Chapter

Diet-Epigenome Interactions: Epi-Drugs Modulating the Epigenetic Machinery during Cancer Prevention

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Abstract

The roles of diet and environment on health have been known since ancient times. Cancer is both a genetic and an epigenetic disease and a complex interplay mechanism of genetic and environmental factors composed of multiple stages in which gene expression, protein and metabolite function operate synchronically. Disruption of epigenetic processes results in life-threatening diseases, in particular, cancer. Epigenetics involves altered gene expression without any change of nucleotide sequences, such as DNA methylation, histone modifications and non-coding RNAs in the regulation of genome. According to current studies, cancer is preventable with appropriate or balanced food and nutrition, in some cases. Nutrient intake is an environmental factor, and dietary components play an importent role in both cancer development and prevention. Due to epigenetic events induce changes in DNA and thus influencing over all gene expression in response to the food components, bioactive compounds and phytochemicals as potent antioxidants and cancer preventive agents have important roles in human diet. Several dietray components can alter cancer cell behavior and cancer risk by influencing key pathways and steps in carcinogenesis, including signaling, apoptosis, differentiation, or inflammation. To date, multiple biologically active food components are strongly suggested to have protective potential against cancer formation, such as methyl-group donors, fatty acids, phytochemicals, flavonoids, isothiocyanates, etc. Diet considered as a source of either carcinogens that are present in certain foods or acting in a protective manner such as vitamins, antioxidants, detoxifying substances, chelating agents etc. Thus, dietary phytochemicals as epigenetic modifiers in cancer and effects of dietary phytochemicals on gene expression and signaling pathways have been widely studied in cancer. In this chapter, current knowledge on interactions between cancer metabolism, epigenetic gene regulation, and how both processes are affected by dietary components are summerized. A comprehensive overview of natural compounds with epigenetic activity on tumorogenesis mechanisms by which natural compounds alter the cancer epigenome is provided. Studies made in epigenetics and cancer research demonstrated that genetic and epigenetic mechanisms are not separate events in cancer; they influence each other during carcinogenesis, highlighting plant-derived anticancer compounds with epigenetic mechanisms of action, and potential use in epigenetic therapy. Recent investigations

involving epigenetic modulations suggest that diet rich in phytochemicals not only reduce the risk of developing cancer, but also affect the treatment outcome.

Keywords: diet, cancer, epi-drugs, epigenetic modulation, phytochemicals

1. Introduction

1.1 Epigenetics

Epigenetics is the study of the variations of genetic expression that has been referred to the heritable changes in gene expression without changes in the DNA sequence and described the interactions between the genome and the environment that leads to the formation of the phenotype [1]. Epigenetic modifications such as DNA methylation and histone modifications are able to affect gene expression mostly by interfering with transcription factors with DNA or may lead to structural rearrangement of chromatin thus promoting the expression of particular genes. These epigenetic mechanisms are those that alter the chromatin structure including DNA methylation of cytosine residues in CpG dinucleotides and post-translational histone modifications. Epigenetic regulations occur not because of differences in DNA structure, but because of chromatin alternations that modulate DNA transcription such as DNA methylation, that can mediate gene and environment interactions at the level of the genome. The mechanisms of epigenetics are thus the link between genome and phenotype [1, 2]. Epigenetic mechanisms play an important role in regulating gene expression. The main mechanisms are methylation of DNA and modifications of histones by methylation, acetylation, phosphorylation. Modifications in DNA methylation are performed by DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) proteins, and by enzymes, such as histone acetyltransferases (HATs), histonedeacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs) that regulate covalent histone modifications. In many diseases, such as cancer, the epigenetic regulatory system is disturbed [2]. MicroRNAs (miRNAs) are another epigenetic regulatory system that influences the regulation of gene expression, which are small RNA molecules, ~22 long nucleotides, that can bind to their target miRNAs and downregulate their stabilities and/or translation [3]. Recent investigations have shown the association of altered expression of noncoding RNAs in general and miRNAs in particular with epigenetic modifications [2–4], suggesting that epigenetic alterations can contribute to the carcinogenesis [3] and are considered a hallmark of cancer [4].

2. Epigenetics and cancer

The progression of cancer is driven not only by acquired genetic alterations but also epigenetic modifications [4]. Epigenetic changes have been reported during cancer development and are found in genes involved in cell differentiation, proliferation, and apoptosis [4, 5]. DNA methylation is the most extensively studied epigenetic mark which occurs on cytosines followed by guanine (CpG), in humans [4, 5]. Methylation of CpGs plays a crucial role in regulation of gene expression [5, 6], which is necessary for orchestrating key biological processes, such as cell cycle, differentiation, and genomic imprinting, where, DNA hypermethylation is found in repetitive genomic sequences to maintain these regions in a transcriptionally inactive chromatin state [4–6].

Cancer cells exhibit a global DNA hypomethylation, which causes chromosome instability leading to various mutations, loss of imprinting, activation of transposable elements disturbances in the genome, eventually, to cancer progression [5, 6]. On the other hand, a DNA hypermethylation of specific promoter regions of tumor suppressor genes leads to loss of expression of specific genes affecting pathways involved in maintenance of cellular functions, including apoptosis, DNA repair, and cell cycle, [5, 6]. Several tumor suppressor genes are silenced by promoter hypermethylation in tumors. Epigenetically mediated silencing of cyclin-dependent kinase inhibitor 2A, which is crucial for control of cell cycle has been reported in several cancers [5–7]. In addition, DNA hypermethylation-dependent silencing have been associated with the pathways regulated by microRNAs [5–7].

In cancer cells, DNA methyltransferases (DNMTs) are able to maintain DNA methylation and to de novo-methylate DNA of tumour suppressor genes [5, 6]. Recently, a new group of enzymes that induce demethylation of the DNA was found, the ten-eleven translocation (TET) enzyme family, that plays crucial roles both in tumorigenesis [5–7]. These aberrant DNA methylations are not limited to cancer cells; abnormal DNMT expressions are also linked to various diseases including cardiovascular diseases, type 2 diabetes, obesity, depression, anxiety disorder, dementia, and autism [7–9].

Gene expression is modulated by interactions between DNA methylation, histone modification, and nucleosome positioning effecting chromatin structure. Chromatin remodellers, chromatin-associated proteins, and methyl DNA binding proteins are important for structural modification of chromatin (**Figure 1**) [10].

Eukaryotic nuclei has histone proteins facilitating the dense packing of DNA and thus playing an essential role in the dynamic accessibility of DNA for transcription factors. In humans, there are two major histone families: linker histone (LH) and the core histones. The dynamic structure of chromatin allows changes in gene regulation [7–10]. The N-termini of histone proteins contain multiple lysine residues that are accessible to covalent modifications such as acetylation, methylation, phosphorylation, glycosylation, thus allowing regulation of gene transcription (**Figures 2** and **3**) [11, 12]. Aberrant expression of histone methyltransferases (HMTs), and histone demethylases (HDMs) has also been associated with cancer development [8–12].

In addition, cell cycle regulation, DNA repair mechanisms, chromosomal integrity, cellular senescence, and transcriptional activity of tumour-associated proteins such as

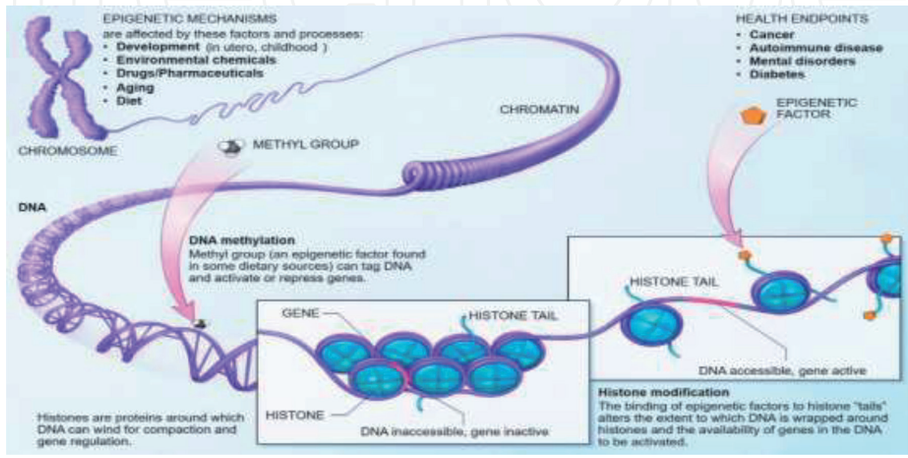

Figure 1.
Gene expression is modulated by interactions between DNA methylation, histone modification, and nucleosome positioning effecting chromatin structure [10].

