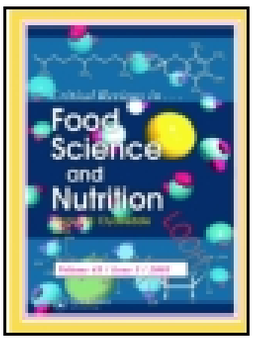

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REVIEW



# Nutrigenomics: Epigenetics and cancer prevention: A comprehensive review

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**ABSTRACT**

Due to change in lifestyle and food habits, people are more at risk of diet-related diseases and cancers. It is also established that dietary modifications significantly reduce the risk of diseases. Nutrigenomics is relatively fresh discipline, but possess an enormous potential that can apply for prevention and management of certain carcinomas and diseases. This review enables us to generate useful information for scientists and health professionals regarding the role of Nutrigenomics in the prevention of diet and lifestyle-related diseases like cancer. It influences health conditions of individuals and susceptibility of disease by defining the metabolic response and gene expression. Epigenetic modifications can perform a significant role in disease occurrence and pathogenesis. DNA methylation and chromatin remodeling are the most common epigenetic mechanisms. Omega 3 fatty acids are the best example of nutrients and gene interaction not involving DNA methylation while certain bioactive food compounds have a proven role in cancer prevention through an epigenetic mechanism. Dietary polyphenols substantially take part in prevention of oral, breast, skin, esophageal, colorectal, prostate, pancreatic and lung cancers. Moreover, minerals and vitamins involve regulatory processes. Zinc, Selenium and folate involve in DNA repairing process have anticancer properties. Consumption of multivitamins prevents methylation of cancer cells.

**KEYWORDS**

Nutrigenomics; epigenetics; cancer; diet and disease

## Introduction and background

The idea of the importance of nutrition in health is not new. About 2000 years ago, Hippocrates, stated that "food may be used instead of medicine as cure remedy". Since that time we have enhanced our understanding in detail how nutrition affects our health in general. Due to the advancement in research and technology, it is explored that how different types of food and bioactive compounds react with our body to promote health (Nepomuceno 2013)

Nutrition can play a direct or indirect role in the pathogenesis of disease or its appearance. Usually, nutrient and gene interaction remains benign but sometimes it is responsible for some deadly consequences. Moreover, it is well established that different individuals differ in the requirement of certain nutrients. Significant heterogeneity has been found in the sequencing of the human genome and genetic difference also considered as a major basis for varied response to the diet among different individuals (Elsamanoudy et al. 2016).

The genetic revolution has highlighted the role of diet in the health and wellbeing. The knowledge about the genes has improved health diagnosis and enhanced the understanding of genomic medicine. In this regard, human genome project had played a vital role to determine mutual relationships between nutrient, genes, and disease. The genomic medicine has ruled out the way for new therapies to cope up with common emerging conditions related to health and nutrition. So, therefore, nutrition research has progressed from physiological and epidemiological facets to genetics aspects and molecular biology as well as nutrigenomics(Nicastro, Trujillo, and Milner 2012). Due to the change in lifestyle and food habits, people are more at risk of chronic diseases and certain sarcomas or cancers.

Cancer considered as a second leading cause of death and 8.8 million deaths occurs due to cancer in 2015 around the globe. Nearly 1 death among 6 occurs due to cancer in the world. Roundabout 70% of cancer deaths happen in underdeveloped countries. According to the epidemiological data, a large portion of the human cancer is significantly associated with lifestyle and diet. One-third of cancer deaths are due to the dietary and behavioral risks like lack of physical activity, high body mass index, lesser vegetable and fruit intake, use of tobacco and alcohol. The diet has the meaningful impact on numerous stages of cancers. Various nutritional factors influence the process of carcinogenesis some of them inhabit and some are responsible for stimulation of this process. Cancer may be caused by endogenous reaction like oxidation or may be the result of some exogenous

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agents like, Aflatoxin (Liver cancer), Tobacco smoking (Lung cancer), Sunlight exposure (Skin cancer) and a high dose of radiations(Nepomuceno 2013; World Health Organization 2018).

There is serious need to lift the understanding of people regarding diet and health relationship through extensive research and publications in the field of nutrition science (Neeha and Kinth 2013). This review enables us to improve our understanding regarding the importance of nutrigenomics in the prevention of cancer. It includes a general overview and role of nutrigenomics in the prevention of carcinoma. This paper will prove to be a useful source of information for researchers, students, nutritionists, clinicians and other reviewers.

Similarly, Zinc is an important mineral act as a cofactor in DNA repair genes OGGI that are responsible for removal of oxidized guanine. Magnesium also acts as a cofactor for various DNA polymerases

## Nutrigenomic or nutritional genomics

Nutrigenomic or Nutritional genomics has become an important discipline due to its significant role in nutrition and medical science. It is a useful remedy for cure and prevention of the numerous types of cancers along with chronic diseases. Nutrigenomic is multidisciplinary knowledge deals with the effect of foods on our genes and response of individual genes towards nutrients absorbed through various foods. It is associated with the molecular relationship between genes and the nutrients in the body (Nutrigenetics) and these influences effect changes in transcript profile (transcriptomics), metabolites (metabolomics) and proteomics. It influences health conditions of individuals and susceptibility of disease by defining metabolic response and gene expression. These associations can particularly exert an impact on digestion, absorption, metabolism as well as excretion of bioactive food components. Nutrigenomics defined as the influence of dietary components on genetic variations and effect of nutrients, bioactive food ingredients on gene expression separately. (Riscuta 2016; Simopoulos 2010).

Nutrigenetics and transcriptomics combined with “omic” like metabolomics and proteomics that actually responsible for the extensive variability in cancer prevention and risk among persons. (Hurlimann et al. 2014; Kaput 2008).

Nutrigenomics includes epigenetics, transcriptomics, and nutrigenomics, combined with other "omic, for example, metabolomics and proteomics that evidently represent the large fluctuation in tumor hazard among people with comparable dietary preferences (Hurlimann et al. 2014; Kaput 2008). Various studies on multiple food constituents including phytochemicals, essential nutrients, and chemicals obtained from bacteria, zoo chemicals, and fungo chemicals had shown different results in cancer and tumor risk reduction behavior. (Vasconcelos 2010). It is proven from a wide range of verdicts that not all persons respond identically to a diet. Nowadays, substantial emphasis is on genome-wide association studies (GWAS) to identify genes that facilitate diseases like cancer and other chronic diseases. Some of the GWAS are in contrast with a large majority and considered as a dietary variable. Moreover, at this stage, GWAS have widely reconfirmed the known facts and still continue to disclose the fact that it will not be a relaxed job to recognize the most significant genetic variables probably due to laid-off cellular controlled methods (Fenech 2008; Ferguson 2009).

It has long been recognized that human response differently to the food they consume. Food components not only affect health but also metabolism, cell, and organs as well. Nutrigenomics is based on two observations (1) effect of nutrients on gene expression (2) nutrient metabolism may differ among individuals genotypes hence effecting health differently. Thus nutrigenomics includes gene and nutritional environment as well as individual’s genotypes in personalizing food and nutrition along with disease prevention (Iacoviello et al. 2008; Kussmann and Van Bladeren 2011).

