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Review

Exploration The Multifaceted Role Of Vitamins In Epigenetic Regulation: Insights Into DNA Methylation And Histone Modification

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ABSTRACT

Background: Recent research underscores the active role of vitamins in regulating epigenetic mechanisms. However, a consolidated synthesis clarifying the distinct and synergistic impacts of various vitamins (A, B, C, D, E, K) on DNA methylation and histone modification, and their comprehensive potential in health and disease, is still developing. This narrative review, therefore, aims to synthesize current evidence on how vitamins A, B, C, D, E, and K influence epigenetic regulation, and to elucidate their potential roles in health maintenance and disease prevention.

Methods: NCBI and ScienceDirect were used to search English-language literature from 2015 to 2024 for a narrative review. To capture vitamins' direct and indirect impacts on epigenetic pathways, selected peer-reviewed papers were qualitatively examined

Results: Vitamin A affects gene expression via receptor-mediated mechanisms which modify chromatin structure. B vitamins provide methyl donors for DNA methylation and histone changes. Vitamin C cofactors TET enzymes and histone demethylases, supporting active DNA demethylation and histone acetylation. The vitamin D receptor (VDR) affects DNA methyltransferases and histone-modifying enzymes, regulating gene transcription. Vitamins E and K modulate oxidative stress and histone changes to stabilize the epigenome, which may benefit cancer treatment and metabolic regulation.

Conclusion: Vitamins' diverse and linked epigenetic regulatory activities are highlighted. These micronutrients may help prevent and treat cancer, metabolic problems, and developmental anomalies by maintaining genomic integrity and influencing gene expression.

INTRODUCTION

The relationship between vitamins and epigenetic regulation is a growing field of study that reveals the complex roles these micronutrients have in cellular processes. Vitamins, traditionally acknowledged for their vital nutritional roles, are increasingly recognized for their ability to induce epigenetic modifications, including DNA methylation and histone modification, which directly influence gene expression and cellular function. This review analyzes the function of different vitamins in epigenetic regulation and emphasizes their impact on health and disease.

While maintaining DNA sequence integrity, epigenetic changes include histone reconfiguration and DNA methylation modify gene expression. With growing evidence pointing to vitamins as co-factor or methyl donors in these mechanisms, the processes are fundamental for both normal development and cellular differentiation. Vitamin C increases the activity of ten-eleven translocation (TET) enzymes, therefore enabling the demethylation of 5-methylcytosine to 5-hydroxymethylcytosine and so stimulates gene reactivation[1,2]. Particularly at H3K9me2, vitamin C encourages histone demethylation, therefore improving the expression of genes linked to pluripotency in embryonic stem cells [2,3]. Processes of DNA methylation depend on vitamins B12 and folate. Acting as ubiquitous methyl donors in biological systems[4,5]. B vitamins are vital methyl donors used in the synthesis of S-adenosylmethionine (SAM). Research on vitamin B12 and folate supplementation shows that low levels of these vitamins are linked with alterations in DNA methylation patterns[6,7]. Research showing significant relationships between maternal B vitamin status and offspring DNA methylation profiles suggests transgenerational epigenetic effects[8,9].

Moreover, because of its connection with both DNA methylation and histone changes, the function of vitamin D in epigenetic control has drawn much study. Via both genomic and non-genomic processes, the bioactive form of vitamin D modulates gene expression. Particularly, vitamin D supplementation has been related to lower DNA methylation at loci relevant to immunological function and bone health[10,11]. Additionally, maternal vitamin D levels have been demonstrated to favorably correlate with offspring DNA methylation patterns, hence influencing developmental outcomes[9,12].

Within the framework of cancer, vitamins become major epigenetic regulators with influence on carcinogenesis. For instance, vitamin C supplements have been found to improve the efficacy of epigenetic medicines including decitabine, therefore enabling a change from a silent to an active state in tumor suppressor genes[13,14]. Likewise, the ability of vitamin D to control genes by histone changes and DNA methylation points to its possible use as a therapeutic companion in cancer treatment plans[10,15].

Recent research had further underlined how vitamin E modulates global DNA methylation levels and gene expression connected to oxidative stress responses, therefore influencing the epigenetic machinery[16,17]. Furthermore, new data suggests that vitamins K2 and E could influence histone methylation mechanisms as well as DNA, which has important consequences for diseases including obesity and liver diseases[18,19]. These results support a more comprehensive knowledge of nutritional effects on treatment frameworks and highlight the complicated interactions among diet, epigenetic control, and disease.

Thus, vitamins form a dynamic interaction basic to development and disease etiology by both direct and indirect processes influencing epigenetic changes. Based on this knowledge could transform into useful health interventions and therapeutic approaches depends on clear understanding of the particular routes via which vitamins exert their effects as research in this subject develops. With an emphasis on DNA

methylation and histone modifications, this review attempts to summarize latest understanding of the function of vitamins inside the framework of epigenetic control and investigate their possible effects on health and disease management.

