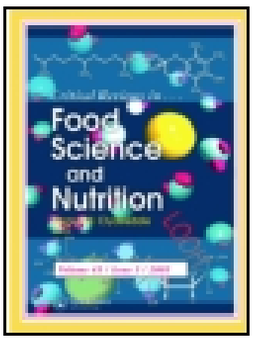

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REVIEW

Nutritive vitamins as epidrugs

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ABSTRACT

Epigenetic modifications play an important role in disease pathogenesis and therefore are a focus of intense investigation. Epigenetic changes include DNA, RNA, and histone modifications along with expression of non-coding RNAs. Various factors such as environment, diet, and lifestyle can influence the epigenome. Dietary nutrients like vitamins can regulate both physiological and pathological processes through their direct impact on epigenome. Vitamin A acts as a major regulator of above-mentioned epigenetic mechanisms. B group vitamins including biotin, niacin, and pantothenic acid also participate in modulation of various epigenome. Further, vitamin C has shown to modulate both DNA methylation and histone modifications while few reports have also supported its role in miRNA-mediated pathways. Similarly, vitamin D also influences various epigenetic modifications of both DNA and histone by controlling the regulatory mechanisms. Despite the information that vitamins can modulate the epigenome, the detailed mechanisms of vitamin-mediated epigenetic regulations have not been explored fully and hence further detailed studies are required to decipher their role at epigenome level in both normal and disease pathogenesis. The current review summarizes the available literature on the role of vitamins as epigenetic modifier and highlights the key evidences for developing vitamins as potential epidrugs.

KEYWORDS

Epigenome; histone modifications; methylation; miRNAs; vitamins

Introduction

Epigenetics is the study of reversible heritable changes in gene expression without altering the DNA sequence and includes DNA methylation, histone modifications, and chromatin remodeling (Feinberg 2007). DNA methylation is one of the major group of epigenetic modifications in which a methyl group (one carbon) is covalently added to the C5 position of cytosine base (Bird 2002). The degree of DNA methylation defines gene expression. Excess DNA methylation known as hypermethylation is with gene inactivation through silencing of the promoter of tumor suppressor genes. Under-methylated DNA known as hypomethylation is linked to the induction of proto-oncogenes (Herceg 2007). The second group of epigenetic changes includes histone modifications which either activate or repress gene expression based on posttranslational modifications in the histone tail at lysine, arginine, and serine residues (Kouzarides 2007). The various posttranslational modifications include methylation, citrullination, acetylation, phosphorylation, SUMOylation, and ADP-ribosylation at the histone tail regions that alter gene expression pattern (Ducasse and Brown 2006). These modifications further regulate the accessibility of DNA to transcription factors by modifying the compactness of the chromatin structure (Luger 2003). Methylation and demethylation of histone proteins are catalyzed by histone methyltransferases (HMTs) and histone demethylases (HDMs) respectively. Similarly, acetylation and deacetylation of histone proteins are catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs) respectively (Shi 2007; Haberland, Montgomery, and Olson 2009). RNA regulatory epigenetic mechanisms include small non-coding RNAs that control various biological processes. These non-coding RNA are 22 nt long microRNAs and degrade target messenger RNA by complementary base pairing toward the 3′ end (He and Hannon 2004).

Several external, as well as internal factors regulate the epigenetic machinery directly or indirectly (Choi and Friso 2010). Among all factors that regulate epigenetic modifications there is a special focus on diet these days (Khan et al. 2018). A growing body of evidence suggests vitamins as major epigenetic modifiers attracting the attention of consumers, nutritionists and scientists. Apart from cancer, vitamins also play major role immunopatho-physiological conditions of the body. Several vitamins including vitamin A, vitamin C, vitamin D affect the one-carbon metabolism in the body and hence regulate the epigenetic machinery (Carlos-Reyes et al. 2019; Montgomery and Srinivasan 2019;

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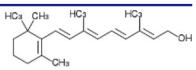
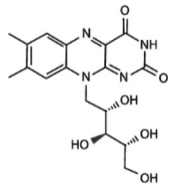
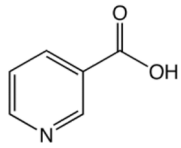
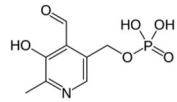
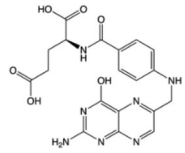
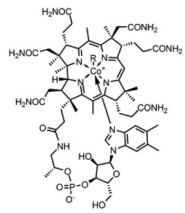
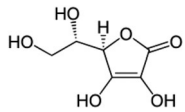
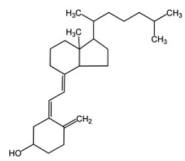
Table 1. Sources and molecular formula of different vitamins.

Types of vitamins	Sources	IUPAC name	Formula	Structure
Vitamin A (Retinol)	Liver Fish oil	(2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraen-1-ol	$C_{20}H_{30}O$	
Vitamin B2 (Riboflavin)	Egg Green vegetables Milk and Meat	7,8-dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl] benzo[g]pteridine-2,4-dione	$C_{17}H_{20}N_4O_6$	
Vitamin B3 (Niacin)	Yeast, meat, fish, milk, eggs and cereal grains	2,4,5,6-tetradeuteriopyridine-3-carboxylic acid	$C_6H_5NO_2$	
Vitamin B6 (Pyridoxine)	Meat, fish, legumes, nuts, bananas, potato	4,5-bis(hydroxymethyl)-2-methylpyridin-3-ol	$C_8H_{11}NO_3$	
Vitamin B9 (Folic acid)	Leafy vegetables, legumes Citrus fruits	(2S)-2-[[4-[(2-amino-4-oxo-1H-pteridin-6-yl)methylamino]benzoyl] amino]pentanedioic acid	$C_{19}H_{19}N_7O_6$	
Vitamin B12 (Cyanocobalamin)	Animal Products	cobalt(3+);[(2R,3S,4R)-5-(5,6-dimethylbenzimidazol-1-yl)-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl] [(2R)-1-[3-[(1R,2R,3R,5Z,7S,10Z,12S,13S,15Z,17S,18S,19R)-2,13,18-tris(2-amino-2-oxoethyl)-7,12,17-tris(3-amino-3-oxopropyl)-3,5,8,8,13,15,18,19-octamethyl-2,7,12,17-tetrahydro-1H-corrin-24-id-3-yl]propanoylamino]propan-2-yl] phosphate;cyanide	$C_{63}H_{88}CoN_{14}O_{14}P$	
Vitamin C (Ascorbic acid)	Fruits and Vegetables	(2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one	$C_6H_8O_6$	
Vitamin D (Cholecalciferol)	Sunlight Fish Fish liver oil	(1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol	$C_{27}H_{44}O$	

Friso et al. 2020).Water-soluble B vitamins like biotin, niacin, and pantothenic acid also play important roles in epigenetic modifications (Park, Friso, and Choi 2012; Friso et al. 2017). In this review, the most recent findings on vitamins-mediated (Table 1) epigenetic regulations that play a major role in disease pathogenesis are summarized and discussed.