### *Principles of nutrigenomics*

Nutritional genomics comprises of following principles.it includes metabolomics, transcriptomics, proteomics and epigenetics.

In some people diet is considered as an important influencing factor for various diseases under a particular condition. Subsequently, diet ingredients change the human genome by altering gene structure or gene expression. The genotype difference among individuals can illuminate the equilibrium between disease and health. Those genes that are dependent in its regulation on dietary factors may have a part in commencement, progression, and extent (Ardekani and Jabbari 2009; Elsamanoudy et al. 2016; Fenech 2008; Hardy and Tollefsbol 2011; Nicastro, Trujillo, and Milner 2012) (Figure 1).

## Epigenetics

Epigenetics was first described by Conrad Waddington in 1942 is a combination of two words epigenesis and genetics involving developmental events from fertilization to the whole organism. Currently, it deals with the chromatin remodeling and DNA methylation. (Choudhuri, Cui, and Klaassen 2010)

The word epigenetics denotes to the continual changes in DNA configuration without mutations in sequence but an expression of genetic material can be altered. It is the transmitted material constructed on gene expression. DNA methylation and chromatin remodeling are the most common epigenetic mechanisms. Epigenetic modifications can perform a significant role in disease occurrence and pathogenesis including cancer. Several studies have shown that genes are involved in DNA methylation and cycle regulation respectively (Nicastro, Trujillo, and Milner 2012). The epigenetic involves the modification of protein material and DNA, the change in chromatin structure occur due to the connection of DNA and histones but the arrangement of nucleotides remains the same (Nielsen and El-Sohemy

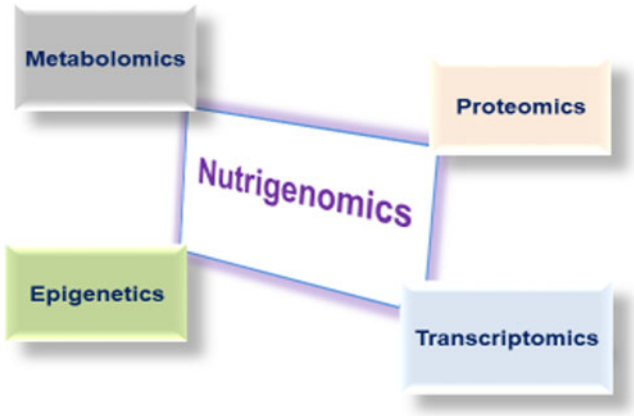


**Figure 1.** Principles of nutrigenomics.

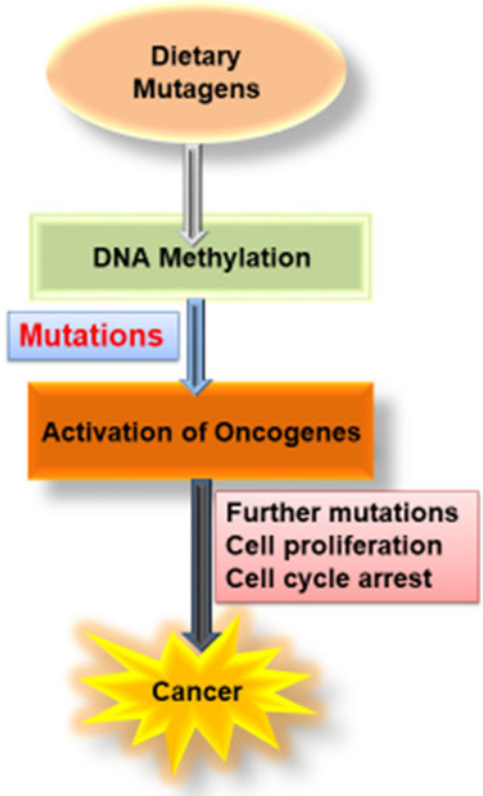


**Figure 2.** Figure depicts that mutagens from diet make changes in DNA methylation and leads to activation of oncogenes and cancer.

2012). It is the information transmitted by gene expression. The changes in epigenetics are slow and progressive but can be reversed possibly Certain nutrients have a role in histone modification and methylation process of DNA (Liu and Qian 2011).

### *Epigenetic molecular events*

Epigenetic events involve three types of regulations. (1) Histone modification (2) DNA methylation (3) gene expressions by nc-RNA. Chromatin structure is said to be a repeated set of nucleosomes that contain DNA and proteins called histones. Histone is a complex of eight proteins so-called octamer structure. The histone octamer consists of two fragments each containing histones H2A, H2B, H3, and H4. H1 histone is called linker histone that links physically, connects nucleosomes with linker DNA. Chromatin structure may undergo changes during metabolic events(Russo et al. 2017).

DNA methylation comprises covalent amendments in cytosine pairs at 5 carbon position of CG dinucleotides termed as CPG dinucleotides. Both DNA strands undergo methylation of cytosine through methyl donors S-Adenosyl methionine and DNA methyltransferase enzymes in replication process parent strand is methylated but the daughter strand remains un-methylated. The maintenance methyltransferase recognizes and methylates cytosine of daughter DNA hence restore methylation. DNA methyl enzymes are of two types one is responsible for methylation while other maintains the methylation process once it established. There are four DNMTs like DNMT1, DNMT2, DNMT3a, and DNMT3b. Any mutation in the replication process and improper restoration of methylation due to lack of enzymes and hypermethylation leads to DNA modification and results in the occurrence of diseases (Choudhuri, Cui, and Klaassen 2010). An example is folic acid metabolism in which folic acid ensures balance and secure amount of deoxyribonucleic acid for replication of DNA (Cozzolino and Cominetti 2013; Liu and Qian 2011). Folic acid act as a cofactor for enzymes responsible for the synthesis of nucleotides and thymidylate (pretentious material in RNA) (Sanhueza and Valenzuela 2012; Vahid et al. 2015).

Epigenetic mechanisms are responsible for variations in gene expression and chromosome structure, for example, histone acetylation and DNA methylation (Ronteltap et al. 2013). According to different studies, it is shown that methylation of DNA is directly related to the transformation of chromatin that in turn provoked by nutrient-dependent enzyme DNA methyltransferase responsible for transferring a methyl group from S-Adenosyl methionine to particular sites on DNA. (Choudhuri, Cui, and Klaassen 2010; Ronteltap et al. 2013). The S-Adenosyl methionine takes up its components from food vitamins like methionine B2, B6 and B12 and folic acid. A lack of these can prompt changes in carbon metabolism and accordingly weaken DNA methylation, increase the risk of NTCD. The hypermethylation of DNA suppress transcriptional genes and hypomethylation in the result of it leads to various malignancies. Prostate cancer and hepatocellular carcinoma are suitable examples of it. (Ronteltap et al. 2013; Sales, Pelegrini, and Goersch 2014; Shukla, Meeran, and Katiyar 2014; Uramova et al. 2018; Vahid et al. 2015).

