



# Nutriepigenomics: Need of the Day to Integrate Genetics, Epigenetics and Environment towards Nutritious Food for Healthy Life

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## Abstract

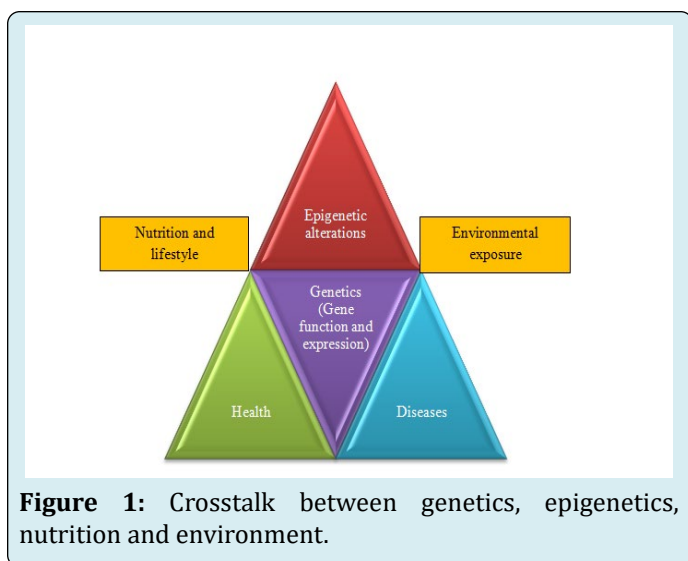
Nutrition, lifestyle, behavior, and other environmental factors affect human health that may control pathogenesis of various diseases, and it is regulated through epigenetic modifications. Nutrition is an indispensable environmental factor that not only impacts our growth and development but also the health by affecting epigenetic phenomena. Furthermore, these changes might impact next generation via transgenerational inheritance of epigenetic alterations; thus, making them important health issues for the society. Certain nutrients and bioactive food components are able to alter epigenetic status at DNA methylation and histone modulation levels, which might modulate expression of the genes associated with patho-physiological processes. In addition to the genetics, health condition of an organism might be affected by the integration of environmental factors/signals acting through epigenetic changes. Therefore, understanding the molecular (epigenetic) basis of environmental factors has become a need of the day towards development of preventative strategies against various pathological conditions like obesity, type II diabetes, cardiovascular diseases, cancer etc, utilizing a personalized dietary chart.

**Keywords:** Bioactive Food Component; Cancer; Disease; Environment; Epigenetics; Genetics; Nutrient

## Introduction

Unravelling the codes of about 2.9 billion nucleotides or nearly 30000 genes has provided tremendous opportunities to understand response of human body to the dietary components, other environmental factors, and how these factors affect human health. Apart from metabolic production of energy, food is now also known to provide conditioning environment that shapes the activities of the genome and physiology of the body [1]. A deeper understanding of how nutrients influence genes and their expression might help managing healthy life in a better way. Explaining the genetic variations and the continuously changing genotype due to

the environmental factors, including dietary/nutritional components, using classical genetics alone has become arduous [2]. Moreover, the rate of genetic mutations and phenotypic variations are considerably different from each other which cannot be explained merely based on genetics [3]. Different tissues in an organism have different phenotype/physiology regardless of possessing the same genome, which is mainly because of differential expression of the genes regulated by the pliable epigenetic landscape of an individual (Figure 1). A better understanding of the epigenetic switching on/off gene might help explaining this enigma [4].



**Figure 1:** Crosstalk between genetics, epigenetics, nutrition and environment.

If epigenetics is contemplated as a harmonizing process with genetics, many of the phenotypic variations can be easily explained [5]. Epigenome refers to the sum total of all the changes in genetic material without altering the underlying nucleotide sequence. Studies of such changes including modification in chromatin architecture, histone protein, DNA methylation and non-coding RNA biogenesis that affect gene expression in a cell/tissue is known as epigenomics [6]. The epigenetic changes might revert back to the previous state after normalization of the environmental conditions. One of the well-known mechanisms of epigenetic change has been methylation of cytosine at the 5<sup>th</sup> carbon [5]. In addition,

certain amino acids located at the tail of the histone proteins are post-translationally modified by methylation, acetylation or biotinylation [7]. Similarly, non-coding RNAs also play very important role in epigenetic modifications and gene regulation. More importantly, some of the epigenetic changes may be inherited to the next generation that might result in phenotypic variations [8]. It is becoming apparent that changes in epigenome of living organism play crucial role in tolerance to environmental stresses, nutrient availability, and the evolution processes [9].

