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Metallothionein Defensive Strategies against Metal Overload in Farm Animals

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Abstract

The comprehensive research highlights the possible health effects of metal overload, which is the condition of farm animals having an excess of metallic components like lead or copper. The study, which spans the years 2019 through 2023, offers a thorough review of defense mechanisms with a particular emphasis on metallothionein (MT) defensive strategies. Utilizing information from 37 pertinent research studies, the paper discusses important metals such as Ni, Cd, Cu, Fe, Zn, As ,Co, Pb, Hg and Cr, clarifying their effects and limits, particularly concerning topical and intramuscular applications. Particular focus is placed on the harmful effects of mercury pertaining to the reproductive, immune and central neurological systems. To lessen the negative impacts of metal overload on animal health, the article supports regulatory actions as well as environmental pollution mitigation. Together with antioxidants, metal-binding proteins, enzymatic and non-enzymatic defense mechanisms, MT becomes an essential defensive strategy. The importance of vitamins, minerals, proteins and phyto-nutrients in preventing oxidative stress brought by an excess of metals is covered in the last section. MT induction provides farm animals with a useful defense against metal overload while preserving physiological balance because metal-binding proteins like metalloreductase and ceruloplasmin maintain copper-iron balance. Metallothionein, crucial for farm animals' metal homeostasis, is essential for protecting against metal overload. Understanding its regulation is crucial for sustainable animal husbandry practices.

Keywords: Metal Overload, Metallothionein (MTs), proteins and minerals, animal's health

INTRODUCTION

Farm animals that are overexposed to metals run a serious danger of oxidative damage, stunted growth and even death. The MT protein family is essential for controlling metal concentrations and offering strong resistance to overabundance buildup (1). Farm animals in India, where the cattle industry generates a large portion of the country's agricultural GDP, are exposed to different metals via their environment, food and water (2). The necessity for efficient preventive measures is highlighted by the possible overconsumption of certain metals (3). As essential metal buffers, MTs regulate the concentration of metals in cellular environments, maintaining the delicate balance necessary for essential biological functions. Farm-raised animals have a greater production of metal-tolerant molecules (MTs) in response to metals, indicating that they can adapt to variations in metal concentrations (4). As part of the defense mechanism against metal overload, complex interactions occur between metal ions and metalloproteins (MTs). Reactive oxygen species (ROS) generated during metal-induced stress is scavenged by MTs, who actively take part in detoxification procedures (5). MTs play a crucial role in farm animals' antioxidant defense mechanisms, raising resistance to oxidative damage caused by metals, contributing to the overall well-being of farm

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animals in agricultural settings (6). The study sheds light on the potential health risks associated with metal overload, a condition in which farm animals have an excess of metallic elements such as lead or copper in figure (1).