METHOD

Design and Search Strategies

This narrative review was conducted by searching the literature available in English through the NCBI and ScienceDirect databases. The search strategy involved the use of key terms and combinations such as “vitamins,” “epigenetics,” “DNA methylation,” “histone modification,” and “epigenetic regulation.” Although no formal systematic review protocol was followed, the search aimed to capture a broad range of relevant studies published between 2015 and 2024. Both MeSH terms and free-text keywords were utilized to ensure comprehensive coverage of the topic.

Criteria for Inclusion and Exclusion

Articles were chosen according to their relevance to the several functions of vitamins in epigenetic control. Studies published in English in peer-reviewed journals, papers directly or indirectly addressing the impact of vitamins on epigenetic mechanisms (e.g., DNA methylation and histone modifications) and studies published during the past ten years comprised the inclusion criteria. Articles not published in English, Articles lacking Digital Object Identifier (DOI), studies not mostly focused on epigenetic control or those with tangential relevance to the topic, and Conference abstracts, non-peer-reviewed sources, book chapter and grey literature will be excluded.

Data Extraction and Data Analysis

Relevant studies were identified, and key data were extracted independently by the authors. The extracted information included study design, vitamin(s) examined, the epigenetic mechanisms investigated (e.g., specific modifications in DNA methylation or histone structure), and the main findings of each study. The extracted data were then organized into thematic categories to facilitate a qualitative synthesis of the literature. Although this review did not employ a quantitative meta-analysis, the narrative synthesis highlights major trends, critical insights, and areas requiring further investigation regarding the epigenetic roles of vitamins.

RESULTS

This study identified and reviewed a collection of relevant studies based on the conducted literature search. This research investigates the role of vitamins in epigenetic regulation, particularly concerning DNA methylation and histone modification. A total of 67 pertinent studies conducted between 2015 and 2024 were chosen for analysis. Figure 1 demonstrates that most studies included in this review were published in 2016, whereas the least were published in 2024.

Several studies explicitly elucidated the relationship between particular vitamins and epigenetic mechanisms, specifically DNA methylation and histone modification, as reflected in their titles. Some individuals, however, characterized these associations more indirectly or addressed supplementary vitamins that seem to be interrelated, though without significant emphasis, indicating a need for further correlation. The discussion section will provide a more detailed exploration of these interconnections. The findings related to vitamins and their association with epigenetic mechanisms are summarized in Table 1.

As demonstrated in Table 1, our findings indicate that the studies most frequently reporting a direct association between vitamins and genetic mechanisms predominantly focused on vitamin C, whereas vitamin K was reported the least. Notably, vitamin K ranked third in terms of indirectly described epigenetic mechanisms, following vitamin A and vitamin B. Overall,

vitamin A appears to be the vitamin most commonly associated with epigenetic mechanisms, although most of its effects are described indirectly and warrant further investigation. In contrast, the literature on the epigenetic involvement of vitamin E and vitamin K remains relatively scarce

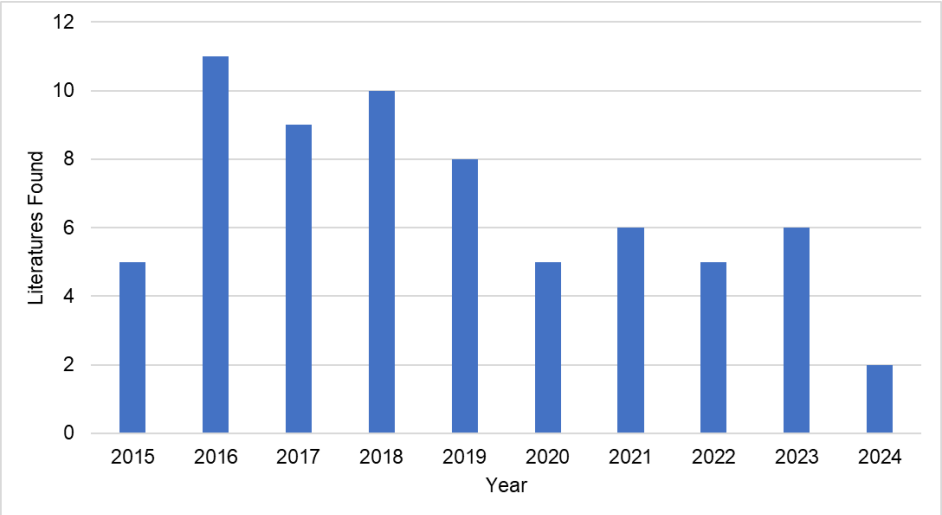

Figure 1. Distribution of related studies found that will be discussed in this study (n=67)

This study's findings suggest a relationship between one vitamin and another within the epigenetic mechanism. Multiple B vitamins (B9, B6, B2, and B12) play a crucial role in the one-carbon cycle, facilitating the production of S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methylation. Vitamins A and D are known to indirectly interact with B vitamins involved in the One-carbon cycle, in addition to their own mechanisms through respective receptors that influence epigenetic enzymes. Vitamins B5, B3, and B7 appear to operate through distinct mechanisms outside the One-carbon cycle within the epigenetic framework, which remains inadequately elucidated. Similarly, vitamin E is primarily associated with its antioxidant properties, which reduce reactive oxygen species (ROS) and subsequently regulate epigenetic enzymes. Vitamin K, in addition to enhancing the activity of the enzyme γ-Glutamyl Carboxylase in the regulation of epigenetic enzymes, may also have an indirect interaction with vitamin D in epigenetic mechanisms. Figure 2 illustrates the schematic relationship between one vitamin and another.