The on-going researches on nutritional epigenetics justify the direct association between dietary nutrients and epigenetic alterations. Various nutrients possess the ability to alter the epigenetic pattern via availability of the substrate and activities of the related enzymes. In the field of nutritional science and technology, epigenetic changes have gained exceptional importance because of the ability of nutrients and bioactive food components to change the epigenetic status of gene/genome which can alter the gene expression [10]. Bioactive food compounds like folic acid, vitamin-B<sub>12</sub>, methionine and choline might affect epigenetic modifications through one-carbon metabolism [11,12]. In principle, any nutrient/bioactive compound or condition that can affect AdoMet (S-adenosylmethionine) or AdoHcy (S-adenosylhomocysteine) level in a tissue can alter methylation of DNA/histone proteins [13]. Different vitamins play important roles in histone modification, and affect the enzymes involved in the epigenetic mechanisms [14]. The roles of epigenetic alterations in certain patho-physiological processes are summarized in Table 1.

Dietary components	Patho- physiological state	Epigenetic modification	References
Butyrate	Stem cells	Histone acetylation, DNA Methylation	[15]
Folate	Embryonic growth and development	DNA methylation, imprinting	[16,17]
Choline		DNA methylation	[18]
Alcohol		DNA methylation	[19]
Choline	Neurocognition	DNA methylation	[18]
		Histone methylation	[20]
Fat rich diet	Obesity and insulin resistance	DNA methylation, miRNA biogenesis, Histone acetylation	[21]
Curcumin			
Resveratrol	Inflammation	Histone acetylation	[22]
Methyl-deficient diet		MicroRNAs	[23]
Folate	Immune system functioning	DNA methylation	[24]
Calorie restriction	Aging	DNA methylation	[24]
		Histone acetylation	[25]

**Table 1:** Dietary components associated with patho-physiological conditions and epigenetic modifications.

The present review discusses the influence of environmental factors (including the food/dietary components) on epigenetic behavior of living organism, and their effects on human health and diseases, and the future prospective of an emerging branch of science namely nutriepigenomics.

### Nutrition and Genomics: Nutrigenomics

Nutritional genomics (nutrigenomics) deals with the identification, classification, and characterization of genetic variations in the genome that modulate metabolism of various nutrients present in the food/diet. Thus, nutrigenomics focuses on understanding the pathways that are modulated by gene-nutrient interaction for the management of pathophysiological conditions and healthy life. It is now well-understood that chronic diseases are quite complex in their etiology, and comprise of a substantial genetic component as every individual has a different response to food and its nutrients [26,27]. This clearly indicates that the linkage between genes and environment is bidirectional, and the environment including food and nutrients can indirectly affect gene expression/response of the organism.

### Role of Dietary Components in Genome Stabilization and Gene Expression

Different components of a diet may affect expression of genes and stability of the genome. For example, loss of amino acids in the extra-cellular environment enhances expression of asparagine synthetase (AS) gene [28]. AS encodes the enzyme that catalyses the reaction responsible for conversion of aspartic acid to asparagine. The diets rich in carbohydrates, primarily glucose, induce transcription of some of the glycolysis and lipogenic pathway genes [29]. It is also known that carbohydrate-rich diets are linked to pathophysiological conditions like obesity, type II diabetes and hyperlipidemia. Vitamins play significant part in repair and maintenance of DNA, and thus genome stability. Deficiencies of vitamin create hindrance in DNA repair mechanism and cellular dysfunction, such as cancer and aging. Reactive oxygen species (ROS) generated due to catabolism of the dietary components and cellular metabolic processes are very harmful for DNA and enzymes. On the other hand, carotenoids act as an antioxidant and quench the harmful free-radicals, thereby reduce the damage caused by ROS. Concentration of carotenoids in human plasma was reported to be negatively associated with oxidative lymphocyte damage [30]. Similarly, expression of interleukin 6 (IL-6), type I and type II proto-oncogenes, and growth factors like tumor growth factor- $\beta$ 1 are regulated by vitamin A [31].