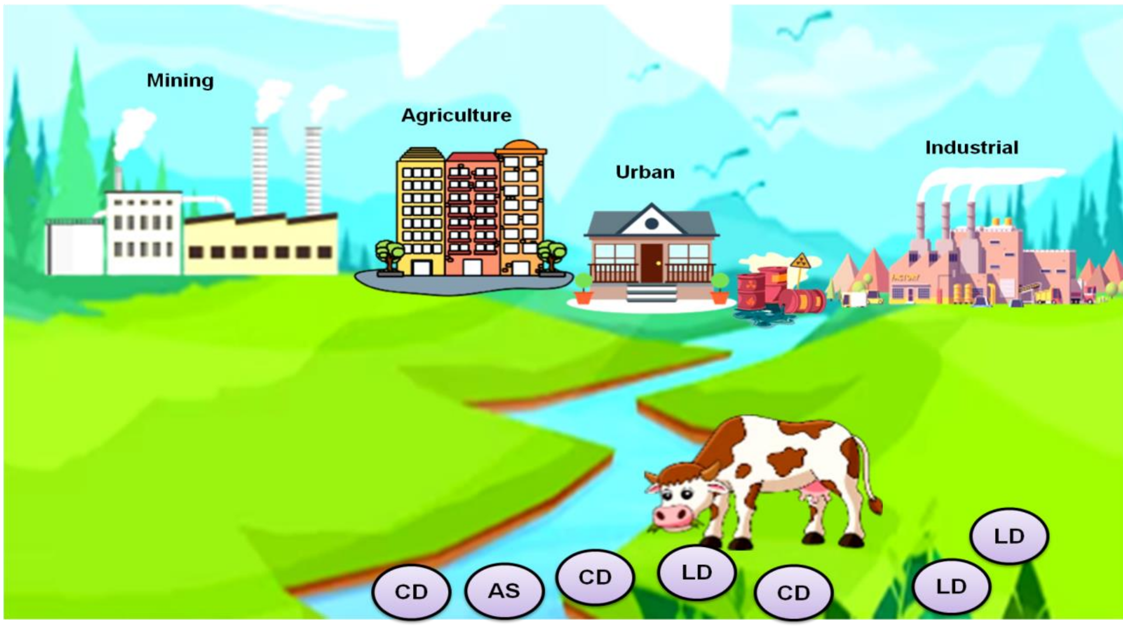

Figure (1). Metal overloading in farm animals (Source: https://www.frontiersin.org/articles/10.3389/fvets.2023.1149720/full**)**

Characteristic of metal overload in farm animals

Metallic substances associated with potential toxicity and pollution is referred as "metal overload". Regarding toxicity, components used in industry, are hazardous to aerobic and anaerobic processes as well as animals, however not all of them are completely metallic or denser (7). Figure (1) shows the characters of metal overload. Consists of: As, Co, Cd, Cr, Cu, Pb, Hg, Ni, Fe, Ni and Zn. Table (1) represents the limits of heavy metal.

Table (1). Constraints of Overloaded Metal (Source: Author)

Huge Metals	**Regular Dosage**	
	Intramuscular	**Topical**
Ni	25	250
Cd	0.5	5
Cr	25	250
Ar	1.5	15
Hg	1.5	15
Co	250	2500
Pb	1	10

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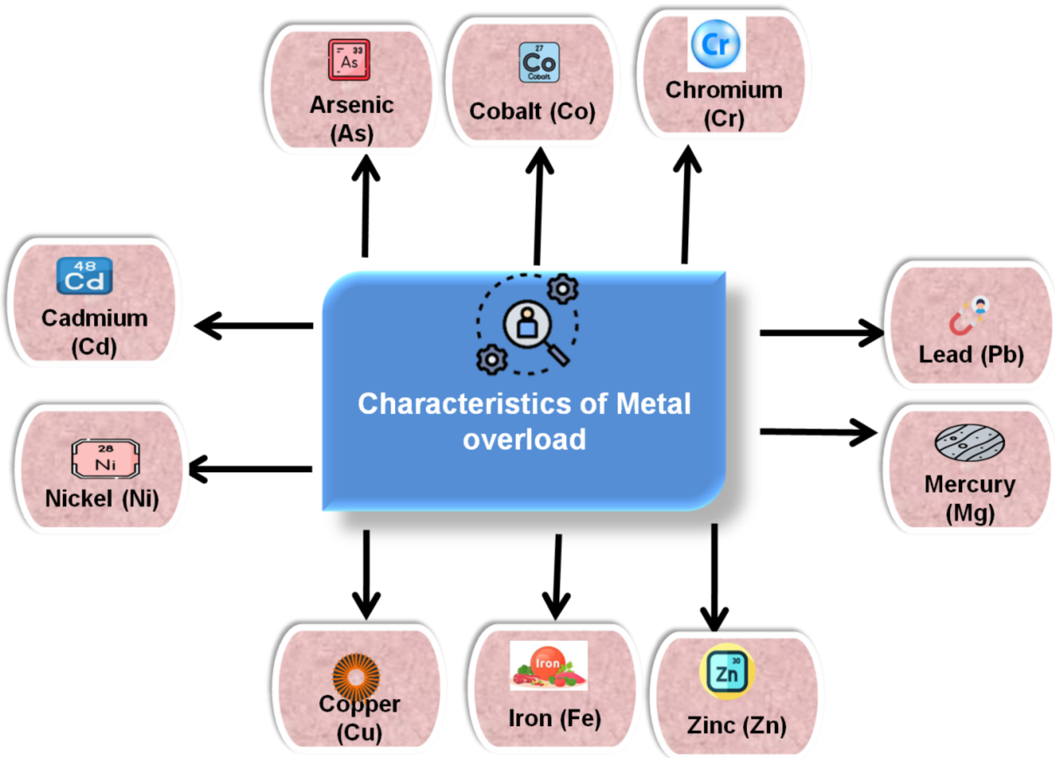

