

# Nutrient-Mediated Activation of Cellular Signaling Pathways: Mechanistic Insights into Attenuation of Toxin-Induced Inflammation in Food-Animals

Md. Emran Hossain\*

## Abstract

*Dietary and environmental toxins remain a persistent challenge in food-animal production, where subclinical and clinical inflammation compromises health, productivity, and food safety. The toxin-induced inflammation is driven by oxidative stress, mitochondrial dysfunction, and dysregulated immune signaling, resulting in impaired metabolic efficiency and increased disease susceptibility. Recent advances in nutritional science have revealed that nutrients act not only as substrates for growth but also as signaling molecules capable of modulating key cellular pathways involved in inflammatory regulation. This review synthesizes current knowledge on nutrient-mediated activation of cellular signaling pathways and their mechanistic roles in attenuating toxin-induced inflammation in food-animals. Major nutrient-sensing and stress-responsive pathways, including AMP-activated protein kinase, mechanistic target of rapamycin, nuclear-factor-erythroid-2-related-factor-2, nuclear-factor-kappa-B, and mitogen-activated protein kinases, are discussed in the context of toxin exposure. The review highlights how specific nutrients, such as amino acids, fatty acids, vitamins, minerals, and functional phytochemicals influence these pathways to restore redox balance, regulate cytokine production, enhance cellular detoxification, and maintain mitochondrial integrity. Species-specific responses in poultry, ruminants, and swine are also considered, reflecting differences in digestive physiology and metabolic regulation. In addition, emerging tools including nutrigenomics, metabolomics, and systems biology approaches are evaluated for their potential to clarify complex nutrient-toxin signaling interactions. By integrating mechanistic insights with applied nutritional strategies, this review provides a framework for developing precision feeding interventions aimed at reducing inflammation, improving resilience to toxins, and enhancing sustainable food-animal production. The findings underscore the importance of signaling-based nutrition as a promising avenue for mitigating toxin-related challenges in modern livestock systems.*

**Keywords:** AMPK, inflammation, mTOR, Nrf2, nutrient signaling, oxidative stress, toxin exposure

### \*Author for Correspondence

Md. Emran Hossain  
E-mail: [emran@cvasu.ac.bd](mailto:emran@cvasu.ac.bd)

Professor, Department of Animal Science and Nutrition,  
Chattogram Veterinary and Animal Sciences University,  
Khulshi, Chattogram, Bangladesh

Received Date: January 27, 2026  
Accepted Date: January 30, 2026  
Published Date: January 31, 2026

**Citation:** Md. Emran Hossain. Nutrient-Mediated Activation of Cellular Signaling Pathways: Mechanistic Insights into Attenuation of Toxin-Induced Inflammation in Food-Animals. International Journal of Toxins and Toxics. 2026; 3(1): 1–12p.

## INTRODUCTION

Dietary and environmental toxins represent a continuing and often underestimated constraint to efficient food-animal production worldwide [1–3]. Feed contamination with mycotoxins, exposure to heavy metals, plant secondary metabolites, and microbial toxins frequently occurs at subclinical levels, yet these exposures are sufficient to disrupt physiological homeostasis [4–6]. One of the most consistent biological consequences of toxin exposure in food-animals is the induction of inflammatory responses that impair nutrient utilization, compromise immune competence, and reduce growth, reproductive performance, and

product quality [7–9]. The economic and welfare implications of toxin-induced inflammation extend beyond overt toxicity, making mitigation strategies a priority for sustainable livestock systems [10–12].

Traditionally, nutritional interventions against toxins have focused on physical binding, dilution, or detoxification using feed additives [13–16]. While these approaches provide partial protection, they do not adequately address the intracellular mechanisms by which toxins initiate and sustain inflammatory cascades. Increasing evidence indicates that toxin-induced inflammation is closely linked to oxidative stress, mitochondrial dysfunction, and dysregulation of cellular signaling pathways that govern energy balance, redox status, and immune responses [17, 18]. These processes highlight the need to move beyond conventional toxin control strategies toward mechanism-driven nutritional solutions.