## Mutations in cancer

Programmed cell death is a normal mechanism in the human body. As it was discussed above that genes are involved in DNA sequencing as well as biological processes. Mutations in genetic pathways lead to abnormal cell production or neoplasm. In different studies up-regulation of genetic pathways has been observed in malignant cells. Carcinogens present in diet and environment causes

Table 1. Dietary constituents, polymorphic genes, and location of the cancer.

| SR No | Dietary constituents | Phentype1 or Polymorphic genes | Site of cancer |
|---|---|---|---|
| **Carcinogens** | | | |
| 1 | Aflataxins | EPHX, GSTM 1 | Liver |
| 2 | Alcohol | ADH (CYP2E1, ALDH) | Colorectal, Liver, Oral |
| 3 | Heterocyclic amines | CYP1A1 | Multiple places |
| 4 | Nitrosamines | CYP2E1 | Liver and other sites (Hirose Y et al. 2002) |
| 5 | Polycyclic hydrocarbans | GSTM1, CYP1A1 | Stomach, GIT, Nasophrangeal |
| **Anticarcinogens** | | | |
| 1 | Calcium and Vit D | The receptor of Vit D<br>Receptors of retinoic acid | Prostate, Colorectal, promyelocytic leukemia,<br>Skin, Head and neck |
| 2 | Cruciferous vegetables | GST, CYP1A1 | Colorectal and other places |
| 3 | Folate, methionine | Synthase | Colorectal and cervix |
| 4 | Fruits and vegetables | GST, CYP1A1 | Multiple sites |
| 5 | Retinoids | Methionine, variant MTHFR | Breast |

ADH, alcohol dehydrogenase; CYP, cytochrome p450; EPHX, epoxide hydrolase; GST, glutathione-S-transferase; MTHFR, Methylenetetrahydrofolate reductase.
Data references: Nepomuceno (2013).

modifications in cell cycle regulation and leads to abnormalities. Carcinogenesis is defined as the accumulation of mutagens or epigenetic events in genes, in other words, proto-oncogenes become activated to oncogenes and there is the silencing of tumor suppressor genes (TP35) in the result of mutational shift and chromosomal rearrangements. Transcriptional deregulations in the result of epigenetic modifications may result in unfortunate expression of genes and may activate expressions for oncogenes and leads to cancer development. According to different studies genome irregularities like hyper or hypomethylation, down-regulation of mRNA and histone deacetylation are determined as proven markers in cancerous cells. (Ardekani and Jabbari 2009).

As it was discussed above that nutrients in diet interact with genes and epigenetics are influenced by dietary and environmental factors. Certain bioactive food ingredients or micronutrients are normally involved in DNA methylation, gene expressions, histone modifications, biological and metabolic regulatory pathways. Deficiency of any key nutrient, the absence of methyl donors or hindrance in methyltransferases can lead to mutations in genes by activating promoter genes and DNA hypo or hypermethylation resulting into silencing of tumor suppressor genes with age and cell proliferation leads to cancer development (Figure 1 and Table 1).

## Diet and cancer

According to epidemiological and clinical studies dietary factors are involved in cancer development. Dietary mutagen leads to mutations in normal pathways as they are involved in many biological and pathological conditions. Similarly, dietary based regimens and dietary components also have a preventive effect against cancer as DNA metabolism and repair depends on dietary factors served as a cofactor in metabolic pathways. Certain bioactive food compounds have proven role in cancer prevention through epigenetic mechanism genetic modification and nutrient-gene interactions and prevention from damage due to oxidative stress (Bull and Fenech 2008). Not only food preferences but also the amount of specific food components also affects genes. Plants phytochemicals and polyunsaturated have proven role in diet and cancer relationship. Not only these but also vitamins and minerals have a significant part in it. Polyphenolic compounds, phenolic compounds, carotenoids, flavones, flavanols, isoflavones from soy and sulfur compounds are still under the discussion. Lycopene from tomatoes, resveratrol from grapes and berries, numeric acid from cinnamons, hesperidin from citrus fruits, carotenoids from red vegetables and fruits, ascorbic acid, coffee acid from coffee, types of soluble fibers, polyunsaturated and fatty acids from marine animals have protective role in the cancer development (Hardy and Tollefsbol 2011). Minerals and vitamins from diet involve in regulatory and enzymatic processes. The deficiency of micronutrients leads to abnormalities. Moreover, zinc and folate involve in DNA repairing process but all compounds have the same mechanism. Some of the compounds have proven role in epigenetics while others may interact with genes other than DNA repairing and methylation. Some have a protective role against oxidative stress while some inhibit cell proliferation by modifying the inflammatory process (Elsamanoudy et al. 2016).

For example, there is an association between inadequate intakes of folate with colorectal cancer but the risk varies from person to person due to the genetic variation of individuals. Similarly, the risk of colorectal cancer due to consumption of red meat is also varied among individuals due to the difference in the genetics related to the metabolism.

Higher consumption of cruciferous vegetables decreases the hazard of lung and colorectal cancer among individuals with the low manifestation of enzymes responsible for secretion of sulforaphane (bioactive compound). These examples are few of many defining nutrient-gene associations in cancer (Table 2).

## Nutrigenomics/epigenetics: role of dietary components in cancer prevention

Several pieces of evidence have shown remarkably effect of dietary components in cancer prevention.

As discussed above a list of dietary regimens, food components, minerals and vitamins are involved in it but not all have the same mechanism. In nutrigenetics and nutrigenomics, nutrients interact with genes involved in the genesis of cancer while epigenetic role includes nutrients specifically targeting DNA methylation and histone modifications. In this review, we only discuss only those nutrients that have

**Table 2.** Key plants elements with epigenetic modifications.

| SR No | Key plants | Bioactive element | Epigenetic functions |
|---|---|---|---|
| 1 | Apples | Phloretin | Demethylation, reexpression TSGs, HDAC inhibition |
| 2 | Broccoli | Isothiocyanates | Chromatin remodeling, activation of P21gene |
| 3 | Cashew nuts | Anacardic Acid | Inhibition of histone acetyltransferase, DNA repair |
| 4 | Citrus | Hesperidin | DNMT inhibitor |
| 5 | Cinnamon | Coumaric acid | DNMT ihibitor |
| 6 | Coffee | Caffeic acid | DNMT inhibitor |
| 7 | Garlic | Allyl mercaptan | Histone acetylation, HDAC inhibitor |
| 8 | Grapes | Resveratrol | DNMT inhibitor |
| 9 | Soybean | Genistein | DNMT inhibitor |
| 10 | Tea | Epigallocatechin gallate (EGCG) | DNMT inhibitor |
| 11 | Tomatoes | Lycopene | Unknown |
| 12 | Tumeric | Curcumin | DNMT inhibitor |

DNA, deoxyribonucleic acid; DNMT, dinucleotide methylase transferase; HDAC, histone deacetylases.
Data references: Link, Balaguer, and Goel (2010); Nicastro, Trujillo, and Milner (2012).

proven potential effect in preventing cancer by interacting with genes other than DNA methylation (Nutrigenomics) and epigenetics (DNA methylation and modifications). Omega 3 fatty acids are the best example of nutrients and gene interaction not involving DNA methylation while in nutrients that modify DNA.