Figure (1). Attributes of metal overload (Source: Author)

Nickel (Ni)

Ni is a crucial trace element for many organisms. Reduced growth, altered iron, copper and zinc levels in the liver, skin eruptions, anemia, longer gestation, fewer children, decreased levels of hematocrit and hemoglobin, the production of hem, decreased activity of various enzymes, including transaminases, α-amylase, as well as hydrogenases, have been associated with an animal lacking nickel (8). The quantities of nickel were highest in the lungs and kidneys, yet lowest in the liver. Numerous studies have shown that animals can transfer nickel through their placenta. Male adult rats did not exhibit any signs of metal accumulation in their testes, liver, brain, hair, small intestine, liver, or digestive tract after receiving 10 or 20 Ni/kg body weight for 14 days (9).

Copper (Cu)

Cu is a crucial trace element that is required for the preservation of metabolic balance in plant and animal nutrition as well as the activation of oxidative enzymes. Pig growth is enhanced by high dietary Cu, which can attributed to its bacteriostatic action, feed intake increase, enhanced enzyme activity and neuropeptide release (10). Cu can promote the growth of microorganisms and the breakdown of agricultural waste, however, this process can take longer in large quantities. Cu is far more harmful than Zn to Gobiocypris rarus when it comes to the soil-microbial breakdown of polycyclic aromatic hydrocarbons. Both people and animals can be harmed by high Cu consumption, as they can livestock themselves (11).

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Zinc (Zn)

Zinc is a trace mineral that is critical to metabolism that is present in over 300 metallo-enzymes and genes. Keeps the gut mucosa intact, guards against enteric infections and improves the performance of weaned piglets. Misusing it increases the diversity of drug-resistant (14). Zinc resistance and Enterococcus faecalis are associated. High zinc concentrations can be harmful to Gobiocypris rarus embryos and soil microbes. It's the most studied alternative since it stimulates growth as an antibiotic does.

Cadmium (Cd)

Due to fertilization and atmospheric deposition, the nation's soil has a low lead (Cd) background. Mineral supplements including phosphates and zinc sulfate include cadmium as an impurity. 1.0-3.6% Cd is present in pig feed and 150-370 mg/kg Cd is present in 5% of premixed feeds that are purchased. Feces contain the majority of the CD discharged. In Beijing and Fuxin farmlands, PM plays a significant role in contributing to soil Cd levels (15). Vegetables and certain animal haslets contain Cd at levels higher than recommended by national food hygiene regulations. When Cd is transported from soil to food crops, creature exposure to this category I carcinogen, which can result in mutagenesis, teratogenesis, carcinogenesis and medical anomalies occurs (16). Cadmium affects animal development in pigs by increasing the feed/gain ratio and decreasing the average daily feed intake.

Iron (Fe)

Iron is the most common trace element in the body and it is a part of many different enzyme systems, such as cytochrome, myoglobin, as well as hemoglobin. Hemoglobin, the molecule in charge of oxygen supply, makes up around 60% of the iron in the body (12). It returns via venous circulation as carboxy-hemoglobin, which uses arterial blood to transport oxygen from the lung and CO2. Iron participates in the electron transport chain as a member of the cytochrome enzyme. A simpler version of myoglobin is the ferrous porphyrin that is present in muscle. About 25% of the iron in the body is found in the storage forms magnetite and the hemosiderin, which are found in the liver, spleen, bone marrow and other organs (13).

Cobalt (Co)

Cobalt, a mineral in vitamin B12, plays a crucial role in nerve tissue preservation and red blood cell production. It aids in the rumen's synthesis of cyanocobalamine. Australian studies in 1935 confirmed cobalt's dietary requirement for cattle, sheep, horses and ruminants primarily need it due to stomach bacteria converting it into vitamin B12. For ruminants, the daily intake is 0.10 ppm (17). Cobalt is involved with molybdenum in hematopoiesis, iron and copper.