Vitamin A

Vitamin A is categorized as an essential micronutrient required for growth and development of an organism. It is not synthesized in mammals but is available through animal as well as plant based β carotenes (Doldo et al. 2015). Vitamin A and its derivatives play a critical role in various biological processes that include cellular reproduction, differentiation as well as embryogenesis (Dadon and Reifen 2017). Retinoic acid (RA), a natural derivative of vitamin A participates in cellular signaling events by inducing cell differentiation in stem cells and some cancer cells. Nuclear receptor for retinoic acid, retinoic acid receptor alpha (RAR α), forms a heterodimer with retinoid X receptor (RXRs) which further binds to RA response elements (RAREs) on promoters of RA-target genes. These genes are further involved in epigenetic regulation in the cells (Fazi et al. 2005). Several studies provide evidence of RA-mediated cancer treatment alone or in combination with various drugs by modifying the epigenetic landscape of the body (Urvalek, Laursen, and Gudas 2014). Another study (Ferrari, Pfeffer, and Vidali 1988) demonstrated in vivo binding of retinol to the nucleosome complex, which further modifies the chromatin structure and regulates its function. Deregulation of

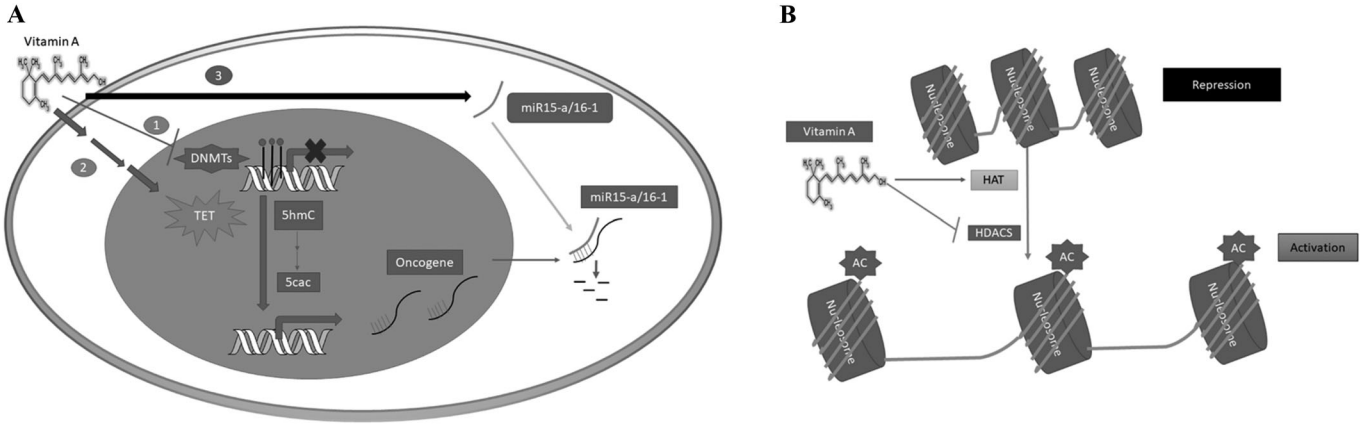


Figure 1. (A) Schematic representation of Vitamin A mediated mechanism of epigenetic modifications in cell. 1: DNMTs has methylation activity on gene is to be transcribed, hence transcription halts. Retinoic Acid (Vit A) blocks the DNMTs, leads to transcriptional inhibition or DNA hypomethylation. 2. Vit A also alters the TET activity through conversion of 5hmC to 5mc so that gene transcription proceed. 3. RA can also actas an inducer for some miRNA by modulating epigenome. (B) Vitamin A blocks HDACs and simultaneously activate histone acetyltransferases (HAT) leading to acetylation of chromatin structure further leading toward activation of gene expression.

retinoid signaling is linked with carcinogenesis (Dragnev, Rigas, and Dmitrovsky 2000). Beneficial effects are found in various types of cancers including breast, ovarian, renal, head and neck, melanoma, leukemia, and prostate with the treatment of retinoic acid (Tang and Gudas 2011). Vitamin A helps to regulate the immunity of the body as demonstrated by researchers who showed the immunomodulatory effect of vitamin A through epigenetic changes of innate immune cells (Arts et al. 2015). The detailed mechanisms of Vitamin A-mediated epigenetic changes are discussed in the following sections.

Vitamin A and DNA methylation

Vitamin A-mediated DNA demethylation is closely associated with various patho-physiological conditions (Figure 1A). RARs and specifically RARα involved in specific promoter hypomethylation and reduced expression of RARα may trigger leukemogenesis development (Urvalek, Laursen, and Gudas 2014). Involvement of Vitamin A in the embryonic reprograming of stem cells is well studied and is mediated through the ten-eleven translocation (TET) demethylases, which erase DNA methylation marks. TET enzymes oxidize 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) and 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) and hence play a major role in regenerative medicine (Hore 2017).The pluripotency of human embryonic stem cells (hESCs) are maintained by regulating DNA methylation status around CpG island which is also controlled by vitamin A abundance (Cheong et al. 2010). RA induced DNA methylation and differentiation pattern during embryogenesis is well studied. Further, studies demonstrated enrichment of 5-hydroxymethylcytosine (5hmC) around the promoter of homeotic (*Hoxa*) gene cluster after RA treatment of NT2 human embryonal carcinoma stem cells (Bocker et al. 2012). This 5mC-5hmC conversion is catalyzed by TET2 enzyme upon RA treatment, which helps to maintain the open chromatin state. Hence, RA treatment plays a key role in maintaining the development pattern of body plan in mammalian embryo.

