambreena Tunio¹, Fayaz Ali Ujjan², Meena Memon³, Sarfaraz Ali Fazlani⁴, Faisal Ayub Kiani⁵ and Muhammad Azhar Memon^{1*}¹Livestock and fisheries department, Govt. of Sindh, Pakistan²Vaccine production unit Sindh Tando jam livestock and fisheries department, Pakistan³Richmond Crawford Veterinary Hospital, Karachi Livestock & Fisheries Dept., Govt. of Sindh, Pakistan⁴Lasbela University of Agriculture, Water and Marine Sciences, Pakistan⁵Bahauddin Zakariya University, Pakistan

*Corresponding author

Muhammad Azhar Memon, Livestock and fisheries department, Govt. of Sindh, Pakistan.

Received: August 05, 2024; Accepted: August 14, 2024; Published: August 19, 2024

ABSTRACT

Cadmium is an element of heavy metal which can be harmful to environment and human beings with the rapid development of industry, cadmium as an important raw material causes serious pollution to the environment. It is stable in the environment and the biological half-life of it can be 10 to 30 years, difficult to degrade but easy to accumulate. Cadmium can exert toxic effects to many organs and tissues of human being and experimental animals, and its toxic effect on reproductive system has caught more and more attentions many research being done on it. This paper tries to over view the relative research about Cadmium toxicity on male reproduction.

Keywords: Male, Cadmium, Reproductive Toxicity, Sexual gland, Accessory Sex Gland, Endocrine Secretion

Introduction

Cadmium (Cd) is a toxic metal that is widely present in the environment. One of the heavy metal elements is listed by the United States Poisons Control Commission (ATSDR). No. 6 Toxic substances that endanger the health of animals. Ali et al. found that cadmium has an effect on testicles when studying the pharmacological effects of cadmium [1]. The pill had a strong necrotic effect, but it did not attract enough attention at that time. The occurrence of “painful disease” in Japan in the 30s was proved to be associated with cadmium exposure. As a result, people began to pay attention to the harm of cadmium to the human body 50s [2]. Bomhard found that within hours of subcutaneous injection of cadmium salts in the testes of animals. Visible macroscopic changes may be present. Since the 50s of this century especially since the 80s, people have begun to pay attention to the reproductive toxicity caused by cadmium many scholars have paid attention to and conducted a lot of research in the United States to this day there are about 100 research topics on cadmium and health Field [3]. The research on the toxicity and toxicology of cadmium in China has also been carried out

more extensive. In this paper, we will study the male reproductive toxicity of cadmium Contribute to the review.

Gonadal Toxicity of Cadmium

The two important functions of the testicles are the production of male hormones and sperm. Most of the research subjects on the reproductive toxicity of cadmium have focused on cadmium Effects on the testicles [4-6]. This is because the testicles are Cd²⁺ primary targets one of the officials. Experimentally confirmed for Cd²⁺ Detoxifying metallic sulphur eggs The gene for white (MT) cannot be induced in the testes The amount of conductive expression or synthesis is insufficient, so it is compared with other organs such as the liver Cd²⁺ More likely to cause testicular damage [7-10]. More research is mainly focused on: Morphological aspects. Most scholars believe that the early manifestations are mainly manifested in the injury of the blood late supratubal damage to testicular parenchymal cells, extensive spermatogenesis, epithelial cells Degeneration, necrotic cell nucleus shrinkage, lytic cytoplasmic eosinophilic staining The chromogenic part of the spermatogenic epithelium is shedding, separated and the seminiferous tubule is fibrosis Often the structure disappears [11,12]. However, the results of Abarikwu et al. suggest that cadmium can be straight Lesions

