23

An Overview of Copper Toxicity and Public Health Concerns with Mitigation Strategies

AUTHORS DETAIL

Maria Jamil[1], Aisha Khatoon[1*], Muhammad Kashif Saleemi[1*], Al-Hafiza Shafia Tehseen Gul[1], Muhammad Imran[1], Wafa Majeed[2], Muhammad Waseem Tahir[1] and Muhammad Tahir Aleem[3]

[1]Department of Pathology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Department of Pharmacy, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[3]MOE Joint International Research Laboratory of Animal Health and Food Safety, College of Veterinary Medicine, Nanjing Agricultural University, 210095 Nanjing, P.R. China
*Corresponding author: aisha.khatoon @uaf.edu.pk; drkashif313@gmail.com

Received: Oct 21, 2022 Accepted: Dec 23, 2022

INTRODUCTION

Copper is considered as a trace element found on the planet Earth (Dai et al. 2020). It denoted by Cu (from latin: *cuprum*), having atomic No. 29. It is malleable, ductile and soft metal having high electrical and thermal conductivity. Fresh color of copper is pinkish orange. It is commonly used in building material, metal alloys, coins, jewelry, marine hardware, thermocouples for measurement of temperature and in strain gauges (Mehta and Badheka 2016).

Copper is used in electrical wire, plumbing, cooking utensils, coins, jewelry and decorative objects (Thompson 2007). It is also used in agriculture and veterinary medicine as copper salt. Supplementation of copper obtained from both inorganic and organic source have the positive effects in poultry yield (Das et al. 2010). It is also used as growth promoter if fed at the rate of 250 ppm, but supplementation at high quantity leads to decreased in feed intake, poor FCR and depressed growth in broiler (Rahman et al. 2001).

Copper may contaminate the environment when it accumulates abundantly in environment producing many hazards (Hefnawy and El-khaiat 2015; Dai et al. 2020). It is a one of major cause of environment pollution (Ray et al. 2006). Copper is essential part of many enzymes, which are necessary for the normal biological mechanism of body (Gaetke and Chow 2003). It is present in many cells of body but its highest quantity present in brain and liver. It is present in biological system as cupric form (Cu++), but in copper containing enzyme, it is present as bound cation form. Copper is required for all living organism for normal biochemical process (Gaetke et al. 2014). It is a part of many enzymes as a cofactor like metalloenzyme which include lysyl oxide, ceruloplasmin, cytochrome oxidase, superoxide dismutase and tyrosinase. It is also required for free radical defense, cellular respiration, tissue biosynthesis and neurotransmitter functions (Hefnawy and El-khaiat 2015). It also possesses antioxidant activity. It is used in cytochrome copper oxidase and C oxidase as prosthetic group. It is essential part of enzyme as is required for the conformation and integrity of enzyme. It is required for oxidation reduction reaction (Dai et al. 2020). Lysyl oxidase is Cu enzyme which is vital for cross linkage of collagen and elastin. These are required for connective tissue formation. Protein having Cu like ferroxidase and ceruloplasmin transfer from storage site to site of erythropoiesis. Myelin protects the neuron as covering layer which is formed and maintained by Cu. It is also essential for the development of eyes, hair and skin pigment i.e., melanin (Gaetke et al. 2014). Copper is a part of cytochrome C oxidase, which catalyzes the reduction of oxygen to water, the crucial step in cellular respiration, and is a part of copper, zinc-superoxide dismutase (Cu, Zn-SOD). Nonspecific Cu++-binding to thiol enzymes transform the catalytic activities of cytochrome P450 monooxygenase, and Cu++ could both oxidize and bind to some amino acid residues of the P450 monooxygenase, but not to its heme group (Letelier et al. 2009). In brain, copper present in numerous synaptic membranes, hippocampus, basal ganglia and cerebellum (Madsen and Gitlin 2007). Many enzymes present in central nervous system like ceruloplasmin, Cu/Zn superoxide dismutase, cytochrome C oxidase and dopamine β-hydroxylase are dependent on copper for normal functioning (Pal et al. 2013).