## Omega 3 fatty acids

Omega 3 fatty acids are considered as polyunsaturated fatty acids contains double bond at carbon number 3 in omega naming system. It is found in fatty and greasy fish while some amounts present in oils extracted from plants like flaxseed oil. Omega 3 fatty acids are proven anti-inflammatory agents against many diseases including cardiovascular and cancers. They have also proven their nutrigenetics role in which they interact with genes involved in inflammation and cancers. (Deckelbaum, Worgall, and Seo 2006) .The various animal in vitro studies has shown the effect of omega 3 fatty acids especially docosahexaenoic acid against prostate cancer (Groeger et al. 2010). Docosahexaenoic acid and eicosapentaenoic acid are mostly found in greasy fish, and late epidemiological investigations prove that continuous consumption of oily fish is associated with decreased risk of prostate tumor. Polyunsaturated unsaturated fats, both n-3 and n-6, are changed over in the body to eicosanoids, for example, prostaglandins and thromboxanes. These compounds usually remain involved in cell growth and differentiation, immune modulation and anti-inflammatory process. (Gu et al. 2013).

The mechanism by which omega 3 fatty acid prevents from carcinogenesis is the inhibitory effect on arachidonic acid synthesized eicosanoids (Wang et al. 2014). Eicosanoids are normally synthesized in our body from fatty acids. Eicosanoids that are derived from arachidonic acid have a pro-inflammatory effect while omega 3 fatty acid derived eicosanoids have anti-inflammatory effect and protection from prostate cancer. In the synthesis of eicosanoids cyclooxygenase -2 act as a key enzyme. Studies have shown that there is over production of COX-2 in case of prostate cancer.(Fradet et al. 2009; Sikka et al. 2012). Also, utilization of NSAID which suppress the Production of COX -2, is related to a decreased risk of prostate cancer (Sikka et al. 2012; Wang et al. 2014). Overproduction of Cyclooxygenase when the human diet is higher in arachidonic acid and leads to cancer. Eicosanoids derived from omega 3 fatty acids have an inhibitory effect on the overproduction of COX-2 and hence preventing prostate cancer as shown in the Figure 3 below.

In a case-control study conducted in Sweden observed a significant association between the use of salmon type fish, rich in n-3 unsaturated fats and a hereditary variation of COX-2 in deciding the danger of prostate malignancy (Hedelin et al. 2007). Among heterozygotes or homozygotes of the variant allele of +6365T/C SNP of COX-2, high consumption of salmon fish was related with a remarkable reduction in the risk of prostate malignancy, while there was no significant association found between fish use and tumor risk in wild-type allele carriers (Stefanska et al. 2010).

Marine n-3 unsaturated fats have been likewise producing defensive effect against carcinoma of the breast in postmenopausal women. This inhibitory effect is associated with the degree of lipid peroxidation produced in tumor tissues or cells (Hedelin et al. 2007; Iacoviello et al. 2008).

## Dietary polyphenols

Polyphenols also are known as polyhydroxy phenols are found in fruits and vegetables and present in human diet so-called dietary polyphenols (Gomez-Casati, Zanor, and Busi 2013). They are also called as secondary metabolites of plants produced by Shikimate pathway (Santhakumar, Battino, and Alvarez-Suarez 2018). Based on their chemical properties and structure they are classified into ten groups like phenolic compounds, flavonoids, benzoquinones, xanthones, lignins and acetophenones (Kok, Breda, and Manson 2008; Santhakumar, Battino, and Alvarez-Suarez 2018).

All polyphenols contain aromatic ring and at least one hydroxyl group. They derived from phenylalanine or their precursor shikimic acid. It has a huge range of chemical properties and structure from simple to complex. They comprise one or more than one sugar residue at one or more hydroxyl group (González-Vallinas et al. 2013) (Figure 4).

There are more than 800 polyphenols are available. Epigallocatechin is common polyphenols found in human diet from green tea, turmeric acid from cinnamon, resveratrol from the grape and curcumin from turmeric. Various studies have proved that dietary polyphenols have potential

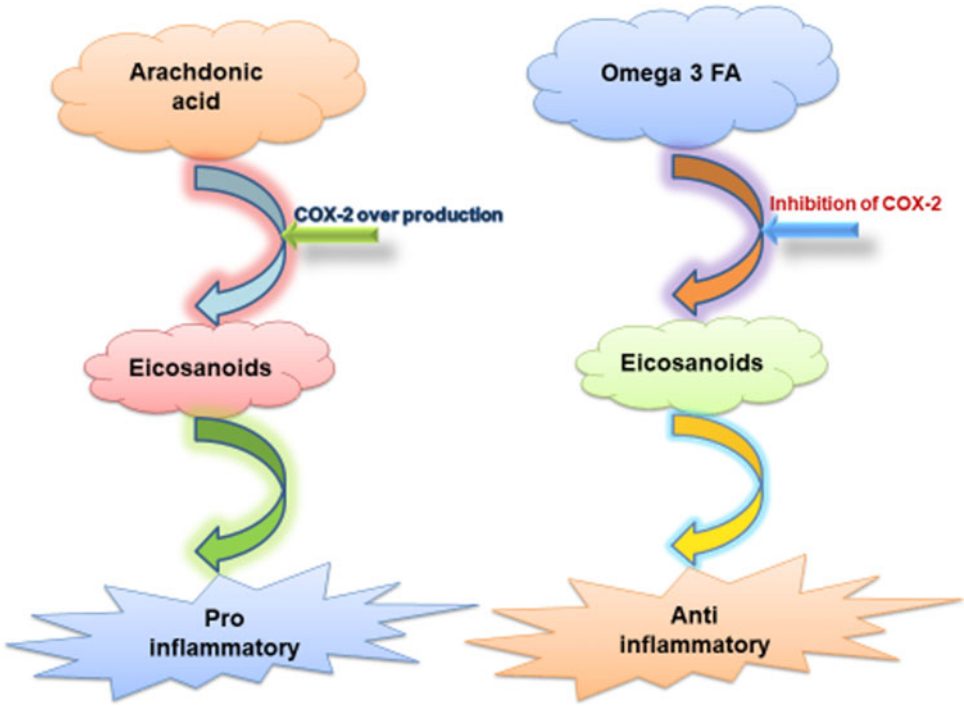


**Figure 3.** Figure showing that eicosanoids from ARA have pro inflammatory effect while eicosanoids from Omega 3 FA have anti-inflammatory effect.