In recent years, nutrients have emerged as critical regulators of cellular signaling rather than passive contributors to metabolism [1, 19–22]. Amino acids, fatty acids, vitamins, minerals, and bioactive phytochemicals can directly activate or suppress signaling pathways like AMP-activated protein kinase, mechanistic target of rapamycin, nuclear-factor-erythroid-2-related-factor-2, and nuclear-factor-kappa-B. Through these pathways, nutrients influence antioxidant defense, inflammatory gene expression, autophagy, and cellular repair processes [23–26]. This signaling-based perspective of nutrition provides a novel framework for understanding how dietary composition can enhance resilience against toxin-induced inflammatory stress. The objective of this review is to integrate current mechanistic evidence on nutrient-mediated activation of cellular signaling pathways involved in the attenuation of toxin-induced inflammation in food-animals. By synthesizing findings across species and experimental models, this review aims to identify knowledge gaps and inform future nutritional strategies that support animal health, productivity, and food safety under conditions of unavoidable toxin exposure.

## **MAJOR TOXINS AFFECTING FOOD-ANIMALS**

### **Mycotoxins and Feed-Borne Contaminants**

Mycotoxins are secondary metabolites produced by filamentous fungi that contaminate feed ingredients during crop growth, harvest, storage, and processing. Common mycotoxins affecting food-animals include aflatoxins, ochratoxin A, fumonisins, deoxynivalenol, and zearalenone. These toxins impair intestinal integrity, disrupt hepatic metabolism, and suppress immune function [3, 27, 28]. Chronic exposure, even at low concentrations, induces oxidative stress and inflammatory signaling, leading to reduced feed efficiency, poor growth, reproductive disorders, and increased susceptibility to infectious diseases.

### **Heavy Metals and Environmental Pollutants**

Heavy metals, such as lead, cadmium, mercury, and arsenic enter animal production systems through contaminated water, soil, forages, and industrial emissions. Persistent environmental pollutants, including pesticides and industrial chemicals, further contribute to toxic burden. These compounds accumulate in tissues due to limited excretion and interfere with enzyme systems, mitochondrial respiration, and antioxidant defenses [29, 30]. At the cellular level, heavy metals promote reactive oxygen species generation and activate inflammatory transcription factors, resulting in chronic low-grade inflammation and potential residue risks in animal-derived foods.

### **Plant-Derived and Microbial Toxins**

Plant-derived toxins include alkaloids, glycosides, tannins, and saponins that are naturally present in certain forages and feedstuffs. Microbial toxins originate from pathogenic bacteria and include endotoxins and exotoxins that trigger strong immune responses. These toxins disrupt cell membranes, inhibit protein synthesis, and alter gut microbial balance [8, 31–34]. In food-animals, ingestion or absorption of these compounds activates innate immune pathways, compromises nutrient absorption, and contributes to intestinal and systemic inflammation, particularly under stress or high production demands.

### **Common Inflammatory Outcomes**

Despite differences in chemical structure and origin, most toxins elicit similar inflammatory outcomes in food-animals. These include oxidative stress, activation of proinflammatory cytokines, disruption of gut barrier function, and impairment of mitochondrial energy metabolism. Sustained activation of inflammatory signaling pathways diverts nutrients away from productive functions toward immune responses [1, 2, 7, 13, 35]. Over time, this inflammatory burden reduces growth, reproductive efficiency, and overall resilience, underscoring the need for nutritional strategies that target shared mechanistic pathways rather than individual toxins alone.

## **TOXIN-INDUCED INFLAMMATION**

### **Oxidative Stress and Redox Imbalance**

Toxin exposure in food-animals frequently generates excessive reactive oxygen species (ROS) that overwhelm the antioxidant defense system, including enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. This imbalance between pro-oxidants and antioxidants, known as oxidative stress, leads to lipid peroxidation, protein oxidation, and DNA damage [36–38]. The resulting cellular injury activates stress-responsive pathways, amplifies inflammatory signals, and compromises nutrient utilization, growth, and immune competence.

### **Mitochondrial Dysfunction and Energy Disruption**

Many toxins interfere with mitochondrial function by inhibiting electron transport chain components, altering membrane potential, and impairing ATP synthesis. Reduced energy availability disrupts normal cellular processes, including ion homeostasis, protein synthesis, and repair mechanisms. Damaged mitochondria also release signaling molecules, such as ROS and cytochrome c, which further amplify inflammatory responses and programmed cell death [39–44]. Consequently, toxin-induced mitochondrial dysfunction contributes to systemic inflammation and metabolic inefficiency in food-animals.