Copper is an essential micromineral in animal's diet. It is necessary for cellular breakdown and enzymatic action such as Cu-Zn superoxide dismutase (SOD1), cytochrome C oxidase, lysyl oxidase and tyrosinase that are involved in several important procedures essential for maturation and growth (Gupta 2012). Improving diet with inorganic and organic Cu source has beneficial impacts on poultry production (Das et al. 2010; Attia et al. 2011; Samanta et al. 2011). It has been recognized that as compare to inorganic copper, supplementation of organic copper at the dose rate of 8 mg/kg is essential for the development of White Pekin ducks up to first 56 days of age. The supplementation of Cu enhanced the plasma copper cholesterol level and reduced the

Citation: Jamil M, Khatoon A, Saleemi MK, Gul AHST, Imran M, Majeed W, Tahir MW and Aleem MT, 2023. An overview of copper toxicity and public health concerns with mitigation strategies. In: Abbas RZ, Saeed NM, Younus M, Aguilar-Marcelino L and Khan A (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 2, pp: 162-167. https://doi.org/10.47278/book.oht/2023.56

level of zinc. It has been stated that by organic copper supplementation liver Cu concentration improved along with Cu excretion and retention (Attia et al. 2012). Supplementation of copper at 10 mg/kg was effective for reproductive and productive efficacy and also improved the quality of eggs for laying hens (Attia et al. 2011). In poultry and livestock feed, $CuSO_4$ is commonly applied as feed additives (Wen et al. 2019). Supplementation of copper at 250 ppm has been certified as growth promoter (Gupta 2012).

Causes of Copper Toxicity

While excessive copper in diet is linked with several detrimental effects on poultry. Supplementation of Cu in excess amount reduced the feed intake, growth and feed conversion ratio in birds (Hashem et al. 2021). Numerous studies have verified the harmful effects of copper on birds (Yigit et al. 2012; Hefnawy and El-khaiat 2015; Huang et al. 2021). Moreover, by adding 325 ppm in poultry feed leads to initiate the muscle atrophy and growth retardation (Cinar et al. 2014). The excessive consumption of copper through feed leads to morphological modifications in the soft interior organs of the body (Attia et al. 2011). Previously, it has been described that in copper intoxicated bird's variation in liver tissue signified by necrotic and hyperplastic biliary epithelium with several deteriorative and necrotic alteration is seen at the 3rd week. Additionally, at 6th week necrosis of bile duct epithelia, cholestasis, fibroblast proliferation and lymphocytic portal aggregation occur. Long term exposure of Cu also leads to hemolytic anemia and disturb the central nervous system (CNS) (Hashem et al. 2021). Exposure to extreme level of Cu may result in oxidative distress in birds (Min et al. 2010; Yang et al. 2018), reduced the action of Cu-Zn superoxide dismutase (SOD1) and glutathione peroxidase (GSH-Px) along with increase in the contents of malondialdehyde (MDA) in duckling (Zhao et al. 2008). One of the best-known consequences of excess Cu is peroxidative damage to membrane lipids. Lipid peroxidation occurs by the reaction of lipid radicals and oxygen to form peroxy radicals. Lipid peroxy radicals may damage cells by changing the cell membrane's fluidity and permeability or by directly attacking DNA and other intracellular molecules such as proteins. In the mitochondria lipid peroxidation occurs along with in the inner membrane (cristae) Cu-damaged liver cells. Cu also leads to peroxidation in the membranes of hepatocyte lysosomes (Gaetke and Chow 2003).

Source of Copper Toxicity

Main source of copper toxicity is the accidently consumption of water supplies which contain high concentration of copper. Water may be adulterated by industrial waste or farm operation that run off into nearby public wells or reservoirs. Water running through the copper pipes may absorb copper particles and become pollutant with high copper, specifically if the pipes are corroded. Copper may be found in several types of food, drinking water and also in air. The renowned amount of copper is absorbed each day by drinking, eating and breathing. Copper level in air is typically low that's why copper exposure by breathing is minor. While people that live near smelters that process copper ore into metal, do experience this type of exposure. Occupational exposure to copper usually occurs. In the working environment copper infection may lead to flu like condition which is well known as metal fever (Royer and Sharman 2022).