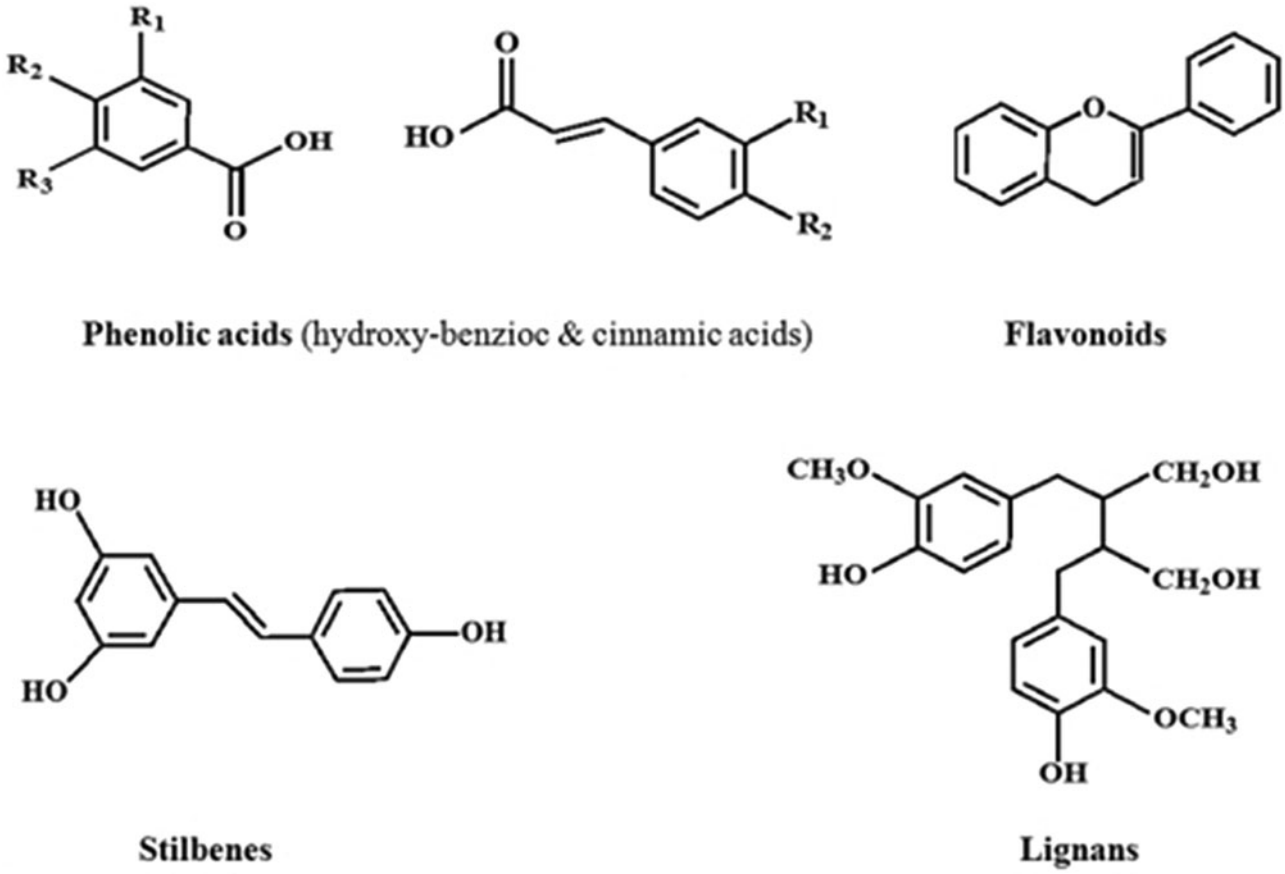


**Figure 4.** Structures of plant polyphenols.

health benefits including cancer prevention (Cui et al. 2010; Gomez-Casati, Zanor, and Busi 2013). Several mechanisms have been found by which dietary polyphenols prevent certain disease including their epigenetic role in cancer prevention by remodeling of chromatin material and activation of gene silencing. Cancer preventing the effect of dietary polyphenols may be outlined due to their ability to inhibit DNA methyltransferase and to modify histones. All

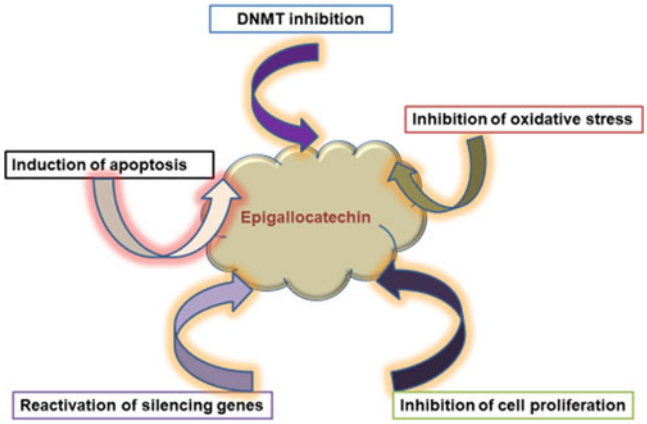


**Figure 5.** figure summerizing the epigenetic mechanism of eppigallocatachin in cancer prevention.

these characteristics of polyphenols can fundamentally alter the epigenome of tumor cells and are perceived as interesting potential outcomes for cancer prevention (Chen et al. 2017; Sehitoglu et al. 2014).

### *Epigallocatechin*

Polyphenols from tea and green tea have proven their role in many diseases including cancer. One subcategory of tea polyphenols are catechins that include, epicatechin 3 gallates, epicatechin, and epigallocatechin. All of these are similar in properties and proven their role in preventing cancer. Epigallocatechin accounts for 50% of all the bioactive compounds present in tea studied for anticarcinogenic properties. A number of studies significantly showed a positive correlation with consumption of epigallocatechin and prevention of oral, breast, skin, esophageal, colorectal, prostate, head, neck and pancreatic cancer (Fei et al. 2014). The mechanism by which epigallocatechin and EPC 3 gallate prevent cancer involves DNA methylation. Catechol-O-methyltransferase is the enzyme responsible for inactivating catechol molecules methylate epigallocatechin. S-adenosyl methionine donates a methyl group to catecholamines catalyzes by COMT enzyme. After the donation of methyl group SAM is called S-adenosyl Homocysteine (SAH). SAH is a potent inhibitor of DNA methyltransferases (Link, Balaguer, and Goel 2010; Ullah et al. 2016).

EPGC 3 gallate exerts its epigenetic role in preventing cancer by modifications in the epigenetic mechanism, cell cycle arrest and programed cell death, prevention from oxidative stress and angiogenesis. It inhibits the proliferation of tumor cells and regulates a single transduction pathway (González-Vallinas et al. 2013). As methylation cause silencing of genes, EPGC reactivates silenced genes by directly interacting with DNMT and involves in demethylation of the enzyme (Balasubramanian, Adhikary, and Eckert 2010; Farabegoli et al. 2010; Khan et al. 2018). Treatment of an esophageal cancer cell with EPGC studies had shown a reduction in DNMT activity, time and the dose-dependent relationship between restoration of methylation in genes including hMLH1, p16, RARb, and MGMT (Nandakumar, Vaid, and Katiyar 2011; Rady et al. 2018). Various Animal studies have shown that green tea treat prosttae cancer cells had significant decrease in tumor markers including MMP9, MMP2, VEGFA and alteration of PI3K pathway(Shankar, Montellano, and Gupta 2016b).

In human prostate cancer studies had showed that introduction of LNCap cells to green tea polyphenols cuases reexpresion of GSTP1 genes, GSTP1 prevent DNA damge due to recative oxygen species produced by $H_2O_2$(Guo et al. 2017; Jacob, Khan, and Lee 2017; Kanwal et al. 2014; Shankar, Montellano, and Gupta 2016b) .