Citation: Sambreena Tunio, Fayaz Ali Ujjan, Meena Memon, Sarfaraz Ali Fazlani, Faisal Ayub Kiani, et al. Research Progress of Cadmium Toxicity on Male Reproduction Health. J Biomed Sci Biotech Res. 2024. 2(3): 1-6. DOI: doi.org/10.61440/JBSBR.2024.v2.14

to the spermatogenic epithelium and testicular blood vessels, and sensitization of the spermatogenic epithelium to cadmium. Sensibility is higher than that of testicular blood vessels [13]. In recent years, studies have confirmed: cadmium on the testicles at the same time, the tissue produces pathological damage, and it can also promote the occurrence of testicular tissue tumors, which are usually benign and malignant, and the degree of malignancy is not high without metastasis, it can also cause testicular teratomas or other tumors in animals reported. Different doses of cadmium damage to the testicles at different times after poisoning the injuries are also different. It is generally believed that 1~7 days after poisoning acts on sperm 8~21d acts on sperm cells, and 22~35d acts on spermatozoa. After 35 days, the cell acts on spermatogonia. Only very large doses can damage to spermatogonial cells in the spermatogenic epithelium leads to irreversible damage. Medium and low doses of cadmium mainly act on spermatocytes and spermatocytes the damage caused is reversible [14,15].

Epigonadal Toxicity of Cadmium

Animal epigonads are less sensitive to cadmium than testes. Generally, look at the epididymis, seminal vesicles, prostate volume reduction and weight loss after cadmium injection. Light. The effect of cadmium on the epididymis is different from the effect of cadmium on the blood vessels of the epididymis. Only the epididymis in the testicles have a brief small amount of reduced blood supply and capillaries to the head. Vascular permeability is increased with no significant changes in the body and tail [16-20]. There are newspapers after cadmium treatment, the number of sperms at the tail of the epididymis decreased significantly the spermatozoa in the testicles and in the semen also decreases with the duration of administration. Prolongation, sperm count decreases more dramatically, until the end of the sperm is free. This is because cadmium can make alkaline phosphatase, lactate dehydrogenase, and carbon in the epididymal tissue the activity of anhydrase and α -ketovalulase dehydrogenase was significantly inhibited. Sperm-specific marker enzyme --- lactate dehydrogenase-X viability. Also, it is possible that cadmium staining causes the increase in the P H value of the epididymal luminal fluid. Acidic environment required. In vitro experiments in rats showed acidic rings in the epididymal duct the environment plays an important role in the development of sperm motility [21,22]. Epididymal luminal fluid Alkalinization is the loss of tight junctions between the main cells of the epididymis and the blood epididymal barrier tile solution. Damage to the structure of the main cell leads to its synthesis and secretion. Hypotropia affects the acquisition of sperm motility. Ali et al., For adult rats epididymis to Cd the sensitivity is the same as that of young mice. The dose can cause intracapillary coagulation and epithelial in adult rat epididymis. Cell-cell tight junction disintegration and interstitial hemorrhage, while the young mice did not develop. Giving birth to such pathological changes is still in the abdominal cavity of the young mouse epididymis to make it capillary. Vascular endothelial cells may have some kind of defense against Cd 2+ mechanics [4,23,25]. Effect of cadmium on seminal vesicles. Nordberg has been reported: long-term in mice the weight and volume of seminal vesicles stained with cadmium were significantly lower than those of the control group. Previous report showed the changes in the ultrastructure of seminal vesicles caused by

cadmium were mainly manifested online semineral swelling, enlargement of Golgi complex vesicles, myeloid structure, and autophagy. Increased number of bodies as well as an increase in lipid droplet lysosomes. The effect of cadmium on the prostate is well studied on the effect of cadmium on prostate damage. Few. A large number of experiments have confirmed that cadmium is a prostate carcinogen in rats. Meantime Cd may disrupt the body by affecting the hypothalamic-pituitary-gonadal axis [26-30].