Table 1. The Number Of Research Findings Reporting Associations Between Vitamins And Epigenetic Mechanisms, Either Directly Or Indicrectly Explained

Vitamin	The number of studies reporting associations between vitamins and epigenetics		
	Directly Explained	Indirectly Explained	Overall
A	5	16	21
B	10	5	15
C	16	1	17
D	12	1	13
E	3	1	4
K	1	3	4

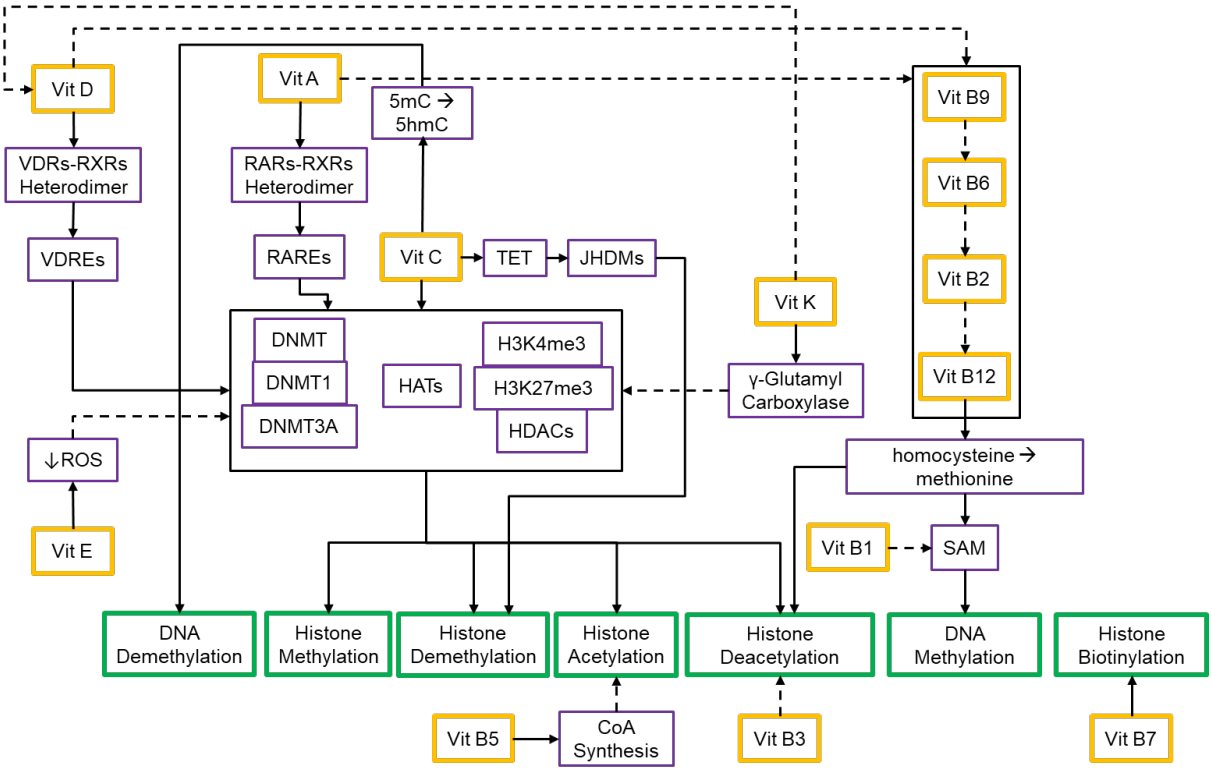

Figure 2. The interaction of vitamins within the context of epigenetic mechanisms. The yellow box illustrates the function of vitamins, while the purple box delineates the process culminating in the epigenetic outcome indicated by the green box. The dotted line represents indirect interactions, whereas the solid line indicates direct interactions.

DISCUSSION

Role of Vitamin A in Epigenetics

Vitamin A, mainly via its active metabolite retinoic acid (RA), significantly influences gene expression regulation through the modulation of epigenetic modifications. Retinoic acid functions by binding to nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which form heterodimers that engage with retinoic acid response elements (RAREs) located in the promoter regions of target genes[20–22]. This receptor-mediated action is crucial for regulating transcription and modulating essential epigenetic processes, such as DNA methylation and histone modifications, which collectively affect chromatin structure and gene accessibility.

Regarding DNA methylation, retinoic acid coordinates intricate control of gene expression is required for appropriate cellular differentiation and organogenesis, is the interaction between retinoic acid signaling and DNA methylation[24]. Retinoic acid has also been demonstrated to affect the expression of genes linked in one-carbon metabolism a route necessary for producing methyl donors such S-adenosylmethionine (SAM), synthesised from methionine which underpins methylation reactions[25,26]. Both essential for one-carbon metabolism chemical activities vital throughout embryonic development and cellular differentiation. Retinoic acid helps transcription of genes linked in differentiation and development by assembling coactivators and chromatin remodeling complexes[20,23]. Particularly important during embryogenesis, where exact, retinoic acid's interaction with vitamins B12 and folate points to a complicated network whereby Vitamin A indirectly controls DNA methylation[6,27].

