**Role of Nutrition in Epigenetics and its Impact on Milk Production in Farm Animals: A Review**

**Abstract:**

 Milk production in farm animals is a cornerstone of global agriculture, significantly influenced by epigenetic mechanisms, and it plays an important role in mammary gland function, milk quantity, and quality traits. In this review, we discuss how nutrition can play a role in epigenetic mechanisms via mammary gland development and milk production, such as histone modifications, DNA acetylation, and DNA methylation, in addition to non-coding RNAs. We highlight the nutrients, such as methionine, choline, omega-3 fatty acids, and resveratrol, and how they directly affect epigenetic marks, and increase the yield, composition, and quality of milk. Adding methionine to milk improves the production of protein and fat, while omega-3 fatty acids increase milk production by acetylating histones. However, there remain major gaps in knowledge of species-specific epigenetic responses to nutritional interventions. Nonetheless, many issues about the epigenetic pathways remain unresolved. Particularly, their lack of understanding of the role of epigenetics in milk production across species and the influence of various nutritional components. This review summarizes from beginning to current knowledge about nutrition specific components, how it influences epigenetics and its impact on the udder environment and milk production, identifies the research gaps and offers insightful information about its applicability to enhancing animal nutrition and dairy production for research scholars, veterinarians, and livestock farmers.

**Keywords**: Epigenetics, Milk Production, Livestock, Nutrition, DNA Methylation, Histone Modifications, Non-Coding RNAs, Dietary Interventions, Methionine, Choline, Omega-3 Fatty Acids, Mammary Gland, Gene Expression, Sustainable Agriculture, Animal Health.

1. **INTRODUCTION**

All over the world, billions of people depend mainly on milk and dairy products to meet their nutritional needs. This demand provides livelihoods for millions of people involved in milk and dairy product supply chains worldwide. Currently, livestock products contribute 28% of the total agricultural output, with a 2.6% annual growth rate, and it is predicted that this contribution will increase to 31% by 2032. India, globally ranked first for milk production, is a primary driver of this growth, especially in dairy products. In global milk production, contributions from cows (81%), buffalo (15%), and a combination of goats, sheep, and camels (4%) are expected to grow by 1.5% annually over the next decade, reaching 1039 million tonnes (Mt) by 2032. At the same time, the population is projected to increase by 7–9%, resulting in a huge demand for milk and dairy products, particularly in regions with high growth rates. This growth underscores the importance of understanding the biological mechanisms underlying milk production. In particular, the role of epigenetic mechanisms has emerged as a key factor that could unlock higher milk production in livestock (Riggs et al., 1996). This understanding could lead to innovative breeding strategies and improved management practices that enhance productivity while ensuring animal welfare. As researchers delve deeper into the epigenetic factors influencing milk yield, the dairy industry may be poised for a significant transformation that aligns with both consumer demand and sustainability goals.

1. **HISTORY AND EVOLUTION OF EPIGENETICS ON MILK PRODUCTION IN FARM ANIMALS**

The study of epigenetics has a rich history, beginning with Conrad H. Waddington’s (1905 – 1975) pioneering work on the relationship between genes and their expression. Waddington introduced the term" epigenetics" to describe the interplay between inheritable and environmental factors in shaping an organism’s development. Over the decades, crucial discoveries have advanced our understanding of epigenetic mechanisms. For illustration,X-chromosome inactivation in mammals (Lyon, 1962), cytoplasmic heritage in Paramecium (Beisson&Sonneborn, 1965), and the identification of nucleosome structure (Kornberg & Thomas, 1974) laid the foundation for ultramodern epigenetics. moment, epigenetics is defined as the study of inheritable changes in gene function that do without changes to the DNA sequence (Riggs et al., 1996). These changes, which include DNA methylation, histone variations, andnon-coding RNAs, play a critical part in gene regulation, cell isolation, and phenotype expression (Singh et al., 2012).