Hormone homeostasis affects the structure and function of the prostate. Hiba and other newspapers atrophy of prostate glands and epithelial folds after cadmium infection; Transmission electron microscopy the endoplasmic reticulum of secretory cells in the ventral lobes of the prostate is swollen and the remnants are increased [31,32]. Some cell matrices are shallow and organelles are absent. Low compared to the control group the organ index of the ventral lobe of the prostate was significantly lower in the dose and high dose groups $P < 0.05$ [33]. The experimental results are different depending on the way of poisoning with a single dose of intraperitoneal Cd (2mg/kg) was found the amount of injection for 4 hours can cause mitochondrial endotochondrial swelling of the main cells of the prostate swelling and myeloidosis; After 24 hours, the main manifestation is swelling of the Golgi apparatus; After 60 days, the ultrastructural changes basically returned to normal. Previously have found that the transoral subchronic toxicity of Cd mainly acts on the prostate the endoplasmic reticulum of the master cell causes endoplasmic reticulum expansion, vacuolarization, and leads to fineness cell disintegration without significant changes in mitochondria and Golgi apparatus. The target site of chronic Cd infection is the endoplasmic reticulum. May cause egg whites disorders of plasmid synthesis and modification. This main cell damage leads to the prostate Acinar atrophy and weight loss. Cadmium not only has a strong toxic effect on the gonadal testes, but also on the epididymis, accessory gonadal organs such as seminal vesicles and prostate also have toxic effects that cannot be ignored. Use. However, it is generally believed that the damage to the attached gonads after cadmium injection is like attachment. Weight loss, structural and functional changes in testicles, seminal vesicles, prostate, etc it can be a direct injury to cadmium or it can be due to testicular injury, testosterone. Secondary changes due to decreased synthesis [34-36].

Effects of Cadmium on Endocrine and Fertility

There are domestic and foreign studies on the effect of cadmium on hormone levels in experimental animals. However, the conclusions are not entirely consistent. This may be related to the various investigators the method of infection, the dose, the time and the experimental animals used. Germline differences. Cadmium is thought to be inhibited in both in vivo and in vitro testes. Cells secrete testosterone. Smoking high cadmium can cause plasma sex hormone testosterone. Ketones (T) and luteinizing hormone (LH) are reduced underwater. Santana et al. Chronic low-dose oral cadmium contamination was found to have an effect on serum testosterone levels in rats the effects have a lot to do with the time of exposure [37,38]. After the first month of poisoning no change in testosterone levels; Three months later, the rats in each group were treated with controls compared with the group, the serum testosterone level increased significantly; after the sixth month of this kind the

difference was only significant in the 200mg/kg cadmium group [39,40,41]. Zhang et al. also confirmed this, and experiments found that one-time injections Serum prolactin levels, growth hormone, thyroid gland after CdCl₂ 26 h Hormones, luteinizing hormone decreased, follicle-stimulating hormone did not change; at Acute administration of CdCl₂ 214d was followed by an increase in serum growth hormone and thyroid hormone, luteinizing hormone, and follicle-stimulating hormone levels, while serum lactation is promoted decreased hormone levels [42,43]. Mognetti et al. also found an increase in cadmium or Decreased prolactin secretion depends on the dose and timing of exposure It is also closely related to the age of rats: 30 days and 60 days Rat-aged rats were injected subcutaneously with CdCl₂ 20.5 or 1.0 mg/kg from an early age dose starts every 4 days, and the dose is exchanged every 4 days, and 90 days after 30 days Serum prolactin in rat-aged rats was averaged half-depletion period, average, absolute Amplitude, duration, relative amplitude shortened [44]. And 60d rat-old rats only the mean halving of serum prolactin was shortened, and the other parameters were not Change. Lahuent et al. found the effect of cadmium on testosterone levels in rats Ringing is also associated with age-related low-dose subcutaneous cadmium toxicity (0.5 mg/kg g) One month causes an increase in testosterone levels in juvenile rats (1-month-old). It is high and decreased in adult rats (2 months of age). According to Sengupta, low-dose injection of cadmium can cause rats Decreased sperm count, low or even no sperm in the epididymis. Hu et al. discovered Thirty-two male Kunming mice were divided into 4 groups, each group per kilogram per day Body weights were injected subcutaneously with CdCl₂ 20, 0.5, 1.0, 2.0mg continuously the results of 5 weeks showed that the sperm concentration in the epididymis of mice in each experimental group was as follows Sperm motility decreased significantly, and the rate of sperm malformation increased significantly and was dosed dependencies [45,46]. The above treated male rats were coped with female rats in a ratio of 1:2 The mating fertility rate, pregnancy rate, litter size and sex of the piglets were calculated the proportion found that these indicators showed a downward trend with the increase of the dose treated the female/male ratio showed an increasing trend, and to a certain extent, after females Proportions of generations. It has been reported that higher levels of cadmium in the body will make humans Sperm maturation and motility are greatly reduced. Relatively contains X-Chromosomes are more resistant to sperm and have a better survival rate than those contained The sperm of the Y-chromosome is high and therefore the chances of bonding with the egg are opposite this increases the proportion of female babies born [47,48]. The above results showed that cadmium had an effect on spermatogenesis and semen quality in mice it has obvious toxic effects and has obvious incompetence in male animal's benign influence [49-52].