Folic acid and vitamin B<sub>12</sub> are required for DNA metabolism. Folate is important for the synthesis of

deoxythymidine monophosphate (dTMP) from deoxyuridine monophosphate (dUMP). Deficiency of folate results in the incorporation of uracil in DNA, resulting in breaks in the DNA and increased requirements of efficient DNA repair mechanisms. Some of the major roles of vitamin B<sub>12</sub> and folate include synthesis of methionine and S-adenosyl-methionine (SAM), which are needed to maintain the epigenomic architecture [32]. Studies indicate that single nucleotide polymorphism (SNP) in the genome of individuals might be responsible for functional variations in the proteins/enzymes necessary for synthesis, transport and metabolism of vitamins [33]. Vitamin B<sub>12</sub> has been reported to have inductive effect on the synthesis of methionine synthase with prompt post-transcriptional modulation in mammalian cell cultures. Vitamin C also acts as an antioxidant, and plays important role in minimizing oxidative damage to DNA. Studies indicate that vitamin C affects expression of the genes for glutathione S-transferase Pi, p73, fra-1, Mut L homologue-1 (MLH1). MLH1 is specifically important in DNA repair pathways, as its up-regulated expression is essential for DNA defense mechanism [34]. Thus, optimal intake of vitamins is essential to protect the genome. It has been established now that nutrients like carbohydrates, amino acids and vitamins are required for defense, repair and maintenance of DNA, and integrity of genome; thereby, nutrients play crucial roles in genome stability and gene expression.

### Epigenetics and Epigenomic Modifications

Epigenome is the sum total of the changes in the genome (without altering the nucleotide sequence), and studies of such changes are known as epigenomics. More importantly, these epigenetic changes are reversible in nature; thereby, play important roles in regulation of gene expression particularly under varying environmental conditions [6]. Epigenetic modifications may alter chromatin conformation either by making it more compact (heterochromatin), and thus suppressing transcription of the genes present in the region, or by making it (euchromatin) easily accessible to transcription machinery [4]. In addition, certain amino acids at the N-terminal tails of histone proteins are post-translationally modified that may have profound impacts on condensation/segregation of chromosomal regions [7]. Non-coding RNAs like small-RNAs (siRNA and miRNA) and lncRNA biogenesis play vital role in DNA methylation through RNA-directed DNA methylation (RdDM) pathway [35]. More importantly, some of the epigenetic changes may be inherited to the next generation that might result in phenotypic variations [8]. Evidence suggests the role of epigenetic changes in regulation of gene expression during growth, development, and environmental fluctuations; hence, it would be crucial to investigate the role of nutrients in managing epigenetic architecture of the genome/epigenome. This may help utilizing dietary components/

nutrients to manage epigenetic landscape, which may help treating various metabolic disorders [9].

### DNA Methylation is Affected by Nutrients

DNA methylation is catalyzed by DNA methyltransferase (DNMT) family of enzymes, which is responsible for modulating transcription in association of the altered chromatin state [4]. Dietary folate contains methyl group and delivers it during the formation of AdoMet. Apart from folate, other dietary components like methionine, betaine, vitamin B<sub>2</sub> and choline are determinants of DNA methylation. A study on mouse indicated that folate concentration is significantly correlated with altered methylation at p16 promoter, and change in expression of the gene in mouse colon [11]. Choline is an essential micro-nutrient that plays a vital role in DNA methylation. Studies showed that supplementation of choline increases DNA methylation with enhanced DNMT expression in hepatic cells (HepG20) of human being [36]. When human T lymphocytes were cultured in a medium containing lower concentration of methionine and folic acid, DNA demethylation and overexpression of certain genes associated with autoimmunity was observed [24]. An *in vivo* study on sheep suggested that dietary deficiency of folate, methionine and vitamin B<sub>12</sub> trigger obesity in offspring along with inadequate immune response. The study indicates that deficiency of dietary components during the periconceptional period may have potential effects on altering DNA methylation pattern even in offspring [16].

Vitamin B<sub>12</sub> is a vital cofactor for methionine synthase, and its availability impacts genomic DNA methylation [37]. Recent study shows that certain bioactive food compounds like polyphenols (tea), isothiocyanates and genistein (soybean) might be involved in decreasing the risks of cancer by reducing DNA methylation from the genes associated with cancer [38]. Polyphenols can have direct inhibitory effects on the catalytic site of DNA methyltransferase 1 or it can have indirect effect on DNA methylation status [39]. Alcohol has profound impacts on methyl group transfer reaction. Study on mouse model shows that expression of certain epigenetically sensitive alleles like Agouti viable yellow (A<sub>vy</sub>) is affected by the exposure of maternal parent to ethanol [19]. It was suggested that ethanol might affect transcriptional silencing, which corroborate with hypermethylation at A<sub>vy</sub>, leading to agouti-colored coat in mouse. Thus, certain nutrients and bioactive dietary components have the potential to alter DNA methylation pattern, and indirectly affect gene expression as well as various patho-physiological conditions.