 In the environment of udder for the milk production, epigenetics has surfaced as a pivotal factor in regulating mammary gland function and milk composition. Epigenetic mechanisms act as molecular switches that control gene expression patterns essential for milk product (Singh et al., 2012). These mechanisms are largely sensitive to environmental factors, particularly nutrition, making them a promising target for optimizing best productivity (Sinclair et al., 2016). Specific nutrients such as methionine, choline, and omega- 3 adipose acids have been shown to modulate epigenetic processes in the mammary gland, impacting milk yield and composition (Weikard et al., 2012). The dynamic and reversible nature of epigenetic variations offers perceptivity into how environmental exposures, including diet, affect milk product (Singh et al., 2010).

 Despite these advancements, there remains a lack of understanding regarding species-specific epigenetic responses to salutary interventions (Sinclair et al., 2016). This gap in knowledge limits the development of targeted approaches to ameliorate dairy product effectiveness. This review synthesizes current knowledge on the part of nutrition in the epigenetic regulation of milk production, with a focus on crucial mechanisms similar as DNA methylation, histone variations, and non-coding RNAs. By exploring the active component of specific nutrients on mammary gland function, we punctuate the eventuality of salutary interventions to optimize milk yield and composition. Likewise, we identify critical exploration gaps, particularly in understanding species-specific epigenetic responses, and emphasize the need for further studies to ground these gaps. Eventually, this review seeks to give precious perceptivity for experimenters, veterinarians, and livestock policymakers, paving the way for innovative strategies to enhance dairy production, better health, and promote sustainable husbandry.

1. **MECHANISMS OF EPIGENETICS**

 Epigenetic mechanisms regulate gene expression without altering the beginning DNA sequence, playing a critical part in mammary gland function and milk product. These mechanisms include histone variations, acetylation, methylation, andnon-coding RNAs, each of which contributes to the dynamic regulation of gene expression in response to environmental and nutritive cues. nutritive factors, similar as methionine, choline, omega- 3 adipose acids, and resveratrol, have been shown to modulate these epigenetic pathways, impacting milk yield, composition, and quality.

* 1. **Histone Tail Modification:**

 Histone post-translational variations encompass chemical differences being on histone proteins, which constitute the primary factors of chromatin, the complex comprising DNA and histone proteins forming chromosomes(Allfrey et al., 1964). Histone tail modification, including acetylation, methylation, and phosphorylation, affect gene expression by altering chromatin structure. Tightly packed thick chromatin turns off genes, while unpacked thin chromatin activates them. Histone variations regulate gene expression, chromatin structure, replication, and DNA form( Rothbart&Strahl, 2014). For illustration, histone acetylation is intermediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which add or remove acetyl groups from lysine residue, independently results modification of histone protein structure leads to tightly packing and unpacking of chromatin structure (Xhemalce et al., 2011). In the mammary gland, histone acetylation is linked to the activation of genes involved in milk composition, such as lactalbumin and lactoferrin (Singh et al., 2012). Again, histone deacetylation is associated with gene silencing during mammary gland development and other udder complications. Nutrients like butyrate and resveratrol can modulate histone acetylation, impacting milk product and quality (Wall & McFadden, 2010). Nutritiveinterventions, similar as resveratrol supplementation, have been shown to enhance histone acetylation, leading to bettered lactose and fat content in milk(Sun et al., 2019). also, omega- 3 adipose acids impact histone variations, regulating enzymes like stearoyl- CoA desaturase(SCD) and lipoprotein lipase(LPL), which are critical for milk fat conflation (Javaheri et al., 2023). These findings punctuate the eventuality of salutary strategies to optimize milk product through epigenetic regulation.

