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Review
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EPIGENETIC MECHANISMS IN ANIMAL NUTRITION: THE IMPACT OF FEED ADDITIVES ON HEALTH AND PRODUCTIVITY

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Abstract: The combination of nutrition and epigenetics has redefined our fundamental understanding of animal physiology and productivity. This review explores the profound influence of feed additives on gene expression through diverse epigenetic mechanisms, including DNA methylation, histone modifications, and the regulatory roles of non-coding RNAs. Dietary bioactive compounds, such as methyl donors, vitamins, minerals, probiotics, and phytobiotics, act as effective biological signals that modulate the epigenome of animal, thereby shaping developmental processes, immune responses, and metabolic homeostasis. Beyond immediate physiological maintenance, these nutri-epigenetic interactions offer a transformative pathway to enhance resilience against environmental stressors and optimize product quality. By synthesizing current findings, this study highlights the potential of "epigenetic programming" as a precision tool for sustainable livestock production and identifies future directions for integrating multi-omics technologies into nutritional management strategies.

Keywords: Epigenetics, Feed additives, Gene expression, DNA methylation, Animal performance

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1. Introduction

In the modern landscape of precision livestock farming, the focus of animal nutrition has evolved from only fulfilling basal metabolic requirements to actively modulating the molecular structure of the organism. At the center of this evolution is the epigenome, which serves as a dynamic interface between environmental stimuli, specifically nutritional inputs, and the genome. Within this context, feed additives are no longer viewed only as supplementary nutrients; they function as biological signals capable of programming gene expression patterns. This emerging field of nutri-epigenetics provides profound insights into how specific nutritional components can induce heritable modifications in health, stress resilience, and productivity without altering the underlying DNA sequence (Sinclair et al., 2016).

As the global demand for animal-derived products increases, the strategic use of feed additives, including vitamins, minerals, probiotics, prebiotics, and bioactive herbal extracts, has become a basis for enhancing growth performance and product quality. Beyond their immediate physiological effects, a growing body of scientific evidence suggests that these additives use their influence through complex epigenetic mechanisms, namely DNA methylation, histone modifications, and the regulatory actions of non-coding RNAs. These mechanisms regulate vital biological processes ranging from embryonic development and immune system maturation to long-term stress tolerance and disease susceptibility (Wang and Ibeagha-Awemu, 2021).

Critically, the impact of nutritional influences can extend beyond the individual level, potentially manifesting as intergenerational phenotypic changes (Murdoch et al., 2016). Therefore, a comprehensive synthesis of how feed additives modulate the epigenetic modifications is essential for optimizing animal welfare and achieving economic sustainability in the livestock sector. This review evaluates the current understanding of these epigenetic pathways, explores the transformative potential of "epigenetic programming" in animal nutrition, and identifies the challenges in translating these molecular insights into robust, large-scale production strategies.

1.1. Feed Additives

Feed additives are substances added to animal feed in small amounts to improve growth, development, product quality, and health. They are divided into various categories according to their functional properties and chemical structures; these include nutritional supplements, vitamins, minerals, amino acids, fatty and fatty acids, enzymes, probiotics, prebiotics, antibiotics, antioxidants, aromatic substances, and preservatives.

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Particularly in poultry production, ensuring consistent feed availability and maximizing nutrient utilization using conventional and unconventional feedstuffs remain major global challenges (Ravindran, 2010). To address these issues and promote gut integrity, especially in the era of phasing out in-feed antibiotics, additives such as probiotics (Ezema and Ugwu, 2014) and prebiotics (Gibson and Roberfroid, 1995) are widely employed to combat intestinal challenges like necrotic enteritis (Williams, 2005; M'sadiq et al., 2015). Although these substances have traditionally been used to increase yield and meet other metabolic needs in animals, the molecular-level effects of bioactive components (plant extracts, methyl donors, etc.) are now understood. Thus, it has been proven that feed additives not only affect animal physiology but also have indirect effects on epigenetic mechanisms (Coustham and Pitel, 2025).

1.2. DNA Methylation and Feed Additives

DNA methylation plays a crucial role in controlling gene expression and does not alter the DNA sequence. The mechanism involves the covalent attachment of a methyl (CH_3) group to the 5th carbon of the cytosine base. The methyl group is usually attached to CpG islands located in the initiation regions (promoters) of genes. This process is managed by DNA methyltransferase enzymes (*DNMT1*, *DNMT3a*, and *DNMT3b*) (Halušková et al., 2021). Demethylation leads to increased gene expression by removing the methyl group. DNA methylation varies depending on environmental factors, developmental stage, and cell type (Marttila et al., 2015).

