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Role of Nutrition in Epigenetic Modulation as a Preventive and Therapeutic Approach for Cancer

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ABSTRACT

Epigenetics is defined as heritable changes in gene expression and chromatin structure without changing the nucleotide sequence. Epigenetic effects are reversible and occurred mainly by changes in acetylation and methylation based on DNA. Epigenetic changes, through affecting the gene expression, can play preventive and therapeutic roles for several disorders including cancer. Recent studies have demonstrated that nutrition can modulate epigenetic and environmental factors which consequently have preventive and therapeutic effects on different cancers. The present study comprehensively reviews the role of some nutrients and micronutrients in the prevention and treatment of cancer and discusses their epigenetic aspects and modulations for different cancers.

Keywords: Epigenetic, Nutrition, Methylation, Acetylation, Cancer

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INTRODUCTION

A brief history of Epigenetics: The term epigenetics was introduced first by a biologist named Conrad Waddington in 1942 (1). Epigenetics generally refers to heritable changes in gene expression and chromatin structural changes that occur without any change in nucleotides of DNA. Most epigenetic changes occur through methylation of DNA and changes in histones.

DNA methylation usually occurs in the CPG islands that are located within or near the gene promoter. More than 70% of genes have these islands. CPG islands refer to a rich sequence of *CG dinucleotides* that are between 200 and 500 bp in length and their Cgbase measurement is at least 50-55%. DNA methylation usually takes place through the enzyme methyltransferase (DNAMTs). Through the enzyme methyltransferase, hypermethylation, the CPG islands cause the gene silencing and the transcription process stopping (2). Under normal conditions, in the body's normal cells, CPG islands are usually nonmetylated, but in the tumoral cells these islands can be hypermethylated. This change occurs along with the silencing of the tumor suppressing genes; so, abnormal methylation patterns at the promoter site are associated with the process of becoming malignant cells (3). Studies show that change in the

expression and activity of the enzyme methyltransferase is seen in many diseases such as autism, cardiovascular disease, type 2 diabetes and cancer (4-7); in addition, general hypermethylation can be seen in all cancers (8).

Changes in histones are among other epigenetic mechanisms that are carried out mainly after translation and the changes are done on *histone N-terminal*. These modifications include acetylation, methylation and phosphorylation (9-11). Changes in the histones take place through enzymes of histone methyltransferase (HMTs), histone demetylases (HDMs), histone acetyl transferases (HATs) and histone deacetylases (HDACs). Histone methyltransferase adds methyl groups to amino acids lysine and arginine in the histones. And histone demethylases cause separation of these groups from histones (12, 13). Methylation lysine can enable or stop the process of transcription, whereas methylation lysine normally activates the transcription (14). The balance between the enzymes of histone acetyltransferase (HAD) and histone deacetylases (HDAC) is also of great importance. So that if chromatin in a region is more acetylated, expression of genes available in the area will be more and deacetylation of histones (by histone deacetylases) will be combined with condensing chromatin and gene silencing (15).During recent years non-medication based techniques including physical and herbal agents have been dramatically developed for the treatment of different disorders (16-29). In the recent studies the relationship between nutritional factors and chronic diseases has been shown(30-34). On the other hand, nutrition is one of the important and influential elements in the epigenetic field and many foods show their role through an epigenetic process in the treatment and prevention of diseases. One of the diseases that are discussed in this context is cancer. Many studies have shown that nutritional factors found in vegetables and fruits can cause activation of tumor suppressor gene, apoptosis and suppression of cancer genes (35-37). Food phytochemicals, such as polyphenols in tea, genistein, resveratrol and curcumin have shown anti-cancer activities through the epigenetic effects(38, 39).

Dietary polyphenols: Dietary polyphenols found in fruits and vegetables includes an important part of the human diet (40, 41). Polyphenols found in food include epigallocatechingallate (found in green tea), curcumin (found in turmeric), and resveratrol (found in grapes). These polyphenols have a protective role against diseases, and play a noteworthy role in the prevention of cancer (42-45). These polyphenols have a potential to inhibit DNMTs and make changes in the histones that they may have anti-cancer effect through these two mechanisms.