Protection of Cadmium Against Male Reproductive Toxicity

Cd has been used with various chelating agents for a long time Poisoned Pro The most commonly used drug for bed therapy is edetate disodium disodium acid. But due to chela The mixture is non-specific and binds to metal ions not only to increase Cd²⁺ platoons Leakage also increases Zn²⁺, Ca²⁺ the discharge of plasma causes the battalion Nutritional imbalance [53]. Ran et al. proposed that the use of dredging chelating agents should be used at the same time the addition of vitamin B1 can both

enhance and reduce the function of chelating agents Urine Zn²⁺ and fecal Cu²⁺ excreted but still needs to be confirmed by clinical trials. At present, many studies have focused on the antagonism of Chinese herbal medicines to the reproductive toxicity of cadmium Function [54-56]. Liou found that mice were intraperitoneally injected with gynostemma Glycoside solutions at various concentrations can antagonize Tunnel positive fine compared with the cadmium chloride group, there was a significant decrease in the total gynostemma glycosides Cadmium chloride-induced apoptosis of mouse testicular germ cells [57]. Its mechanism may It protects cells, enhances immune function and promotes DNA synthesis strong DNA damage repair and antioxidant effects and improved ATPase function [58-60]. Wang et al. antagonized cadmium to tea polyphenols in male rats preliminary studies of reproductive toxicity have shown that tea polyphenols can be used at the same time as poisoning Apparent antagonism of cadmium causes testicular atrophy in rats; Cadmium-induced LDH-X enzyme activity reduction has a certain restorative effect; decreased sperm motility and survival due to cadmium there are changes in the rate of decreasing, counting decreasing, and increasing deformity rate significant antagonism. The mechanism may be related to antioxidant and cadmium stimulation relate [61-65]. In short, with the further understanding of the mechanism of action of cadmium poisoning new treatments or regimens will be available in the near future.

Credit Authorship Contribution Statement

Sambreena Tunio: Writing- Original draft preparation. Fayaz Ali Ujjan, Meena Memon, Sarfaraz Ali Fazlani, Faisal Ayub Kiani and Muhammad Azhar Memon: Writing- Reviewing and Editing.

Funding: Funding not available.

Declaration of Competing Interest: The authors declare that there are no conflicts of interest

References

1. Ali W, Ma Y, Zhu J, Zou H, Liu Z. Mechanisms of cadmium-induced testicular injury: a risk to male fertility, Cells. 2022. 3601.
2. Vahter M, Berglund M, Åkesson A. Toxic metals and the menopause, British Menopause Society Journal. 2004. 10: 60-65.
3. Bomhard E, Vogel O, Löser E. Chronic effects on single and multiple oral and subcutaneous cadmium administrations on the testes of Wistar rats, Cancer letters. 1987. 36: 307-315.
4. Ali W, Bian Y, Ali H, Sun J, Zhu J, et al. Cadmium-induced impairment of spermatozoa development by reducing exosomal-MVBs secretion: a novel pathway, Aging (Albany NY). 2023. 15: 4096.
5. Feng T, Liu M, Li C. How do vertical fiscal imbalances affect energy efficiency? The role of government spending on science and technology, Environmental Science and Pollution Research. 2023. 30: 42327-42338.
6. Ali W, Buriro RS, Gandahi JA, Chen Y, Aabdin Z, et al. A critical review on male-female reproductive and developmental toxicity induced by micro-plastics and nano-plastics through different signaling pathways, Chemico-Biological Interactions. 2024. 110976.