* 1. **DNA Acetylation**

 DNA acetylation is a less discussed area but inversely important epigenetic mechanism. DNA acetylation adds an acetyl groupto DNA, primarily at cytosine bases, turning on the gene. X-chromosome inactivation in mice (Lyon, 1961) exemplifies this epigenetic mechanism. It involves the addition of acetyl groups to DNA, which can impact gene expression by altering the commerce between DNA and histone proteins. While DNA acetylation is not as well- studied as histone acetylation, arising substantiation suggests that it plays a part in regulating gene expression in the mammary gland. For illustration, acetylation of DNA can enhance the availability of recap factors to gene promoters, thereby transcribing the genes involved in milk production and secretion (Zhang et al., 2020). Nutritive factors, similar as butyrate and resveratrol, have been shown to impact DNA acetylation. Butyrate, a short-chain adipose acid produced by ruminal microbiota utilising national fibres, which acts as an HDAC asset, leading to increased acetylation of both histones and DNA(Davie, 2003). This, in turn, enhances the expression of genes involved in milk production. Resveratrol, a polyphenolic emulsion set up in grapes and berries, has also been shown to modulate DNA acetylation, perfecting milk composition and increasing yield in dairy animals (Sun et al., 2019).

3.3 **DNA Methylation**

 DNA methylation involves adding a methyl group to the coding region of a DNA sequence (gene), turning off the gene. DNA methylation, first detected in shin thymus cells (Hotchkiss, 1948), was latterly linked to gene expression and suppression (Riggs, 1975; Holliday & Pugh, 1975). Methylation occurs substantially on cytosine base of GCrich regions of DNA sequence, impacting gene expression and cell division (Jurkowska et al., 2011). These functions intricately regulate gene expression and contribute to the development of inheritable diseases and early and post embryonic development of livestock (Esmaeili et al., 2020 Izzo, et al., 2016; Martire, et al., 2020). Some specific nutritional molecules play a pivotal part in DNA methylation. For case, methionine is essential for the production of S-adenosylmethionine (SAM), is the universal methyldonor. Methionine supplementation in dairy cows has been shown to enhance milk protein and fatyield and fat percentage by modulating DNA methylation patterns in genes involved in mammary gland function (Qi et al., 2018). also, choline and folate, which are also methyl donors, influence DNA methylation and gene expression, impacting milk yield and composition (Salah et al., 2014).

* 1. **Non-Coding RNAs**

 Non-coding RNAs (ncRNAs), including microRNAs(miRNAs) and long non-coding RNAs(lncRNAs), play a vital part inpost-transcriptional regulation of gene expression. In the mammary gland, miRNAs similar as miR-21 and miR-148aare regulatory genes involved in milk composition and production (Singh et al., 2010). For illustration, miR-148a targets the DNA methyltransferase 1 (DNMT1) gene, creating a response loop between DNA methylation and miRNA expression. Also, lncRNAs are involved in mammary gland development and lactation, although their mechanisms remain less understood s(Dysin et al., 2021). The interplay between ncRNAs and other epigenetic mechanisms highlights the complexity of gene regulation in milk production. Nutritive factors can impact ncRNA expression, thereby affecting milk production. For case, high- fat diets have been shown to drop DNA methylation and increase miRNA- 152 expression, which regulates mammary gland development and lactation processes(Wang et al., 2014). also, energy restriction alters miRNA expression patterns, impacting milk production and composition in cattle (Billa et al., 2021). These findings emphasize the significance of salutary interventions in modulating ncRNA-intermediated epigenetic regulation.

1. **EPIGENETIC REGULATION GROUNDED ON NUTRITIVE CHANGES AND ITS EFFECT ON MILK PRODUCTION IN FARM ANIMALS**

 Epigenetic regulation plays a vital part in milk product among various livestock species. Throughout lactation, mammary gland cells undergo substantial epigenetic variations that essential for milk production and secretion. A crucial epigeneticmechanism in milk production involves DNA methylation, intricately regulates milk production (Xie et al., 2012) and positively correlates with the protein and fatyield in milk. Recent findings by Wang et al. (2021) showcased differentially methylated CPGregions of DNA sequences associated with quantitative trait loci (QTLs) for milk protein and fat yield. Hypo-methylation of the lactation enhancer, binding to the activator of recap STAT5, in bovine lactating mammary glands regulates casein expression. Specifically, an increase in methylation of the STAT5 binding CPG Island was observed with prolongedpost-milking duration, potentially linked to mammary gland complication and the decline in milk protein components (Vanselow et al., 2006; Singh et al., 2010). Nutrition exerts a profound influence on epigenetic regulation in the mammary gland, during gestation and lactation and altering gene expression and milk composition. For case, specific amino acid restriction during gestation and lactation was shown to modify DNA methylation patterns in the mammary gland leading to changes in the expression of genes involved in milk production in cattle and goats (Singh et al., 2012; Tian et al., 2017; Liu et al., 2017). DNA methylation patterns and gene expression in the mammary gland are subject to revision with the supplementation of certain nutrients like choline and folic acid. Certain amino acids, specially methionine, choline, betaine, and folate give methyl benefactors for methyl transferases, pivotal in regulating S-adenosylmethionine (SAM) (DelCurto et al., 2013; Sutter et al., 2013).