Mechanism of Copper Toxicity

It is a microelement which is essential for normal functioning of body but when it accumulate in body at higher concentration, induced toxicity in aquatic life (Zeeshan et al. 2016). It is found in bounded form with protein but some time it released and in free form it catalyzed to form the reactive hydroxyl radicals. These radicals are reactive in nature, which leads to cellular toxicity. It produced oxidative stress by accumulating chronically or excessive exposure. Cu deficiency also produce oxidative stress (Gaetke and Chow 2003). When copper accumulation occurred in body, it leads to oxidative tissue damage through free radical formation (Kadiiska and Mason 2002). When Cu is found in the supply in excessive quantity than the cells demand, it excites the formation of reactive oxygen species and the abrupt deterioration of protein, fat and DNA. Several tools have been recommended to validate the Cu induced toxicity. Free Cu ions behave as an effective catalyst for the creation of free radicals. In redox reaction cupric and cuprous copper ion may execute as a vital component, i.e., cupric ion (Cu^{2+}) may be condensed to cuprous (Cu^{+}) in the presence of superoxide (O_2^{-}) that may catalyze the generation of reactive OH^{-} radicals from hydrogen peroxide (H_2O_2) breakdown by the Haber-Weiss reaction. Hydroxyl radicals are the most effective oxidative radicals possibly exist in living system and can arouse the peroxidation of lipid leading to destruction of tissues (Hashem et al. 2021). Pathogenesis of copper toxicity depend upon disruption of Cu homeostasis, due to which Cu accumulation occurred in body. Accumulation of Cu in body leads to neurodegenerative changes and hepatic disorder. Copper induced the cellular injury which leads to oxidative damage. Cellular injury result in the disruption of lipid metabolism, altered cellular events, alpha-synuclein aggregation, gene expression, Cu induced hepatic damage, initiation of acidic sphingomyelinase and release of ceramide and interaction of protein and copper in the nervous system (Gaetke et al. 2014).

Effects of Copper Intoxication

Accumulation of copper in excessive quantity leads to toxic effects such as degeneration of basal ganglia, hemolytic anemia and liver cirrhosis (Hefnawy and El-khaiat 2015).

Copper is microelement which is essential but can be harmful if its quantity increased or decreased. When copper ingested in abundant quantity, it effects adversely to the gut microflora. Liver toxicity occurred in chicken fed with CuSO4 at 1000 mg/Kg feed (Persia et al. 2003).

When rat fed with copper at 0.2 and 1.0 mg/kg BW, the AST, ALP and ALT increased significantly which showed the liver damage. Result showed that the early exposure of copper had effects on liver damage and gut microflora (Dai et al. 2020). When there is impaired copper excretion or accumulation of copper in body due to excessive intake, it leads to oxidative tissue damage through free radical formation (Kadiiska and Mason 2002). When oxidative damage occur, it causes many anomalies like Wilson's disease (Kido et al. 2017) and Indian childhood cirrhosis (Nayak and Chitale 2013).

In a study, Male Wistar rats were injected intraperitoneally with copper lactate at 0.15 mg Cu/100 g BW daily for 90 days. Serum acetylcholinesterase (ACHE) activity was decreased significantly. The spatial memory and decreased neuromuscular incoordination was also observed as compared to control rates. Copper contents in hippocampus and in liver increased significantly to 73% and 99.1% respectively while zinc content in liver reduced to 40.7%. The hippocampus zinc content increased by 77.1% with concomitant increase in level of zinc and copper in urine and serum in those rates which were intoxicated with copper as compared to control group (Pal et al. 2013).

Copper and Oxidative Damage

Copper induced the oxidative stress through ROS production. Intoxication of copper at concentrations of 0.06 mg & 0.1 mg/L for 24 hour or 48 hour which is sub lethal concentration, showed the significant production of intracellular reactive oxygen species (ROS) in Hydra (Zeeshan et al. 2016). Copper intoxication caused the redox activity through production of reactive oxygen species (ROS) (Valko et al. 2005). It generates the hydroxyl radicals and superoxide as a result of reactive oxygen species (ROS) production via Haber–Weiss and Fenton reactions.

According to another study, body weight of the broiler birds was found decreased at 6th week which was fed with copper at the concentration of 300mg/kg feed. Feed conversion ratio (FCR) was also poor in these birds as compared to control birds feeding with normal diet. Erythrocyte superoxide dismutase, alanine aminotransferase, Plasma aspartate aminotransferase, iron, alkaline phosphatase activities, copper concentrations, and malondialdehyde were increased in copper intoxicated birds while in plasma vitamin A and C concentrations were decreased, in copper intoxicated bids as compared to control birds (Cinar et al. 2014).