### Histone Modifications and Effects of Bioactive Food Components

Histone modulation works with DNA methylation

to epigenetically regulate gene expression. Numerous evolutionary conserved lysine (K) residues in the histone proteins are subjected to various modifications like acetylation, methylation, ubiquitylation, biotinylation, etc [7]. Two enzymes, namely histone acetyltransferase (HAT) and histone deacetylase (HDAC), control acetylation level of the histone protein towards regulation of gene expression [40]. More importantly, certain bioactive food components impact the activity of HAT and HDAC [41]. Bioactive food compounds like sulforaphane (found in broccoli and sproutes), diallyl sulfide (from garlic) and short chain fatty acid (e.g. butyrate) act as HDAC inhibitors. *In vitro* melanoma cell (B16 and S91) culture study inferred that sulforaphane has the potential to reduce deacetylation activity, thereby inhibits growth and proliferation of cancerous cells [42]. Diallyl sulfide was reported to have the potential to enhance H3 and H4 acetylation in rat colon cells [43]. Another study showed that tributyrates can increase hepatic nuclear H3K9 acetylation by 4-fold in preneoplastic lesions in rat, which also increases expression of p21 protein by 1.5-fold that acts as HDAC inhibitory effect [44]. Acetylation/deacetylation of histone proteins is associated with expression of pro-inflammatory genes (e.g. interleukin-1, 8, 12) and anti-inflammatory genes (like IL-10) [45,46,25]. Resveratrol present in grape skin acts as activator of Sirt1, and has anti-inflammatory effects against colitis and colitis-associated colon cancer [22,47]. Studies also indicate that resveratrol can repress NF-κB and acetylation of histone proteins. Histone methylation/demethylation was reported to be linked with obesity in mice [48]. Loss of activity of H3K9-specific demethylase (Jhdm2a) resulted in obesity and hyperlipidemia, suggesting that H3K9 methylation plays important role in regulation of metabolism associated genes. Biotin also play important role in modification of H3 and H4 via covalent attachment of biotin to specific lysine residues. Thus, dietary deficiency of biotin might have impacts on chromatin structure and gene expression [49].

### Non-coding RNAs Helps Modulating Gene Expression

Non-coding RNA (ncRNA), a functional RNA produced through transcription but not translated into proteins, is another epigenetic mark that affects gene expression, and thus many cellular processes [50]. Epigenetic modifications like DNA methylation and histone modifications are mediated through ncRNAs, these may lead to some pathological conditions like cancer [51]. Various bioactive food components affecting miRNA biogenesis and cancerous growth are listed in Table 2. Study also indicated that diet deficient in methyl group donor, cause formation of tumors in rat liver along with the changes in biogenesis of miRNAs like miR34a, miR127, and miR16a that are involved in the regulation of programmed cell death, proliferation of cells

and intercellular connection [52]. Cirera, et al. [53] reported 1.4-fold reduced expression of miR122 in pigs when they were fed with high-cholesterol diet compared to those

fed with the standard diet, which indicates implication of miRNA/epigenetics in obesity.

Bioactive food component	Effect	References
Genistein	Represses human uveal melanoma cells and murine chronic lymphocytic leukemia cells by altering miR-16.	[54]
Curcumin	Represses human pancreatic cancer cells by upregulating and downregulating miR-22 and miR-199a respectively.	[55]
Retinoic acid	Retinoic acid receptor antagonists sufficiently effectively repress miR-10a expression and block metastasis and miR-34a functions as a potential tumor suppressor in neuroblastoma cells.	[56]
Polyunsaturated fatty acids	During initial stage of cancer progression several microRNAs such as let-7d, miR-15b, miR-107, miR-191 and miR-324-5p were significantly affected by diet-carcinogen interactions. It is inferred that fish-oil-fed animals differentially expressed smallest microRNAs thus, concluding the potential of fish oil in protecting the colon from carcinogen-induced microRNA dysregulation.	[57]
Curcumin	Upregulation of miR-15a and miR-16 expression, both of which could inhibit the expression of B-cell lymphoma 2 (Bcl-2), thereby inducing apoptosis in MCF-7 breast cancer cells.	[58]