Nutrients and bioactive components in feed additives have the potential to influence DNA methylation. For example, choline, methionine, folate, and vitamin B12 directly affect the synthesis of S-adenosylmethionine (SAM), which is essential for DNA methylation. Therefore, the levels of these substances may influence DNA methylation and gene expression. In other words, methyl donors (methionine, choline, etc.) used in animal feed can directly affect phenotypic performance by altering the methylation status of the relevant genes (McKay and Mathers 2011, Feil and Fraga 2012). Furthermore, the supplementation of specific amino acids, such as threonine, arginine, and glutamine, alongside essential vitamins like Vitamin E, not only improves carcass characteristics and immunological responses in broilers (Ezeokeke et al., 2008; Bortoluzzi et al., 2018; Debnath et al., 2019), but their broader nutritional significance is increasingly linked to downstream epigenetic regulatory pathways that govern overall health and productivity (Alagawany et al., 2021).

Studies have shown that phytobiotics, probiotics, prebiotics, and some trace minerals affect the gut microbiota (Yadav and Jha, 2019). Therefore, they can cause changes in DNA methylation by affecting intracellular signaling pathways. This epigenetic change can have effects on phenotypic characteristics such as growth, development, immune response, metabolic health, and resistance to disease in animals (Mukherjee et al., 2015).

1.3. Histone Modifications

Histone modification is an important epigenetic mark that affects gene expression by regulating the packaging of DNA in the cell nucleus. DNA is wrapped around histone proteins (H2A, H2B, H3, H4) to form nucleosomes and, in nucleosomes, the denser chromatin. Covalent modifications of the amino-terminal tails of histone proteins (such as methylation, phosphorylation, acetylation and ubiquitination) alter the structure of the chromatin and affect the delivery of genes to the transcriptional machinery (Bannister and Kouzarides, 2011).

1.3.1. Histone acetylation

Histone acetyltransferase (HAT) enzymes add an acetyl group to histone lysine residues. This weakens the interaction between DNA and histones, thus relaxing the chromatin and increasing gene expression. Histone deacetylase (HDAC), on the other hand, removes acetyl groups, leading to chromatin condensation and suppression of gene expression (Molina-Serrano et al. 2019). In animal nutrition, some feed additives can directly affect this balance. For example, butyrate is a potent HDAC inhibitor. Through this inhibition, the chromatin structure relaxes (euchromatin), thereby increasing the expression of genes related to intestinal development and immune response, directly affecting the animal's health and overall performance. It improves intestinal health and growth performance (Chen et al., 2025).

1.3.2. Histone methylation

Histone methylation occurs through the addition of a methyl group to the arginine or lysine tails of histones. The number and location of methylations can increase or decrease gene expression. These are catalyzed by histone methyltransferase (HMT) enzymes and reversed by histone demethylase (HDM) enzymes (Greer and Shi, 2012).

Components in feed additives can directly or indirectly affect histone modifications. Methyl donors used in feed (methionine, B12, etc.) control gene expression bi-directionally by affecting not only DNA methylation but also histone methylation. In another example, short-chain fatty acids (such as butyrate) act as histone deacetylase inhibitors. This leads to increased histone acetylation levels and increased expression of related genes. Consequently, they affect gut health. Butyrate is produced from fibers fermented by the gut microbiota. Butyrate-induced histone acetylation contributes to the development of intestinal epithelial cells and also enhances the expression of immune genes, thereby contributing to the overall growth performance of the animal (Hamer et al., 2008). Minerals also act as cofactors for histone-modifying enzymes. In another example, antioxidants and phytobiotics regulate epigenetic mechanisms by affecting the activity of histone-modifying enzymes or reducing intracellular oxidative stress (Gliozheni, 2018).

1.4. Non-Coding RNAs (ncRNAs)

While it is known that genetic information is transferred from DNA to RNA and then to protein, studies have identified RNA molecules that occupy a large portion of the genome and do not code for proteins but influence gene expression. These molecules are called non-coding RNAs. They have the function of controlling biological processes in living organisms. ncRNAs are an important target for understanding the epigenetic effects of feed additives (Hu et al., 2022). Specifically, there are two main classes of ncRNAs: microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). miRNAs are generally short molecules of 18-25 nucleotides. They work by cleaving the target mRNA or inhibiting translation. lncRNAs, on the other hand, are molecules longer than 200 nucleotides and have complex tasks such as chromatin remodeling (Li et al., 2025). Mining and profiling these long non-coding RNAs in livestock have revealed their crucial roles in regulating diverse physiological, metabolic, and production traits (Weikard et al., 2017). ncRNA modulations offer a novel epigenetic strategy to increase feed utilization and improve resistance to stress factors in farm animals.