Vitamin A and histone modification

Histone modification pattern is also affected by the availability of RA (Figure 1B). For example, heat map of Hox (homeobox) gene cluster that plays an important role during embryonic development, shows increase in H3K4me3 and H3ac activation mark and decrease in repressive mark H3K27me3 in response to RA treatment. It also increases H3K9 and H3K14 acetylation, which further leads to transcriptional activation (Urvalek, Laursen, and Gudas 2014). Another example of epigenetic change that occurs in response to RA and their relationship to cell differentiation is discussed by Gudas (2013). PHF8 (also called ZNF422, JHDM1F), a histone lysine demethylase that preferentially acts on histones in the monomethyl or dimethyl states, is involved in the response of stem cells to RA. Loss of mono-methylation mark and a genetic reduction in expression of lysine methyltransferase SETD6 is achieved after RA treatment. SETD6 is involved in maintenance of renewal of mouse embryonic stem cells (Binda et al. 2013).Vitamin A deficiency is known to cause memory loss. Hou et al. (2015) demonstrated that vitamin A deficiency mediated decrease in RARα signaling, followed by significant decrease in HAT activity as well as H3 and H4 histone acetylation. This further downregulates expression pattern of some memory related genes due to lack of H3ac and H4ac enrichment in the promoter region of these genes.

Vitamin A and miRNA regulation

Vitamin A regulates the expression of various miRNAs during embryonic development, in normal as well as neoplastic cells (Nervi and Grignani 2014). RA regulated miRNAs play a significant role during cancer progression (Figure 1A). For example, RA acts as an anticancer agent by upregulating tumor suppressor miR-10 function in breast cancer cells (Khan et al. 2015). Anti-proliferative nature of RA is further studied in acute myeloid leukemia (AML) cells. All-trans retinoic acid (ATRA) upregulates miR-663 expression, which further induces differentiation and inhibits proliferation of HL-60cells (Jian et al. 2011). A very recent work

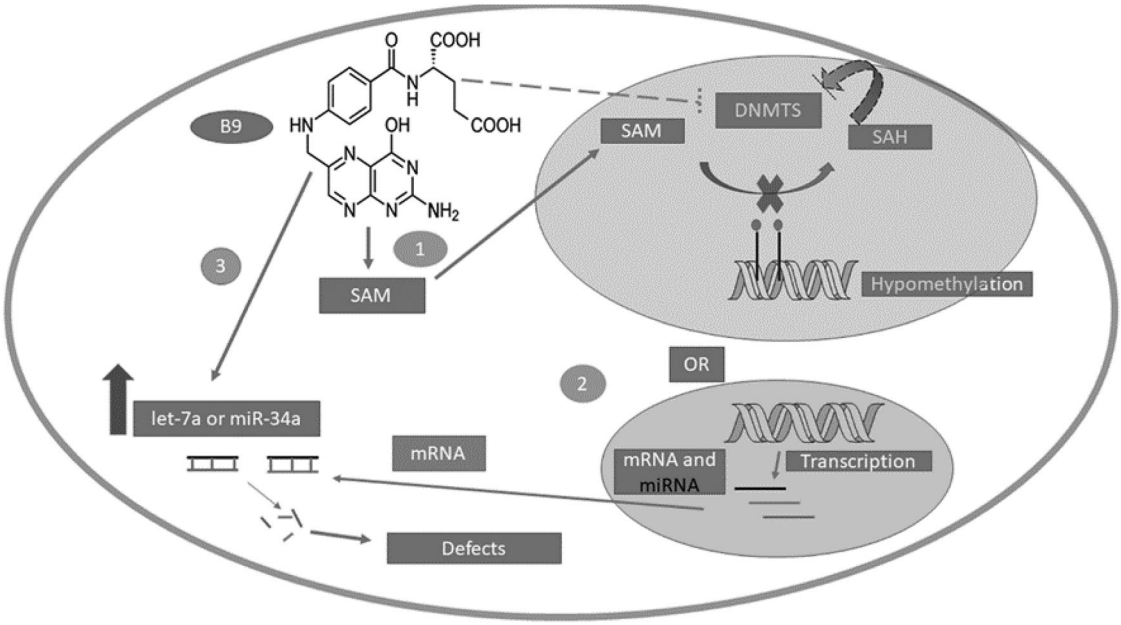


Figure 2. Vitamin B9 or folate (water-soluble form of vitamin B9), after dietary intake through series of enzymatic reactions is subsequently converted into SAM which is important for DNMTs activity. In a static cellular condition, folate induces mRNA and miRNA transcripts that are necessary for normal embryonic development. However, in folate deficiency some miRNA are upregulated that silenced the normal developmental genes.

Table 2. Target of different vitamins related to epigenetic modifications.

Type of vitamin	Epigenetic modifications	Disease involved	References
Vitamin A	DNA methyl transferase↓ Histone deacetylase↓ miR-15a/16-1↑	1. Acute promyelocytic leukemia 2. Leukemia	16, 105
Vitamin B2	miR-203 up regulation and inhibited c-Jun expression↑	Provides neuroprotection	106
Vitamin B6	Hypermethylation	Skeletal Muscle Myopathy	107
Vitamin B7	K12H4 biotinylation↓	Choriocarcinoma cells	108
1. Vitamin B9 high dose treatment 2. Vitamin B9 treatment	1. Sperm DNA hypomethylation↑ 2. miR-222 and -22↑	1. Male idiopathic infertility 2. human lymphoblast cells	109, 52
1. Vit B12 deficient 2. Vit B12 supplementati on	1. BRCA1 promoter hypermethylation ↑ 2. miR21 promoter methylation ↑	1. Breast cancer 2. Type II diabetes	110, 59
1. Vitamin C treatment 2. Vitamin C treatment	1. H3K9m3, H3K27m3 downregulation and removes repressive marks 2. Tet 2 DNA hypomethylation	1. Parkinson's Disease 2. Leukemia	111, 112
1. Vitamin D intake 2. Vit D intake	1. Antagonists dickkopf 1 (DKK1) and WNT5A methylation↓ 2. miR-126-3p, miR 154-5p and miR-21-5p↑	1. Colorectal Cancer 2. Prostate cancer	113, 103

correlates embryogenesis and RA function by regulating miRNA expression. Wu et al. (2017) demonstrated upregulation of miR-219, which further targets Foxj3 and Zbtb18 genes involved in neural tube differentiation after RA treatment in embryonic stem cells (ESCs). Work done by Zhang et al. (2015) showed RA-mediated modulation of miR-200b and miR-200c expression involved in the maintenance of pluripotency in embryonic stem cells. RA-induced microRNA-31-5p targets Wnt5a/calcium/calmodulin-dependent protein kinase II delta (CamkIIδ), which further suppresses myogenic proliferation and differentiation (Liu et al. 2017). Few more example of vitamin A-mediated miRNA regulations are summarized in (Table 2).