Chromium (Cr)

In animals, balancing the metabolism of fats, carbohydrates and proteins depends on Cr (III), which binds to cell wall receptors to improve insulin activity. The effects of various chemical forms of Cr (III) on cattle development, carcass features, immunological response, reproduction and tissue deposition have been investigated (18). Piglet growth performance can be enhanced by chromium nanocomposite, nicotinate, propionate, tripicolinate, chromium-l-methionine and chromium picolinate. Blood, muscle and a few other organs have much higher Cr contents are dietary supplements of chitosan nanoparticles (19). It is thought that organic Cr (III) has a higher biological availability than inorganic Cr (III).

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Lead (Pb)

Lead accumulates in the kidneys of animals. The lead concentrations in the liver and kidneys of wild boars were nearly identical, although they were much greater than those in the muscles (20). Pb profoundly alters steroid production and reduces gonadotropin binding in vitro. Breastfeeding eliminates lead in the milk. Pb can accumulate in the growing fetus starting in the second trimester. Furthermore, Pb (II) damages and deforms the circulatory system in zebra-fish embryos. Lead pollution has been traced back to zinc oxide used in the early post-weaning phases of animal mounting.

Mercury (Hg)

Hg is a harmful substance that builds up in individual follicular fluid as well as in pigs' kidneys, liver and muscles. The kidneys of wild boars have the greatest quantity of mercury. The primary reason for the rise in mercury levels in animal tissues is the usage of fish meal (21). When a meal is fed to animals, particularly ruminants, mono-methyl mercury can bio-concentrate in protein matrices including eggs, meat and dairy products.

Arsenic (As)

As is a metalloid, which is necessary for animal growth, but a deficit can lead to changes in mineral concentrations, aberrant reproduction and decreased growth or heart injury. When added to feed, organo-arsenics such as roxarsone and arsanilic acid introduce contaminants. The most found contaminants in feeds are As (III) and As (V). The trivalent and pentavalent oxidation states of soil are harmful, much as the pollution caused by concentrated animal feeding operations that pollutes the soil (22). As inorganic molecules are more dangerous than organic, the limited absorption of organic As leads to low bioavailability levels.

Most Toxic Metal Overload

Metal overload in animals is an overabundance of metals building up in their blood vessels, leading to toxic effects and potential harm. Mercury, a highly toxic metal, can cause severe damage to the central nervous system, disrupt reproductive processes and weaken immune responses. Monitoring and managing metal overload is crucial for wildlife and domesticated species' well-being (23). Mitigating environmental contamination and enforcing regulations to limit industrial discharges are essential steps to prevent metal overload and its adverse effects on animal health. Table (2) demonstrates the negative impacts of Cadmium, Mercury, Arsenic and Lead**.**

Table (2). Complications Related to Lead, Mercury, Cadmium and Arsenic (Source: Author)

Excess Metals	Negative impacts
Pb	Both eating and breathing it in might allow it to enter the body. To determine the elemental impurities limit, the highest permitted amounts might be 5 µg/L. It can lead to altered Hb biosynthesis, anemia, elevated kidney damage, issues with reproduction as well as fertility and harm to the brain or neurological system.

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As	Inorganic chemicals that dissolve in water are easily absorbed by the digestive system. As in inorganic form is extremely harmful. Some of the negative effects include skin issues, inflammation of the stomach, intestines and lungs, along with decreased production of RBCs and WBCs. Infertility, skin issues, heart issues, brain damage, poor immunity to infections and even death can result from high amounts of inorganic As. As has a 10–300 mg/kg oral acute lethal dosage (LD50).
Hg	Its environmental presence can cause the food chain to become biomagnified. Because organic mercury is more easily absorbed by the animal body than inorganic mercury (like methyl mercury), organic mercury is more toxic. Numerous health issues, such as kidney damage, nervous system disruption, brain damage, chromosomal and DNA damage, allergic responses, sperm destruction, birth deformities and miscarriages, can be brought by mercury exposure. Mercury in tiny animals has a low half-life (LD50) of 1 mg/kg.
Cd	Cadmium is absorbed more readily by the lungs than by the digestive system. The CNS, kidneys and immunological systems can be harmed. Additionally, it might lead to fractured bones and problems with reproduction. It could cause diarrhea, vomiting and stomachaches. The oral LD50 animal samples varied from 63 to 1125 milligrams per of Cd.