**Table 2:** Bioactive food components affecting cancer through miRNA biogenesis.

### Nutrieigenomics: Integration of Epigenetics, Nutrition and Health

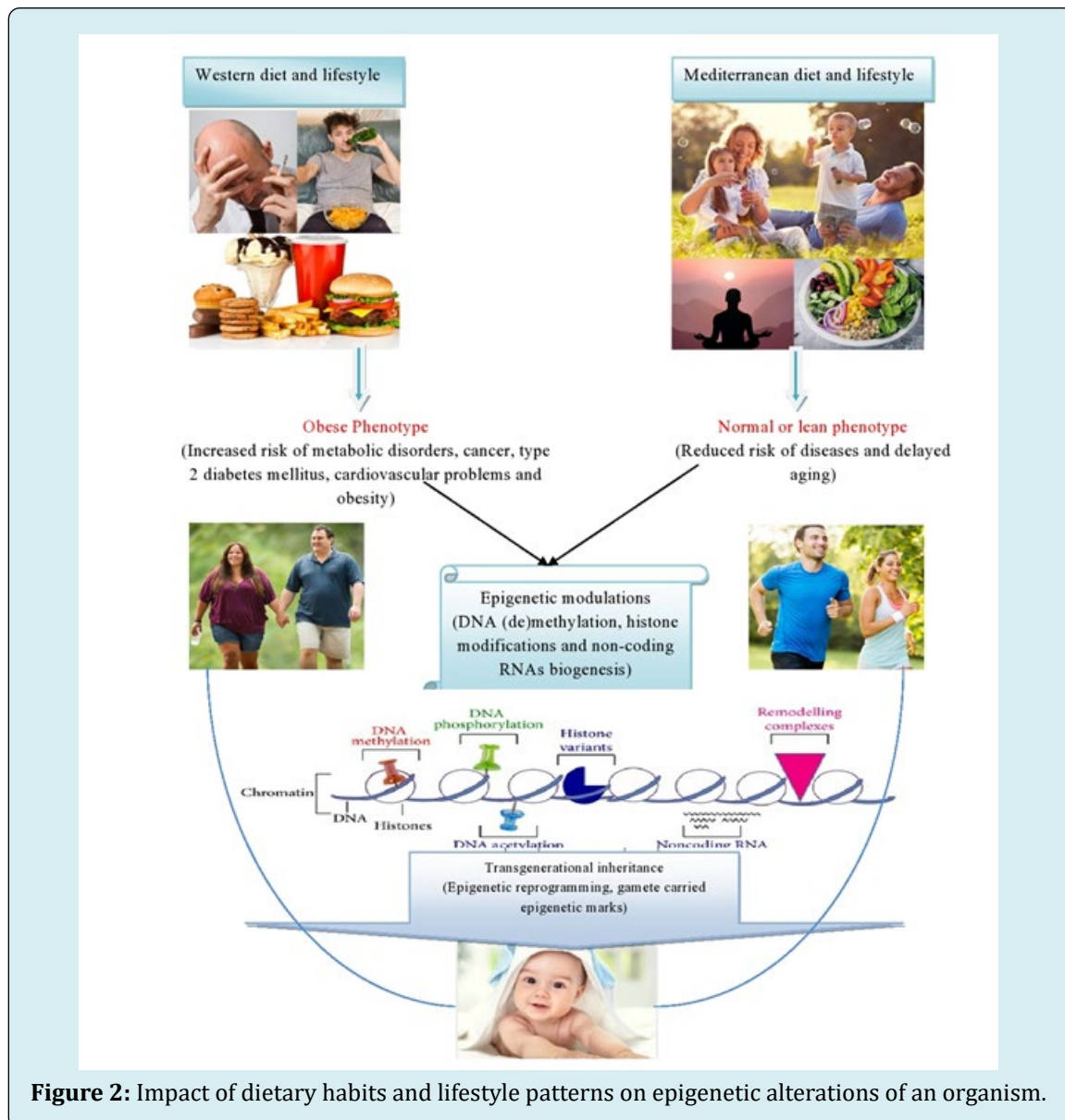
Dietary behavior not only affects nutritional requirements of the body but also have influence on epigenome and phenotype of the individual as well as its offspring. Westernized diets are mainly comprised of the food rich in saturated fats and meat, lesser carbohydrates, cereals/grains, fruits and fresh vegetables. When westernized diet is combined with static lifestyle, severe alcohol consumption, smoking, it may lead to the occurrence of diseases like hypertension, cardiovascular disorders (CVDs), obesity and cancer [59]. The impact of the diet rich in saturated fatty acid and other harmful components was assessed towards the development of non-alcoholic fatty liver disease (NAFLD) in rodent. An imbalanced ratio of n-6 polyunsaturated fatty acids (PUFA) and n-3 PUFA in Western diets increases the risk of NAFLD. Non-alcoholic steatohepatitis (NASH), a type of NAFLD, results in the accumulation of lipids in liver, fibrosis and cirrhosis/liver cancer. The risk increases due to the reduced content of linoleic acid [60]. Decreased n-6:n-3 ratio was reported to prevent NASH by attenuating oxidative stress [61]. Studies suggest strong correlation between DNA methylation level in peripheral blood and eicosapentaenoic acid/arachidonic acid content in milk-fed infants and adult men [62,63]. Dyslipidemia in pregnant mother was reported to cause epigenetic alterations in placenta and liver of the fetus [64]. On the other hand, Mediterranean diets have been