Moreover, studies show that retinoic acid controls the expression of DNA methyltransferases (DNMTs), including DNMT1 and DNMT3A, hence producing changes in global DNA methylation patterns[19,21]. In cancer biology, this regulation is especially important since abnormal DNA methylation patterns usually cause the epigenetic silence of tumor suppressor genes.

Retinoic acid has thus been suggested as a therapeutic agent in some malignancies, including acute promyelocytic leukemia, where its capacity to reverse epigenetic silencing helps to explain its efficiency in inducing cellular differentiation and stopping proliferation[19,28]. Beyond oncology, retinoic acid affects DNA methylation in metabolic control; for example, by altering the expression of genes linked in adipogenesis, retinoic acid may influence the development of obesity and metabolic diseases[21,29]. In the context of maternal health, the action of retinoic acid on placental DNA methylation is crucial for fetal development, therefore underlining the need of sufficient Vitamin A consumption during pregnancy for appropriate epigenetic programming[30,31].

Parallel to its effects on DNA methylation, retinoic acid significantly regulates histone modifications, a process essential for the dynamic control of gene expression. Retinoic acid primarily influences histone modifications by regulating histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone acetyltransferases (HATs) add acetyl groups to lysine residues on histones, promoting a more open chromatin structure that facilitates active transcription. In contrast, histone deacetylases (HDACs) remove these acetyl groups, resulting in chromatin condensation and transcriptional repression[32]. Retinoic acid enhances the expression and activity of specific HATs, facilitating histone acetylation and the transcription of target genes[33].

Apart from acetylation, retinoic acid affects histone methylation, a crucial post-translational alteration whose lysine residue change either stimulates or inhibits transcription. For instance, whereas trimethylation at lysine 27 (H3K27me3) is linked to transcriptional repression, trimethylation of histone H3 at lysine 4 (H3K4me3) is linked with transcriptional activation[34]. Retinoic acid is essential in controlling the methylation level of histones and, hence, the transcriptional results of related genes by adjusting the expression of histone methyltransferases and demethylases[35]. This mechanism is especially relevant during development since retinoic acid-induced histone changes are necessary for the activation of genes engaged in the differentiation of embryonic stem cells and the generation of distinct tissues[36].

Particularly in the therapy of cancer, retinoic acid's regulation of histone alterations has great therapeutic consequences. Many times, seen in cancer, aberrant histone modification patterns help to silence tumor suppressor genes and activate oncogenes. Retinoic acid has thus been investigated as a possible therapeutic agent in diseases including acute promyelocytic leukemia, with its capacity to reverse epigenetic silencing by means of changes in histone acetylation and methylation hence improving the efficacy of current treatment strategies[37]. Moreover, the action of retinoic acid reaches to immune system control. Retinoic acid modulates histone changes to influence the development and function of immune cells including T cells and dendritic cells so boosting the expression of genes involved in immunological tolerance and anti-inflammatory responses[38].

Role of Vitamin B in Epigenetics

The B vitamins, a collection of water-soluble vitamins such as B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin), are essential for various metabolic processes and are gaining attention for their significant role in epigenetic regulation. Their role in epigenetic processes is complex, affecting DNA methylation and histone modifications via interconnected mechanisms related to one-carbon metabolism, cofactor functions, and the regulation of essential enzymatic activities. The epigenetic effects have significant implications for health and disease, encompassing cancer prevention, metabolic regulation and neurodegenerative disorders. The primary mechanism through which these vitamins influence epigenetics is their involvement in one-carbon metabolism, supplying the methyl groups necessary for methylation reactions. Folate (B9) is essential in this context, providing the one-carbon units required for the conversion of homocysteine to methionine, a reaction that produces S-adenosylmethionine (SAM), the primary methyl donor for DNA and histone methylation[5]. Similarly, Vitamin B12 functions as a crucial cofactor for methionine synthase, the enzyme

responsible for the remethylation of homocysteine to methionine. Deficiencies in folate or B12 can result in decreased SAM levels, leading to global hypomethylation of DNA and abnormal gene expression, along with altered histone methylation patterns that may increase susceptibility to cancer and other chronic diseases[5,39,40].

Vitamin B6 (pyridoxine) enhances methylation processes by regulating homocysteine levels through the transsulfuration pathway, thus ensuring a sufficient supply of methyl donors. Vitamin B2 (riboflavin) is essential for the synthesis of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are crucial cofactors for the function of several enzymes that participate in the demethylation of DNA and histones[41]. The activity of these enzymes is crucial for sustaining appropriate epigenetic patterns, underscoring riboflavin's significant role in genomic regulation.