Vitamin B

B-group vitamins are water-soluble vitamins and include Thiamin (vitamin B1), Riboflavin (B2), Niacin (B3), Pantothenic acid (vitamin B5), Pyridoxine (B6), Biotin (B7), Folic acid (B9), Cyanocobalamin (B12). Out of these vitamins B2, B6, B9, and B12 are active members of one-carbon metabolism pathway that induces biological methylation reactions of proteins, phospholipids, and nucleic acids including methylation of DNA (Gruber 2016). This section of the review underscores the epigenetic role of B group of vitamins.

Riboflavin (vitamin B2)

Riboflavin is member of one-carbon metabolism and component of FAD (flavin adenine dinucleotide). FAD is a cofactor for methylenetetrahydrofolate (MTHF) reductase which catalyzes the conversion of 5,10-MTHF to 5-MTHF, a substrate for homocysteine remethylation to methionine (Stefanska et al. 2012). Vitamin B2 is abundantly present in various dietary sources including eggs, meat, milk and cheese (Sharma and Litonjua 2014). Role of this group of vitamin in the epigenetic regulatory mechanism is not widely studied. Available few reports support its role in DNA methylation. Genomic DNA stability through DNA methylation and the involvement of riboflavin is reported in the literature (Figure 2).

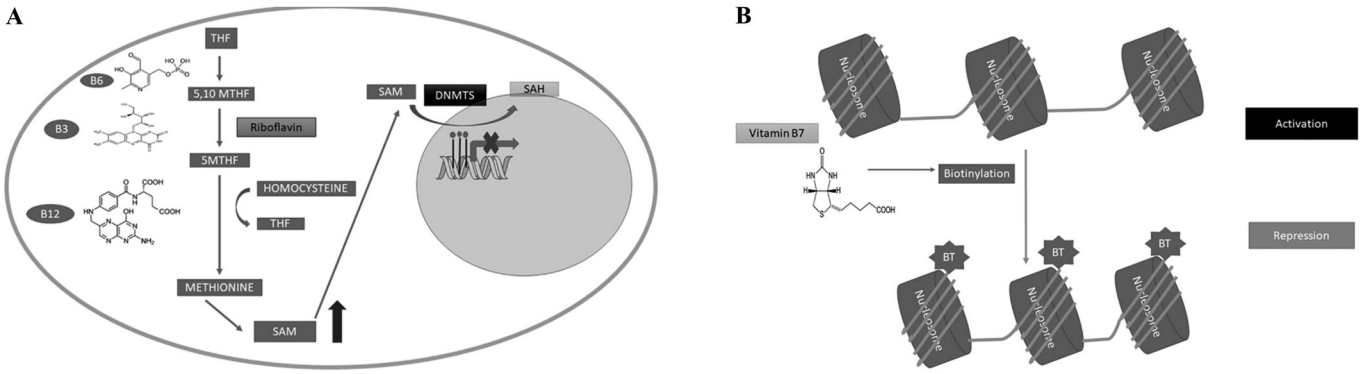


Figure 3. (A) Vitamin B3 (riboflavin), B6, B3, and B12 are involved in one carbon metabolism pathway where they acts as co-factor for enzymatic reaction pathways. THF acts as a precursor, which converts into 5MTHF, later metabolized into methionine to SAM with help homocysteine. This SAM further act as effector for DNMTs to converts SAH through methylation of DNA. (B) Biotin (Vitamin B7) leads to biotinylation of histones cause of transcriptionally repressed heterochromatin formation.

Insufficient riboflavin supply in food is found to be associated with increase in the risk of carcinogenesis (Pangrekar, Krishnaswamy, and Jagadeesan 1993).

Niacin (vitamin B3)

Niacin is available in various forms like nicotinic acid, nicotinamide, and tryptophan and is required for formation of Nicotinamide-adenine dinucleotide (NAD) and Nicotinamide-adenine dinucleotide phosphate (NADP). Niacin deficiency interferes with various biochemical processes. For example, niacin deficiency leads to delayed DNA excision repair, deregulated p53 expression, impairment of cell cycle arrest as well as apoptosis in rat bone marrow cells (Kostecki et al. 2007; Spronck, Nickerson, and Kirkland 2007). The relationship between niacin deficient diet and cancer incidence remains poorly understood. A few studies suggest higher cancer rates in niacin deficient condition in human subjects. Niacin plays a crucial role in maintaining chromatin structure in an NADP dependent manner (Kirkland 2009). Niacin also regulates the expression level of various miRNAs in certain pharmacological concentrations. Couturier et al. (2014) demonstrated differential expression of 42 out of a total number of 259 miRNAs between the niacin treated group and the control group. Among the 42 differentially expressed miRNAs, a total number of 22 miRNAs were found to be down regulated and 20 were found to be up regulated in the niacin treated group when compared to the control group. These results were further validated by using quantitative RT-PCR and showed a significant up regulation of four miRNAs (miR-29b-3p, miR-145-5p, miR-24-2-5p, miR-665), along with significant down regulation of three miRNAs (miR-21-3p, miR-466b-2-3p, miR-466d) and non-regulation of one miRNA (miR-34a-5p) in skeletal muscle of obese zucker rats.

Pyridoxine (vitamin B6)

Vitamin B6 or pyridoxine is abundantly present in fish, beef liver, fruits, vegetables, and grains (Sharma and Litonjua 2014). Pyridoxine is actively involved in *trans*-sulfuration reaction (homocysteine to glutathione conversion) as well as acts as a cofactor for serine hydroxymethyl transferase in the synthesis of 5,10-MTHF from THF (Maruti et al. 2009; Selhub 2002). It plays a significant role in the synthesis of neurotransmitters like dopamine, serotonin, gamma-aminobutyric acid (GABA), noradrenaline and the hormone melatonin in which it acts as a rate-limiting cofactor in amino acid synthesis (Kennedy 2016). Pyridoxine depletion is associated with epigenetic modifications. The insufficiency of pyridoxine supply is found to be linked with an increase in the S-adenosyl-L-homocysteine (SAH) level, which further leads to DNA hypomethylation through inhibition of methyltransferases (Figure 2; Maruti et al. 2009). The mechanism for vitamin B mediated epigenetic modifications are presented in Figure 3.