### **Activation of Inflammatory Transcription Factors**

Toxins can activate key transcription factors, such as nuclear-factor-kappa-B (NF- $\kappa$ B), activator protein 1 (AP 1), and signal transducer and activator of transcription (STAT) proteins. Once activated, these transcription factors drive the expression of proinflammatory cytokines, chemokines, adhesion molecules, and inducible enzymes such as cyclooxygenase 2 and inducible nitric oxide synthase [8, 45, 46]. This molecular cascade promotes local and systemic inflammation, leading to tissue damage, impaired immune regulation, and reduced animal performance.

### **Crosstalk between Metabolic Stress and Immune Signaling**

Metabolic stress induced by toxins, such as nutrient depletion or energy deficit, interacts with immune signaling pathways to amplify inflammation. Key nutrient-sensing pathways, including AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR), modulate immune cell function in response to cellular energy status. Dysregulation of this crosstalk results in excessive cytokine production, impaired autophagy, and prolonged inflammatory responses, creating a feedback loop that exacerbates toxin-induced tissue damage in food-animals [47, 48].

## **NUTRIENT SENSING AND SIGNALING PATHWAYS**

### **AMPK Signaling Pathway**

The AMP-activated protein kinase (AMPK) pathway serves as a central energy sensor in cells, detecting changes in the AMP/ATP ratio to maintain metabolic homeostasis. Under nutrient or energy stress, AMPK is activated to promote catabolic pathways generating ATP while inhibiting energy-consuming anabolic processes. Beyond metabolism, AMPK exerts anti-inflammatory effects by suppressing NF- $\kappa$ B activation, reducing proinflammatory cytokine production, and enhancing autophagy. Nutritional interventions, such as supplementation with specific amino acids, polyphenols, or fatty acids, can modulate AMPK activity, improving cellular resilience against toxin-induced energy deficits and oxidative stress in food-animals [22, 49–51].

### **mTOR Signaling Pathway**

The mechanistic target of rapamycin (mTOR) integrates nutrient availability, particularly amino acids and glucose, with cellular growth and immune regulation. Activation of mTOR promotes protein synthesis, cell proliferation, and immune cell differentiation. Toxin exposure can dysregulate mTOR signaling by inducing oxidative stress and nutrient scarcity, leading to impaired growth, suppressed immune responses, and exaggerated inflammation. Nutritional strategies targeting mTOR, including balanced amino acid supply and antioxidant support, can restore pathway homeostasis, regulate immune cell activation, and mitigate the inflammatory consequences of dietary and environmental toxins [9, 28, 49, 52].

### **Nrf2-Keap1 Pathway**

Nuclear-factor-erythroid-2-related-factor-2 (Nrf2) is a transcription factor that regulates the expression of antioxidant enzymes and detoxification genes. Under basal conditions, Nrf2 is bound to Keap1 and targeted for degradation, but oxidative stress or certain nutrients trigger its release and nuclear translocation. Once active, Nrf2 enhances cellular defenses against reactive oxygen species, electrophilic toxins, and inflammatory mediators. Nutrients, such as vitamins C and E, selenium, polyphenols, and sulfur-containing amino acids can activate Nrf2, reinforcing detoxification pathways and reducing tissue injury in toxin-exposed food-animals [22, 23, 44, 53–55].

### **Nf- $\kappa$ b and MAPK Pathways**

Nuclear-factor-kappa-B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) pathways are central mediators of toxin-induced inflammatory responses. NF- $\kappa$ B controls the transcription of proinflammatory cytokines, chemokines, and adhesion molecules, while MAPKs transduce stress signals to regulate apoptosis, proliferation, and inflammation. Nutritional modulation, including antioxidants, omega-3 fatty acids, and bioactive compounds, can suppress NF- $\kappa$ B activation and fine-tune MAPK signaling. This interaction helps attenuate inflammation, restore cellular homeostasis, and enhance resilience of food-animals to toxin exposure [29, 35, 56–60].

## **NUTRIENTS AS MODULATORS OF CELLULAR SIGNALING**

### **Amino Acids**

Amino acids play a critical role beyond protein synthesis by directly modulating cellular signaling and immune responses. Sulfur-containing amino acids, such as methionine and cysteine, enhance antioxidant capacity through glutathione synthesis, reducing oxidative stress triggered by toxins. Glutamine supports intestinal integrity and immune cell proliferation, while arginine regulates nitric oxide production, promoting vascular function and inflammatory control. Through these mechanisms, amino acids influence key nutrient-sensing pathways including AMPK, mTOR, and Nrf2, enhancing cellular resilience and mitigating toxin-induced inflammation in food-animals [14, 18, 61].