Tea polyphenols: After water, tea is the most consumed beverage in the world (46). Studies have shown that compounds found in tea can prevent many diseases, including cancer. Tea contains phenolic compounds that these compounds have the protective effects against reactive oxygen species(38, 47). Epigallocatechingallate (EGCG) include over 50% of the active ingredients of tea and its anti-cancer role has been studied frequently (48) and its inhibitory effects on many cancers have been proven (49, 50). By several different mechanisms such as apoptosis induction, Inhibition of the cell cycle, inhibition of oxidative stress and angiogenesis as well as reducing the proliferation of cancer cells, EGCG applies its anticancer effects (51-54). Preliminary studies by Fang et al. showed that EGCG reduces *hypermethylation* in the tumor suppressor genes by reducing the activity of DNMT activity in esophageal cancer cells and thereby increases the activity of these genes (55). By inhibiting the HAT, EGCG reduces acetylation in factor of P65 transcription and thus reduces the amount of production of Kappa nuclear factor (*NFκB*) and interleukin 6 (IL6) (54). In addition, a tumor suppressor gene RECK *hypermethylation* adjustment in oral cancer cells, resulting in a significant increase in the expression of these genes will be (56). Recent studies have shown that EGCG modifies miRNA expression in liver cancer cells (57).

Curcumin: Curcumin is a polyphenol that its origin is turmeric (Curcuma longa). Curcumin is the main composition of turmeric and responsible for its yellow color. This nutrient ingredient has inflammatory and antioxidant activity as well as anticancer properties and as a therapeutic factor is used in, Indian and Chinese medicine (58, 59). Evidence suggests that curcumin is an effective factor in *hypomethylation* of *DNA*that could facilitate the expression of inactive proto-oncogenes (60, 61). Curcumin has epigenomic effects on DNA of cancer cells and general hypomethylation has been seen after treatment with curcumin (62) and also causes GADD153 expression and induction of apoptosis in lung cancer cells (63). By inhibiting histone acetyltransferase (HAD) and histone deacetylase (HDAC), curcumin causes changes in the histones. Studies show that curcumin is associated with inhibition of HAD activity, thereby reduction in the H3 and H4 acetylation in brain cells. In addition, curcumin causes *histone methylation* of several promoters and silencing of genes. While inhibition of both enzymes of HAD and HDAC contradict each other, recent studies show that inhibition of HAD plays a potential role in cancer treatment, but inhibition of both enzymes is a strong strategy for the treatment of cancer and it normally causes stop of cell cycle and apoptosis (64, 65). Several studies have shown that curcumin can inhibit the activity of p300 / CBP

in leukemia and the uterus cancer (66). There is also evidence that curcumin prevents hypermethylation of histones induced by HDAC inhibitors in peripheral blood lymphocytes and cancer cells (67).

Resveratrol: Resveratrols are found in polyphenolic food and are usually seen in several plants, including peanuts, strawberries, blueberries and most of it is found in grape skins(68) . Antioxidant, anti-inflammatory and anticancer properties of resveratrol occur through different and molecular biochemical pathways (69). Antiproliferative properties of resveratrol have been reported in cancers of liver, breast, prostate, lung and colon (70, 71). Studies have shown inhibitory effects of resveratrol DNMT compared with EGCG is less. However, resveratrol can prevent the silencing of tumor suppressor genes (BRCA1) (72). Resveratrol activates the SIRT1 and the P300, which are known as inhibitors of histone deacetylase (HDAC) (73). Enzymes converting acetyl groups to HDAC are among histone lysines. To date, at least 18 HDAC isoenzymes have been identified that are divided into several categories. Several studies have reported the relationship between class I HDACs with malignant tumors progress while the relationship is rarely seen in the Class two of these enzymes (74). Many studies have examined the anti-aging effects of resveratrol. In a study, Bauer *et al.* reported that resveratrol can increase longevity and improve health in mice with a high-calorie diet (75). The inhibitory effects of resveratrol in oxidative conditions today are approved over the past. Resveratrol prevents oxidative DNA damage in the presence of metal ions such as iron and copper (76).

Isoflavones (genistein): Isoflavones are among the flavonoids group and the largest class of polyphenolic compounds. Polyphenols are found in a number of plants such as soybean and bean. Reviews on isoflavones have shown that these compounds have anti-cancer properties. Among the isoflavones, most studies have been conducted on genistein and their results have shown that genistein is a phytoestrogen, which due to have pseudo-estrogen compounds can have a role in the prevention of several cancer types (77). Several mechanisms have been attributed to anti-cancer properties of genistein, including the ability to regulate gene transcription with effect on *histone acetylation* and *DNA methylation* (78). According to the studies conducted on prostate cancer cells, by making changes in histone methylation and promoter, genistein induces the expression of tumor suppressor genes (P16 and P21) (79). Genistein inhibits DNA methyltransferase (DNMT1, 3a and 3b) and increases acetylation by the increased activity of HAT. In addition, genistein and other isoflavones help regulate miRNA expression in cancer cells (80, 81).