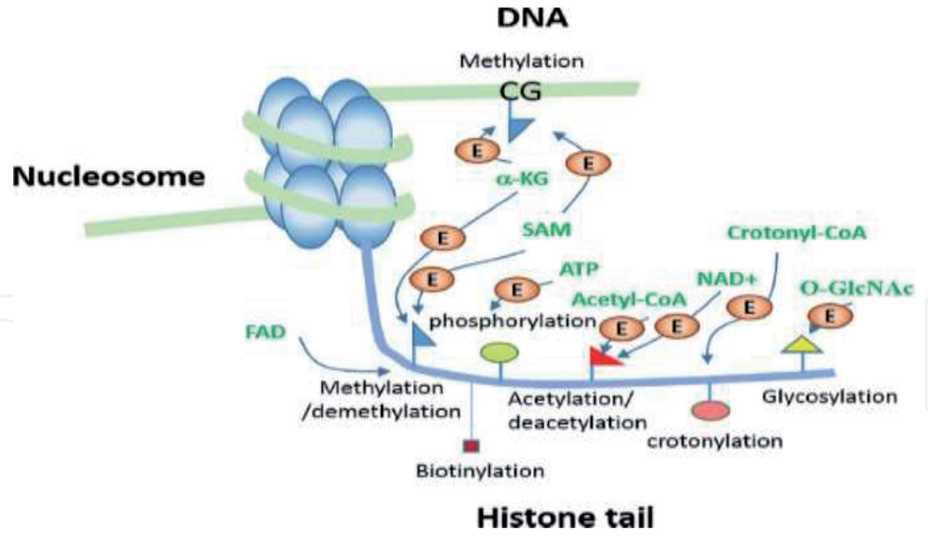

Figure 2.
Epigenetic markers on histone tails and DNA strand. Various enzymes (E) are responsible for the generation of epigenetic modification including DNA methylation/demethylation, histone acetylation/deacetylation, histone methylation/demethylation, histone biotinylation, crotonylation, phosphorylation and glycosylation [11].

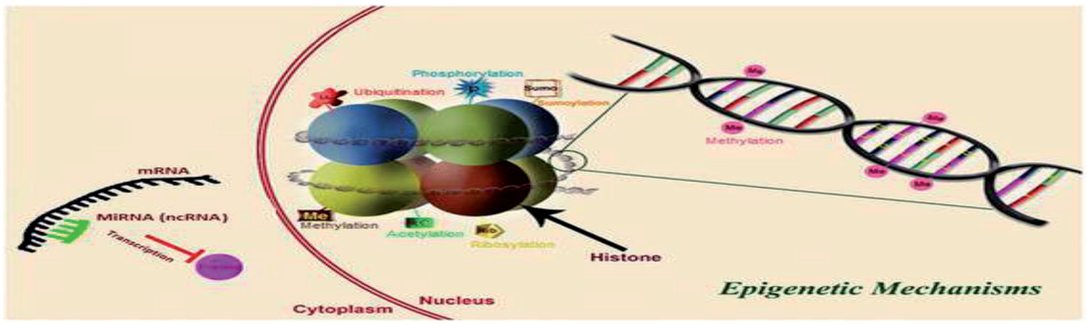

Figure 3.
Epigenetic mechanisms [12].

p53, nuclear factor kappa-lightchain- enhancer of activated B cells (NF-κB), and the FoxO family [10–14] rely on a stable cellular metabolic state. In majority of cancer cells genomic instability is found causing an increased vulnerability against DNA damaging agents [12–14]. Therefore, cancer cells might be more susceptible to exogenous compounds causing oxidative stress by production of reactive oxygen species than healthy tissues [13]. Oxidative stress plays an important role in epigenetic reprogramming of expression of tumour suppressor genes, cytokines, and oncogenes, thereby setting up a ground for carcinogenesis [13, 14].

Unlike genetic defects, epigenetic modifications are reversible and represent a promising field in therapeutic interventions [15]. Due to epigenetic aberrations occur in early stages of cancer, approaches in targeting the epigenome have been proposed as preventive and therapeutic strategies [15, 16], that aim to reverse cancer-associated epigenetic changes and restore normal gene expression. A synergistic combination of epigenetic modifying agents, including miRNAs, may provide a clinically important reversal of epigenomic cancer states.

It is known that the cause of cancer is a complex interplay mechanism of genetic and environmental factors. Dietary nutrient intake is an environmental factor and a marked variation in cancer development with the same dietary intake between individuals has been identified [17]. The effects of dietary phytochemicals on gene

expression and signaling pathways have been widely studied in cancer [17, 18]. The present review aims to clarify the basic knowledge about the vital role of nutrition-related genes in cancer, focusing on the role of dietary phytochemicals as epigenetic modifiers in cancer, and summarizing the progress made in cancer chemoprevention with dietary phytochemicals.

3. Diet and cancer

Cancer is a multi stage process composed of complex stages in which gene expression, protein and metabolite function operate aberrantly [19]. Inherited mutations in genes can increase one's susceptibility for cancer; while the risk of developing cancer can be increased markedly, if there is a gene-diet interaction [19, 20]. Epigenetic functions has reversible nature which made them attractive as targets for drug development. Epigenome is continuously changing due to environmental factors such as diet, and lifestyle factors such as stress and exercise. Diet has been demonstrated to have important impact on epigenetic mechanisms [19–21]. Changes in dietary intake have been shown to affect epigenetic functions providing a significant reduction in cancer risk and also contributing to disease prevention [19–21]. In addition, revision of diet in cancer patients has shown to be resulted in changes in gene expression, that can enhance therapeutic efficacy. Diets rich in fish, fibers, fruits, vegetables, and reduction in consummation of red meat have affected the epigenome, providing therapeutic efficacy [21].

The impact of diet and environment on human health has been known since ages. Diet can either be a source of carcinogens present in certain foods or a source of protective contituents (vitamins, antioxidants, detoxifying enzyme-activating substances, etc.) [22]. Cancer initiation and progression have been linked to oxidative stress by DNA mutations, genome instability, and cell proliferation; therefore antioxidant agents could interfere with carcinogenesis. Natural herbs have been used for prevention or treatment of diverse diseases for thousands of years; depending on the presence of bioactive components in plants that makes them appropriate choices to be used as food or medicinal purposes. Plant derived bioactive components confirmed the anticancer activities of natural dietary phytochemicals which resulted in an increase in comprehension of these compounds as a biological functional agent which has a theuropetic effect on human health [22]. Epidemiological studies reported that diet rich in fruits and vegetables have cancer preventive properties and several phytochemicals originated of edible plants have defensive mechanisms that prevent the induction of carcinogenesis by scavenging free radicals and by transducting signals in response to stress factors that activate proteins associated to cellular signaling pathways [22]; thus, dietary phytochemicals are able to be a chemopreventative agent toward cancer by inflection of the cancer cell cycle, proliferation inhibition, and initiation of apoptosis [22, 23].

Common dietary compunds can act on the human genome, directly or indirectly, by altering gene expression or structure; some dietary constituents affect post translation events [23]. Acetylation of histones and non-histone proteins has been shown to affect cell metabolism and can be targeted by inhibitors of histone deacetylases (HDACs) and histone acetyl transferases (HATs) [23, 24]. Natural compounds from broccoli, garlic, curcumin speculated to have inhibitory effects of HDACs and HATs with their influence on epigenetic mechanisms for normalization of the deregulated cancer cell metabolism [23, 24]. Dietary factors can also interact with hormonal regulation such as obesity that strongly affects hormonal status such as phytoestrogens [23, 24].