7. Vistro WA, Zhang Y, Bai X, Yang P, Huang Y, et al. In vivo autophagy up-regulation of small intestine enterocytes in chinese soft-shelled turtles during hibernation, *Biomolecules*. 2019. 9: 682.
8. Chen H, Huang Y, Bai X, Yang P, Tarique I, et al. Apoptotic-like changes in epididymal spermatozoa of soft-shelled turtles, *Pelodiscus sinensis*, during long-term storage at 4°C, *Animal reproduction science*. 2019. 205: 134-143.
9. Ahmed N, Yang, P Chen H, Ujjan IA, Haseeb A, et al. Characterization of inter-Sertoli cell tight and gap junctions in the testis of turtle: Protect the developing germ cells from an immune response, *Microbial pathogenesis*. 2018. 123: 60-67.
10. Wagan SA, Memon AA, Kalwer Q, Korejo RA, Khokhar TA, et al. Efficacy of Estrous Synchronization protocols ovsynch and cosynch in kundhi buffalo heifers.
11. Tarique I, Tariq M, Bai X, Wenjia, Q Yang P, et al. Interaction of Epididymal Epithelia and their Secretions with Spermatozoa Supports Functional and Morphological Changes During Long-Term Storage in the Chinese Soft-Shelled Turtle (*Pelodiscus sinensis*), *Microscopy and Microanalysis*. 2020. 26: 542-550.
12. Tarique I, ShiY, Gandahi NS, Ding B, Yang P, et al. In vivo cellular evidence of autophagic associated spermiophagy within the principal cells during sperm storage in epididymis of the turtle, *Aging (Albany NY)*. 2020. 12: 8987.
13. Abarikwu SO, Wokoma AF, Mgbudom-Okah CJ, Omeodu SI, Ohanador R. Effect of Fe and Cd co-exposure on testicular steroid metabolism, morphometry, and spermatogenesis in mice, *Biological Trace Element Research*. 2019. 190: 109-123.
14. Ali W, Chen Y, Shah MG, Buriro RS, Sun J, et al. Ferroptosis: First evidence in premature duck ovary induced by polyvinyl chloride microplastics, *Science of The Total Environment*. 2024. 933: 173032.
15. Ali W, Khatyan U, Sun J, Alasmari A, Alshahrani MY, et al. Mitigating effect of pomegranate peel extract against the furan induced testicular injury by apoptosis, steroidogenic enzymes and oxidative stress, *Chemosphere*. 2024. 358: 142086.
16. Vistro WA, Huang Y, Bai X, Yang P, Haseeb A, et al. In vivo multivesicular body and exosome secretion in the intestinal epithelial cells of turtles during hibernation, *Microscopy and Microanalysis*. 2019. 25: 1341-1351.
17. Vistro WA, Tarique I, Haseeb A, Yang P, Huang Y, et al. Seasonal exploration of ultrastructure and Na⁺/K⁺-ATPase, Na⁺/K⁺/2Cl⁻-cotransporter of mitochondria-rich cells in the small intestine of turtles, *Micron*. 2019. 126: 102747.
18. Haseeb A, Bai X, Tarique I, Chen H, Yang P, et al. Characterization of in vivo autophagy during avian spermatogenesis, *Poultry Science*. 2019. 98: 5089-5099.
19. Ali Vistro W, Liu Y, Xu M, Yang P, Haseeb A, et al. Mitochondria-rich cells: A novel type of concealed cell in the small intestine of chinese soft-shelled turtles (*Pelodiscus sinensis*), *Animals*. 2019. 9: 717.
20. Shi Y, Vistro WA, Bai X, Wu R, Chen C, et al. Effect of seasonal variance on intestinal epithelial barriers and the associated innate immune response of the small intestine of the Chinese soft-shelled turtles, *Fish & Shellfish Immunology*. 2020. 97: 173-181.