Copper is also toxic to aquatic animals, depends upon its quantity/concentration (Vieira et al. 2009). Accumulation of copper in body leads to ROS production resulted in oxidative damage by oxidizing protein and lipid molecules (Wang et al. 2012). When the quantity of copper increased in aquatic medium, it resulted in the copper accumulation in hydrobionts. Lipid peroxidation occurred through ROS production in copper intoxication (Barata et al. 2005), initiation of apoptosis (Krumschnabel et al. 2005), DNA damage (Bopp et al. 2008) and agitation of embryonic development (Kong et al. 2013). Numerous effects of copper excess in human and animals have been shown in Fig. 1.

Effects of Copper Deficiency

Copper deficiency also effects adversely and shows many clinical signs like anemia, pale coat, decrease the fleece quality in sheep, decrease the capillary integrity, bone fracture, poor reproductive performance, spinal cord hypomyelinization, decreased immunity and diarrhea (Tessman et al. 2001), which leads to the economic losses. In grazing animals copper deficiency ranked at 2nd most widespread deficiency among all mineral deficiencies. When animal suffered from copper deficiency, it leads to change in blood chemistry and enzyme system (Hefnawy and El-khaiat 2015). Its deficiency adversely effects the cardiovascular system by affecting the lysyl oxidase, ceruloplasmin and Cu superoxide dismutase which are essential for the strength and integrity of blood vessels (Al-Bayati et al. 2015). It leads to fatty liver disease, if copper intake is improper (Antonucci et al. 2017). Copper deficiency may also lead to the peripheral neuropathy (Coyle 2016) and anemia (Nakagawaa et al. 2014). Numerous effects of copper deficiency on human and animals have been shown in Fig. 2.

Amelioration of Toxic Effect of Copper

The toxic effects of copper are ameliorated by Vitamin E and ascorbic acid by reversing the oxidative damage. Zinc also ameliorates the toxic effects of Cu by reversing the free radical formation after binding on that site where the Cu bound and produced toxicity. Alpha-lipoic acid, polyphenols and beta-carotene also ameliorated the oxidative stress induced by the Cu (Gaetke and Chow 2003).

In a study, liver toxicity occurred in chicken fed with CuSO4 at 1000 mg/Kg feed. Supplementation of Zn at 1 g/kg, cysteine at 5 g/ kg and of ascorbic acid 1 g/kg feed, ameliorated the toxic effects of Cu toxicity by reverting the accumulation of Cu in liver. Supplemental $ZnSO_4$ also decreased the food intake, weight gain and reduced the Cu concentration in liver (Persia et al. 2003). Copper intoxication at 300 mg/Kg feed caused the oxidative damage while supplementation of vitamin E and vitamin C at 250 mg/kg and 250 mg/kg feed respectively ameliorated the toxic effects of copper in broiler (Cinar et al. 2014). Myo-inositol (MI) ameliorate the toxic effects of Cu through reverting the ROS production, protein oxidation and induction of lipid peroxidation in fish muscle. Molybdenum also have the capability to decline the copper absorption from the intestine and stored in the liver by enhancing the copper excretion. The ratio of copper to molybdenum in total diet of sheep must be 6:1 respectively (Jiang et al. 2015).