Another study on A431 skin malignancy cells revealed that EGCG therapy reduces levels of global DNA methylation, as well as decreases the 5 methylcytosine levels, mRNA and DNMT action along with protein levels of DNMT1, DNMT3a and DNMT3b causing re-articulation of p16(INK4a) mRNA and p21/Cip1 mRNA. It was observed that EGCG has the potential to reactivate estrogen receptor-an (ER-an) articulation in ERa-negative MDA-MB-231 malignancy cells of the breast (Li et al. 2010; Uramova et al. 2018; Vahid et al. 2015).

For the very fisrt time taniguchi's group had showed that there is reduction of average number of nodules in lung and inhibition of lung metastases of B16 malignant cells upon admisnistration of 0.05 and 0.1% solution of EPCG in C57BL/6 mice (Fujiki et al. 2018).

DNA microassay studies from wild type versus Nrf-2-knockout mouse have shown that Nrf2 independent and Nrf2 dependet genes in liver and small inteestine were siginficantly modulated through epigallocatechins gallate. In addition to this EPCG activate Nrf2-ARE, Akt, ERK1/2 and HO-1 expression in endothellial cells while in B lymphoblasts it activates p38 and MAPK.

Another study had showed EPCG casues expression of Nrf2-mediated antioxidant and activation of ERK and P13K in epithelial cells of human breast (Qin and Hou 2016) (Figure 5).

### *Curcumin*

Curcumin is a polyphenolic compound present in commonly used spice turmeric and curry has proven its role as a wound healer, anticancer, anti-inflammatory agents with other health benefits. Multiple studies have demonstrated that curcumin inhibits DNMT action by covalently binding and blocking the reactive sites of thiolate of C1226 of DNMT1. Being hypomethylating agent curcumin inactivates the protooncogenes and prometastatic genes activity. Moreover, curcumin has an epigenomic impact on genomic DNA of leukemia cells by global hypomethylation of MV4-11 cells after curcumin intake. Wide analysis of genome demonstrated the role of curcumin in the prevention of colon cancer after time and dose-dependent intake due to its ability to modify methylation activities (Khan et al. 2018; Link, Balaguer, and Goel 2010).

Moreover, curcumin can perform an anti-inflammatory role said by Valinluck and Sowers. Halogenated cytosine initiates these kinds of impacts that stimulate 5-methylcytosine in DNA methylation and shows a significant association

between inflammation and epigenetic alterations (Hardy and Tollefsbol 2011; Vahid et al. 2015).

In addition to DNA methylation, curcumin also works as histone modifying agent and also has potential to inhibit HDAC and HAT while this effect is less as compared to other dietary polyphenols. Kang et al proved that there is a reduction in global acetylation of H3 and H4 in brain tumor cells after curcumin treatment. Moreover in an independent study conducted by Cui and Pollack revealed that promoter hypoacetylation of a few histones was facilitated by curcumin and related to silencing of genes. The ability of curcumin to hinder HDACs and Caps in a few infection models including tumorigenesis has been shown in various in vitro animal studies. While inhibition of the HATs and HDACs at the same time may appear to be contradictory. HATs inhibitors have a potential role in cancer treatment has been proven from various studies. It is proven from various studies that HAT inhibitors have a potential role in the treatment of cancer and that hindrance of HATs and HDACs together may give a powerful strategy against tumor treatment (Hardy and Tollefsbol 2011; Uramova et al. 2018).

### Apigenin

Apigenin is plant flavone (4, 5, 7-trihydroxyflavone), present in many fruits and vegetables. Parsley, celery and dried chamomile flowers also contain ample amount of apigenin. Apigenin is known potent anticancer agent by interacting with cancerous cell genes. Various studies have shown that apigenin prevents the expression of, MMP-9, cyclinD1, iNOS and COX-2. Apigenin prevents from cancer by inducing apoptosis in various cancerous cells including breast, hepatoma, skin, thyroid, prostate and leukemia by inhibiting DNA replication; inhibition of protein kinase, caspase activation, ROS generation and mitochondrial damage(Shukla et al. 2015). In study conducted by Shankar et al., it has been shown that feeding of 20 and 50 microgram apigenin per day for 20 weeks in TRAMP mice had reduce prostate cancer by inhibiting activation of NF-$\kappa$B (Shukla et al. 2015). Apigenin also inhibits invitro DNMT and HDAC-1 activity and reduce tumor growth through its epigenetic modifications. (Choi et al. 2014; Guizani et al. 2018; Khan et al. 2018; Pandey et al 2012; Shankar et al. 2016a).

### Resveratrol

Resveratrol is a bioactive compound known for its anticancer ability and it is available from red grapes, wine, blueberries, and mulberries. Anticancer properties of resveratrol have a preventive role in lungs, skin, prostate and breast cancer. However, it has less DNMT inhibitory movement than epigallocatechin of tea. It has also an epigenetic role to prevent silencing of tumor suppressor genes BRCA1(Weng et al. 2010). Various studies have shown restoration of mono methylations of H3K9, DNMT1, and MBD2 at the BRCA1 promoter in resveratrol-treated MCF-7 cancer cells(Khan et al. 2018)

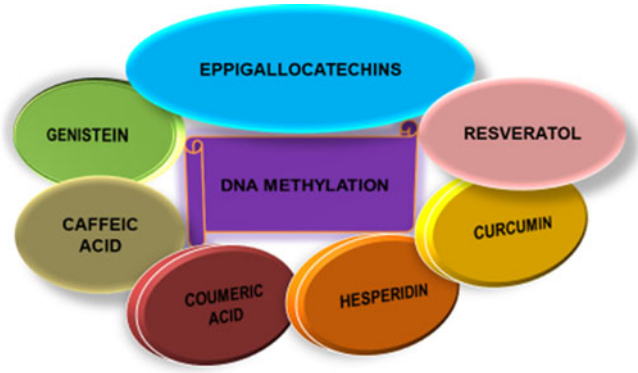


**Figure 6.** Figure represents the plant polyphenols that have effect on DNA methylation.

DNMT inhibition has appeared in nuclear concentrates from MCF-7 breast cancer cells treated with resveratrol despite the fact that resveratrol unable to return the methylation of certain tumor suppressor genes. Moreover, resveratrol is also impotent to hinder MGMT promoter methylation and RARb2 in MCF-7 cells (Hardy and Tollefsbol 2011; Papoutsis et al. 2010; Vahid et al. 2015).

### Genistein

Genistein is isoflavones belongs to the largest class of polyphenols known as flavonoid group. They are abundantly found in soybeans and also known as phytoestrogens or an estrogen-like compound having anti-cancer properties. Genistein has proven their dose-dependent epigenetic role in DNMT inhibition, gene transcription, and histone acetylation. Treatment of esophageal squamous cell carcinoma with genistein has shown a significant reverse of hypermethylation of DNA and also recurrence of p16, RARb along with MGMT Moreover, the same results were observed in prostate malignancy cells.

In prostate cells, genistein triggers the reactivation of the tumor suppressor genes including p16 and p21 by modifying histone and promoter methylation(Shankar, Montellano, and Gupta 2016b). Similarly, studies on breast malignancy cells treated with a low dose of genistein (3.125 $\mu$M) cause demethylation of the promoter of the GSTP1 genes. Genistein treated renal and prostate cells demonstrated a reversal of hypermethylation quality of a tumor suppressor gene known as BTG3(Shankar et al. 2016a).