Biotin (vitamin B7)

Biotin is involved in various signaling pathways and has a significant role in cancer development (Zempleni 2005). Chromatin structures are affected by biotinylation of histone proteins, which further controls gene expression. For example, Histone H4, lysine 8 (K8)-, and lysine 12 (K12)-biotinylation induces gene silencing by the formation of heterochromatin structures. A greater degree of histone biotinylation is evident in proliferating cells as compared to quiescent cells (Figure 3B). Biotinidases are the enzymes that catalyze both histone biotinylation and debiotinylation (Hassan and Zempleni 2006). Cellular response to DNA damage is linked with biotinylation status of histone molecules. For example, decreased biotinylation of H4K12 is evident when double-stranded DNA breaks are introduced in etoposide-treated lymphoid and choriocarcinoma. This is consistent with a role for histone biotinylation in signaling DNA damage. But the detailed correlation between biotinylated histones and apoptosis mechanism are not yet fully understood (Kothapalli et al. 2005). So, biotin deficiency enhances decreased biotinylation of histones that might be associated with various diseases (Zempleni et al. 2008).

Folic acid (vitamin B9)

Folate is a water-soluble form of vitamin B9, which is involved in DNA synthesis, repair, and methylation. After

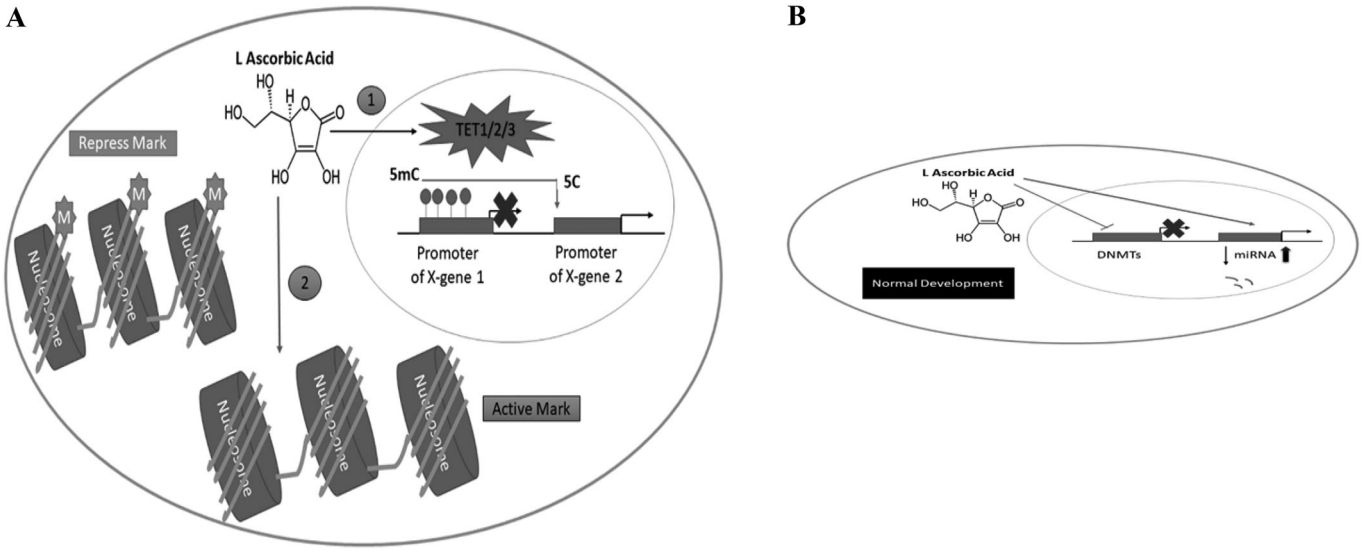


Figure 4. (A) L-Ascorbic (vitamin C) acid mediated modification of epigenome. 1. CpG islands of promoter X-gene is hypermethylated (5mC) hence transcriptionally repressed. Vitamin C induce TET1/2/3, which demethylates 5mC to unmethylated cytosine (5C) leads to transcriptionally active gene promoter. 2. Vitamin C also demthylates methylated histone in TET independent way to unmethylated histone in nucleosome structure. (B) Vitamin C mediated miRNA upregulation, which further maintain the pluripotent state of mouse embryonic stem cells.

dietary intake, folate is converted to dihydrofolate and subsequently to tetrahydrofolate by dihydrofolate reductase, which is involved in the re-methylation of homocysteine to methionine (Selhub 2002). Methionine acts as a precursor of S-adenocyl methionine (SAM), which is the primary methyl group donor for most methylation reactions. After transferring a methyl group, SAM is converted to SAH, an inhibitor of methylation reactions (Figure 4; Waterland 2006). Insufficient folate supply is linked to cancer development and malignant transformation by altering the methylation status and expression pattern of tumor suppressor genes as well as oncogenes. Components of DNA methylation machinery are regulated by the availability of dietary folate and hence affect the carcinogenic process. For example, in hepatocarcinoma, development folate deficiency increases mRNA and protein level of various components of DNA methylation machinery including DNMT1, DNMT3B, MBD2, and MBD4 (Stefanska et al. 2012). Development of childhood cancer is also linked to dietary intake of folate, which regulates DNA methylation status of proto-oncogenes (Yiu and Li 2015). Folate-rich diet also affects DNA methylation in an age-dependent manner. For example, genomic as well as p16 promoter DNA methylation is enhanced by the availability of dietary folate in the aged mouse colon as compared to the young ones (Park, Friso, and Choi 2012). Folate deficiency is also linked to neural tube defects (NTDs) worldwide. Maternal folic acid supplementation causes a significant increase in methylation at the DMR of Insulin-like growth factor 2 (IGF2) gene in infants which is regulated by imprinting (Friso et al. 2017). Folate status may influence miRNA profiles via alteration of DNA methylation of genes coding for miRNA, or via modulation of expression of genes upstream of miRNA signaling pathways (Beckett, Veysey, and Lucock 2017). Folate deficiency during embryonic development leads to various birth defects. In a rat model of maternal folate deficiency, upregulation of let-7a and miR-34a, and subsequent downregulation of their regulatory targets, such as TRIM71 and notch, which are involved in embryogenesis and neurogenesis, occurs in the brain (Geoffroy et al. 2017). Folate deficiency is also linked with miRNA-mediated deregulation in cancer. miR-222 is upregulated in cultures with low folate concentration which is an oncogenic miR (Stefanska et al. 2012). Fola-miRs are the new group of miRNAs, which are conjugated with folate for their targeted delivery into the cancer cells expressing folate receptor. Therefore, these miRNAs have a significant contribution to target cancer cells, scientists demonstrated suppression of tumor growth in human lungs and breast cancer cells after treatment with folate-conjugated miR-34a (Orellana et al. 2017).