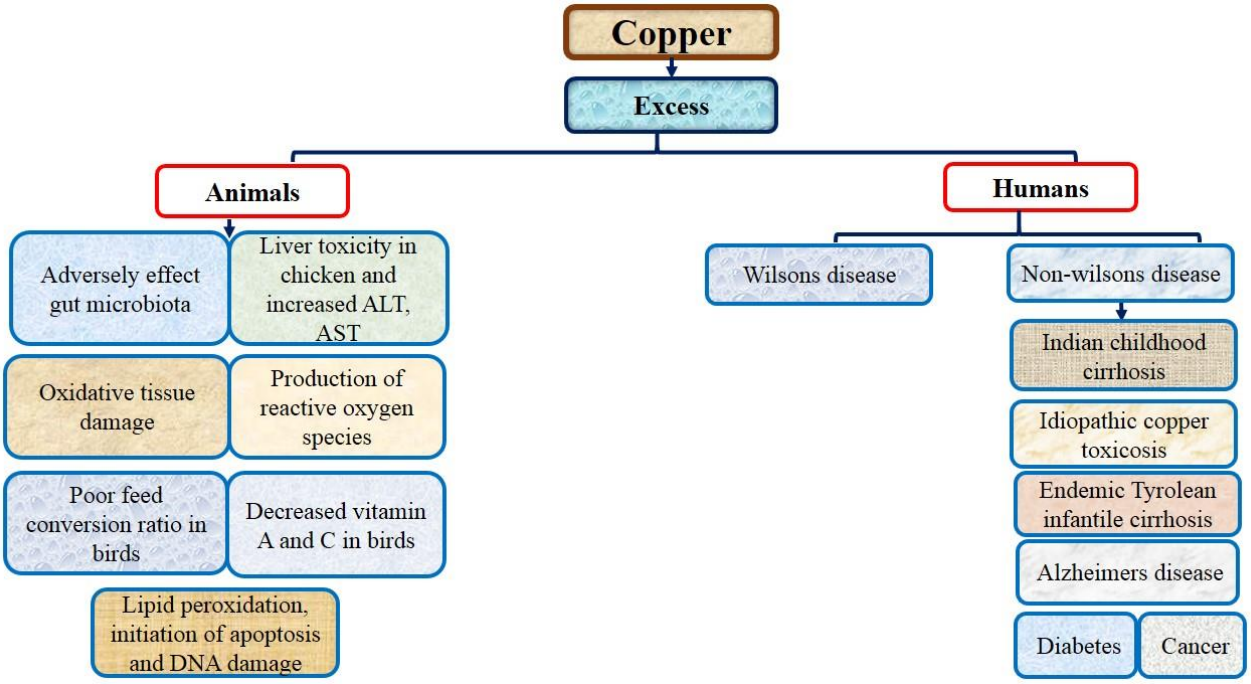

Fig. 1: Effects of copper excess on human and animals.

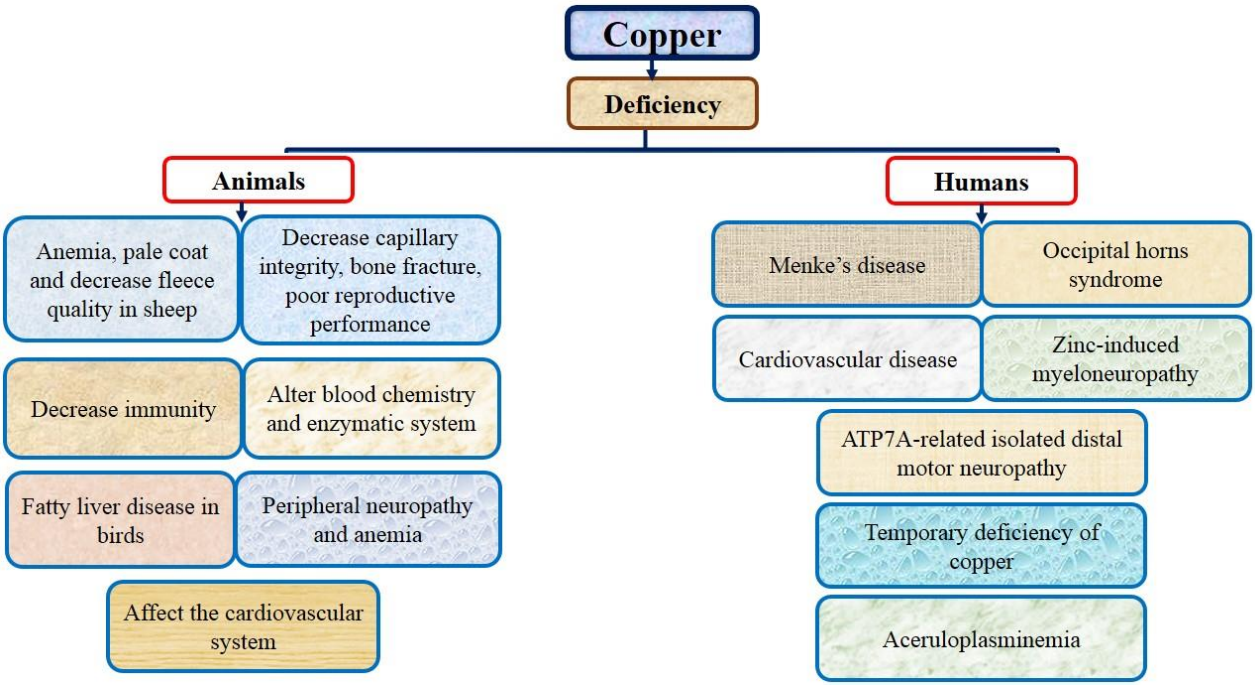

Fig. 2: Effects of copper deficiency on human and animals.