### **Fatty Acids**

Fatty acids, particularly omega-3 and omega-6 polyunsaturated fatty acids, act as potent modulators of inflammation and signaling pathways. Omega-3 fatty acids inhibit NF- $\kappa$ B activation and reduce the production of proinflammatory cytokines, while omega-6 fatty acids serve as precursors for both pro- and anti-inflammatory eicosanoids, depending on metabolic context. Fatty acids integrate into cell membranes, influencing receptor function and signal transduction [42, 62–64]. Nutritional manipulation of fatty acid profiles can, therefore, regulate immune cell function, control inflammatory mediator release, and enhance antioxidant defenses in animals exposed to dietary or environmental toxins.

### **Vitamins**

Vitamins serve as cofactors, antioxidants, and regulators of gene expression, interacting with multiple transcriptional and signaling pathways. Vitamin E acts as a lipid-soluble antioxidant, protecting membranes from peroxidation. Vitamin A modulates immune cell differentiation and cytokine production. Vitamin D regulates innate and adaptive immune responses, while B-complex vitamins participate in energy metabolism and methylation reactions affecting gene expression [65, 66]. Through

these roles, vitamins can modulate NF- $\kappa$ B, Nrf2, and other nutrient-sensing pathways, reducing toxin-induced oxidative stress and inflammation in food-animals.

### **Minerals and Trace Elements**

Essential minerals and trace elements, such as zinc, selenium, copper, and iron are vital for enzyme function, antioxidant defense, and signaling regulation. Zinc stabilizes protein structure and modulates NF- $\kappa$ B and MAPK signaling. Selenium is integral to glutathione peroxidase activity, reducing oxidative stress. Copper and iron are cofactors for redox enzymes and contribute to mitochondrial function. Adequate mineral nutrition enhances cellular resilience, modulates inflammatory responses, and supports detoxification mechanisms in animals exposed to toxins [18, 24, 29, 67].

### **Phytogenic and Functional Nutrients**

Phytogenic compounds, including polyphenols, carotenoids, and other bioactive plant metabolites, exhibit synergistic effects on cellular signaling and inflammation. These compounds scavenge reactive oxygen species, activate Nrf2-mediated antioxidant pathways, and inhibit proinflammatory transcription factors, such as NF- $\kappa$ B. They also modulate gut microbiota composition, further influencing immune and metabolic signaling [8, 31, 33]. Inclusion of phytogenic and functional nutrients in diets offers a natural strategy to attenuate toxin-induced inflammation while enhancing cellular homeostasis and overall animal health.

## **MECHANISTIC INTERACTIONS**

### **Nutrient-Driven Attenuation of Oxidative Stress Signaling**

Nutrients, such as sulfur-containing amino acids, vitamins, minerals, and phytochemicals reduce toxin-induced oxidative stress by enhancing cellular antioxidant defenses. These nutrients activate signaling pathways like Nrf2, upregulating antioxidant enzymes including glutathione peroxidase, superoxide dismutase, and catalase. By neutralizing reactive oxygen species and preventing lipid, protein, and DNA damage, nutrients restore redox balance, reduce inflammatory signaling, and protect tissues from the oxidative consequences of toxins in food-animals [64, 68, 69].

### **Of Cytokine Production and Immune Cell Activation**

Dietary nutrients influence the production and release of pro- and anti-inflammatory cytokines, shaping the immune response to toxins. Amino acids, fatty acids, vitamins, and trace elements modulate NF- $\kappa$ B, MAPK, and mTOR signaling in immune cells, reducing overproduction of inflammatory mediators while enhancing protective responses. This fine-tuning of cytokine networks prevents excessive inflammation, improves pathogen defense, and supports recovery of tissue function during toxin exposure [38, 70, 71].

### **Modulation of Mitochondrial and Cellular Homeostasis**

Toxins often impair mitochondrial function, leading to energy deficits and increased reactive oxygen species. Nutrients, such as arginine, B-complex vitamins, omega-3 fatty acids, and polyphenols enhance mitochondrial biogenesis, stabilize membrane potential, and improve ATP production. By supporting mitochondrial efficiency, these nutrients maintain energy homeostasis, reduce oxidative stress, and improve the resilience of cellular systems against toxin-induced injury [16, 54, 72–74].