Plant-derived natural bioactive compounds (phytochemicals) have acquired an important role in human diet as potent antioxidants and cancer chemopreventive agents [23, 24]. Recently, the role of epigenetic alterations such as histone modifications, DNA methylation, and non-coding RNAs in the regulation of genome have been addressed (**Figure 4**) [25].

The present review outlines epigenetic mechanisms in the regulation of genome and the role of dietary phytochemicals as epigenetic modifiers in cancer; summarizing the progress made in cancer chemoprevention with dietary phytochemicals, and the challenges in the future.

3.1 Cancer control and prevention by diet and epigenetic approaches

Epigenetic mechanisms are known to be essential for normal development and maintenance of adult life. Disruption of epigenetic processes results in deregulated gene expression and leads to life-threatening diseases, in particular, cancer, which is defined as both a genetic and epigenetic disease. Genetic and epigenetic events are suggested to be susceptible to environmental and lifestyle factors such as radiation, toxins, pollutants, infectious agents, and diet (**Figures 5** and **6**) [26, 27], that affect the phenotype of cells and organisms. Diet is defined as more easily studied and therefore better understood environmental factor in epigenetic changes [26, 27].

Cancer is known to take many years to develop from initiation to progression, as the long period of development may represent an opportunity to use multi-functional preventive drugs to block or reverse tumorigenesis. Unlike genetic mutations, epigenetic alterations are potentially reversible and can be restored to their normal state, thus one path to cancer prevention can be to target and reverse these epigenetic defects. According to epidemiological studies there is a close link between rich diets in bioactive compounds and the low incidence of different types of cancer; regarding the impact of bioactive nutrients on the epigenetic mechanisms of gene expression, such as genomic DNA methylation, altered activity and expression of DNA methyl transferases and ten-eleven translocation enzymes, local DNA hypermethylation of gene promoters of tumor suppressor genes or of non-coding RNAs (microRNAs and long-noncoding RNAs), as well as global hypomethylation (**Figures 5** and **6**) [26, 27].

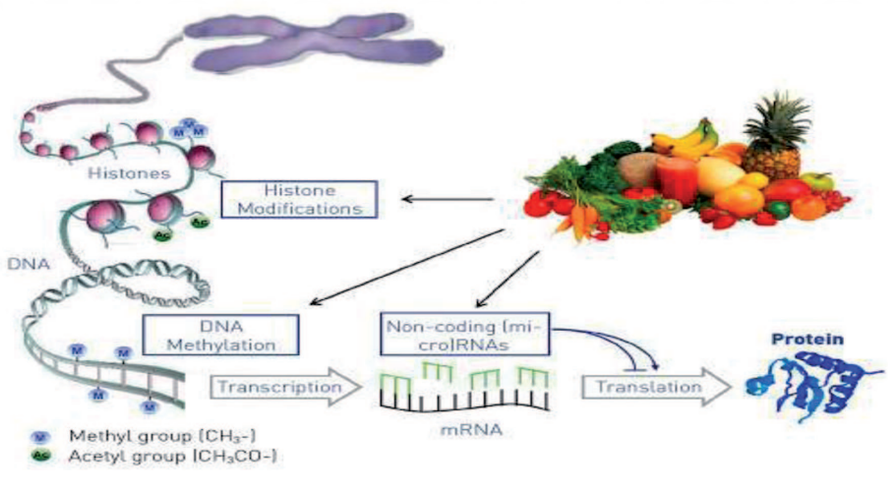

Figure 4.
Plant-derived natural bioactive compounds (phytochemicals) have acquired an important role in human diet as potent epigenetic modulators such as histone modifications, DNA methylation, and non-coding RNAs in the regulation of genome (from Daniele Segnini) [25].

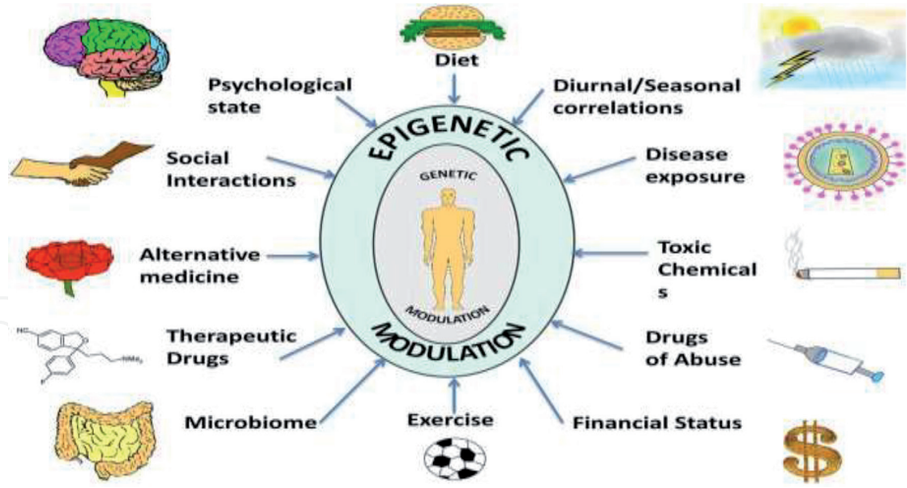

Figure 5.
Epigenetic events are suggested to be susceptible to environmental and lifestyle factors such as radiation, toxins, pollutants, infectious agents, and diet [26].

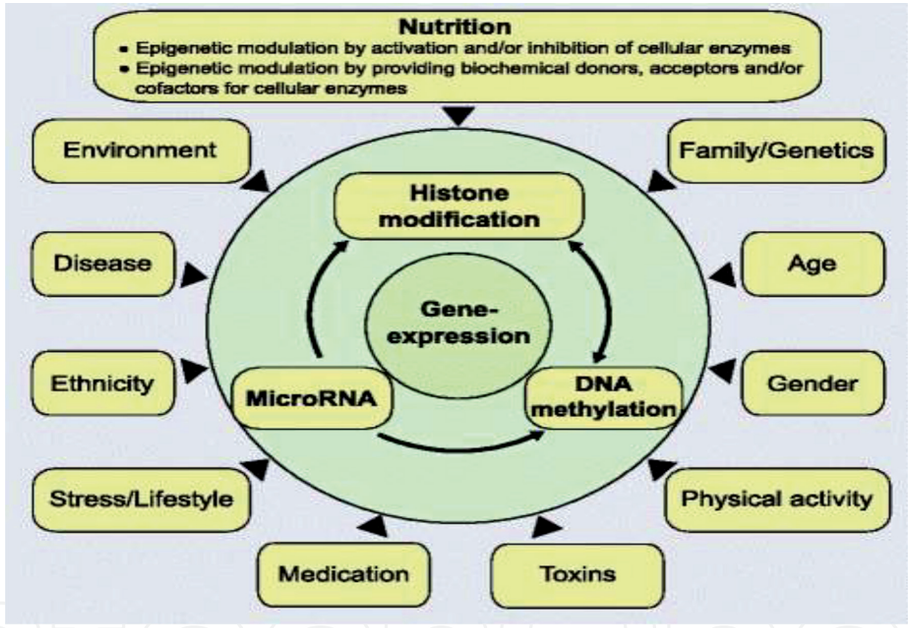

Figure 6.
Modulation and interaction of epigenetic mechanisms [27].

Dietary components play important roles in either cancer prevention or cancer development [28–31]. Intake of certain bioactive food components such as resveratrol (grapes), polyphenol-catechins (green tea), genistein (soybean), curcumin (turmeric), sulforaphane (cruciferous vegetables), and other bioactive components such as isothiocyanate (cruciferous vegetables), apigenin (parsley), silymarin (milk thistle), cyanidins (grapes), and rosmarinic acid (rosemary) (**Figure 7**) [28] is identified to play significant roles in modulating tumor risk and development [28–31].