The consequences of Cu toxicity may be reduced by antioxidant protection system i.e., glutathione, catalase, dismutase, superoxide and vitamin C and E (Cinar et al. 2010). The dietary administration of several antioxidants i.e., selenium and vitamin C and E were effectively practiced, which mitigated the oxidative distress in animal products (Gouda et al. 2020; Amer et al. 2021; Ibrahim et al. 2021). Vitamin E is an antioxidant which protects the intracellular structure of animals and humans. It works by alleviating the harmful impacts of reactive oxygen species (ROS) and free radicals which stimulate the destruction of sulfhydryl groups and phospholipids, and leads to the altered cell membrane

structure. Similarly, vitamin C is significantly critical water-soluble antioxidant, as it defends biofilms from peroxidation of lipid by eradicating the peroxyl radicals in the aqueous phase prior to the deterioration process starts (Leskovec et al. 2018). It also acts to reload the declined vitamin E. The lipophilic radicals form in the membranes may be eradicated directly by vitamin C, while it declines the quantity of tocopheroxyl radicals that are observed in the membrane during the conversion of the lipophilic to aqueous phase. Several studies exposed good performance by the supplementation of vitamin C and E in poultry (Cinar et al. 2014; Zhu et al. 2019; Gouda et al. 2020; Amer et al. 2021) or fish diet (Ibrahim et al. 2020; Ibrahim et al. 2021; Azeez and Braimah 2020; Ahmed et al. 2021). Currently, several distinct information's have stated that vitamin E and C may defend from lethal impurities of xenobiotics and minerals due to their vital role as an antioxidant (Ajuwon and Idowu 2010). Both vitamins may work synergistically to prevent the harmful effects of copper toxicity (Cinar et al. 2014). Previously it was described that concurrent impacts of vitamin C and E may alleviate the DNA and histological alterations in the liver of birds intoxicated with CuSO4. Vitamin C and E alleviate the oxidative stress, Leukogram, erythrogram alterations and histopathological alteration in kidney induced by CuSO4 toxicity in birds (Hashem et al. 2021).

As copper is able to catalyze the development of reactive oxygen species, while the nutrients having the antioxidant abilities may protect against copper induced oxidative injury. Possible mechanism for antioxidant action of nutrients comprises of; constrain the formation of mitochondrial superoxide, scavenge or chelate the reactive oxygen species, or withdraw the transitional metal ions from the site of reactive oxygen species formation, declining the hydroperoxides formation, and restoration of impaired molecules. Significant enzymatic antioxidant systems in the body comprise of Mn-SOD, CU, Zn-SOD, GSH-Px and catalases, while non-enzymatic antioxidant system comprises of vitamin C, GSH and beta-carotene (Gaetke and Chow 2003).

Conclusion

Copper is a vital nutrient and a redox-active transition metal which can stimulate oxidative injury. High level of Cu may lead to enhanced oxidative destruction of protein, lipid and DNA and subsidize to neurodegenerative syndromes. Alternatively, copper is necessary for optimum antioxidant protection, and copper deficiency declines the body capability to deal with oxidative distress. Several nutrients can intermingle with copper and change its toxicity. Available evidences indicate that vitamin C and E, ascorbic acid, zinc, alpha-lipoic acid, beta-carotene, molybdenum and polyphenol primarily protects against the copper induced oxidative injury.

REFERENCES

Ahmed SA et al., 2021. Chitosan vitamin E nanocomposite ameliorates the growth, redox, and immune status of Nile tilapia (Oreochromis niloticus) reared under different stocking densities. Aquaculture 541: 1-12.

Ajuwon OR and Idowu O, 2010. Vitamin C attenuates copper-induced oxidative damage in broiler chickens. African Journal of Biotechnology 9: 7525-7530.

Al-Bayati MA et al., 2015. Cardiovascular effects of copper deficiency on activity of superoxide dismutase in diabetic nephropathy. North American Journal of Medical Sciences 7: 41-46.

Amer SA et al., 2021. Changes in the growth, ileal digestibility, intestinal histology, behavior, fatty acid composition of the breast muscles, and blood biochemical parameters of broiler chickens by dietary inclusion of safflower oil and vitamin C. BMC Veterinary Research 17: 1-18.