By influencing histone biotinylation, a post-translational alteration that can change chromatin structure and gene accessibility, biotin (B7) also greatly helps to regulate epigenetics. Often interacting with other epigenetic markers, the biotinylation of histones further fine- tunes gene expression and DNA methylation patterns[42]. Additionally, thiamine (B1) also supports energy metabolism and nucleotide synthesis, which are essential for SAM synthesis and, hence, for preserving appropriate methylation patterns on DNA and histones[34,35].

Crucially for the action of sirtuins NAD+-dependent deacetylases controlling histone acetylation, vitamin B3 (niacin) is a precursor of nicotinamide adenine dinucleotide (NAD+). Through changing chromatin accessibility, sirtuins indirectly regulate DNA methylation by modifying histone acetylation [43,44]. In a same line, the synthesis of coenzyme A (CoA), a chemical needed for the acetylation of histones, depends on vitamin B5 (pantothenic acid). This acetylation process loosens chromatin structure, therefore facilitating transcriptional activation and impacting DNA methylation dynamics as well as histone modification[1].

Maintaining appropriate gene expression and cellular function depends on the combined and synergistic actions of the B vitamins on histone modifications and DNA methylation. By means of their involvement in one-carbon metabolism and as indispensable cofactor for many enzymes, the B vitamins guarantee the availability of SAM and assist the proper operation of methyltransferases, deacetylases, and other histone-modifying enzymes. This multifarious participation not only maintains genomic integrity but also modifies gene expression in ways that are important for preventing and controlling chronic diseases like cancer, cardiovascular disease, neurodegenerative disorders, and metabolic dysfunction. Furthermore, the epigenetic programming of children depends much on mother consumption of B vitamins during pregnancy. Appropriate supplements, especially with folate and vitamin B12, can change the DNA methylation patterns and histone modification profiles in the growing baby, therefore influencing long-term health outcomes and disease susceptibility[8,45].

Role of Vitamin C in Epigenetics

Vitamin C, or ascorbic acid, is an essential nutrient involved in various biological processes, especially in epigenetic regulation. Its influence encompasses DNA methylation and histone modifications, impacting gene expression, cellular differentiation, developmental processes, cancer progression, and immune responses. Vitamin C regulates DNA methylation primarily by serving as an essential cofactor for ten-eleven translocation (TET) enzymes. These enzymes facilitate the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), which is a crucial step in the process of active DNA demethylation[46,47]. Vitamin C supplies the required reducing power for optimal TET enzyme activity, facilitating the conversion of 5mC to 5hmC and promoting demethylation. This process is essential for preserving proper gene expression patterns, especially during developmental phases and in reaction to environmental stimuli[47,48].

Furthermore, studies have shown that vitamin C can cause particular demethylation of histones, such lowering of H3K9me2 levels in embryonic stem cells by means of Jumonji domain-containing histone demethylases[49].

This observation emphasizes how closely DNA and histone methylation coordinate to create the larger epigenetic terrain controlling gene expression and cellular differentiation [2,48].

There are also major clinical ramifications from vitamin C's effect on DNA methylation. For example, maternal vitamin C intake has been linked to a decrease in both hypermethylated and hypomethylated loci[50,51]. Furthermore, in relation to cancer, vitamin C has become a possible treatment agent. Its capacity to reawaken suppressed tumor suppressor genes by improving the efficacy of DNA methyltransferase inhibitors such decitabine emphasizes its function in correcting aberrant methylation patterns in colon cancer cells[52,53].

In addition to its direct impact on methylation, Vitamin C influences immune responses. This process enhances the stability of Foxp3 expression in regulatory T cells by facilitating active demethylation of the Treg-specific demethylated region (TSDR), a modification essential for sustaining immune tolerance and averting autoimmune diseases[54]. Additionally, Vitamin C exhibits a synergistic interaction with other nutritional components involved in one-carbon metabolism, including folate and Vitamin B12, which are crucial for the synthesis of S-adenosylmethionine (SAM), the primary methyl donor in DNA methylation reactions[55,56]. Adequate levels of Vitamin C may support proper DNA methylation processes and overall genomic stability.

Beyond its established function in DNA methylation, Vitamin C also plays a significant role in histone modifications. A primary mechanism through which it exerts this effect is associated with its role as a cofactor for TET enzymes. These enzymes catalyze DNA demethylation and indirectly influence histone modifications by modifying the chromatin environment[57,58]. Vitamin C facilitates the efficient oxidation of 5mC to 5hmC, thereby supporting the preservation of gene expression patterns crucial for development and environmental adaptation. Additionally, directly fostering histone demethylation is vitamin C. Studies have indicated that it increases the activity of histone demethylases (JHDMs), which remove methyl groups from Jumonji domain-containing histones. Treatment with vitamin C has been linked in mouse embryonic stem cells to a marked decrease in histone methylation markers, including H3K9me2, therefore promoting a more permissive chromatin state that enhances gene expression[49]. Establishing an epigenetic terrain supporting both stem cell pluripotency and differentiation depends on this direct influence on histone demethylation.