Despite the investigations that epigenetic changes are heritable in somatic cells and epimutations are rare in healthy tissues, it is of interest to note that epigenetic modulations are potentially reversible. Depending on this property targeting epigenetic mechanisms have been a promising approach for cancer prevention [32]. Interestingly, altered diet is found to have transgenerational effects [33]. In a study done by Heijmans *et al.* [33] pregnant mothers during the Dutch Hunger Winter of

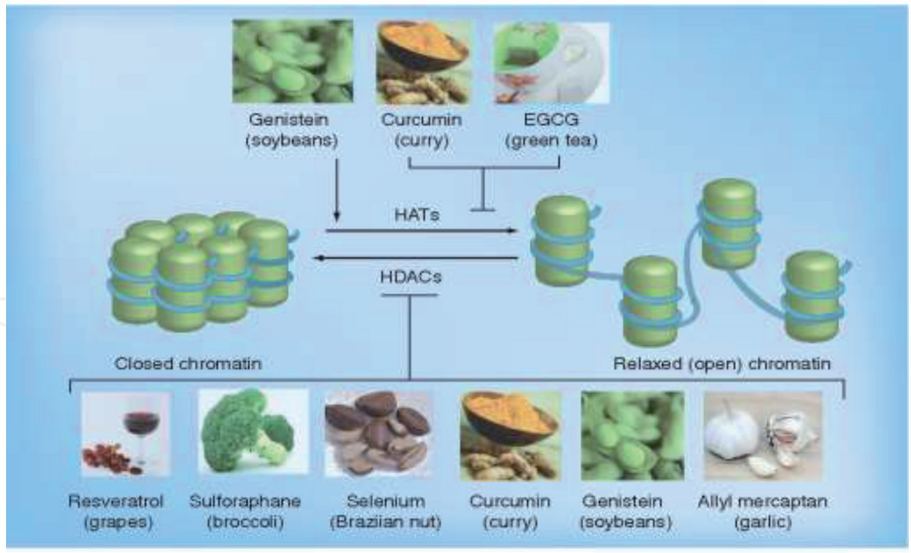

Figure 7.
Certain bioactive food components such as resveratrol (grapes), polyphenol-catechins (green tea), genistein (soybean), curcumin (turmeric), sulforaphane (cruciferous vegetables), and other bioactive components such as isothiocyanate (cruciferous vegetables) playing significant roles in modulating tumor risk and development [28].

1944 to 1945; methylation profiles of the mothers' offspring six decades later are followed and compared them with the profiles of their unexposed, same-sex siblings. The data indicated hypomethylation of insulin-like growth factor 2 (*IGF2*) and hypermethylation of interleukin-10 (*IL-10*), *LEP*, *ABCA1*, and *MEGF*; indicating the significance of diet components in the development of diseases including cancer [34].

Several diet components are demonstrated to alter tumor cell behavior and cancer risk by influencing key pathways and steps in carcinogenesis, including inflammation, cell signaling, cell cycle control, hormonal regulation, apoptosis, differentiation, and carcinogen metabolism [31–34]. While, antioxidant compunds such as polyphenols and resveratrol, are known to modulate proliferating cell nuclear antigen, *p21*, and *p27* [34, 35]; and indole-3-carbinol inhibiting cellular proliferation in human breast cancer cells [34, 35]; xenobiotic compounds, such as tobacco-specific carcinogens known to induce lung cancer [36].

Epigenetic modifications such as DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs are the most common epigenetic mechanisms. Dietary agents such as sulforaphane (SFN) found in cruciferous plants and epigallocatechin-3-gallate (EGCG) in green tea are demonstrated to exhibit various epigenetic mechanisms such as histone modifications via histone deacetylase (HDAC), histone acetyltransferase (HAT) inhibition, DNA methyltransferase (DNMT) inhibition, or noncoding RNA expression [37, 38]. These phytochemicals are shown to have an enhanced effect on epigenetic changes, which play a crucial role in cancer prevention [37, 38]. Meanwhile, restriction of glucose has been suggested to decrease the incidence of cancer and diabetes. Diet rich in compounds such as SFN and EGCG are reported to modulate the epigenome positively and lead to many health benefits; while reducing glucose in the diet is conferred to reduced cancer incidence [37, 38]. As a result, due to change in lifestyle and food habits, people can reduce risk of diet-related diseases and cancers. This review is focused on the phytochemicals that can affect various epigenetic modifications such as DNA methylation and histone modifications as well as regulation of non-coding miRNAs expression for treatment and prevention of various types of cancer.

3.2 Dietary compounds as epigenetic modulating agents in cancer

Drugs targeting epigenetic processes are called "epi-drugs", which are mostly plant-derived compounds that work through epigenetic mechanisms such as polyphenols, alkaloids, organosulfur compounds, and terpenoids [39]. Epigenetic mechanisms such as DNA methylation and posttranslational histone modifications regulate expression of various genes of changes in the DNA sequence, that play important roles in controlling cellular functions, including the cell cycle, signal transduction and immunoresponses [40]. On the other hand, epigenetic aberrations are associated with proliferation of cancer cells and oncogenesis, that these epigenetic alterations have been identified in many human cancer cells [40, 41]. This review focuses on the plant-derived anticancer drugs with epigenetic mechanisms of action, and their potential use in epigenetic therapy.

3.2.1 Therapeutic potential of polyphenols on DNA methylation

Plant-derived flavonoids as a therapeutic agents for cancer, attributed to their ability for epigenetic regulation of cancer pathogenesis [42]. The epigenetic mechanisms of various classes of flavonoids including flavonols, flavones, isoflavones, flavanones, flavan-3-ols, and anthocyanidins, such as cyanidin, delphinidin, and pelargonidin, are demonstrated [43]. These phytochemicals are mainly contained in fruits, vegetables and seeds, as well as in dietary supplements; that act as powerful antioxidants and anti-carcinogen agents; such as curcumin, catechins, genistein, quercetin and resveratrol.

As known, epigenetic modifications of chromatin are reversible and inherited, so they represent promising targets for the development of novel drugs targeting the epigenome which can contribute to amelioration of conventional therapies in cancer [44]. It has been reported that a diet rich in phytochemicals may act through epigenetic mechanisms such as modulation of DNMTs and HDACs activities that can significantly reduce the risk of cancer development by regulating the expression of oncogenes and tumor suppressor genes [45]. Cancer treatments are involved using chemo-radio therapeutic agents, kinase inhibitors, antibodies as well as certain compounds that stimulate the immune system, generally. Meanwhile, demethylating drugs modified gene expressions by reversing the aberrant epigenetic alterations acquired during tumorigenesis [44, 45]. In this context, polyphenolic flavonoid compounds may represent an alternative therapeutic option for cancer treatment.

Flavonoids are natural phenolic molecules that form a large group of secondary plant metabolites with important biological activities; subgroups of flavonoids are: flavonols such as quercetin, kaempferol, and myricetin; that are found in onions, curly, broccoli. The flavanones as hesperetin and naringenin that are found in grapefruit, oranges, and lemons. Isoflavonoids including daidzein and genistein are found in leguminous. The flavones as apigenin and luteolin that are present in cereals. The flavanols as catechin are found in green tea and chocolate, and the anthocyanins including cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin are present in berries, pears, apples, grapes and peaches [46]. The biological effects of flavonoids have been linked to their antioxidative activities, that these compounds inhibit cell proliferation, induce cytotoxicity, suppression of angiogenesis; and situmulation of apoptosis, in cancer (**Figure 8**) [27]; displaying diverse properties affecting epigenetic mechanisms such as modulation of the DNA methylation and histone acetylation [23–25].