Studies by Fang et al showed that 2-20 $\mu$M genistein causes methylation of silenced genes including p16INK4a, (RAR$\beta$) and MGMT in KUSE 510 esophageal cancer cells and LNCaP & PC3 cells of prostate cancer (Fang et al. 2005). Similarly King Batoon et al. had showed re administration of low dose of genistein (3.125 $\mu$M) for 1 week after every 48 hour cuses partial demethylation of tumor suppressor gene GSTP1 in MCF-7, MCF10A and MDA-MB-468 breast cells(King-Batoon et al. 2008).

Moreover, genistein combined with DNA methylation inhibitors or different DNMTs can improve the reactivation of qualities silenced by methylation. It was determined that genistein hinders DNMT1, 3a, 3 b, and expression of

hTERT. Genistein builds acetylation by enhancing HAT action(Khan et al. 2018). Moreover, various studies have determined that genistein initiated hypomethylation and hyperacetylation rejuvenate tumor suppressor genes in the prostate cancer cells (Hardy and Tollefsbol 2011; Link, Balaguer, and Goel 2010; Stefanska et al. 2010) (Figure 6).

## Micronutrients (minerals and vitamins)

Minerals and vitamins are an essential part of the human diet and a huge range of micronutrients (Minerals and Vitamins) available subsequently. Both minerals and vitamins play an important role in metabolism based reactions, they regulate certain important events by acting as a cofactor and key nutrient. The best example is the methylenetetrahydrofolate gene responsible for folic acid metabolism and maintaining normal blood homocysteine levels.

Low dietary intake of Folic acid leads to high homocysteine levels that are a marker of cardiovascular diseases (Elsamanoudy et al. 2016; Fenech 2008). As discussed above DNMT catalyzes the transfer of methyl group from S-adenosyl methyltransferase to particular sites in DNA and in return, it takes its deficient molecules from folic acid, vitamin B12, B6, choline, and methionine hence it is highlighting the role of vitamins in the epigenetic mechanism. In addition, significant protection against methylation in cancer cells of the lung was also observed after consumption of multivitamins. (Stidley et al 2010). Deficiency in any of dietary methyl donors can modify DNA methylation status and leads to tumorigenesis. As folate is an important methyl donor, its deficiency can cause liver, breast, brain, lung and colorectal cancer (Hardy and Tollefsbol 2011).

Selenium is recognized as epigenetic mineral found in nuts and beef. Se possesses anticancer properties due to antioxidant effect and DNA repairing mechanism along with pro-apoptotic ability. Se deficiency leads to cancer progression and it is proven that several Se binding proteins are involved in cancer development. Se exhibit DNA demethylation and reappearance of GSTP1 genes in prostate cancer cells. It also decreases histone deacetylase activity and increases acetylation of H3K9. Animal studies have shown the effect of Se in the prevention of colon and liver cancer. Similarly, Zinc is an important mineral act as a cofactor in DNA repair genes (OGGI) that are responsible for removal of oxidized guanine. Magnesium also acts as a cofactor for various DNA polymerases (Fenech 2008).

## Gaps and challenge and future perspectives

Nutrigenomics came into force in order to step forward from physiology and epidemiology to molecular genetics. On the basis of profound research in the emerging area of epigenetics, several directions in future could be pursued:

- At the level of gene expression, fighting cancer with dietary phytochemicals could be valuable and effective approach. It has also become an emerging area of research. It has been shown by the studies that many dietary compounds prevent cancer by targeting 22 epigenetic pathway but additional studies are needed with untested dietary agents.
- The emerging field of nutrigenomics and epigenetic explains the effect of nutrients on the epigenome and how it brings about a change by targeting DNA methylation, activity of HDAC and miRNA. The study of dietary phytochemicals about their combined effects and their course of action and targets is still at an early stage which may lay as strong foundation for epigenetic studies later on.
- The phenotype is evolved due to complex interaction of gene and environment. The gene-environment interaction in the ancestral, past and current environment is life longing process which results in remolding of epigenome. For designing personalized and advanced regimen for preventing and curing cancer, it is important to understand the role of different dietary phytochemicals as some of them are cell type while other are organ specific.
- It is evident by several studies that immune functions can alter if epigenetic mechanisms are disrupted which may lead to various disease phenotypes. It is an effective approach to target immune related pathway by understanding and manipulating the epigenome, with a focus on histone methylation of inflammatory genes and DNA modulation, with dietary phytochemical.
- Any defect in epigenetic may lead to irreversible genetic defect. Use of dietary phytochemicals by keeping appropriate time of intervention in consideration might be effective to reverse or slow down the progression of cancer.
- It is demonstrated by several studies that bioavailability and effects of chemoprevention can be enhanced by using nanomaterial encapsulation technology. Many dietary phytochemicals such as curcumin, resveratol, EGCG and genistein are encapsulated in nanoparticles to resolve the issues of poor absorption and bioavailability. This should be considered for further studies.
- The effect of different food ingredients and diet may differ from individual to individual and their biological systems. Nutrients and diet may alter the hormonal environment of a living being and may responsible for controlling switching on and off particular pathways (Endocrinomics) while Nutrigenomics deals with how each bioactive food ingredient effect gene expression. These two emerging fields could be combining in order to prevent and cure diseases.

Epihenetic treatment has appeared a glistening ray of hope in area of cancer therapies. Epigenetic variations help researcher to set biomarker profiles for different types of cancers as they are the primary events in cancer development and give consideration about nature and course of modifications. Dietary phytochemicals have a strong potential to modulate all major epigenetic pathways which involves methylation of DNA and modification of histones