Vitamin C has been shown to affect histone acetylation, a modification typically linked to active transcription. Histone acetylation is modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Additionally, Vitamin C has been demonstrated to increase the expression and activity of HATs. This enhancement promotes histone acetylation, resulting in a relaxed chromatin structure that facilitates transcription[1,59]. This modulation of histone acetylation by Vitamin C can lead to enhanced gene expression, especially in situations characterized by epigenetic silencing.

The effects of vitamin C on histone changes reach even into oncology. Often helping to silence tumor suppressor genes and activate oncogenes in cancer is aberrant histone modification patterns. By encouraging histone demethylation and reactivating suppressed tumor suppressor genes vitamin C has been suggested as an adjuvant treatment agent able to improve the effects of DNA methyltransferase inhibitors such azacitidine[52,60].

Furthermore, important for developmental processes and immunological control is the function of vitamin C in histone modification. Vitamin C has been demonstrated in embryonic stem cells to cause histone changes that support the expression of pluripotency proteins, hence preserving stem cell identity and enabling differentiation[3]. Furthermore underlining its significance in immunological tolerance is Vitamin C's ability to sustain Foxp3 expression in regulatory T cells by encouraging active demethylation of the TSDR, same as it affects DNA methylation[54].

Role of Vitamin D in Epigenetics

Vitamin D, a fat-soluble vitamin with hormonal functions, is crucial in various

biological processes, especially in regulating gene expression and epigenetic modifications. The active form, calcitriol (1,25-dihydroxyvitamin D_3), significantly influences DNA methylation and histone modifications, impacting transcriptional activity, cellular differentiation, development, immune regulation, and cancer progression. This review synthesizes existing research on the modulation of epigenetic processes by Vitamin D via its interaction with the Vitamin D receptor (VDR) and related molecular mechanisms. Vitamin D regulates DNA methylation primarily through its interaction with the Vitamin D receptor (VDR). Upon binding to calcitriol, the vitamin D receptor (VDR) forms a heterodimer with the retinoid X receptor (RXR) and translocate to the nucleus, where it binds to vitamin D response elements (VDREs) in the promoter regions of target genes[61,62]. This interaction recruits' coactivators and chromatin remodeling complexes that alter chromatin structure, thus influencing the transcriptional activation or repression of genes essential for key biological processes. VDR interacts with histone modifiers, which can influence DNA methylation patterns.

Studies indicate that Vitamin D influences the function of DNA methyltransferases (DNMTs), the enzymes that add methyl groups to DNA. Vitamin D is linked to the downregulation of DNMT1, an enzyme essential for preserving DNA methylation patterns during cell division. Vitamin D may enhance gene expression by inhibiting DNMT1, which promotes a hypomethylated state in specific gene regions. This effect has been observed in various contexts, including cancer, where Vitamin D deficiency is associated with abnormal DNA methylation patterns that may silence tumor suppressor genes[11].

Studies indicate that Vitamin D affects global DNA methylation levels. Observational studies indicate an inverse relationship between Vitamin D status and DNA methylation in leukocytes, suggesting that increased Vitamin D levels are associated with reduced overall methylation[12,61]. This relationship holds particular importance in populations susceptible to Vitamin D deficiency, such as African-American adolescents, where notable variations in DNA methylation patterns have been observed in relation to Vitamin D status.

Vitamin D also plays a part in DNA methylation that relates to developmental processes. Pregnancy-related maternal vitamin D levels have been demonstrated to affect fetal epigenetic programming. For instance, gestational vitamin D supplementation has been linked to lowered DNA methylation of genes essential in fetal development, thereby stressing the need of enough vitamin D during pregnancy for correct epigenetic control[7,12]. On the other hand, mother Vitamin D insufficiency has been related to changed DNA methylation patterns in children, thereby perhaps predisposing them to metabolic problems, autoimmune diseases, and other health difficulties later in life[9,63]. Regarding cancer, the ability of vitamin D to change DNA methylation has attracted great interest. Studies show that by means of demethylation mechanisms, vitamin D can reawaken repressed genes. For colorectal cancer, for example, vitamin D intake has been linked to the methylation status of genes engaged in the Wnt signaling pathway, implying its possible therapeutic use for cancers marked by hypermethylation of tumor suppressor genes[39].

The impact of Vitamin D on DNA methylation extends beyond its direct interactions with DNMTs and VDR. It also contributes to the broader context of one-carbon metabolism, a critical pathway for DNA methylation processes. Vitamin D interacts with other nutrients, including folate and Vitamin B12, which are crucial for the synthesis of S-adenosylmethionine (SAM), the principal methyl donor for methylation reactions[61]. Adequate Vitamin D levels may enhance the availability of methyl donors, thereby supporting proper DNA methylation and overall genomic stability.

In addition to its effects on DNA methylation, Vitamin D is essential for the regulation of histone modifications, which in turn affects chromatin structure and gene accessibility. Calcitriol, the active form of Vitamin D, binds to the Vitamin D receptor (VDR), subsequently forming a heterodimer with retinoid X receptor (RXR) and translocating to the nucleus. The complex binds to VDREs, which initiates the recruitment of coactivators

and chromatin remodeling complexes that modify the chromatin landscape[61]. The conformational changes enable the release of corepressors and enhance interaction with histone acetyltransferases (HATs), thus promoting histone acetylation.