 The impact of Methionine (Met) supplementation on cows has been considerably studied both in vivo and in vitro. Met, an essential amino acid, is integral to colourful natural processes similar as growth and milk product. Duringthe periparturient period Met has been shown to upregulate gene expression via the SNAT2- PI3K signalling pathway, adding milk protein and fat composition and mammary cell proliferation (Qi et al., 2018). likewise, methionine supplementation enhances the methylation of protagonist regions of PPARα target genes, leading to bettered lipid metabolism, vulnerable function, and milk product in dairy cows (Osorio et al., 2016).

**Table 1: Epigenetic changes due to alteration in nutrition, and related phenotypic effects in milk production in farm animals.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sl. No** | **Nutritional Factors** | **Epigenetic change** | **Phenotypic effects in milk production** | **References** |
|  | Protein restriction | α-S1 casein encoding gene region methylated at 3 CPG dinucleotides | Shutdown the synthesis of alpha S1 casein during mammary involution and mastitis | Singh *et, al.* 2012 |
|  | Long-term feeding of high concentrate diet in goats | Methylation in the promoter regions of SCD and ACACA genes | Decrease in production of milk fat | Tian *et, al.* 2017 |
|  | Protein restriction | Hypomethylation of first CpG island in the promotor region of EEF1D gene during dry period | mRNA expression of EEF1D gene was higher during dry period | Liu *et, al.* 2017 |
|  | Supplementation of methionine during third trimester in cows | Changes in mRNA expression | Changes in immune function and abundance of microRNA and mRNA in Holstein calf polymorphonuclear leukocytes | Jacometo*et, al.* 2018 |
|  | Supply of methionine and choline during the periparturient period | Upregulation of gene expression | Alter Polymorphonuclear Leukocyte Immune Response in Holstein Cows | Zhou *et, al.* 2018 |
|  | Supply of methionine during the periparturient period | Phosphorylation of the antioxidant transcription regulator NFE2L2 | Alters mammary gland antioxidant gene networks in cattle | Han *et, al.* 2018 and Liang *et, al.* 2019 |
|  | Supplementation of methionine | Upregulation of gene expression via SNAT2-PI3K signalling pathway | Increased milk protein and fat synthesis and mammary cell proliferation | Qi *et, al.* 2018 |
|  | Supplementation of methionine in cows | Methylation of promotor region of PPARα target genes leads to upregulation of gene expression | Leads to improved lipid metabolism, immune function and milk production in dairy cows | Osorio et.al., 2016 |
|  | Dietary resveratrol supplementation during gestation and lactation of sows | Upregulation of gene expression | Improved the lactose content in the colostrum and fat content in milk at day 21 of lactation and also increased the HDL and LDL in the plasma of piglets. | Sun *et, al.* 2019 |
|  | Omega-3 fatty acid supplementation in Sannen goats | Histone acetylation patterns decrease the activity of LPL and SCD enzymes. | It leads to increase in milk production in goats | Javaheri*et, al.* 2023 |
|  | Feeding a high-Concentrate Corn Straw Diet | Decrease in Histone H3 acetylation | Leads to higher lipopolysaccharide concentrations in mammary tissue in dairy cows | Dong *et, al.* 2014 |
|  | Feeding a high-Concentrate Corn Straw Diet | Methylation of the stearoyl-coenzyme A desaturase gene | Increase in milk fat synthesis but decrease the protein synthesis in dairy cows | Dong *et, al.* 2014 |
|  | Linseed oil supplementation in dairy cows | DNA methylation patterns altered | It regulates the fatty acid synthesis in dairy cows | Li *et, al.* 2017 |
|  | High fat supplementation | It leads to decreased DNA methylation increases the microRNA-152 expression | Development and lactation processes in the mammary glands of dairy cows | Wang *et, al.* 2014 |
|  | Energy restriction | MiRNA expression patterns altered | Milk production and composition incattle | Billa*et, al.* 2021 |