reported to reduce the risk of CVDs, obesity and other health problems. Mediterranean diet is composed of fruits, fresh vegetables, multigrain food, fish, egg, and healthy fats. Human population fed with Mediterranean diet along with olive oil and nuts showed lower risk of CVDs and cancer compared to their counterparts [65,66]. Regular Mediterranean diet during the early pregnancy was reported to be linked with positive cognitive behavior in the offspring [67] (Figure 2).

Nutrition, being the most extensively studied environmental factor, is associated with epigenetic changes in the genome (epigenome), health of the organism, and metabolic disorders [68]. Common dietary components like folate and choline can modulate DNA methylation and impact gene expression. Methyl-enriched diet is essential during the early days of pregnancy is essential for proper growth and development of fetus, otherwise chances of diseases and cancer increase significantly [69]. An NAD<sup>+</sup>-dependent HDAC (Sirtuin 1) has been reported to be activated by several dietary components like resveratrol, and Sirtuin 1 delays some of the physiological processes related with aging via its impact on DNA methylation [70]. Balanced nutrition during the early life prompts epigenetic alterations that affect individual's health and disorders. Nutrients directly affect the activity of enzymes (DNMT and HDAC) linked with epigenetic modifications [71]. Malnutrition during the early months of pregnancy have higher risk of diseases in fetus through epigenetic variations, and these might have

impacts throughout the life. The effects of nutritional status of grandmother's life (who faced malnutrition/famine) on the health of female grandchildren, in terms of the risks of

mortality due to CVDs and body mass index (BMI), were observed to be higher compared to that in its counterpart [72,2].



Studies report significant association between epigenetic changes in the genes involved in glucose/insulin metabolism and obesity [73-77]. Increased methylation of *HIF3A* was reported to be correlated with higher BMI [73]. Number of studies has been carried out to analyze DNA methylation and its association with obesity. DNA methylation drastically changes during ageing, and it has become clear that better nutrition during early life has the potential to modulate DNA methylation and improve longevity [71]. Thus, consumption of junk food and negligible exercise affect the risk of obesity, which might be controlled through genetic predisposition

and/or epigenetic alterations [78].