Antonucci L et al., 2017. Non-Alcoholic Fatty Liver Disease and Nutritional Implications: Special Focus on Copper. Nutrients 9: 1-12.

Attia Y et al., 2011. Effect of inorganic or organic copper additions on reproductive performance, lipid metabolism and morphology of organs of dual-purpose breeding hens. European Poultry Science 3: 169-178.

Attia YA et al., 2012. Effect of different dietary concentrations of inorganic and organic copper on growth performance and lipid metabolism of White Pekin male ducks. British Poultry Science 53: 77-88.

Azeez O and Braimah S, 2020. Mitigating Effect of Vitamin-E on Copper Sulphate-Induced Toxicity in African Catfish (Clarias gariepinus). European Journal of Medical Research 2: 1-10.

Barata C et al., 2005. Antioxidant enzyme activities and lipid peroxidation in the freshwater cladoceran Daphnia magna exposed to redox cycling compounds. Comparative Biochemistry and Physiology, Part C 140: 175-186.

Bopp SK et al., 2008. Copper-induced oxidative stress in rainbow trout gill cells. Aquatic Toxicology 86: 197-204.

Cinar M et al., 2010. Effects of vitamin C or vitamin E supplementation on cadmium induced oxidative stress and anaemia in broilers. Revenue de Medicine Veterinaire 161: 449-454.

Cinar M et al., 2014. Effects of dietary supplementation with vitamin C and vitamin E and their combination on growth performance, some biochemical parameters, and oxidative stress induced by copper toxicity in broilers. Biological Trace Element Research 158: 186-196.

Coyle L, 2016. The perfect storm: copper deficiency presenting as progressive peripheral neuropathy. American Journal of Emergency Medicine 34: 340-346.

Dai J et al., 2020. Toxicity, gut microbiota and metabolome effects after copper exposure during early life in SD rats. Toxicology.

Das T et al., 2010. Influence of level of dietary inorganic and organic copper and energy level on the performance and nutrient utilization of broiler chickens. Asian-Australasian Journal of Animal Sciences 23: 82-89.

Gaetke LM and Chow CK, 2003. Copper toxicity, oxidative stress, and antioxidant nutrients. Toxicology 189: 147-163.

Gaetke LM et al., 2014. Copper: toxicological relevance and mechanisms. Archives of Toxicology 88: 1929-1938.

Gouda A et al., 2020. Effect of dietary supplemental ascorbic acid and folic acid on the growth performance, redox status, and

immune status of broiler chickens under heat stress. Tropical Animal Health and Production 52: 2987-2996.

Gupta RC, 2012. Veterinary Toxicology: Basic and Clinical Principles, Academic Press, Cambridge, MA, USA.

Hashem M et al., 2021. Mitigation effects of vitamin C and E against copper toxicity in broiler chickens, with reference to biochemical, genotoxicity and pathological studies, Research Square, Durham, NC, USA.

Hefnawy AE and El-khaiat HM, 2015. The importance of copper and the effects of its deficiency and toxicity in animal health. International Journal of Livestock Research 5: 1-20.

Huang C et al., 2021. Effects of subchronic copper poisoning on cecal histology and its microflora in chickens. Frontiers in Microbiology 12: 1-13.

Ibrahim RE et al., 2020. Influence of vitamin C feed supplementation on the growth, antioxidant activity, immune status, tissue histomorphology, and disease resistance in Nile tilapia, Oreochromis niloticus. Aquaculture Reports 18: 1-8.

Ibrahim RE et al., 2021. The effects of chitosan-vitamin C nanocomposite supplementation on the growth performance, antioxidant status, immune response, and disease resistance of Nile tilapia (Oreochromis niloticus) fingerlings. Aquaculture 534: 1-9.

Jiang WD et al., 2015. Copper exposure induces toxicity to the antioxidant system via the destruction of Nrf2/ARE signaling and caspase-3-regulated DNA damage in fish muscle: Amelioration by myo-inositol. Aquatic Toxicology 159: 245-255.

Kadiiska MB and Mason RP, 2002. In vivo copper-mediated free radical production: an ESR spin-trapping study. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 58: 1227-1239.

Kido J et al., 2017. Plasma exchange and chelator therapy rescues acute liver failure in Wilson disease without liver transplantation. Hepatology Research 47: 359-363.

Kong X et al., 2013. Effects of copper exposure on the hatching status and antioxidant defense at different developmental stages of embryos and larvae of goldfish Carassius auratus. Chemosphere 92: 1458-1464.