Phytochemicals and other bioactive dietary compounds are reported to restore global and gene-specific promoter DNA methylation patterns by reactivating

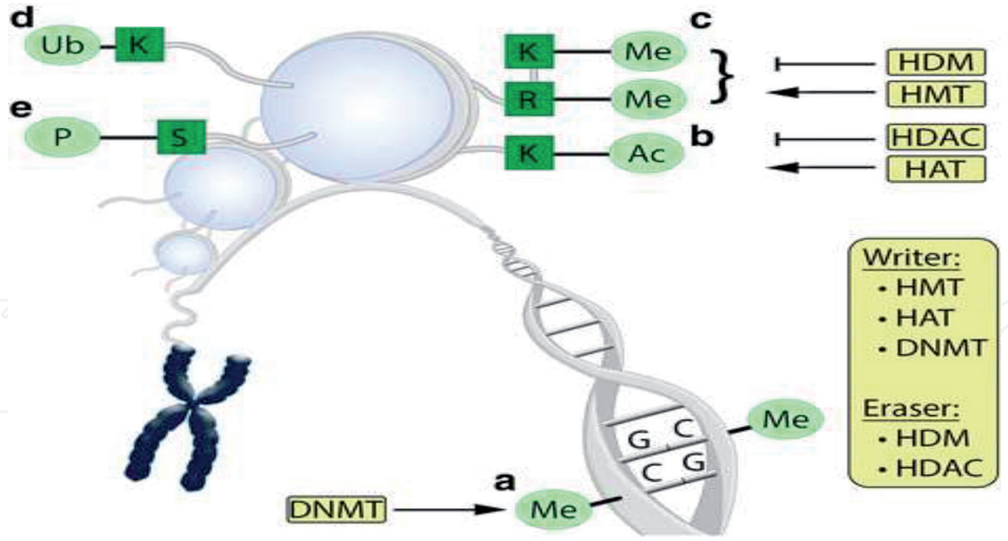

Figure 8.
Epigenetic machinery that is included the regulation of DNMTs and HDACs activities [27] (from Jan Frank).

DNA methyltransferases or by providing the provision of methyl groups [47]. This review focuses on the impact of modified DNA methylation pattern on early carcinogenesis and summarizes the effects/mechanism of phytochemical interventions on this type of epigenetic alterations. Recent investigations reported that flavonoids blocked the development and progression of tumors by targeting key signaling transducers resulting in the restoration of tumor suppressor genes, and inhibition of oncogenes expression [44–47] by modulating epigenetic machinery that is included the regulation of DNMTs and HDACs activities (**Figure 8**) [27].

Depending on epidemiological studies, dietary flavonoid intake is strongly suggested to reduce the risk of numerous cancer entities. According to current studies, cancer is preventable with appropriate or balanced diet and avoidance of obesity [48–50], in some cases. Multiple biologically active food components are strongly suggested to have protective potential against cancer formation, examples are methyl-group donors such as phytochemicals, flavonoids, isothiocyanates, allyl compounds, selenium and fatty acids [49–51].

3.2.1.1 Epigenetic effects of curcumin in cancer prevention

The yellow pigment curcumin (diferuloyl methane), a polyphenolic compound derived from turmeric (*Curcuma longa* Linn), a major ingredient of the spice curry, possessing remarkable antioxidant properties and has been studied for its potential anti-anticancer effects [52]. It has a broad spectrum of activities and acts on signaling pathways, particularly NF-κB signaling; has been shown to induce apoptosis and block invasion, metastasis, and angiogenesis for all major tumor entities [52]. It has been reported to modulate epigenetic changes in cancer cells, and has been shown to be a DNA hypomethylation agent in colon, prostate, and breast cancer, thus serving as a chemopreventive agent [53], other epigenetic studies include histone acetylation/deacetylation, and histone methylation/demethylation [52, 53]. Curcumin is first identified as an inhibitor of HAT activity; as a specific inhibitor of p300, also identified as inhibitor of acetylation of the tumor suppressor protein p53 as a non-histone protein target of p300 [52, 53], considering acetylation of p53 to be essential for

p53-dependent growth arrest and apoptosis; curcumin and its derivatives have also been identified as potent modulators of miRNAs [53].

3.2.1.2 Epigenetic effects of isothiocyanates in cancer prevention

Organosulfur compounds, isothiocyanates (ITCs), are the most investigated glucosinolate-derived bioactive diet components. The chemopreventive properties of ITCs on cancer, are well demonstrated [18, 38, 54]. Although the anticancer effects of ITCs, little attention has focused on their ability about the epigenetic processes that lead to epigenetic changes in cancer. Regular intake of organosulfur compounds is reported to protect cardiovascular health [18, 38, 54], besides prevent carcinogenesis stimulated by N-nitrosodiethylamine [18, 38, 54].

3.2.1.3 Epigenetic effects of green tea polyphenols in cancer prevention

Green tea polyphenols constitute a mixture of flavan-3-ols containing a catechol moiety. Biochemical compounds from green tea such as (−)-epigallocatechin gallate have been demonstrated to alter DNA methyltransferase activity in studies of various cancer cells. Mouse model studies have confirmed the inhibitory effect of (−)-epigallocatechin gallate on DNA methylation [27, 55].

3.2.1.4 Epigenetic effects of quercetin in cancer prevention

Quercetin is reported to have a broad spectrum of cancer-preventive activities: acting as an antioxidant and modulating enzymes and signaling cascades involved in detoxification, inflammation, proliferation, apoptosis, angiogenesis, autophagy, immune defense, and senescence; besides it has been suggested to have potential to inhibit DNMT activity *in vitro*, associated with p16 up-regulation at the mRNA and protein level and inhibition of cell proliferation [27, 56].

3.2.1.5 Epigenetic effects of resveratrol in cancer prevention

Resveratrol is a plant-derived stilbene derivative found in fruits, especially in the skin of red grapes [45]. It has been reported to have a broad spectrum of health-beneficial effects, including antioxidant, cardioprotective, and antitumor activities, which have mechanistically been linked to effects on cell signaling related to cell survival, apoptosis, inflammation and tumor angiogenesis [45, 46]. Resveratrol was shown to prevent carcinogenesis in animal models for various cancer typesi, and reduced xenograft growth of various tumor cell lines. For example, activation of the aryl hydrocarbon receptor (AhR) has been shown to lead to epigenetic silencing of the DNA repair gene BRCA1 in breast cancer [57–59].

3.2.1.6 Epigenetic effects of anacardic acid in cancer prevention

A component of cashew nut shell liquid, anacardic acid (6-nonadecyl salicylic acid), is identified as a natural-product inhibitor of the HAT enzyme which is involved in the activation of key enzymes of DNA damage response, which is also found to inhibit p300-mediatedacetylation of the p65 subunit of NF-κB (nuclear factor "kappa light-chain enhancer" of activated B cells) as a non-histone substrate of HATs, and inhibited NF-κB-mediated signaling involved in inflammation, cell survival, proliferation, and invasion [60–62].

3.2.1.7 Epigenetic effects of gallic acid in cancer prevention

Gallic acid (3,4,5-trihydroxybenzoic acid), having high antioxidant activity is found in various fruit, tea and coffee, witch hazel, sumach, oak bark, walnuts, berries and other plants, as free tannins and as part of hydrolyzable tannins (gallotannins) [63]; has been shown to reduce oxidative DNA damage and to induce apoptosis in cancer cells [64]. It is identified as a specific inhibitör of HAT activity *in vitro*, and finally reduced NF-κB activation and expression of anti-apoptotic genes in response to pro-inflammatory stimuli [64].

3.2.1.8 Epigenetic effects of delphinidin in cancer prevention

Fruit, particularly blueberries contain anthocyanidins that have high antioxidant potential; possessing antiproliferative activity, inducing apoptosis and cell differentiation, and inhibiting angiogenesis and invasiveness, contributing to their high chemopreventive potential [60, 61, 65]. Overall, anthocyanidins have been shown to prevent cancer, and delphinidin has been identified as a HAT inhibitor [65]. HAT-mediated acetylation of histones and non-histone proteins seems to play an important role and; as gallic acid, delphinidin is proved to reduce pro-inflammatory signaling by preventing acetylation of the NF-κB [65], contributing to the anti-inflammatory activity of chemopreventive polyphenols [65].

3.2.1.9 Epigenetic effects of flavolignan silymarin in cancer prevention

Milk thistle (*Silybum marianum*) is used to protect liver against various diseases, and poisions. Silymarin is derived from milk-thistle seeds contains at least seven flavolignans and additional components. The most abundant compound is silybinin (or silibinin), existing as isomers, silybin A and B. Cancer-preventive potential of milk-thistle has been attributed to the inhibition of cell growth, angiogenesis, tumor invasion, metastasis, and inflammation [66, 67]. It is reported that silybinin treatment reduced the growth of human liver cancer xenografts through induction of apoptosis, and this was associated with an increase in histone H3 and H4 acetylation [68].