Histone acetylation serves as a significant post-translational modification that typically enhances gene expression by loosening the chromatin structure, thereby facilitating the access of transcription factors to DNA. Vitamin D enhances HAT activity, leading to increased acetylation of histones H3 and H4, which is crucial for regulating genes associated with immune responses and cellular differentiation[61].

Besides acetylation, Vitamin D also affects histone methylation. Histone methylation can activate or repress transcription, contingent upon the specific lysine residue that is modified. Trimethylation of histone H3 at lysine 4 (H3K4me3) correlates with active transcription, while trimethylation at lysine 27 (H3K27me3) is associated with transcriptional repression[64]. Studies indicate that Vitamin D can regulate the expression of histone methyltransferases and demethylases, consequently affecting the methylation status of histones and the expression of related genes[10]. The relationship between Vitamin D and histone modifications is significant in the realm of immune regulation. Research indicates that Vitamin D enhances T cell differentiation and promotes the expression of anti-inflammatory cytokines via its influence on histone modifications[15,61]. In $CD4^+$ T cells, Vitamin D induces specific histone modifications that enhance the expression of genes related to T cell differentiation and the function of regulatory T cells, contributing to immune homeostasis.

Moreover, in cancer the capacity of vitamin D to affect histone changes has important therapeutic consequences. Many times, aberrant histone modification patterns in cancer cause oncogenes to be active and tumor suppressor genes to be silenced. Studies have indicated that vitamin D can boost the effects of DNA methyltransferase inhibitors by encouraging histone demethylation and reactivating suppressed tumor suppressor genes in cancer cells thereby suggesting it as a possible auxiliary treatment agent[10,12].

the function of vitamin D in histone modification reaches developmental stages as well. While deficits have been connected to changed histone modification patterns in offspring, enough vitamin D levels during pregnancy have been linked to appropriate fetal development[64,65]. Studies point to mother's vitamin D supplements improving the epigenetic programming of the fetus, therefore influencing long-term health effects.

Role of Vitamin E in Epigenetics

Group of fat-soluble molecules mostly known for their antioxidant effects, vitamin E has attracted interest for its possible function in controlling DNA methylation, a crucial epigenetic alteration affecting gene expression. Because Vitamin E can control oxidative stress, one of the main ways it affects DNA methylation is through that. Linked in many disorders, including cancer, oxidative stress can cause DNA damage and changes in DNA methylation patterns. Strong antioxidant vitamin E scavenges reactive oxygen species (ROS) hence lowering oxidative damage to DNA. This lower oxidative stress helps to preserve normal DNA methylation patterns and stop aberrant gene expression linked with oxidative damage[4,16]. Studies have indicated, for example, that vitamin E supplements can raise global DNA methylation levels in cell lines, implying that their antioxidant effects could help to stabilize the epigenome[16,17].

Studies show that vitamin E might directly affect the expression and activity of DNA methyltransferases (DNMTs), the molecules that add methyl groups to DNA. Particularly vitamin E has been found to raise DNMT1 expression, which is essential to preserve DNA methylation patterns throughout cell division. This overexpression of DNMT1 can cause increased methylation of particular gene promoters, therefore affecting gene expression. For colorectal cancer cells, for instance, vitamin E has been linked to higher methylation of the MLH1 gene, a fundamental actor in DNA mismatch repair, which is usually suppressed in cancer[16,17]. This implies, depending on the context and cellular environment, Vitamin E could have a dual function in both preserving and enhancing DNA methylation.

Furthermore, the effect of vitamin E on DNA methylation spans its interactions with other epigenetic controllers. Vitamin E has been shown to affect the expression of genes linked in the control of chromatin structure and histone modifications, which are fundamental for the formation and preservation of DNA methylation patterns 4,16. For example, vitamin E might increase the activity of histone acetyltransferases, therefore producing a more open chromatin structure that helps DNMTs to bind to their target genes[4,16]. This interaction between Vitamin E and histone changes emphasizes the intricacy of epigenetic control and the possibility of Vitamin E to affect gene expression via several channels.

Vitamin E not only directly affects DNMTs and oxidative stress but also regulates microRNAs (miRNAs), which are small non-coding RNAs essential for post-transcriptional gene regulation. Specific miRNAs are recognized for their ability to target DNMTs and various epigenetic regulators, thus affecting DNA methylation patterns[4]Vitamin E has the potential to influence the expression of particular miRNAs, which can subsequently alter the methylation status of target genes, thereby enhancing its involvement in epigenetic regulation.

The effects of Vitamin E on DNA methylation have significant implications for chronic diseases and cancer. Aberrant DNA methylation patterns characterize numerous cancers, and Vitamin E's capacity to affect these patterns may offer insights into its potential therapeutic applications[4,16]. For example, studies indicate that Vitamin E supplementation can reverse hypermethylation of tumor suppressor genes in various cancer models, suggesting potential enhancement of existing cancer therapies[4,16]. The antioxidant properties of Vitamin E may mitigate oxidative stress linked to cancer progression, thereby supporting its role in cancer prevention and treatment.