Cyanocobalamin (vitamin B12)

Cyanocobalamin, a water-soluble B vitamin, is a common methyl group donor and essential cofactor of methionine synthase. In one-carbon metabolism, cyanocobalamin catalyzes the conversion of homocysteine to methionine which is further converted to SAM and therefore plays a crucial role in RNA and DNA methylation (Figure 3A; Uekawa et al. 2009).Vitamin B12 is required for red blood cell formation, DNA synthesis, and proper neurologic function (Gille and Schmid 2015). Vitamin B12 deficiency is linked with DNA methylation status, as it is one of the major components of one-carbon metabolism. There is correlation between vitamin B12 concentrations and genomic DNA methylation status in tissue samples of squamous cell lung cancer and adjacent normal bronchial mucosa (Piyathilake et al. 2000). Their results showed decreased vitamin B12 concentration is followed by genomic DNA hypomethylation in the cancer tissue as compared to the normal control. Another study provided evidence of low vitamin B12 intake and DNA hypomethylation in neurological pathology. Furthermore, correlation is also found between neural tube defects in the trans-cobalamin receptor (TCblR)/CD320

knock out (KO) mouse models and DNA hypomethylation (Fernandez-Roig et al. 2012).Vitamin B12-mediated miRNA regulation is also described in the literature. For example, vitamin B12-mediated methylation of miR21 affects type-2 diabetes associated genes (Yadav et al. 2018). Combinatorial supplementation of vitamin B12 along with folic acid affects genome-wide DNA methylation status of leukocytes which further affects normal developmental process as well as carcinogenesis (Kok et al. 2015). Some of the vitamin B12 deficiency related diseases are summarized in Table 2.

L-ascorbate (vitamin C)

Vitamin C or L-ascorbate is a water-soluble antioxidant that acts as a cofactor of collagen prolyl hydroxylases which induces recycling of Fe(III) to Fe(II) (Ebata et al. 2017; Yu et al. 2018). All mammals can participate in *de novo* synthesis of ascorbate in liver except primates and guinea pigs because of a mutation in gluono-lactone oxidase (GULO) enzyme. GULO is an important catalyzing enzyme, which helps in the conversion of L-gulono-G-lactone into ascorbic acid. Diet is the sole source of vitamin C (Young, Zuchner, and Wang 2015; Drouin, Godin, and Page 2011).Deficiency of vitamin C in the diet induces scurvy due to loss of proline hydroxylase and incomplete collagen cross-linking (Camarena and Wang 2016). Various reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, singlet oxygen, and hypo-chlorous acid are generated during normal metabolic respiration/mitochondrial oxidative phosphorylation (aerobic ATP generation). Vitamin C acts as an electron donor and reduces these reactive oxygen species and hence protects against mutations and maintains protein integrity (Padayatty and Levine 2016).

Role of vitamin C in epigenetic regulation has recently been investigated and mainly affects DNA methylation and histone modifications. Vitamin C acts as a cofactor for TET dioxygenases that catalyze the oxidation of 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) which is the main step in the DNA methylation process. Demethylation of 5mCs to 5hmC followed by 5fC and 5caC and finally to un-methylated cytosine is catalyzed by TET enzymes (Camarena and Wang 2016; Sajadian et al. 2016). TET1, TET2, and TET3 are the major groups of TET enzymes for which ascorbic acid acts as a cofactor and binds to the catalytic domain of the TET enzyme to facilitate TET-mediated DNA demethylation (Ito et al. 2010). TET1 is located at chromosome 10q22 while TET2 and TET3 are at 4q24 and 2p12 respectively of the human genome. Any mutation in the members of the TET gene family leads to various disease conditions (Lorsbach et al. 2003; Delhommeau et al. 2009).

Vitamin C and methylation

Vitamin C is one of the major regulators of methylation–demethylation cycle. The first demethylation step was identified by Tahiliani et al. (2009) when they demonstrated the involvement of TET1 in the oxidation of 5mc to 5hmc. Later studies further showed TET2 and TET3 mediated oxidation of 5mc to 5hmc (Figure 4; Ito et al. 2010). As previously mentioned vitamin C regulates TET activity, which is the key step during DNA methylation and the concentration of TET enzyme dictates DNA methylation status. In addition, vitamin C modulate the activity of Jumonji-C domain-containing histone demethylases (JHDMs) (Lee Chong, Ahearn, and Cimmino 2019). DNA hypermethylation is induced by a lower concentration of TET enzyme. For example, in diffuse large B-cell lymphoma (DLBCL), TET-2 mutation is observed in 13% of the cases which induces a high degree of methylation disruption and intra-tumor methylation heterogeneity and is associated with poor patient outcome (Cerami et al. 2012). Ascorbic acid treatment-mediated demethylation as well as re-expression of tumor suppressor gene SMAD1 in DLBCL patients manifest enhanced chemosensitivity (Shenoy et al. 2017). Further, a recent study also showed that normalization of plasma vitamin C by oral supplementation leads to an increase in the 5hmC/5mC ratio compared to placebo-treated patients and might enhance the biological effects of DNA methyltransferase inhibitors (Gillberg et al. 2019). Another study showed protective role of vitamin C against UV-mediated apoptosis by demethylating and reactivating silenced tumor suppressor genes p21 and p16 in a TET-dependent DNA demethylation manner in human skin cancer cells (Lin et al. 2014).Vitamin C acts as a major factor in stem cell differentiation and function(Cimmino, Neel, and Aifantis 2018). Vitamin C induces TET mediated DNA demethylation in embryonic stem cells which further induces pluripotency (Hore 2017). Germline genes expression in embryonic stem cells (ESCs) is reported by enhancing vitamin C-mediated TET activity by demethylating at CpG Island (CGIs) sites (Blaschke et al. 2013). Epigenetic reprograming of embryonic stem cells is maintained by TET enzymes in a Vitamin C-mediated manner and insufficient vitamin C leads to severe birth defects (Camarena and Wang 2016). Mesenchymal to epithelial transition (MET) is also regulated by vitamin C availability, which controls TET1 enzyme activity. TET1 mediated somatic cell reprograming is independent of MET in absence of vitamin C. Further, the formation of 5-hydroxymethylcytosine (5hmC) at loci critical for MET is regulated by TET1 in a vitamin C-dependent fashion (Chen et al. 2013).