21. Wang X, Zhang K, Ali W, Li J, Huang Q, et al. Luteolin alleviates cadmium-induced metabolism disorder through antioxidant and anti-inflammatory mechanisms in chicken kidney, *Poultry Science*. 2024. 103: 103817.
22. Huang Y, Yang P, Chen H, Bai X, Wang X, et al. A “Lamellar structure” contributes to autophagosome biogenesis and mitophagy in zebrafish hepatocytes, *Fish & shellfish immunology*. 2018. 81: 83-91.
23. Sun J, Chen Y, Wang T, Ali W, Ma Y, et al. Baicalin and N-acetylcysteine regulate choline metabolism via TFAM to attenuate cadmium-induced liver fibrosis, *Phytomedicine*. 2024. 125: 155337.
24. Sun J, Chen Y, Wang T, Ali W, Ma Y, et al. Role of Mitochondrial Reactive Oxygen Species-Mediated Chaperone-Mediated Autophagy and Lipophagy in Baicalin and N-Acetylcysteine Mitigation of Cadmium-Induced Lipid Accumulation in Liver, *Antioxidants*. 2024. 13: 115.
25. Sun J, Chen Y, Wang T, Ali W, Ma Y, et al. Cadmium promotes nonalcoholic fatty liver disease by inhibiting intercellular mitochondrial transfer, *Cellular & molecular biology letters*. 2023. 28: 87.
26. Malyar RM, Li H, Liu D, Abdulrahim Y, Farid RA, et al. Selenium/Zinc-Enriched probiotics improve serum enzyme activity, antioxidant ability, inflammatory factors and related gene expression of Wistar rats inflated under heat stress, *Life sciences*. 2020. 248: 117464.
27. Memon IA, Raza MA, Vistro WA, Leghari MF, Nizamani AW, et al. Marker assisted molecular investigation of kappa-casein gene in *Bos indicus* Sindhi genetic group using HINFI restriction enzyme, *Int Arch BioMed Clin Res*. 2016. 2: 34-39.
28. Duan Y, Zhao Y, Wang T, Sun J, Ali W, et al. Taurine alleviates cadmium-induced hepatotoxicity by regulating autophagy flux, *International Journal of Molecular Sciences*. 2023. 24: 1205.
29. Zhang K, Li J, Dong W, Huang Q, Wang X, et al. Luteolin Alleviates Cadmium-Induced Kidney Injury by Inhibiting Oxidative DNA Damage and Repairing Autophagic Flux Blockade in Chickens, *Antioxidants*. 2024. 13: 525.
30. Duan Y, Zhang Y, Wang T, Sun J, Ali W, et al. Interactive mechanism between connexin43 and Cd-induced autophagic flux blockage and gap junctional intercellular communication dysfunction in rat hepatocytes, *Heliyon*. 2023.
31. Hiba EI O, Laaradia MA, Azzaoui FZ, Brahim MAS, Bitar A, et al. Prostate Cancer and Environmental Exposure: A Focus on Heavy Metals and Pesticides, in: *Handbook of Research on Global Environmental Changes and Human Health*, IGI Global. 2019. 130-151.
32. Azhar M, Gadahi JA, Bhutto B, Tunio S, Vistro WA, et al. Babesiosis: current status and future perspectives in Pakistan and chemotherapy used in livestock and pet animals, *Heliyon*. 2023. 9.
33. Khan SA, Kalhor IB, Gandahi JA, Vistro WA, Kalwer Q, et al. Puberty associated micro anatomical modification in testes and epididymis of Teddy goat (*Capra hircus*), *Pure and Applied Biology (PAB)*. 2019. 8: 1281-1286.
34. Mangi M, Kamboh A, Rind R, Dewani P, Nizamani Z, et al. Seroprevalence of brucellosis in Holstein-Friesian and indigenous cattle breeds of Sindh Province, Pakistan. *J. Anim. Health Prod*. 2015. 3: 82-87.