3.2.1.10 Epigenetic effects of genistein and soy isoflavones in cancer prevention

Isoflavones (genistein and daidzein) are a class of flavonoids found in plants of the *Fabaceae* family abundantly, and characterized by phytoestrogenic properties. They are contained in high amounts in soybean (*Glycine max* L.) and are enriched in soy products. Epidemiological studies indicates an inverse correlation between a traditional soy-rich, low-fat Asian diet and the risk of developing breast and prostate cancer [69, 70]. As soy isoflavones and phytoestrogens bind to the estrogen receptor and modulate ER signaling; genistein has been shown to affect several additional chemopreventive mechanisms, including inhibition of oxidative stress, activation of carcinogens, cell signaling, angiogenesis, modulation of cell-cycle regulation, induction of apoptosis and inhibition of inflammation [71]. Recent investigations of a growth-promoting effect of genistein in ER-positive breast-cancer cell lines and xenograft models have indicated a potential risk of genistein for human health [72]; while another recent review does not support these concerns that genistein is tested in various clinical trials for the treatment and prevention of prostate, bladder, kidney, breast, and endometrial cancer [73]. Nutrients are classified that supply methyl

groups have been shown to have a protective effect in various cancer types, such as curcumin, isothiocyanates, green tea polyphenolics, quercetin, resveratrol, anacardic acid, gallic acid, delphinidin, silymarin, silybidin, and genistein that are found in various food components and medicinal plants are summerized in this chapter (**Figure 9**) [74].

These were the best known bioactive food compounds; besides these dietary components folic acid, alliin and allicin in garlic, omega 3 fatty acids, pigments such as licopene, carotenoids and anthocyanins, multivitamins such as vitamine A, C, E, vitamine B12 moreover, minerals such as zinc and selenium are the examples of nutrients that have a proven role in cancer prevention through an epigenetic mechanism [59–61, 74–77]; that substantially take part in prevention of various cancer types such as oral, breast, skin, esophageal, colorectal, prostate, pancreatic and lung cancers (**Figure 10**) [74].

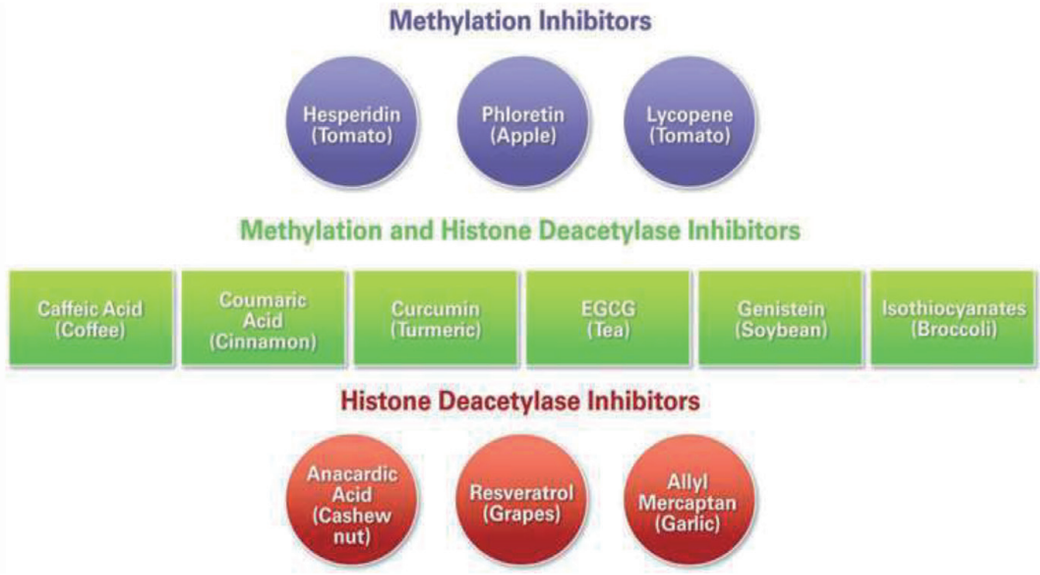

Figure 9.
Natural food components with epigenome altering properties [74].

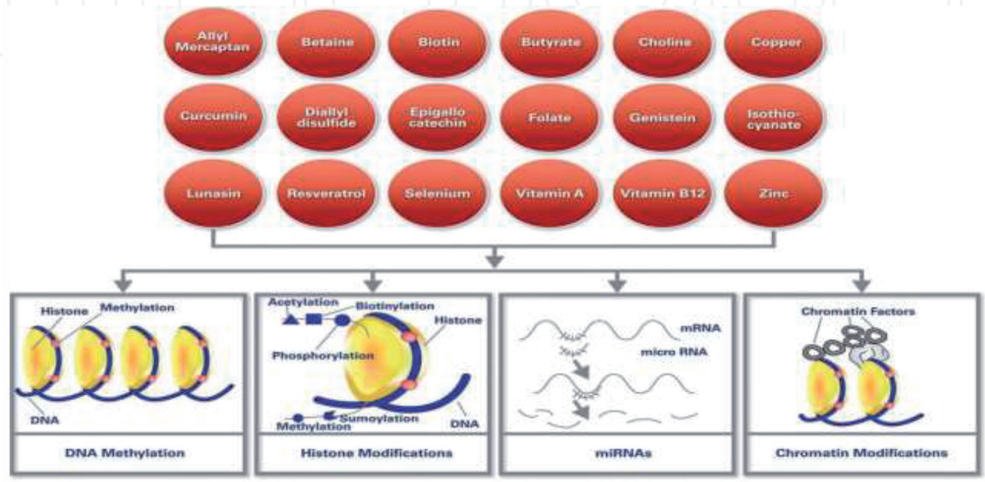

Figure 10.
Dietary components and their interaction with epigenetic regulation [74].

4. Conclusion

Epigenetic modifications is observed to perform a significant role in disease occurrence and pathogenesis. DNA methylation and chromatin remodeling are the most common epigenetic mechanisms, as described as a phenomenon of modifications in gene expression caused by heritable, but reversible, alterations in the chromatin structure, DNA methylation, and post-transcriptional effects of small noncoding microRNAs (miRNAs), without changes in the DNA sequence. The relationship between epigenome, epigenetic mechanisms and gene expression form a complicated feedback network that regulates and organizes cellular functioning at the molecular level; when this regulatory circuit is disrupted by internal or external factors, normal physiological functions are affected, leading to tumor initiation process [59]. Epigenetic mechanisms represent novel targets for natural products in prevention and treatment of cancer and other diseases. The influence of various classes of diet phytochemicals on the enzymatic activities of enzymes involved in epigenetic gene regulation; such as DNA and histone methyltransferases (DNMTs and HMTs), histone acetyltransferases (HATs), histone deacetylases (HDACs), and histone demethylases (HDMs) are also emphasized.

As a conclusion, the present review provided an overview of the most frequent epigenetic alterations in cancers, then described the most studied dietary phytochemicals and their potential use in the reversion of cancer hallmarks through epigenetic mechanisms, and finally discussed their potential use as an alternative strategy for cancer therapy. Above all, this review focused on modulation of epigenetic activities by epi-drugs that will allow the discovery of novel biomarkers for cancer prevention, as a potential alternative therapeutic approach in cancer, summarizing the progress made in cancer chemoprevention with dietary phytochemicals, and challenges in the future.

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References

[1] Loscalzo J. and Handy DE. Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series). Pulmonary Circulation 2014;**4**(2):169-174.

[2] Tchurikov NA. Molecular Mechanisms of Epigenetics. Biochemistry (Moscow); 2005; **70**(4): 406-23

[3] Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, Agarwal S, Iyer LM, Liu DR, Aravind L, Rao A. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science 2009; 324; 930-935

[4] Fraga MF, Esteller M. Towards the human cancer epigenome: a first draft of histone modifications. Cell Cycle. 2005;4:1377-81

[5] Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013; 38(1):23-38

[6] Miller JL, Grant PA. The role of DNA methylation and histone modifications in transcriptional regulation in humans. Subcell Biochem. 2013;61:289-317

[7] Fetahu IS, Höbaus J, Kállay E. Vitamin D and the epigenome. Front Physiol. 2014;5:164.