1.4.1. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs)

These are single-stranded RNA molecules 18–25 nucleotides long. Typically, they bind specifically to the non-coding region (3'UTR) of messenger RNA (mRNA). Therefore, mRNA can repress protein synthesis. They can target multiple mRNAs. They are involved in many biological processes, including cell growth, differentiation, metabolism, and stress responses. They can also regulate genes affecting productivity traits in animals (Coutinho et al., 2007).

On the other hand, long non-coding RNAs (lncRNAs) are molecules longer than 200 nucleotides and regulate more complex processes such as chromatin modification (Li et al., 2025). Feed additives can directly affect animal nutrition and can alter gene expression and change the animal's phenotype by modifying ncRNAs. For example, methyl group donors (such as methionine, choline, and vitamins B9 and B12) play a crucial role in the single-carbon metabolism pathway in the cell. S-adenosylmethionine (SAM) is synthesized along this pathway. Excess and deficiency of these nutrients can affect the methylation status in the promoter regions of ncRNA genes, leading to changes in lncRNA and miRNA expression. For example, phytobiotics (such as carotenoids) and antioxidants (such as selenium) can affect ncRNA expression by reducing intracellular oxidative stress. Furthermore, unsaturated fatty acids (such as omega-3s) alter gene expression by affecting cell membrane structure and signaling, thus potentially altering ncRNA expression as well (Hu et al., 2022).

2. Discussion

The use of feed additives in animal nutrition has traditionally been evaluated primarily on the basis of meeting basal metabolic requirements or enhancing performance parameters (Yadav and Jha, 2019). However, current literature suggests that these bioactive compounds may act as "molecular operators" on the genome through epigenetic mechanisms (Wang and Ibeagha-Awemu, 2021). This dynamic interplay between nutrition and the epigenome (nutri-epigenetics) appears to have the profound potential to shape not only the immediate phenotype of the animal but also the adaptive capacity of subsequent generations (Feeney et al., 2014).

The critical role of methyl donors (e.g., methionine, choline, and vitamin B12) in one-carbon metabolism is thought to provide a pivotal control mechanism for gene silencing or activation by potentially modulating DNA methylation profiles (Chen et al., 2025). Furthermore, the function of short-chain fatty acids, such as butyrate, acting as histone deacetylase (HDAC) inhibitors, has been shown to improve intestinal epithelial development and immune responses not only at the cellular level but also at the transcriptional level by promoting chromatin relaxation (euchromatin). This paradigm shift suggests that incorporating specific additives into the diet transcends a simple "feeding strategy"; it may serve as a potent instrument for "epigenetic programming" (Wang and Ibeagha-Awemu, 2021).

Moreover, the modulation of non-coding RNAs (ncRNAs) by feed additives opens a promising new prospect for stress management and disease resistance in livestock. For example, mitigating oxidative stress via antioxidants and phytobiotics through the regulation of ncRNA expression could establish a critical line of defense, particularly in combating heat stress, a pressing challenge exacerbated by climate change (Feil and Fraga, 2012). In species expected to adapt to harsh environmental conditions, such as small ruminants (e.g., Awassi sheep and Honamlı goats), integrating these targeted epigenetic interventions with population genetics data could be of vital importance for developing sustainable and resilient breeding strategies (Alberto et al., 2018).

Nevertheless, the effectiveness of these epigenetic modulations appears to depend upon a complex interaction among dosage, timing of application (critical developmental windows), and species-specific metabolic pathways (Funston et al., 2019). Future research should look beyond conventional performance metrics and map the complex molecular landscape of these interactions using advanced omics technologies, including transcriptomics and methylomics. Finally, the accurate and targeted application of epigenetic tools in animal nutrition has the potential to form the basis of an environmentally robust and economically sustainable animal production model (Funston et al., 2019).

3. Conclusion

In conclusion, this review highlights that feed additives are no longer only nutritional supplements but powerful epigenetic modifiers capable of reprogramming the gene expression landscape of livestock. The change from basic metabolic maintenance to exact "epigenetic programming" offers a transformative strategy for enhancing animal welfare, productivity, and resilience against environmental challenges, such as heat stress. While mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation provide the molecular basis for these changes, the practical success of such approaches depends on a detailed understanding of the complex interactions between nutrition, the genome, and species-specific metabolic pathways. In the future, the integration of advanced multi-omic technologies will be crucial to fully understanding these complex relationships, opening the way for more resilient herds as well as an environmentally sustainable and climate-friendly livestock sector.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	R.T.	F.K.T.	H.M.
C	30	30	40
D	30	30	40
S			100
DCP	50		50
DAI	50		50
L	30	30	40
W	30	30	40
CR	30	30	40
SR			100

C= concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declared that there is no conflict of interest.

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