### **Restoration of Apoptosis and Autophagy**

Toxins can trigger uncontrolled apoptosis or suppress protective autophagy, leading to tissue damage and inflammation. Nutrients modulate these processes by activating AMPK, mTOR, and Nrf2 pathways, promoting controlled autophagy for the removal of damaged organelles while preventing excessive cell death. This regulation maintains cellular homeostasis, reduces inflammatory damage, and enhances recovery, highlighting the integrative role of diet in counteracting toxin-induced cellular stress [19, 47, 75, 76].

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## SPECIES-SPECIFIC CONSIDERATIONS

### Poultry

Poultry species, including broilers and layers, are particularly susceptible to dietary toxins due to rapid growth rates and high metabolic demand. Their relatively short gastrointestinal tract limits detoxification and microbial degradation of toxins. Toxins, such as aflatoxins and ochratoxins rapidly induce oxidative stress, suppress immune responses, and impair liver function. Nutritional interventions targeting amino acids, vitamins, and phytochemicals are critical to enhance antioxidant defenses, modulate inflammatory signaling, and maintain productivity in poultry exposed to contaminated feed [77–79].

### Ruminants

Ruminants possess a complex forestomach microbiome capable of partially detoxifying certain compounds, including some mycotoxins and plant secondary metabolites. However, chronic exposure to toxins, such as heavy metals, nitrates, or persistent mycotoxins can overwhelm microbial and hepatic detoxification systems. Nutrients including sulfur amino acids, selenium, and trace minerals support liver metabolism, antioxidant defenses, and immune modulation. Additionally, feed formulation strategies that optimize rumen fermentation can reduce toxin absorption and inflammatory responses in cattle, sheep, and goats [42].

### Swine

Swine are highly sensitive to dietary toxins due to their monogastric digestive system and limited detoxification capacity compared to ruminants. Toxins, such as deoxynivalenol, zearalenone, and heavy metals rapidly affect intestinal integrity, immune function, and growth performance. Nutritional interventions emphasizing amino acids, vitamins, trace elements, and fatty acids are effective in modulating signaling pathways, restoring redox balance, and attenuating inflammation. Swine also benefit from feed additives like binders, probiotics, and phytochemicals to reduce toxin absorption and support cellular resilience [80].

### Comparative Insights

Species differences in digestive anatomy, metabolic rate, and detoxification capacity influence the response to toxins and nutrient-mediated mitigation. Ruminants rely on microbial detoxification, poultry have high metabolic demands but limited gut length, and swine are sensitive to both intestinal and systemic toxin effects. Understanding these differences is essential for designing species-specific nutritional strategies that modulate signaling pathways, attenuate inflammation, and improve resilience to toxins while optimizing animal health and productivity [13, 22, 44, 81].

## ANIMAL HEALTH, PRODUCTIVITY, AND FOOD SAFETY

### Improvement of Growth, Reproduction, and Immunity

Nutrient-mediated modulation of cellular signaling pathways helps food-animals maintain physiological homeostasis under toxin exposure, supporting optimal growth, reproductive performance, and immune competence [1, 8–10, 12, 82]. By reducing oxidative stress, controlling inflammatory responses, and preserving mitochondrial function, nutrients enable better nutrient utilization, protein synthesis, and energy allocation. This improves feed efficiency, enhances resistance to infections, and ensures consistent production outcomes even in environments with unavoidable dietary or environmental toxins.

### Reduction of Toxin Residues in Edible Tissues

Effective nutritional strategies not only mitigate inflammation but also reduce the accumulation of toxins and their metabolites in edible tissues, such as meat, milk, and eggs. Activation of detoxification pathways, enhancement of hepatic metabolism, and improved gut barrier function limit systemic toxin absorption and facilitate excretion. This reduces the risk of foodborne contamination, enhances product safety for human consumption, and supports regulatory compliance for residue limits in animal-derived foods [1, 8–10, 12, 82].