Isothiocyanates: Cabbage family is rich in *glucosinolate*. Hydrolysis of glucosinolates by plant enzymes of *myrosinase* causes the production of indole and isothiocyanate (82). Studies show that isothiocyanates have preapoptosis and antiproliferative properties as well as anti-cancer properties with the effect on the genome (83). Treatment with use of Isothiocyanate has been reported to prevent esophageal tumorigenesis in mice (84). Allyl isothiocyanate found in broccoli can increase histone acetylation in *mouse erythroleukemia cells*. *Phenylhexyl isothiocyanate* (*PHI*) is a synthetic isothiocyanate that cause inhibition of histone deacetylases (HDAC), hypomethylation of P16 and hypermethylation of histone H3 (85). In addition, by inhibiting the activity of HDAC, PHI plays a role in the reconstruction of chromatin for activation of P21 and stop of cell cycle in prostate cancer and leukemia cells (86). Another main compound of isothiocyanate is *Sulforaphane* (*SFN*) can be found in the cabbage family such as broccoli. Studies have shown that dietary SFN has anticancer activity in several types of cancer (87, 88). SFN can induce apoptosis and affects cell cycle through inhibition of HDAC. HDAC inhibition by SFN represents its epigenomic effects that can cause histone acetylation of a large number of genes that could be involved in the regulation of cancer-related genes(89, 90). The studies showed that treatment with the SFN cause inhibition of HDAC activity in colon and prostate cancer cells. In addition, SFN can cause inhibition of DNMT in breast cancer cells and inhibition of gene expression of human telomerase (Htert) that can be seen in more than 90% of cancers (91, 92).

Alliums: Garlic, onions and shallots are from Allium family that has organosulfur compounds soluble in fat and soluble in water, some of which are discussed in the prevention and treatment of cancer (93, 94). Allyl derived from garlic was one of the first compounds that its effect was examined on the change in histone. Allyl mercaptan (AM), *Diallyl disulfide* (*DADS*), *S-Allyl cysteine* (SAC), *S-allylmercapto*-L-cysteine (*SAMC*) and allicin increase the acetylation of histones in human cancer cells. Among organosulfur compounds derived from garlic, AM has a stronger impact on the inhibition of HDAC. In the human colon cancer cells, AM causes *hyperacetylation* of *histones H3* and facilitation of action of Sp3 and p53 on the P21WAF1 promoter (95). Recently, it was found that DADS and DATS react directly in response to DNA damage in cancer cells (96, 97). According to some studies, by activating *Chk1*/*Chk2*/*Cdc25C pathway the* DATS causes stop of cell cycle in prostate cancer cells (98).

Butyrate: Butyrate is short-chain fatty acids that are created by the intestinal microbiota microbes via fermentation of dietary fiber and resistant starch in the colon. For the first time in almost forty years ago, it was found that by inhibition of HDAC, butyrate can cause a rapid rise in the *hyperacetylation* cells medium (99). Recent studies indicate butyrate, by inducing distinction and apoptosis in transformed cells, causes the prevention of cancer of the colon (100). Treatment of *HT-29 and HCT-116* human *colon cells* with butyrate caused the promoter demethylation and increased activity is RARβ2. On the other hand, butyrate does not cause general DNA demethylation and applies its demethylation' effects only on certain genes, such as RARβ2 promoter (101). In addition, butyrate is a HDAC inhibitor, and with increasing acetylation of histones, leads to increased expression of genes involved in cell differentiation and apoptosis in several types of cancer (102). Sodium butyrate alone or in combination with folate in mice with colorectal cancer, significantly increases acetylation of histones H3 and P21 gene expression (103). Although most natural foods have beneficial effects on the epigenome, this issue is not generalized to all the food products; so that alcohol consumption is associated with harmful epigenetic variations and with catching all kinds of cancers. For example, by examining patients with colorectal cancer, researchers found patients who consume alcohol have the amount of hypermethylation of gene promoter higher than people who do not consume alcohol (104, 105). There are many foods that can have useful epigenetic effects, including most important ones, i.e. tomatoes, parsley, coffee, etc., which are not mentioned in this article (106, 107). In line with our recent studies on cancer (108-117), this study designed and role of nutrition in molecular mechanisms involving in preventive and therapeutic approaches for cancer investigated.

CONCLUSION

Nutrition can play an important role through several mechanisms in the etiology, prevention, and treatment of various diseases, including cancer. In this context, epigenetic change is a new mechanism, which has been of interest to researchers. Based on a review of the literature, we can conclude that nutrients can be effective in the prevention and treatment types of cancer. On the other hand, Substances such as alcohol and endocrine disruptive may facilitate the carcinogenic via epigenetic changes. It seems that more animal and human studies are needed to achieve a epigenetic regime for the treatment and prevention of cancer.

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