Metallothionein (MT) based Defensive Techniques for Protecting Farm Animals in Metal Overload

In living organisms, the generation of free radicals is regulated by several defense mechanisms. Metal-binding proteins, several defensive mechanisms include enzymatic and non-enzymatic defense systems, additional endogenous antioxidants; Oxidative stress and an abundance of free radicals are present in every system used for farming animal production. The excess of oxidants that expose biomolecules is a significant issue (24). Farm animals need defense mechanisms that lower stress and prevent the creation of free radicals to perform better, be healthier and produce more. Farm animals need additional nutrients in their meals to help them use the basic nutrients and energy in the food in a coordinated way. These nutrients include antioxidants, trace elements and other bioactive chemicals are shown in Table (3).

Table (3). Enzymatic Defense Techniques (Source: Author)

Enzyme Defense methods	**Functions**
Glutathione Reductases	Defend mitochondria and DNA from oxidative damage
Glutathione Transferases	bind to glutathione to detoxify chemicals
Superoxide Dismutases	Transform superoxide radicals into hydrogen peroxide and oxygen
Glutathione Peroxidases	Reduce hydrogen peroxide to prevent lipid peroxidation
Catalases	Disassemble the hydrogen peroxide solution

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Enzymatic Defense methods

Enzymatic defense systems, including glutathione reductases, glutathione transferases, catalases, superoxide dismutases and glutathione peroxidases, protect DNA and mitochondria from the damaging effects of oxidative stress. Changes in these enzymes can affect an individual's ability to fend against certain diseases. Antioxidant enzymes neutralize or deactivate free radicals, depriving them of electrons and energy before they interact with molecules or other components of the cell (25). By interfering with antioxidant enzyme activity, they lessen harm. Over the last decade, studies have shown a positive correlation between more than sixty medical disorders and free electrons, together with diabetes, heart attacks, cancer, atherosclerosis, Alzheimer's disease and aging. Superoxide reductase and superoxide dismutase are two enzymes.

Superoxide reductase (SOR) and superoxide dismutase (SOD)

Superoxide radicals are broken down by metalloenzymes called SODs and SOR into oxygen coupled with hydrogen peroxide. All living things include SODs, however, prokaryotes and unicellular eukaryotes contain ROS (26). SORs exclusively include iron, whereas SODs comprise elements. There are many isoforms of SODs, such as extracellular SOD (EC SOD), mitochondrial MnSOD and systolic CuZnSOD.

Non-Enzyme Defense Methods

Non-enzymatic defense systems include scavenger antioxidants such as coenzyme Q10, glutathione and vitamins C and E, as well as some proteins that bind ROS and RNS to act as proteins with antioxidant properties. SS-peptides and Thioredoxin (Trx), proteins with acute phases such transferrin and albumin, ceruloplasmin as well as haptoglobin are examples of antioxidants (27). Therefore, the tissues are protected against ROS by these antioxidant systems in Table 4.

Table (4). Non-Enzymatic Defense Techniques (Source: Author)

Defense methods	Components of Antioxidants
Antioxidants that Scavenger	Glutathione, Coenzyme Q10 and Vitamins C and E
Proteins Rich in Antioxidants	Acute phase proteins, Thioredoxin and SS-peptides
Antioxidant properties of Vitamins	Beta-carotene, B complex vitamins, C, E and
Effects of Mineral and Trace Elements as Antioxidants	Zinc, Copper and Selenium
Proteins' Antioxidant Properties	Albumin, haptoglobin, lactoferrin and thioredoxin
Phytonutrients' Antioxidant Properties	Polyphenols, Flavonoids