### **Contribution to Sustainable and Safe Animal Production**

Integrating nutrient-based mitigation of toxin-induced inflammation contributes to more sustainable livestock systems. By enhancing animal health and productivity without excessive reliance on chemical interventions or antibiotics, signaling-focused nutrition promotes welfare, reduces environmental impacts, and ensures safer food products. Such approaches align with global priorities for sustainable agriculture, food security, and public health, emphasizing the dual role of nutrition in protecting both animals and consumers from toxin-related risks [1, 8–10, 12, 82].

## **EMERGING TOOLS AND APPROACHES**

### **Nutrigenomics and Nutriepigenomics**

Nutrigenomics investigates how nutrients influence gene expression, while nutriepigenomics explores nutrient-induced modifications of DNA, histones, and non-coding RNAs that regulate transcription without altering the sequence. These approaches allow identification of genes and signaling pathways modulated by dietary components in response to toxin exposure. By linking specific nutrients to molecular mechanisms, nutrigenomics provides insights for precision feeding strategies that enhance antioxidant defenses, immune regulation, and detoxification in food-animals [14, 83, 84].

### **Metabolomics and Proteomics**

Metabolomics and proteomics enable comprehensive profiling of metabolites and proteins affected by toxins and dietary interventions [39, 50, 83, 85]. Metabolomic analyses detect changes in energy metabolites, oxidative stress markers, and inflammatory mediators, while proteomics identifies alterations in enzyme activity, signaling proteins, and stress-response pathways. Integrating these datasets reveals molecular signatures of toxin-induced inflammation and the modulatory effects of nutrients, facilitating biomarker discovery, early detection of subclinical toxicity, and optimization of targeted nutritional interventions [86].

### **Systems Biology and Pathway Modeling**

Systems biology combines computational modeling with experimental data to map complex interactions between nutrients, signaling pathways, and toxin-induced stress responses. Pathway modeling allows simulation of cellular networks, predicting how dietary interventions can influence inflammatory, metabolic, and detoxification pathways. These tools support hypothesis-driven research, identification of key regulatory nodes, and development of multi-nutrient strategies tailored to specific species or toxin challenges, ultimately improving resilience, productivity, and food safety in livestock systems [3, 47, 53, 87].

## **KNOWLEDGE GAPS AND FUTURE DIRECTIONS**

### **Dose and Timing of Nutrient Interventions**

While the protective effects of specific nutrients against toxin-induced inflammation are established, optimal doses, combinations, and timing remain unclear. Most studies focus on short-term or single-nutrient supplementation under controlled conditions, leaving gaps in understanding cumulative effects, threshold requirements, and interactions with animal age, production stage, or physiological status. Future research should define precise nutrient regimens to maximize cellular signaling benefits while minimizing toxicity or imbalances.

### **Combined Nutrient and Toxin Exposure Models**

Most experimental studies evaluate the effects of individual toxins or single nutrients, which may not reflect the complexity of real-world production systems where animals are exposed to multiple toxins simultaneously. Developing models that simulate combined toxin challenges and multi-nutrient interventions will provide more accurate insights into signaling interactions, synergistic or antagonistic effects, and adaptive responses. Such approaches are critical for designing practical feeding strategies that confer broad resilience to toxin mixtures.

### Translation from Experimental to Field Conditions

Many mechanistic studies are conducted under controlled laboratory or small-scale experimental conditions, limiting direct application to commercial livestock systems. Environmental factors, feed variability, stress, and management practices can influence nutrient efficacy and signaling responses. Future research should focus on large-scale, field-based trials that integrate molecular, physiological, and performance outcomes to validate nutrient-mediated mitigation strategies and ensure their effectiveness, feasibility, and economic viability in real production settings.

### CONCLUSION

Nutrient-mediated activation of cellular signaling pathways represents a promising strategy to mitigate toxin-induced inflammation in food-animals. By modulating oxidative stress, regulating cytokine production, restoring mitochondrial function, and controlling apoptosis and autophagy, nutrients enhance cellular resilience and maintain homeostasis under toxic challenges. Species-specific differences in digestive physiology and metabolic capacity necessitate tailored nutritional approaches. Emerging tools, such as nutrigenomics, metabolomics, and systems biology provide mechanistic insights and support precision feeding strategies. Implementing such approaches improves animal health, productivity, and immunity while reducing toxin residues in edible products, contributing to sustainable and safe livestock production. Continued research addressing optimal nutrient doses, multi-toxin exposures, and translation to field conditions will strengthen evidence-based strategies, enabling effective integration of nutrition and toxin management in modern animal production systems.

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