35. Khan SA, Kalhoro B, Gandahi JA, Tunio AN, Vistro W, et al. Gross anatomical studies on testis and epididymis at pre-pubertal and pubertal stages of Teddy goat, *Acad. Res. Internat.* 2016. 7:51-57.
36. Noreen M, Arijio A, Ahmad L, Sethar A, Leghari M, et al. Biological control of mosquito larvae using edible fish, *Int. J. Inov. App. Res.* 2017. 5: 1-6.
37. Haseeb A, Tarique I, Iqbal A, samad Gandahi N, Bai X, et al. Characterization of multilamellar bodies and telocytes within the testicular interstitium of naked mole rat *Heterocephalus glabe*, *Theriogenology*. 2019. 138: 111-120.
38. Liu Y, Liang Y, Wang S, Tarique I, Vistro WA, et al. Identification and characterization of telocytes in rat testis, *Aging (Albany NY)*. 2019. 11: 5757.
39. Santana VP, Salles ES, Correa DE, Gonçalves BF, Campos SG, et al. Long-term effects of perinatal exposure to low doses of cadmium on the prostate of adult male rats, *International journal of experimental pathology*. 2016. 97: 310-316.
40. Liang Y, Wang S, An T, Tarique I, Vistro WA, et al. Telocytes as a novel structural component in the muscle layers of the goat rumen, *Cell Transplantation*. 2019. 28: 955-966.
41. Soomro ZA, Nizamani ZA, Kalhoro NH, Soomro SA, Hm Yu, et al. Studies on surveillance and pathology of *E. coli* infections in poultry in Sindh province of Pakistan. 2021.
42. Waalkes MP, Coogan TP, Barter RA. Toxicological principles of metal carcinogenesis with special emphasis on cadmium, *Critical reviews in toxicology*. 1992. 22: 175-201.
43. Zhang T, Gao X, Luo X, Li L, Ma M, et al. The effects of long-term exposure to low doses of cadmium on the health of the next generation of mice, *Chemico-Biological Interactions*. 2019. 312: 108792.
44. Mognetti B, Franco F, Castrignano C, Bovolín P, Berta GN. Mechanisms of Phytoremediation by Resveratrol against Cadmium Toxicity, *Antioxidants*. 2024. 13: 782.
45. Sengupta P. Environmental and occupational exposure of metals and their role in male reproductive functions, *Drug and chemical toxicology*. 2013. 36: 353-368.
46. Hu D, Han, Li C, Lv L, Cheng Z, et al. Florfenicol induces more severe hemotoxicity and immunotoxicity than equal doses of chloramphenicol and thiamphenicol in Kunming mice, *Immunopharmacology and Immunotoxicology*. 2016. 38: 472-485.
47. Bai X, Guo Y, Shi Y, Lin J, Tarique I, et al. In vivo multivesicular bodies and their exosomes in the absorptive cells of the zebrafish (*Danio Rerio*) gut, *Fish & Shellfish Immunology*. 2019. 88: 578-586.
48. Bai X, Shi Y, Tarique I, Vistro WA, Huang Y, et al. Multivesicular bodies containing exosomes in immune-related cells of the intestine in zebrafish (*Danio rerio*): Ultrastructural evidence, *Fish & shellfish immunology*. 2019. 95: 644-649.
49. Arbab S, Buriro R, Bhugio SU, Shah AH, Soomro J, et al. Antimicrobial properties of aloe vera gel extracts against bacterial isolates from wound of donkey, *Pakistan Journal of Zoology*. 2020 52: 2333.
50. Oad RK, Rajput N, Laghari IH, Soomro H, Memon MA, et al. Effect of dietary lysine on the meat production and behaviour of broilers. 2021.
51. Ayoob MF, Nizamani ZA, Kamboh AA, Ayoob M, Vistro WA, et al. Pathology of induced Velogenic Viscerotropic Newcastle Disease (VVND) in Japanese Quail and Myna, *Pakistan Journal of Zoology*. 2021. 53.