[8] Saito K., Nishida KM, Mori T, Kawamura Y, Miyoshi K, Nagami T, Siomi H, Siomi MC. Specific association of Piwi with rasiRNAs derived from retrotransposon and heterochromatic regions in the Drosophila genome. Genes Dev. 2006; **20**(16): 2214--2222.

[9] Stepanić V, Kujundzic RN, & Trošelj KG. Epigenome, Cancer Prevention and Flavonoids and Curcumin. In: Epigenetics and Epigenomics. Christopher J. Payne (Ed.) InTech Open; 2014; doi.10.5772/58247

[10] Alain LF. Genetics, Epigenetics and Cancer. Canc Therapy & Oncol Int J. 2017; **4**(2): 555634. doi: 10.19080/CTOIJ.2017.04.555634

[11] Zhao Z., Wang L. & Di LJ. Compartmentation of Metabolites in Regulating Epigenomes of Cancer. Mol Med 2016; **22:** 349-360 https://doi.org/10.2119/molmed.2016.00051

[12] Hodjat M, Rahmani S, Khan F. Niaz K, Navaei–Nigjeh M, Nejad SM, Abdollahi, M. Environmental toxicants, incidence of degenerative diseases, and therapies from the epigenetic point of view. Arch Toxicol. 2017; 91, 2577-2597://doi.org/10.1007/s00204-017-1979-9

[13] Qian Y, Chen X. Senescence regulation by the p53 protein family. Methods Mol Biol. 2013; 965:37-61. doi: 10.1007/978-1-62703-239-1_3.

[14] Rosângela FF de Araújo, Danyelly Bruneska G. Martins and Maria Amélia C.S.M. Borba. Oxidative Stress and Disease. InTechOpen. 2016; 12-21

[15] Kelly TK, De Carvalho DD, Jones PA. Epigenetic modifications as therapeutic targets. Nat Biotechnol. 2010; **28**(10):1069-1078. doi:10.1038/nbt.1678

[16] Baylin SB, Jones PA. Epigenetic Determinants of Cancer. Cold Spring Harb Perspect Biol. 2016; **8**(9):a019505. doi:10.1101/cshperspect.a019505

[17] Elsamanoudy AZ, Mohamed Neamat-Allah MA, Hisham Mohammad FA, Hassanien M, Nada HA.

The role of nutrition related genes and nutrigenetics in understanding the pathogenesis of cancer. J Microsc Ultrastruct. 2016; **4**(3):115-122.

[18] Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. Epigenomics. 2011; **3**(4):503-518. doi:10.2217/epi.11.71

[19] Sharma S, Kelly, TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010; **31**(1), 27-36.

[20] Tiffon C. The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. Int J Mol Sci. 2018; **19**(11):3425.

[21] Lundstrom K. Epigenetics: Diet and Cancer. Austin J Genet Genomic Res. 2016; **3**(1): 1020.

[22] Thakur VS, Deb G, Babcook MA, Gupta S. Plant phytochemicals as epigenetic modulators: role in cancer chemoprevention. AAPS J. 2014; **16**(1):151-163. doi:10.1208/s12248-013-9548-5

[23] Kotecha R, Takami A, Espinoza JL. Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. Oncotarget. 2016; **7**(32):52517-52529. doi:10.18632/oncotarget.9593

[24] Knackstedt RW, Moseley VR, Wargovich MJ. Epigenetic mechanisms underlying diet-sourced compounds in the prevention and treatment of gastrointestinal cancer. Anticancer Agents Med Chem. 2012; **12**(10):1203-1210. doi:10.2174/187152012803833053

[25] https://www.danielesegnini.it/epigenetica-e-nutrizione/ Daniele Segnini, Epigenetica e nutrizione

[26] Kanherkar R, Bhatia-Dey N, and Csoka AB. Epigenetics across the human lifespan. Front. Cell Develop Bio. 2014; **2**(49): 1-19.

[27] Busch C, Burkard M, Leischner C, Lauer UM, Frank J, Venturelli S. Epigenetic activities of flavonoids in the prevention and treatment of cancer. Clin Epigenetics. 2015; **10**;7(1):64. doi: 10.1186/s13148-015-0095-z.

[28] Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. Epigenomics. 2011; **3**(4):503-18. doi: 10.2217/epi.11.71.

[29] Kanwal R, Gupta S. Epigenetic modifications in cancer. Clin Genet. 2012; **81**(4):303-311. doi:10.1111/j.1399-0004.2011.01809.x

[30] Zhang Y, Kutateladze TG. Diet and the epigenome. Nat Commun. 2018; **9**(1):3375. doi:10.1038/s41467-018-05778-1

[31] Shankar E, Kanwal R, Candamo M, Gupta S. Dietary phytochemicals as epigenetic modifiers in cancer: Promise and challenges. Seminars in Cancer Biology. 2016; **40**-41:82-99.

[32] Fardi M, Solali S, Farshdousti Hagh M. Epigenetic mechanisms as a new approach in cancer treatment: An updated review. Genes Dis. 2018; **5**(4):304-311. doi:10.1016/j.gendis.2018.06.003

[33] Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; **105**(44):17046-17049. doi:10.1073/pnas.0806560105

[34] Verma M. Cancer control and prevention by nutrition and epigenetic approaches. Antioxid Redox Signal. 2012; **17**(2):355-364. doi:10.1089/ars.2011.4388

[35] Losada-Echeberría M, Herranz-López M, Micol V, Barrajón-Catalán E. Polyphenols as Promising Drugs against Main Breast Cancer Signatures. Antioxidants (Basel). 2017; **6**(4):88. doi:10.3390/antiox6040088

[36] Tan XL, Spivack SD. Dietary chemoprevention strategies for induction of phase II xenobiotic-metabolizing enzymes in lung carcinogenesis: A review. Lung Cancer. 2009; **65**(2):129-137. doi:10.1016/j.lungcan.2009.01.002

[37] Gao Y, Tollefsbol TO. Impact of Epigenetic Dietary Components on Cancer through Histone Modifications. Curr Med Chem. 2015; **22**(17):2051-2064. doi:10.2174/0929867322666150420102641

[38] Daniel M, Tollefsbol TO. Epigenetic linkage of aging, cancer and nutrition. J Exp Biol. 2015; **218** (1):59-70. doi:10.1242/jeb.107110

[39] Schneider-Stock R, Ghantous A, Bajbouj K, Saikali M, Darwiche N. Epigenetic mechanisms of plant-derived anticancer drugs. Frontiers in Bioscience (Landmark Edition). 2012;17:129-173. DOI: 10.2741/3919.

[40] Moosavi A, Motevalizadeh Ardekani A. Role of Epigenetics in Biology and Human Diseases. Iran Biomed J. 2016; **20**(5):246-258. doi:10.22045/ibj.2016.01

[41] Ducasse M, Brown MA. Epigenetic aberrations and cancer. Mol Cancer. 2006; 5:60. doi:10.1186/1476-4598-5-60

[42] Guo Y, Su ZY, Kong AN. Current Perspectives on Epigenetic Modifications by Dietary Chemopreventive and Herbal Phytochemicals. Curr Pharmacol Rep. 2015; **1**(4):245-257. doi:10.1007/s40495-015-0023-0

[43] Khan H, Belwal T, Efferth T, Farooqi AA, Sanches-Silva A, Vacca RA, Nabavi SF, Khan F, Prasad Devkota H, Barreca D, Sureda A, Tejada S, Dacrema M, Daglia M, Suntar İ, Xu S, Ullah H, Battino M, Giampieri F, Nabavi SM. Targeting epigenetics in cancer: therapeutic potential of flavonoids. Crit Rev Food Sci Nutr. 2020; 1-24. doi: 10.1080/10408398.2020.1763910.

[44] Carlos-Reyes Á, López-González JS, Meneses-Flores M, et al. Dietary Compounds as Epigenetic Modulating Agents in Cancer. Front Genet. 2019;10:79. doi:10.3389/fgene.2019.00079

[45] Pop S, Enciu AM, Tarcomnicu I, Gille E, Tanase C. Phytochemicals in cancer prevention: modulating epigenetic alterations of DNA methylation. Phytochem Rev. 2019; **18,** 1005-1024.