### Nutrieigenomics and Cancer

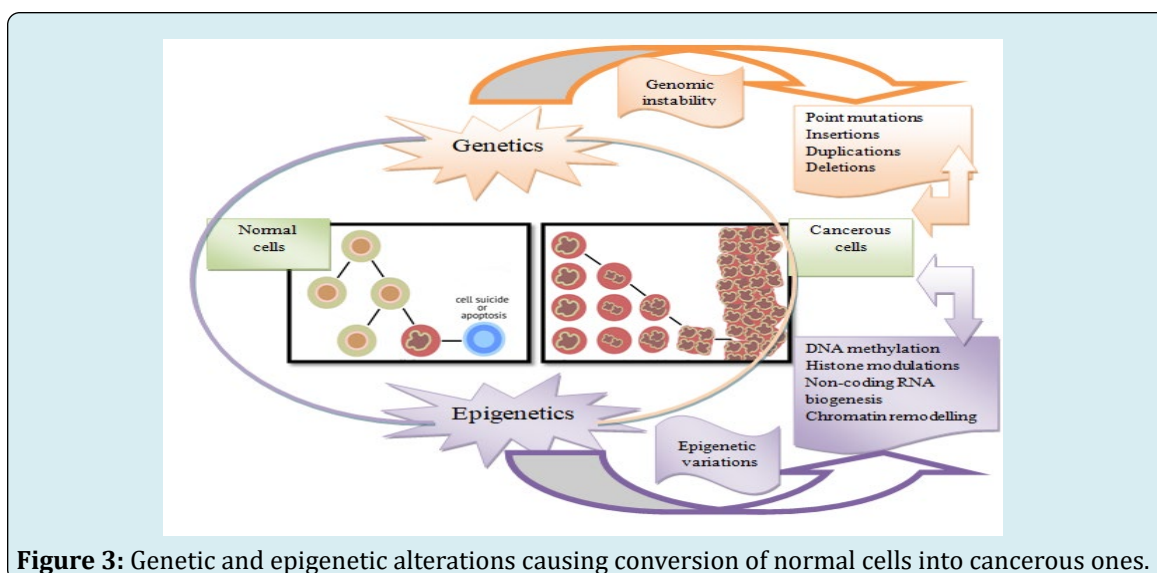
Different nutrients play important roles in epigenetic changes in the genome/epigenome which affect growth, development, and patho-physiological conditions of the organism. Epigenetic alteration in the genetic material is significantly affected by some of the nutrients like folate and vitamin B<sub>12</sub>. *In vivo* study indicates that presence of folate in diet is responsible for the expression of p16 tumor

suppressor gene, which is associated with DNA methylation in its promoter. A tumor suppressor gene (p16<sup>INK4a</sup>) was reported to be target of epigenetic inactivation in human breast carcinogenesis [79]. Low intake of folate has been associated with hypomethylation, increased risks of colorectal and pancreatic cancers. Folate was reported for modifying anticarcinogenic properties via epigenetic alterations [1]. The potential effects of dietary components present in cereals, fruits, vegetables and other Mediterranean

diets via epigenetic changes against cancer have been presented in Table 3. DNA methylation, histone modulations, and ncRNAs are involved in controlling the occurrence of cancer indirectly through epigenetic modifications. Diets deficient in methyl-group donors and folate result in aberrant expression of miRNA; thus, abnormalities in cell proliferation and apoptosis leading to cancer [80]. Genetic and epigenetic alterations causing conversion of normal cells into cancerous cells are represented in Figure 3.

Nutrient	Dietary sources	Epigenetic alteration
Methionine	Spinach, Fish, Peppers, Brazil nuts, Sesame seeds, etc.	S-adenosyl methionine (SAM) synthesis
Folic acid	Leafy vegetables, Sunflower seeds, Baker's yeast, Liver, etc.	Methionine synthesis.
Retinoic acid	Dark green, red and yellow vegetables, fish and cod liver oil, etc.	miRNA regulation
Vitamin B <sub>6</sub>	Vegetable, Nuts, Whole grain products, Meats, etc.	Methionine synthesis
Vitamin B <sub>12</sub>	Milk, Shellfish, Meat, Liver, etc.	Methionine synthesis
SAM-e	Dietary supplements, Supplementary pills, etc. (unstable in food)	With the help of enzymes, transfer methyl group directly to DNA.
Polyphenols	Green tea and other plant sources.	Inhibition of DNA methylation
Curcumin	Turmeric	miRNA regulation
Betaine	Wheat, Spinach, Sugar beet, Shellfish, etc.	Break down the toxic products of SAM synthesis.
Resveratrol	Red wine	Removes acetyl groups from histones.
Butyrate	Produced on fermentation of dietary fibre in intestine.	Increase histone acetylation.
Genistein	Soybean	Increase methylation.
Sulforaphane, Isothiocyanate	Broccoli sprouts	Increase histone acetylation. (Act as HDAC inhibitor)
Diallyl sulphide	Garlic	Increase histone acetylation. (Act as HDAC inhibitor)