52. Malyar RM, Tanha J, Ziauddin Z, Ismail KS, Ibrahim M, et al. Amelioration of heat stress-induced hepatic injury in wistar rats by zinc-enriched probiotics: Role of hepatic antioxidant status and serum enzymes activity. *Pure and Applied Biology*. 2021. 10: 1494-1503.
53. Lochi GM, Shah MG, Gandahi JA, Gadahi JA, Hadi SA, et al. Effect of selenium nanoparticles and chitosan on production performance and antioxidant integrity of heat-stressed broiler, *Biological Trace Element Research*. 2023. 201: 1977-1986.
54. Ran D, Zhou D, Liu G, Ma Y, Ali W, et al. Reactive oxygen species control osteoblast apoptosis through SIRT1/PGC-1 α /P53Lys382 signaling, mediating the onset of Cd-induced osteoporosis, *Journal of Agricultural and Food Chemistry*. 2023. 71: 5991-6002.
55. Sun J, Su F, Chen Y, Wang T, Ali W, et al. Co-exposure to PVC microplastics and cadmium induces oxidative stress and fibrosis in duck pancreas, *Science of The Total Environment*. 2024. 927: 172395.
56. Haseeb A, Tarique I, Bai X, Yang P, Vistro WA, et al. Inhibition of autophagy impairs acrosome and mitochondrial crista formation during spermiogenesis in turtle: Ultrastructural evidence, *Micron*. 2019. 121: 84-89.
57. Liou CJ, Huang WC, Kuo ML, Yang RC, Shen JJ. Long-term oral administration of *Gynostemma pentaphyllum* extract attenuates airway inflammation and Th2 cell activities in ovalbumin-sensitized mice, *Food and Chemical Toxicology*. 2010. 48: 2592-2598.
58. Gandahi NS, Gandahi JA, Yang P, Tarique I, Vistro WA, et al. Ultrastructural evidence of melanomacrophagic centers and lipofuscin in the liver of zebrafish (*Denio rerio*), *Zebrafish*. 2020. 17: 83-90.
59. Gandahi NS, Ding B, Shi Y, Bai X, Gandahi JA, et al. Identification of telocytes in the pancreas of Turtles—A role in cellular communication, *International journal of molecular sciences*. 2020. 21: 2057.
60. Huang Y, Chen H, Yang P, Bai X, Shi Y, et al. Hepatic lipid droplet breakdown through lipolysis during hibernation in Chinese Soft-Shell Turtle (*Pelodiscus sinensis*), *Aging (Albany NY)*. 2019. 11: 1990.
61. Wang W, Sun Y, Liu J, Wang J, Li Y, et al. Protective effect of theaflavins on cadmium-induced testicular toxicity in male rats, *Food and chemical toxicology*. 2012. 50: 3243-3250.

62. Dahiri GN, Memon AA, Kalwar Q, Kaka A, Vistro WA, et al. Improvement of Fertility Rate Using Ovsynch and Biostimulation Protocols with Timed Artificial Insemination in Thari Cattle, Pakistan Journal of Zoology. 2022. 54: 2981.
63. Wajid C, Baloch A, Khosa A, Kaleri H, Bangulzai N, et al. Prop-1 gene a selective marker of wool production in sheep breeds of Balochistan Pakistan, J. Anim. Health Prod. 2022. 10: 238-244.
64. Menghwar MK, Tunio AN, ShahG, Janyaro H, Khoso AS, et al. Comparative study of Propofol and Thiopental Sodium for Gastrotomy in Rabbits, Pure and Applied Biology (PAB). 2021. 10: 1338-1344.
65. Abbasi AG, Abro SH, Kamboh AA, Kalhor DH, Mazari MQ, et al. Epidemiological studies on bacterial respiratory infections in commercial poultry of district Hyderabad, Sindh, Pakistan, Pure and Applied Biology (PAB). 2020. 9: 1253-1265.