Vitamins' Antioxidant Effects

The most researched dietary antioxidants include beta-carotene, vitamin B complex, vitamin E and vitamin C. Whole grains and premium green vegetables are important sources of vitamin E, while fruits as well as vegetables are important providers of carotenoids and vitamin C. For agricultural animals, fresh pasture, legumes, bioactive plants along with herbs, silage and yeasts are natural sources of vitamin E (28). Within the cell membrane, vitamin E functions as a chain-breaking antioxidant to stop the fatty acid membrane lipid peroxidation. Synthetic tocopheryl acetate is less successful than expected tocopherol helping to transfer to muscles from the diet. Other antioxidants, such as vitamin C, carotenoids and phytonutrients, have less of an effect on the quality of dairy products and proteins than vitamin E does. Given that in external fluids, vitamin C is most prevalent soluble in water and antioxidant, it might prevent lipid peroxidation (29). It is thought that vitamin C can restore vitamin E. Furthermore, the antioxidant properties of carotenoids, such as lycopene and beta-carotene, shield lipid-rich tissues in fact; beta-carotene and vitamin E can protect these tissues jointly. Dietary sources that are low in fat might make it more difficult for fat-soluble nutrients like beta-carotene and vitamin E to be absorbed. Studies show that the B group vitamins are active in the reactions associated with either the early phase or the latter phase, with pro-oxidant and antioxidant impact, depending on the conditions of the experiment, on the peroxidation of lipids. Research indicates that B-group vitamins can function as antioxidants to stop lipid peroxidation (30). For instance, vitamin B2 riboflavin functions as a part of the glutathione redox cycle as well as an independent antioxidant. Riboflavin functions as an antioxidant, therefore shielding the organism from oxidative stressors such as reperfusion oxidative damage and lipid per-oxidation.

Mineral and Trace Elements' Antioxidant Effects

Trace minerals, which are cellular pro-oxidants, can produce damaging free radicals. The Fenton reaction, which occurs when metals like Fe2+ and Cu2+ interact with oxygen, can result in ROS. Copper has a 60-fold faster rate of hydroxyl radical production than iron. Hemolexin, ferritin, haptoglobin, lactoferrin, MT, Albumin, myoglobin, hemopexin and ceruloplasmin are a few examples of metal-binding proteins that are essential parts of the antioxidant defense mechanism outside of cells (31). These proteins include trace minerals. Because they function as cofactors of crucial, minerals, antioxidant enzymes like selenium which is a prerequisite for selenoenzymes and necessary for the regeneration of other antioxidants like vitamin C are indispensable.

Antioxidant Functions of Proteins

The majority of the proteins that make up the body's non-enzymatic antioxidant system include thioredoxin, lactoferrin, albumin, haptoglobin, hemopexin and SS peptides. Copper-containing enzyme ceruloplasmin scavenges superoxide and stops lipid oxidation. The most prevalent antioxidant in plasma is albumin, which sequesters iron and copper. Lactoferrin, a glycosylated protein, binds iron and reduces the amount that bacteria in infected tissues can absorb (32). Metal-binding proteins rich in cysteines termed MT are essential for maintaining zinc and copper homeostasis. The iron-binding proteins hemoglobin and hemopexin are made in the liver and released into the bloodstream. The primary antioxidant mechanism in mammalian cells, thioredoxin, keeps the environment conducive to reduction. By scavenging peroxide and hydrogen peroxide, SS peptides shield the inner mitochondrial membrane from lipid peroxidation and provide antioxidants.

Antioxidant Functions of Phytonutrients

Phytonutrients and phytochemicals are plant-based compounds with antioxidant qualities. Flavonoids, referred as phenolic acids are found in abundance in plants, are known to comprise over a thousand distinct chemicals. They could have anti-aging, antiviral, anti-inflammatory, anti-carcinogenic and anti-allergenic effects on animals. They act as a protective barrier against outside threats. In addition to their potential therapeutic effects in animals, flavonoids have heart disease preventative benefits because they inhibit the activity of platelets and the enzymes lipoxygenase and cyclooxygenase in macrophages (33). By-products from orchard, oil, or citrus industries can be used as feed supplements, possibly improving the efficiency, wellness and quality of protein from animals. However, the stomach does not well absorb flavonoid chemicals and their quantities in target tissues are insufficient for them to provide efficient antioxidant protection. Recent research has shown that phyto-nutrients in fruits, vegetables, nuts, grains/seeds and yams can enhance blood lipid profiles, reduce signal transduction and tissue proliferation that improve hormonal status before or after menopause (34). Further investigation, including controlled animal trials, is required to show if feeding these phytonutrients to animals can enhance their deposition in muscle tissues and their association with better meat or milk quality.