Vitamin C and histone modifications

Vitamin C regulates histone demethylation through Fe(II)- and 2-oxoglutarate-dependent dioxygenases (Horton et al. 2010). Chromatin structures are maintained by jumonji-C domain-containing histone demethylases JHDM1A and JHDM1B, which are iron-dependent oxidoreductases (Hore 2017; Pera 2013). Maturation of T cells which is a major step in human immunity is regulated by Jumonji C (JmjC) domain enzymes for which vitamin C acts as a cofactor (Manning et al. 2013). Vitamin C–mediated histone modifications and the induction of pluripotency have been reported in the literature. Chromatin modifications has been also reported during reprograming in the presence or absence of vitamin C (Wang et al. 2011). Their study showed a significant reduction in histone H3 Lys 36

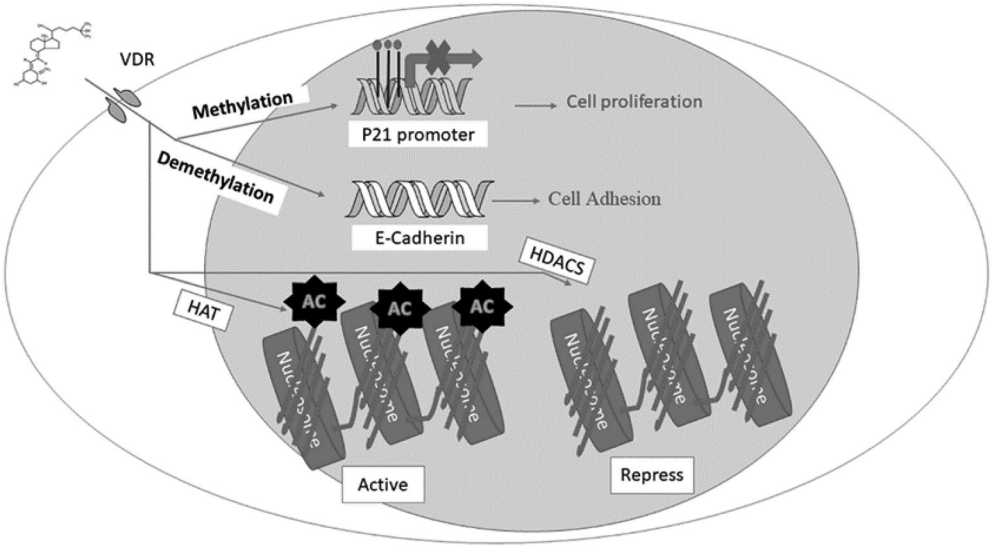


Figure 5. Vitamin D uses VDR to enter the cell and access the nuclear material of epigenome. It can repress p21 promoter transcription, the transcripts accelerate cell proliferation, can demethylate of E-cadherin promoter. It can also activate both HAT (leads active transcription) and HDACs (leads repressed transcription).

dimethylation and trimethylation by two Fe(II) 2OG-dependent histone demethylases, Jhdm1a and Jhdm1b upon vitamin C treatment during reprograming. Vitamin C is also linked with the reduction of histone H3 lysine 9 dimethylation (H3K9me2). In addition, studies also showed that histone demethylases Kdm3a and Kdm3b are required for vitamin C-induced H3K9me2 demethylation, which is independent of TET-mediated DNA demethylation in naïve mouse ES cells (Figure 4; Ebata et al. 2017).

Vitamin C and miRNA

The correlation between vitamin C and miRNA regulation is well established. For example, vitamin C can regulate miRNA functions which further maintain the pluripotent state of mouse embryonic stem cells (Figure 4A, B). Scientific report has been published that a specific miRNA expression pattern in mouse ESCs in vitamin C dependent manner (Gao et al. 2015). miR-290–295, miR-17–92, and the miR-106b–25 clusters are expressed at high levels in mouse ESCs. This study also showed vitamin C–mediated repression of Dnmt3a transcription via miR-143 and promote self-renewal of mouse ESCs. Vitamin C availability and development of bone marrow stromal cells (BMSCs) are linked with each other through miRNA-mediated pathways of selected miRNAs, miR-3619-5p, miR-548a-3p, miR-3942-5p, miR-4741, miR-1825, and miR-1208 play a vital role in BMSC differentiation and musculoskeletal development (Kolhe et al. 2018).

Vitamin D

Vitamin D belongs to a group of secosterols and exists in two forms, vitamin D2, and vitamin D3. This group of vitamins is produced endogenously in the skin from sun exposure or obtained from foods that naturally contain vitamin D, including cod liver oil and fatty fish (Bikle 2014). A biologically active form of vitamin D is 1α, 25-dihydroxyvitamin D3 (1, 25(OH) 2D3, calcitriol) which is involved in cell proliferation, differentiation, survival, metabolism and cell physiology (Pereira et al. 2012). Vitamin D targeted genes are regulated by vitamin D receptor (VDR) which belongs to steroid hormone nuclear receptor family (Carlberg and Seuter 2009).VDR binds and activates genes having VDREs (VDR response element) sites. Various biological functions such as the opening of ion channels, as well as the activity of various enzymes such as kinases, phosphatases, and phospholipases, are regulated by VDR (Haussler et al. 2011). Epigenetic regulation by vitamin D is achieved by regulating both the DNA methylation as well as histone modification status of the cells. Involvement of vitamin D3 in promoter methylation and demethylation status of various carcinogenic genes is well studied (Fetahu, Hobaus, and Kallay 2014). For example, the expression of VDR in triple negative more aggressive breast cancer cells has reported (Lopes et al. 2010). They further investigated the effect of 1Alpha,25-dihydroxyvitamin D3 (1α,25(OH)2D3) and found out a novel mechanism which showed enhanced adhesive property of cells by demethylating promoter region of cadherin 1 (CDH1) gene which encodes epithelial marker, E cadherin (Lopes et al. 2012). Another study showed the effect of 1,25-D3treatment on site-specific methylation of the p21 promoter in malignant prostate epithelial cells (Figure 5; Doig et al. 2013). Maternal vitamin D3 deficiency also affects the maternal as well as infant epigenome. A very recent finding suggests the effect of maternal vitamin D3 status on leucocyte methylation during pregnancy as well as breastfeeding (Anderson et al. 2018).