**Table 3:** Epigenetic role of nutrients and bioactive food components in cancer.



**Figure 3:** Genetic and epigenetic alterations causing conversion of normal cells into cancerous ones.

## Environmental Epigenetics

In addition to the nutritional status, various other environmental conditions like exposure to certain chemicals might contribute to epigenetic changes in the genome. Exposure of organisms to some of the commonly present hazardous metals (arsenic), organic compounds, alcohol, pesticides, and endocrine disrupting chemicals (EDCs) might induce epigenetic alterations. Human beings are frequently exposed to a broad range of EDCs which interfere with pathways of hormone signaling. EDCs related exposure results in epigenetic alterations and play role in carcinogenesis [1]. EDCs have impact on the functioning of epigenetics related enzymes (DNMTs, HATs, and HDACs) [81]. Moreover, smoking and alcohol lead to emphysema (Smoker's disease) and cancers, as smoke and alcohol exert dysregulation of cellular processes through epigenetic changes. *In vitro* and *in vivo* studies indicate that alcohol has deleterious effects on metabolism and nervous system development through down regulated epigenetic changes at early embryonic stage. This may affect learning ability, memory processes and abnormal growth and development of fetus [82]. Human being comes in contact of several chemicals, insecticides, pesticides etc. used in agriculture, society and industries, directly or indirectly. Moreover, chemical/pesticide residues in crop produce/food, pollutants in air/water/soil cause environmental pollutions and health hazards [83]. Tobacco consumption and smoking habits in pregnant mothers have been reported to cause epigenetic alterations in buccal mucosal cells, and serious consequences on child's health and growth with impaired neural development, asthma, allergies, and immune dysfunctions have been reported [84,1].

## Future Perspectives

Nutrition is one of the major environmental factors that affect organism's growth, development and health conditions. Bioactive food components and dietary pattern, along with the other environmental factors, affect epigenomic landscape of the organism. Since nutriepigenomics is quite novel and an emerging branch of science, intensive scientific investigation on the impact of bioactive food components in epigenetic alterations is very much desirable. Moreover, the effects of epigenetic alterations caused by the dietary components and other environmental factors on the organism's phenotype, as well as their inheritance, would be mandatory. In future, the extensive studies on deciphering epigenetic alterations caused by the nutrients might open the way for personalized nutritional interventions to help managing better growth, development, and healthy life. This might also help opening up new therapeutic interventions in cancer research [85,86]. Healthy diets, including fruits and fresh vegetables, have significant effects on metabolic processes which determines cellular environment, and thus affect cellular growth and

immune functions. Changes in DNA methylation in cancer causing genes is a fascinating epigenetic marker that facilitate detecting the tumor at the early stage of development and its efficient treatment [8].

Furthermore, epigenetic manipulation using CRISPR-dCas9 technology might help performing epigenome editing in future not only for sustainable food production but also for curing/preventing patho-physiological conditions [87]. However, several other basic information needs to be generated, challenges to be taken up, and considerable efforts would require to be made to decipher the pathways and epigenetic marks associated with the trait of interest. Such efforts might pave the ways for prognosis and treatment of various life-threatening diseases like cancer [88,89]. However, it would also be essential to maintain the edited epigenetic landscape in the cell/tissue by creating the cellular environment necessary for the epigenetic state either by deploying the essential epigenetic machinery or by supplying the essential nutrient(s). More importantly, the biosafety issues of laboratory research [90] as well as those of the genetically modified organisms [91], as per the regulatory guidelines of the country, must be taken care to maximise the overall benefits [92].

## Conclusions

Nutrients constitute the cellular environment necessary for epigenetic modifications in the cell. Different kinds of epigenetic modifications like DNA methylation, histone protein modifications, biogenesis of ncRNAs, chromatin remodeling are interlinked, and indirectly affected by nutritional status and environmental conditions. Nutrients play vital roles in epigenetic modifications and affect patho-physiological conditions that emergence of a new branch of science namely nutriepigenomics has initiated, which is expected to help managing some of the life-threatening diseases. However, unravelling the role of nutrients on epigenetic alterations toward controlling complex traits can be intimidating process. Moreover, healths, physiological and pathological conditions, aging related complications are the consequences of integrated action of genetics, epigenetics, nutrition and environmental factors. Lifestyle, behavior, eating patterns and various other environmental factors leave epigenetic marks on genetic material that affects expression of genes, tolerance to environmental stresses, and patho-physiological conditions. Therefore, deeper understanding of the cross-talk among nutrition, epigenomics and patho-physiology might help circumventing the health-related issues like CVDs, obesity and cancer. Future research in nutriepigenomics has unprecedented opportunity to benefit public health, and personalized nutrition. Understanding the role of nutrients, particularly in epigenetic modifications, along with their sources and metabolism in the body would



be very essential for targeted discoveries and therapeutic interventions for numerous crucial/chronic diseases.

The views expressed herein are those of the authors only, and these may not necessarily be the views of the institution/organization the authors are associated with.

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