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Metal-Binding Proteins for Antioxidant Defense

Farm animals' antioxidant defense is aided by metal-binding proteins like metallothionein, ceruloplasmin and ferritin, which control vital metals like zinc, copper and iron to avoid oxidative stress and preserve cellular homeostasis. Table (5) represents the immune system defense via metal-binding proteins.

Table (5). Antioxidant Defense via Metal-Binding Proteins (Source: Author)

Metal	Properties of Biological System	Techniques and Implications
Cu	Oxidized (Cu1+), Reduced (Cu2+)	Hepcidin controls the amount of iron that is bound to carriers like ferritin and it is necessary for the transfer of oxygen
Fe	Ferryl, Ferric (Fe3+) and Ferrous (Fe2+)	Different proteins control the absorption, transport and export of copper ions, which exist in numerous configurations.

Iron's Effects on Biological Systems

Biological systems include ferrous, ferric and ferric states of iron. In neutral pH, ferrous iron dissolves and takes part in biological processes. When oxygen is present in anoxic conditions, it is transformed into ferric (Fe3+). By lowering Fe3+ to Fe2+ and acidifying their surroundings, animals can get ferrous iron. Iron solubilization is maintained by low stomach pH and the duodenum, the upper intestine, is where iron absorption takes place. Ferrous iron is exported via ferroportin and it is quickly transformed into Fe3+-bound ferritin. Biological systems include ferrous, ferric and ferric states of iron. In neutral pH, ferrous iron dissolves and takes part in biological processes (35). When oxygen is present in anoxic conditions, it is transformed into ferric (Fe3+). By lowering Fe3+ to Fe2+ and acidifying their surroundings, animals can get ferrous iron. Iron solubilization is maintained by low stomach pH and the duodenum, the upper intestine, is where iron absorption takes place. Hepcidin controls the uptake, storage and entrance of iron into the blood. Since iron transports oxygen to the cellular and muscular systems in the form of hemoglobin, feeding meals high in iron is essential for energy metabolism and active muscle contraction. Pigs lacking iron have reduced this protein activity and anemia; yet, biochemical indicators of oxidative condition are similar in pigs receiving iron supplementation. Pigs seldom get iron toxicities; however, some cases have been documented following iron injections.

Copper Effect Processes in Biological Systems

Copper actions are found in biological tissues in two distinct provides: reduced (Cu2+) and oxidized (Cu1+). Oxidized copper prefers ligands that provide sulfur, whereas reduced copper favors oxygen and nitrogen donors. The copper+1 in a solution of water is volatile. To stabilize it, the user must either oxidize it to a more stable condition or bind it to carriers. In the gut lumen, a metalloreductase converts dietary Cu2+ to Cu1+, which is taken up by a Cu1+ transporter (Ctr1) and delivered into intestinal cells (36). Ctr1 mediates 70% of the Cu uptake by mammalian cells. Cu1+ is expelled from intestinal cells utilizing ATP7A, which appears throughout a number of cells. Cu1+ is carried by the portal vein in the circulation to the liver, where it is combined with ceruloplasmin and released as blood. ATP7B is an additional Cu-transporting ATP that exports excess Cu. Ceruloplasmin is the major binding site for copper, while the rest is bound to low molecular carriers, transcurrent (β-macroglobulin) and albumin (37). Ceruplasmin can be a copper transporter, despite evidence from rodent studies to the contrary. The regulation of Cu transport to tissues is dependent on small Cu carriers (SCC), although little is known about the cellular and systemic components of Cu homeostasis.

CONCLUSION

Overall, MT induction and control are essential components of farm animals' defensive mechanisms against metal overload. The metal-binding protein MT, which stores excess metals and reduces their harmful effects, is responsible for maintaining metal homeostasis. The elevation of MT expression in response to metal exposure is an adaptive mechanism that protects cells from oxidative stress and prevents negative effects on their functioning. Farm animals naturally use these complex MT-mediated defense mechanisms in response to metal-related problems in their environment. By comprehending and using these defensive mechanisms, it would be able to develop novel approaches for enhancing farm animals' resilience to stressors brought by metals, which would eventually improve these animals' health and welfare in a range of agricultural settings.

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