1. **EXPLORATION OF RESEARCH GAPS AND FUTURE DIRECTIONS**

 Despite significant advancements in understanding the part of epigenetics in milk product, several exploration gaps remain.

* 1. **Gap in Species-Specific Response studies:** Utmost studies concentrate on dairy cows, with limited exploration on other beast species similar as scapegoats, lamb, and buffalo. Understanding species-specific epigenetic responses to salutary interventions is pivotal for developing targeted nutritive strategies. For illustration, the epigenetic goods of nutrients like methionine and omega-3 adipose acids may vary across species, challenging acclimatized approaches for each (Sinclair et al., 2016).
	2. **Gap in Long- Term Response trails:** The long- term response trails of specific nutrition on livestock milk production and related epigenetic marks are not well understood. Longitudinal studies are demanded to assess the transgenerational impact of salutary interventions. For case, how the key epigenetic nutrients influenceepigenetic marks duringduring gestation period of differentlivestock species and after gestationhow theyimpact following subsequent lactation periods of animal stages of life that remains an area of active disquisition (Tian et al., 2017).
	3. **Mechanistic perceptivity:** While the part of DNA methylation and histone variations in milk product is well proved, the mechanisms underpinning non-coding RNA regulation remain less explored. farther explorationis demanded to interpret the interplay between ncRNAs and other epigenetic mechanisms. For illustration, how miRNAs like miR- 148a and lncRNAs interact with DNA methylation and histsone variations to regulate milk conflation is still unclear (Dysin et al., 2021).
	4. **Practical operations:** Rephrasing epigenetic exploration into practical salutary recommendations requires large-scale field studies. These studies should estimate the cost-effectiveness and sustainability of epigenetic-nutritive strategies. For case, the profitable viability of supplementing diets with methionine or omega- 3 adipose acids to enhance milk product needs to be assessed (Qi et al., 2018).

 Unborn explorationshould concentrate on addressing these gaps to unleash the full eventuality of epigenetics in enhancing dairy product. By integrating epigenetic knowledge with nutritive wisdom, we can develop innovative strategies to ameliorate milk yield, composition, and beast health, eventually contributing to sustainable husbandry.

1. **CONCLUSION**

 Epigenetic mechanisms, including DNA methylation, histone variations, andnon-coding RNAs, play a critical part in regulating milk product in beast. nutritive interventions, similar as supplementation with methionine, choline, omega- 3 adipose acids, and resveratrol, have been shown to modulate these epigenetic pathways, leading to advancements in milk yield, composition, and quality. For illustration, methionine enhances milk protein and fat conflationby impacting DNA methylation, while omega-3 adipose acids ameliorate milk fat content through histone acetylation (Singh et al., 2012; Javaheri et al., 2023). still, significant gaps remain in understanding species-specific responses and the long- term trials forvaluable interventions. Addressing these gaps through targeted exploration will pave the way for innovative strategies to optimize dairy product. By bridging the gap between nutritive wisdom and epigenetics, this review highlights the eventuality of acclimatized salutary interventions to enhance milk product effectiveness, ameliorate beast health, and promote sustainable husbandry. unborn studies should concentrate on rephrasing these findings into practical operations, icing that the benefits of epigenetic exploration are realized at the ranch position.

**Disclaimer (Artificial intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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**Conflict of Interest:**

The authors declare no conflicts of interest, financial or otherwise, related to this work.

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