[46] Moga MA, Dimienescu OG, Arvatescu CA, Mironescu A, Dracea L, Ples L. The Role of Natural Polyphenols in the Prevention and Treatment of Cervical Cancer-An Overview. Molecules. 2016; **21**(8):1055. doi:10.3390/molecules21081055

[47] Lanzotti V, Carteni F. Drugs based on natural compounds: recent achievements and future perspectives. Phytochem Rev. 2019; **18,** 967-969.

[48] Rodríguez-García C, Sánchez-Quesada C, J Gaforio J. Dietary Flavonoids as Cancer Chemopreventive Agents: An Updated Review of Human Studies. Antioxidants (Basel). 2019; **8**(5):137. doi:10.3390/antiox8050137

[49] Ong TP, Moreno FS, Ross SA. Targeting the epigenome with bioactive food components for cancer prevention. J Nutrigenet Nutrigenomics. 2011; **4**(5):275-292. doi:10.1159/000334585

[50] Wang J, Jiang YF. Natural compounds as anticancer agents: Experimental evidence. World Journal of Experimental Medicine. 2012; **2**(3):45-57. doi: 10.5493/wjem.v2.i3.45.

[51] Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. Anticancer Efficacy of Polyphenols and Their Combinations. Nutrients. 2016; **8**(9):552. doi:10.3390/nu8090552

[52] Sharifi-Rad J, Rayess YE, Rizk AA, Sadaka C, Zgheib R, Zam W, Sestito S, Rapposelli S, Neffe-Skocińska K, Zielińska D, Salehi B, Setzer WN, Dosoky NS, Taheri Y, El Beyrouthy M, Martorell M, Ostrander EA, Suleria HAR, Cho WC, Maroyi A, Martins N. Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Front Pharmacol. 2020; **11**:01021. doi:10.3389/fphar.2020.01021

[53] Hassan FU, Rehman MS, Khan MS, Ali MA, Javed A, Nawaz A, Yang C. Curcumin as an Alternative Epigenetic Modulator: Mechanism of Action and Potential Effects. Front Genet. 2019; 10:514. doi:10.3389/fgene.2019.00514

[54] Montgomery M, Srinivasan A. Epigenetic Gene Regulation by Dietary Compounds in Cancer Prevention. Adv Nutr. 2019; **10**(6):1012-1028. doi:10.1093/advances/nmz046

[55] Henning SM, Wang P, Carpenter CL, Heber D. Epigenetic effects of green tea polyphenols in cancer. Epigenomics. 2013;**5**(6):729-741. doi:10.2217/epi.13.57

[56] Stefanska B, Karlic H, Varga F, Fabianowska-Majewska K, Haslberger A. Epigenetic mechanisms in anti-cancer actions of bioactive food components--the implications in cancer prevention. Br J Pharmacol. 2012;**167**(2):279-297. doi:10.1111/j.1476-5381.2012.02002.x

[57] Ko JH, Sethi G, Um JY, Shanmugam MK, Arfuso F, Kumar AP, Bishayee A, Ahn KS. The Role of Resveratrol in Cancer Therapy. Int J Mol Sci. 2017; **18**(12):2589. doi: 10.3390/ijms18122589. PMID: 29194365; PMCID: PMC5751192.

[58] Pratheeshkumar P, Sreekala C, Zhang Z, Budhraja A, Ding S, Son YO, Wang X, Hitron A, Hyun-Jung K, Wang L, Lee JC, Shi X. Cancer prevention with promising natural products: mechanisms of action and molecular targets. Anticancer Agents Med Chem. 2012; **12**(10):1159-84. doi: 10.2174/187152012803833035.

[59] Varoni EM, Lo Faro AF, Sharifi-Rad J, Iriti M. Anticancer Molecular Mechanisms of Resveratrol. Front Nutr. 2016; **3**:8. doi:10.3389/fnut.2016.00008

[60] Ratovitski EA. Anticancer Natural Compounds as Epigenetic Modulators of Gene Expression. Curr Genomics. 2017; **18**(2):175-205. doi:10.2174/1389202917666160803165229

[61] Shukla S, Meeran SM, Katiyar SK. Epigenetic regulation by selected dietary phytochemicals in cancer chemoprevention. Cancer Lett. 2014; **355**(1):9-17. doi:10.1016/j.canlet.2014.09.017

[62] Sun Y, Jiang X, Chen S, Price BD. Inhibition of histone acetyltransferase activity by anacardic acid sensitizes tumor cells to ionizing radiation. FEBS Lett. 2006; **580**(18):4353-6. doi: 10.1016/j.febslet.2006.06.092. Epub 2006 Jul 10. PMID: 16844118.

[63] Samad N, Javed A. Therapeutic Effects of Gallic Acid: Current Scenario. J Phytochemistry Biochem 2018; 2: 113.

[64] Weng YP, Hung PF, Ku WY, Chang CY, Wu BH, Wu MH, Yao JY, Yang JR, Lee CH. The inhibitory activity of gallic acid against DNA methylation: application of gallic acid on epigenetic therapy of human cancers. Oncotarget. 2017; **9**(1):361-374. doi: 10.18632/oncotarget.23015.

[65] Kuo HD, Wu R, Li S, Yang AY, Kong AN. Anthocyanin Delphinidin Prevents Neoplastic Transformation of Mouse Skin JB6 P+ Cells: Epigenetic Re-activation of Nrf2-ARE Pathway. AAPS J. 2019; **21**(5):83. doi:10.1208/s12248-019-0355-5

[66] Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. Cancer Lett. 2008; **269**(2): 352-362. doi:10.1016/j.canlet.2008.03.053

[67] Deep G, Agarwal R. Antimetastatic efficacy of silibinin: molecular mechanisms and therapeutic potential against cancer. Cancer Metastasis Rev. 2010; **29**(3):447-463. doi:10.1007/s10555-010-9237-0

[68] Cui W, Gu F, Hu KQ. Effects and mechanisms of silibinin on human hepatocellular carcinoma xenografts in nude mice. World J Gastroenterol. 2009; **15**(16):1943-1950. doi:10.3748/wjg.15.1943

[69] Kalaiselvan V, Kalaivani M, Vijayakumar A, Sureshkumar K, Venkateskumar K. Current knowledge and future direction of research on soy isoflavones as a therapeutic agents. Pharmacogn Rev. 2010;4(8):111-117. doi:10.4103/0973-7847.70900

[70] Kalaiselvan V, Kalaivani M, Vijayakumar A, Sureshkumar K, Venkateskumar K. Current knowledge and future direction of research on soy isoflavones as a therapeutic agents. Pharmacogn Rev. 2010; **4**(8):111-117. doi:10.4103/0973-7847.70900

[71] Pudenz M, Roth K, Gerhauser C. Impact of soy isoflavones on the epigenome in cancer prevention. Nutrients. 2014; **6**(10):4218-4272. doi:10.3390/nu6104218

[72] Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, Nabavi SF, Devi KP, Loizzo MR, Tundis R, Nabavi SM. Genistein and cancer: current status, challenges, and future directions. Adv Nutr. 2015; **6**(4):408-19. doi: 10.3945/an.114.008052.

[73] Tuli HS, Tuorkey MJ, Thakral F, Sak K, Kumar M, Sharma AK, Sharma U, Jain A, Aggarwal V, Bishayee A. Molecular Mechanisms of Action of Genistein in Cancer: Recent Advances. Front Pharmacol. 2019; 10:1336. doi: 10.3389/fphar.2019.01336. PMID: 31866857; PMCID: PMC6910185.

[74] Verma M. Cancer control and prevention by nutrition and epigenetic approaches. Antioxid Redox Signal. 2012; **17**(2):355-364. doi:10.1089/ars.2011.4388

[75] Zhang, Y, Kutateladze TG. Diet and the epigenome. Nat Commun 2018; **9,** 3375

[76] Tiffon C. The Impact of Nutrition and Environmental Epigenetics on Human Health and Disease. Int J Mol Sci. 2018; 19(11):3425. doi:10.3390/ijms19113425

[77] Pehlivan, F. Vitamin C: An Epigenetic Regulator. In: Vitamin C: An Update on Current Uses and Functions. Jean Guy LeBlanc (Ed.) InTech Open. 2018. doi. 10.5772/INTECHOPEN.82563