The association between Vitamin E and DNA methylation extends beyond cancer to encompass various health conditions, such as metabolic disorders and neurodegenerative diseases. Research indicates that Vitamin E may influence DNA methylation patterns related to obesity and insulin resistance, suggesting a potential role in metabolic health. In neurodegenerative diseases, Vitamin E influences DNA methylation in genes associated with neuronal function and survival in neurodegenerative diseases, underscoring its significance for brain health[4].

Role of Vitamin K in Epigenetics

Particularly in its forms K1 (phylloquinone) and K2 (menaquinone), vitamin K has attracted interest for its function in epigenetic control, more especially in histone modification. Vitamin K's main mechanism for affecting histone modification is its cofactor function for particular enzymes engaged in post-translational changes of histones. γ-glutamyl carboxylase, which catalyzes the carboxylation of certain proteins, including those implicated in the control of histone modifications, depends on vitamin K for function. This carboxylation can influence histone binding to other proteins and change their modification state, therefore influencing gene expression[18].

Studies indicate that Vitamin K can influence the activity of histone methyltransferases (HMTs), which are tasked with the addition of methyl groups to lysine residues on histones. Vitamin K is involved in regulating the enzyme EZH2, a part of the Polycomb Repressive Complex 2 (PRC2), which catalyzes the trimethylation of histone H3 at lysine 27 (H3K27me3). This modification is commonly linked to transcriptional repression and is essential for preserving cellular identity and regulating gene expression throughout development. The effect of Vitamin K on EZH2 activity indicates its potential role in regulating gene silencing via histone methylation[66].

Furthermore proven to affect histone acetylation, another important alteration usually supporting gene expression, is vitamin K. Histone acetylasers (HATs) and histone deacetylases (HDACs) control histone acetylation. Studies show that vitamin K can boost the expression and activity of several HATs, hence promoting transcription and acetylation of histones[67,68]. Vitamin K's modulation of histone acetylation could help to control genes linked to several biological processes like inflammation and cellular differentiation.

In the framework of cancer, the interaction between Vitamin K with histone changes is especially important. Many different malignancies have aberrant histone modification patterns that cause oncogenes to be activated and tumor suppressor genes to be silenced. By means of its effects on histone alterations, vitamin K has been suggested as a possible therapeutic drug since it can undo epigenetic silencing of target genes. For instance, Vitamin K2 has been demonstrated to lower histone methylation in cancer cells and stimulate histone acetylation, therefore improving the effectiveness of current cancer treatments[2]. This indicates that Vitamin K could function as an adjunct therapy in cancer treatment, especially for tumors with atypical histone modification patterns.

Furthermore, the role of Vitamin K in histone modification also encompasses metabolic regulation and developmental processes. Research indicates that Vitamin K can affect the expression of genes related to lipid metabolism and adipogenesis via its impact on histone modifications[69]. For instance, vitamin K is linked to enhanced histone acetylation at the promoters of genes related to fat metabolism, indicating its potential role in the regulation of metabolic pathways[67].

Vitamin K not only directly influences histone modifications but may also interact with other nutrients and factors that play a role in epigenetic regulation. The interaction of Vitamin K with other dietary elements, including Vitamin D and antioxidants, may improve the epigenetic landscape by fostering a more conducive environment for histone modifications[70]. The synergistic effect highlights the significance of a balanced diet abundant in vitamins for the maintenance of proper epigenetic regulation. This is also consistent with the approach of several researchers who utilized multivitamins in the management of COVID-19 during the pandemic period[71-73].

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CONCLUSION

The data in this study emphasizes the complex function of vitamins in epigenetic control since every vitamin contributes different but linked mechanism influencing both DNA methylation and histone changes. By means of its active metabolite retinoic acid, vitamin A exerts a broad influence by engaging receptor-mediated pathways that coordinate coactivators, chromatin remodeling complexes, and enzymatic activities, so regulating gene expression, cellular differentiation, and tissue development with great consequences for embryogenesis, metabolic control, cancer therapy, and immune function. By acting as a cofactor for TET enzymes and Jumonji domain-containing histone demethylases, as well as by increasing histone acetylation via HAT activity, vitamin C further reinforces epigenetic integrity and ensures the maintenance of suitable gene expression patterns necessary for development, immune control, and cancer therapy. While its involvement in one-carbon metabolism highlights its more general relevance in preserving genomic stability, Vitamin D helps to epigenetically regulate by interacting with its receptor to modulate DNA methyltransferases and recruit chromatin remodeling complexes, so impacting both DNA methylation and histone modifications vital for immune control, development, and cancer treatment. With its strong antioxidant effects, vitamin E interacts with histone modifiers, controls DNA methylation by altering DNMT expression, and influences miRNA expression, so offering great potential for therapeutic intervention in cancer and metabolic diseases. With important consequences for cancer therapy, metabolic control, and developmental processes, vitamin K finally helps to control histone modifications by serving as a cofactor for histone-modifying enzymes and affecting gene expression. These results taken together show the possibility of these vitamins as therapeutic agents in epigenetic control and emphasize the need of ongoing study to completely maximize their advantages in disease prevention and therapy

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