Krumschnabel G et al., 2005. Oxidative stress, mitochondrial permeability transition, and cell death in Cu-exposed trout hepatocytes. Toxicology and Applied Pharmacology 209: 62-73.

Leskovec J et al., 2018. Effects of supplementation with-tocopherol, ascorbic acid, selenium, or their combination in linseed oil-enriched diets on the oxidative status in broilers. Poultry Science 97: 1641-1650.

Letelier ME et al., 2009. Mechanisms underlying the inhibition of the cytochrome P450 system by copper ions. Journal of Applied Toxicology 29: 695-702.

Madsen E and Gitlin JD, 2007. Copper and iron disorders of the brain. Annual Review of Neuroscience 30: 317-337.

Mehta KP and Badheka VJ, 2016. A review on dissimilar friction stir welding of copper to aluminum: process, properties, and variants. Materials and Manufacturing Processes 31: 233-254.

Min L et al., 2010. Effect of dietary high copper on the antioxidase activities of brain tissue in chickens. Chinese Journal of Veterinary Science 41: 220-223.

Nakagawaa M et al., 2014. Copper-deficiency anemia after esophagectomy: A pitfall ofpostoperative enteral nutrition through jejunostomy. International Journal of Surgery Case Reports 5: 311-314.

Nayak NC and Chitale AR, 2013. Indian childhood cirrhosis (ICC) & ICC-like diseases: The changing scenario of facts versus notions. Indian Journal of Medical Research 137: 1029-1042.

Pal A et al., 2013. Biochemical, Histological, and Memory Impairment Effects of Chronic Copper Toxicity: A Model for Non-Wilsonian Brain Copper Toxicosis in Wistar Rat. Biological Trace Element Research 153: 257-268.

Persia ME et al., 2003. Amelioration of oral copper toxicity in chicks by dietary additions of ascorbic acid, cysteine and zinc. Nutrition Research 23: 1709-1718.

Rahman ZU et al., 2001.Effects of copper supplement on haematological profiles and broiler meat composition. International Journal of Agriculture and Biology 3: 203-205.

Ray AK et al., 2006. Assessment of Godavari estuarine mangrove ecosystem through trace metal studies. Environment International 32: 219-223.

Royer A and Sharman T, 2022. Copper toxicity. Statpearls (Internet), Treasure Island (FL), Statpearls publishing.

Samanta B et al., 2011. Effects of dietary copper supplementation on production performance and plasma biochemical parameters in broiler chickens. British Poultry Science 52: 573-577.

Tessman RK et al., 2001. Sensitivity and specificity of serum copper determination for detection of copper deficiency in feeder calves. Journal of the American Veterinary Medical Association 218: 756-760.

Thompson LJ, 2007. Copper. In: Gupta RC editor. Veterinary toxicology basic and clinical principles. Academic Press: USA; pp: 427-429.

Valko M et al., 2005. Metals, toxicity and oxidative stress. Current Medicinal Chemistry 12: 1161-1208.

Vieira LR et al., 2009. Acute effects of copper and mercury on the estuarine fish Pomatoschistus microps: linking biomarkers to behaviour. Chemosphere 76: 1416-1427.

Wang B et al., 2012. Histone deacetylase inhibition activates transcription factor Nrf2 and protects against cerebral ischemic damage. Free Radical Biology and Medicine 52: 928-936.

Wen A et al., 2019. Copper bioavailability, mineral utilization, and lipid metabolism in broilers. Czech Journal of Animal Science 64: 483-490.

Yang F et al., 2018. Autophagy attenuates copper induced mitochondrial dysfunction by regulating oxidative stress in chicken hepatocytes. Chemosphere 204: 36-43.

Yigit A et al., 212. The effects of levamisole on oxidative stress induced by copper intoxication in broilers. New Zealand Veterinary Journal 60: 273-277.

Zeeshan M et al., 2016. ROS dependent copper toxicity in Hydra-biochemical and molecular study. Comparative Biochemistry and Physiology, Part C 185: 1-12.

Zhao L et al., 2008. Effects of high copper on the production of the hydroxy radical and nitrogen monoxide in liver of ducklings. Chinese Journal of Veterinary Science 38: 787-790.

Zhu Y et al., 2019. Effect of in ovo feeding of vitamin C on antioxidation and immune function of broiler chickens. Animal 13: 1927-1933.