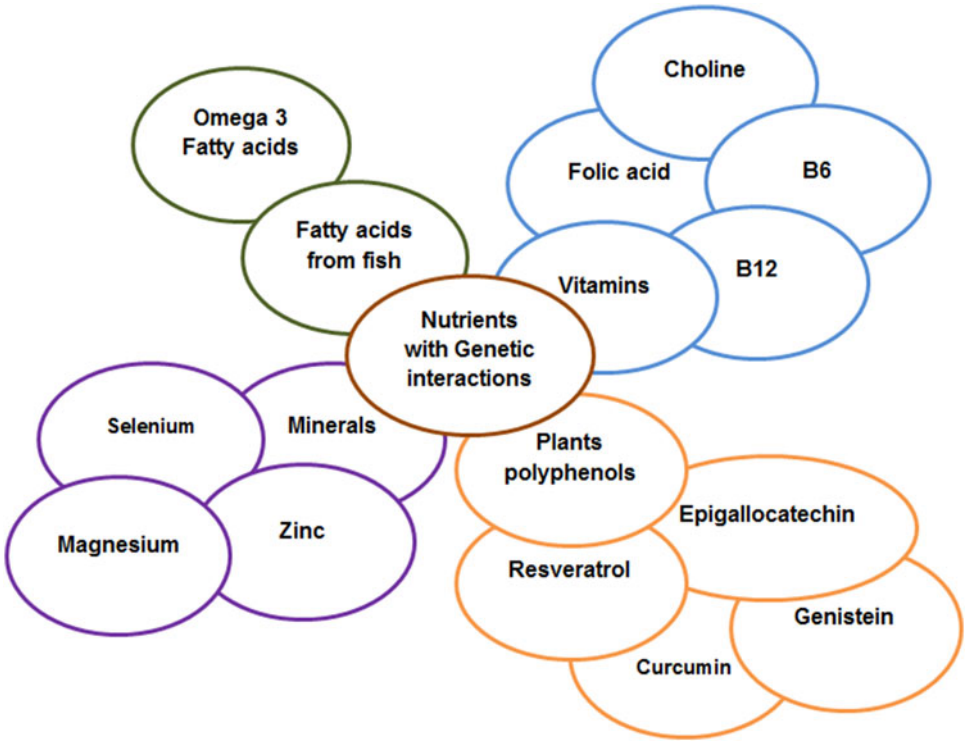


**Figure 7.** Figure summarizes all the nutrients and bioactive compounds discussed in this review.

and miRNA. Cancerous or transformed cells tend to lose their carcinogenicity due to modifications in the cellular activity of metabolic and regulatory pathways. Dietary phytochemicals in natural form are widely available and are less cytotoxic to healthy cells as compared to other chemicals. Advantages like oral bioavailability, cost effectiveness and wide range of gene target have been added due to epigenetically active compounds. In addition to all these advantages, they are capable of functioning for chemotherapeutic drugs as sensitizers when a person develops drug-resistance cancer. In multiple cancers, significant results have been shown by combining epigenetic therapy and chemotherapy. Multiple challenges regarding cure and prevention of cancer are still unsolved in spite of pre experimental and experimental evidences. First, the dietary compound involves several mechanisms. Due to multiple mechanisms, compound lack specificity which poses serious problem in determining the drug ability. Secondly, the epigenetic processes are reversible in nature and unwanted reversal may reduce the effectiveness of cancer therapy. Thirdly, the efficiency of epigenetically active compounds is compromised in immunotherapy whereas it shows better results in chemo-sanitization, chemoprevention and maintenance therapy. On the basis of these observations, epigenetically active compounds can't be used as the first line cancer therapy. In addition to all this, treatment by epigenetic therapy requires early diagnosis as its use at advanced phases of cancer are less effective because of advanced and various changes in cancer cells. Epigenetic modifications provide better understanding of global patterns, chemo preventive strategies and role of dietary phytochemicals to inhibit the cancer progression. Progression of cancer can also be prevented by the development of early diagnostic tools.

In addition to nutrigenomics other omic technologies including microbiomics and metabolomics can be used to fill the gap between research challenges resulting from effect of bioactive food ingredient on health outcome at individual level. Although there are many ingenious studies have been shown interaction between individual phenotype and bioactive food ingredient but there is still need of conducting more researches. By using omic technologies extraordinary data may be generated on bioavailability of food bioactive ingredient and physiological responses. There can be thorough classification of dietary patterns and individual response to bioactive ingredient by undertaking complete characterization of plant metabolome and human gut microbiome variability between the genotype at inter individual level.

There is need to fill the gaps presently frightening the omic restraints to draw strong relationship between bioactive ingredients and health outcome at inter Individual level. Nutrigenomics would categorize the genes or mechanisms showing inter individual variations and addressed the sensitive areas in conducting genetic information studies. Metabolomics would overcome the existing limitations of biomarkers specificity, validation, variation between individuals and quantification. Further limitations in omic studies include expensive studies, limited repeatable results and number of factors influencing results for example individual habits and medications change over time.

In last more efforts are required to assimilate the similar data with proven biomarkers to explore the effect of bioactive plant ingredients at inter individual and population level. The en route for personalized approach may assist in strong interpretation of data which may further benefit in multidisciplinary approaches. Overall there is need to

develop and implement multidisciplinary approaches to totally reveal the relationship between health and effect of bioactive food ingredients in succeeding actual personal based nutritional recommendations of bioactive food ingredients.

## Conclusion

It is well established that food and dietary modifications significantly reduces the risk of diet and lifestyle related diseases. Nutrigenomics in this regard is relatively fresh discipline but possess an enormous potential that can apply for prevention and management of certain carcinomas and diet-related diseases. Various studies suggest that nutrigenomics is a useful remedy for cure and prevention of the numerous types of cancers along with chronic diseases. It influences health conditions of individuals and susceptibility of disease by defining metabolic response and gene expression. Epigenetic modifications can perform a significant role in disease occurrence and pathogenesis including cancer. DNA methylation and chromatin remodeling are the most common epigenetic mechanisms. Certain bioactive food compounds and nutrients have proven role in cancer prevention through an epigenetic mechanism, genetic modification, and nutrient-gene interactions (Figure 7).

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## Financial and competing interests

There is no financial and competing interest of the authors in this publication.

## Author contributions

Principle author Ayesha Nasir (RD) was involved in basic execution, design and write up of the article. Dr. Mir M Hassan Bullo (MBBS, MSPH) has given major input in the write-up, advance execution and formatting of the article. Esha yaqoob was engaged in the literature search. While the final review was completed by the Dr. Zaheer Ahmed (MPhil Ph.D.), Dr. Mahpara Safdar (MPhil, Ph.D.) and Dr. Hajra Ahamed (MPhil, Ph.D.) at AIOU Islamabad.

## Abbreviations

| | |
|---|---|
| AA | Arachidonic acid |
| AIOU | Allama Iqbal Open University |
| BRCA1 | Breast Cancer Susceptibility Gene 1 |
| BTG3 | B-cell Translocation Gene 3 |
| COMT | Catechol-O-Methyltransferase |
| COX-2 | Cyclooxygenase 2 |
| CpG | Cytosine-phosphate- Guanine |
| DHA | Docosahexaenoic Acid |
| DNA | Deoxyribonucleic Acid |
| DNMT | Deoxyribonucleic Acid Methyltransferase |
| EGCG | Epigallocatechin Gallate |
| EPA | Eicosapentaenoic Acid |
| GSTP1 | Glutathione S-Transferase Pi 1 |
| (GWAS) | Genome-wide association studies |
| H3 | Histone 3 |
| H4 | Histone 4 |
| HAT | Histone Acetyltransferase |
| HDAC | Histone Deacetylase |
| HAT | Histone Acetyltransferase |
| H3K9 | Histone 3 Lysine 9 |
| hMLH1 | Human MutL Homolog 1 |
| hTERT | Human Telomerase Reverse Transcriptase |
| MBD2 | Methyl Binding Domain |
| MCF-7 | Michigan Cancer Foundation 7 cells |
| MGMT | O-6-Methylguanine-DNA-Methyltransferas |
| mRNA | Messenger Ribonucleic Acid |
| NTCD | Neural Tube Closure Defects |
| NSALDs | Non-Steroidal Anti Inflammatory Drugs |
| RARB | Retinoic Acid Receptor Bet: ○$ |
| D | Registered Dietician |
| RNA | Ribonucleic Acid |
| SAM | S-Adenosyl Methionine |
| SAH | S-Adenosyl-L-Homocysteine |
| TP 35 | Tumor Protein 35 |

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