Vitamin D3 can also actively participate in histone modifications. Vitamin D3 activates both HATs involved in active transcription and HDACs, which are involved in transcription repression (Figure 5; Fetahu, Hobaus, and Kallay 2014). Not only acetylation, histone methylation is also regulated by vitamin D3. Histone methylation as well as demethylation are regulated by HMTs and HDMs(7). Histone demethylases like JmjC which include KDM2A/JHDM1A affect lysine demethylation regulated by vitamin D3 (Tsukada et al. 2006). VDR

recruited many coactivators which includes p160 steroid receptor coactivator proteins (SRC1, 2, and 3), p300, or CBP have lysine acetyltransferase activity. 1,25-D3 treatment enhanced acetylation at H3K27 at the promoter of several early VDR target genes in human monocytic leukemia cells, THP-1 (Seuter et al. 2013). Another study showed that inhibition of bone morphogenetic protein 2 (BMP2) by 1,25-D3 involves H3 deacetylation and H3K9 di-methylation in genetic hypercalciuric stone forming rats (Fu et al. 2013). As that of histone acetylation, Vitamin D3 can also regulate histone demethylation. For example, vitamin D3 catalyzes site-specific demethylation of mono-, di-, and trimethylated lysines such as jumonji domain containing 3 and 4 (JMJD3 and JMJD4), by regulating histone demethylase enzyme containing JmjC domain in colon cancer cells. A number of studies suggest that JMJD plays a significant role in epithelial to mesenchymal transition (EMT) and metastasis processes. Elimination of H3K27me3 mark and re-expression of cancer associated genes are regulated by histone demethylases like JMJD3 and Lysine-specific demethylase 6A also known as ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) (Hong et al. 2007; Agger et al. 2007). Heightened expression of the EMT-associated genes such as SNAIL1, ZEB1, and ZEB2are detected in JMJD3 deficient conditions while expression of epithelial proteins claudin-1 and claudin-7 are downregulated under similar conditions (Pereira et al. 2011).Vitamin D exerts some anticancer effect by regulating HAT activity. The interaction between VDR/RXR dimmer and HATs such as SRC-1 and CBP/p300 induces transcriptional activation. Vitamin D can also mediate histone deacetylation and transcriptional silencing in which the VDR/RXR complex binds to the negative VDREs (Stefanska et al. 2012).

Vitamin D is reported to control miRNA mediated oncogenic progression. In various cancer cells such as benign prostate epithelium, colon cancer, melanoma, and human leukemia cells miR expression is regulated by 1,25(OH)2D (Giangreco and Nonn 2013).Vitamin D3-mediated p27 upregulation is dependent on miR-181a and miR-181b suppression is related with differentiation of human myeloid leukemia cells (Parasramka et al. 2012). More interestingly, this effect of vitamin D3 appears to be interrupted by miR-125b that negatively regulates VDR expression through a potential miR-125b recognition element identified within 3′-UTR of human VDR mRNA. Vitamin D3 deficiency is closely associated with the development of autoimmune diseases by regulating miRNA expression. As an example miRNA-342, miRNA-10a, miRNA374b, and miRNA-125 are downregulated in T-cells of patients with systemic lupus erythematosus (SLE) in a vitamin D deficient serum concentration (Chen et al. 2017). 1,25-(OH)2 D3 mediated inhibition of fibroblast-like synoviocytes (FLS) proliferation and expression of pro-inflammatory cytokines in a rat model of rheumatoid arthritis (RA) through down-regulation of miR-22 is recently reported (Fan et al. 2017). 1,25(OH)2D mediated regulation of miR-132-5p and miR-212-3p has been described as negatively correlated with metastatic progression in prostate cancer cells (Dambal et al. 2017). Effect of certain anti-tumoral drugs is enhanced after vitamin D3 treatment (Sun et al. 2016). For example, vitamin D treatment enhances the antitumor activity of irinotecan (a topoisomerase I inhibitor) which is used for the treatment of colorectal cancer. Vitamin D mediated miR-627 expression further targets cytochrome P450 drug resistance enzyme CYP3A4 that is responsible for irinotecan inactivation in colorectal cancer (Sun et al. 2016). Other examples of vitamin D mediated epigenetic regulations are summarized in Table 2.

Conclusion and future perspectives

Vitamins have recently emerged as major epigenetic regulators and their role in various epigenetic modifications have been discussed in this review. Although these investigations are preliminary, it is necessary to undertake detailed studies on the mechanism of vitamin mediated epigenetic regulation to delineate its relation to disease pathogenesis. Most of the studies in this field are in cell culture in vitro conditions and there is a need to conduct in vivo studies to further understand their role in realistic physiologic conditions. Other important conditions such as safe dose and time duration of vitamin exposure need to be taken into account. Simultaneous treatment of two or more vitamins might have a significant positive effect as compared to single treatment; therefore, combinatorial treatments of two or more vitamins need to be studied in detail. The main goal of these types of studies must be to enhance the bioactivity and efficacy of these vitamins. Few reports explain the effect of maternal vitamin supply on infant epigenetic variations, but in-depth analysis must be conducted on pregnant women to better understand how to protect new born from various diseases. Although the field is still in its infancy, systematic as well as detailed studies may uncover the role of these vitamins on epigenetic modifications in normal and pathological conditions.

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Abbreviations

AML	Acute myeloid leukemia
TRA	All trans retinoic acid
BMSCs	bone marrow stromal cells
5caC	5-carboxylcytosine
DLBCL	Diffuse large B-cell lymphoma
mt	Epithelial to mesenchymal transition
SCs	Embryonic stem cells
AD	Flavin adenine dinucleotide
FLS	Fibroblast-like synoviocytes
5fC	5-formylcytosine
GABA	Gmma aminobutyric acid
GULO	Gulonolactone oxidase
HATs	Histone acetyltransferase
HDACs	Histone deacetylases
HDM	Histone demethylase
HMTs	Histone methyltransferases
5-hmC	5-hydroxymethylcytosine
JmjC	Jumonji C

MET	Mesenchymal to epithelial transition
MTHF	Methylenetetrahydrofolate
miRNA	microRNAs
5-mC	5-methylcytosine
NTDs	Neural tube defects
UTX	Ubiquitously transcribed tetratricopeptide repeat, X chromosome
RA	Retinoic acid
AR α	Retinoic acid receptor alpha
RAREs	RA response elements
ROS	Reactive oxygen species
SAH	S-adenosyl-L-homocysteine
SAM	S-adenocyl methionine
TET	Ten-eleven translocation
A	Vitamin
DR	Vitamin D receptor
DREs	VDR response elements

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