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REVIEW ARTICLE

Nutri-epigenetics and synthetic analogs in cancer chemoprevention

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Summary

Nutri-epigenetics has lately emerged as a new field in cancer epigenetic research. Cancer represents a multistage and heterogeneous disease that is driven by progressive genetic and epigenetic abnormalities. Epigenetic activity is influenced by several exogenous and endogenous factors including, nutrition, environment, disease, ethnicity, life style, medication, toxins, physical activity, age, gender and family genetics. Epigenetic therapy including mainly natural phenolics is a new area for drug development in cancer prevention. The current generation of epigenetic synthetic analogs are primarily target to inhibit the activity and expression of methyltransferases and histone deacetylases. Epigenetic mechanisms underlying nutrition seem very important tools nowadays in further understanding human health in general. New targeted natural and synthetic agents, along with the application of modern genomic methods, could substantially offer more specific armamentarium towards the prevention and therapy of cancer. The present short review demonstrates a selection of natural and recent synthetic chemopreventing compounds, in relation to their epigenetic mechanisms and current/future uses/limitations in therapeutics.

Key words: *cancer chemoprevention, epigenetic mechanisms, nutri-epigenetics, synthetic agents*

Introduction

Cancer is an alerting growing health problem around the world, particularly related with the steady rise in life expectancy. According to a recent report by the World Health Organization, there are now more than 10 million cases of cancer per year worldwide. Cancer results from a multistage, multi-mechanism carcinogenesis process that involves mutagenic, cell death and epigenetic mechanisms, during the three distinguishable but closely allied stages: initiation, promotion, and progression. Since reducing the initiation phase to a zero level is impossible, the most effective intervention would be at the promotion phase to eliminate premalignant cells before they become malignant [1]. In general, tumor growth is associated with both epigenetic and genetic aberrations resulting in altered gene expression [2] According to current data, cancer is in, at least, 30-40% of the cases preventable with appropriate or balanced food and nutrition, regular physical activity and avoidance of obesity [3].

Natural metabolic products, in general, have been always the most significant source of drugs in science. Throughout history, these products have afforded a rich source of compounds that have found many applications in the fields of medicine/oncology, pharmacy and biochemistry [4]. The fact that about 7 million people die of various types of cancer every year, making this disease responsible for 12.5% of deaths worldwide, raises an overwhelming demand to develop new, more potent and effective anticancer, as well as

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chemopreventing agents [5]. Therefore, the concept of delaying or preventing this transformation remains a viable and attainable goal for the future [6]. Epigenetic aberrant modifications are described in neurodegenerative diseases, cardiovascular diseases, diabetes mellitus type 2, obesity and cancer. The general reversibility of epigenetic changes makes them an attractive and promising target in the treatment of cancer [7].

Nutri-epigenetics has lately emerged as a new field in current epigenetic research. During carcinogenesis, major cellular functions and pathways, including drug metabolism, cell cycle regulation, potential to repair DNA damage or to induce apoptosis, response to inflammatory stimuli, cell signaling, and cell growth control and differentiation become deregulated. Recent evidence now indicates that epigenetic alterations contribute to these cellular defects, for example epigenetic silencing of detoxifying enzymes, tumor suppressor genes, cell cycle regulators, apoptosis-inducing and DNA repair genes, nuclear receptors, signal transducers and transcription factors by promoter methylation, and modifications of histones and non-histone proteins such as p53, NF-κB, and the chaperone HSP90 by acetylation or methylation [8].

Vegetables and fruits are excellent sources of cancer-preventive substances. Intervention to slow down, arrest or reverse the process of carcinogenesis by the use of either natural or synthetic substances individually or in combination therapy has emerged as a promising medical approach to reduce cancer risk. Epidemiological and experimental evidence emphasizes that specific compounds may positively inhibit carcinogenesis at various sites, including the oral cavity, esophagus, stomach, colon/rectum, lung, breast, and prostate, but at the same time, another compelling body of evidence, together with the data from animal and *in vitro* studies, strongly supports the relationship between dietary constituents and the risk of cancer development [9]. The American National Cancer Institute has identified about 35 plant-based foods containing 1,000 different phytochemicals, that possess cancer-preventive properties. The most exciting findings have been achieved with antioxidant vitamins and their precursors, which are found in dark, leafy green vegetables and yellow/orange fruit and vegetables. Recently, the focus and emphasis have shifted to the non-nutritive phytochemicals [4].

The present short review demonstrates a number of natural and recent synthetic chemopreventing compounds, in relation to their epigenetic mechanisms and current/future uses/limitations in therapeutics.

Chemopreventing mechanisms

The term *epigenetics* refers to heritable changes in gene expression (active versus inactive genes) that does not involve changes to the underlying DNA sequence; a change in *phenotype* without a change in *genotype*. Hence, epigenetic research seeks to describe dynamic alterations in the *transcriptional* potential of *a cell*. These alterations may or not be *heritable*, although the use of the term "epigenetic" to describe processes that are not heritable is controversial [10]. The mechanistic insight into chemoprevention includes induction of cell cycle arrest and apoptosis or inhibition of signal transduction pathways, mainly the mitogen-activated protein kinases (MAPK), protein kinases C (PKC), phosphoinositide 3-kinase (PI3K), glycogen synthase kinase (GSK) which leads to abnormal cyclooxygenase-2 (COX-2), activator protein-1 (AP-1), and nuclear factor kappa-light chain-enhancer of activated B cells (NF-kB). Effectiveness of chemopreventive agents reflects their ability to counteract certain upstream signals that leads to genotoxic damage, redox imbalances and other forms of cellular stress. Targeting malfunctioning molecules along the disrupted signal transduction pathway in cancer represents a rational strategy in chemoprevention. NF-kB and AP-1 provide mechanistic links between inflammation and cancer. Thus cell signaling cascades and their interacting factors have become important targets of chemoprevention and phenolic phytochemicals and plant extracts seem to be promising in this endeavor [11].

Epigenetic mechanisms are also involved in carcinogenesis. Carcinogenesis is a long-term process and both genetic and epigenetic factors contribute to cancer development. Epigenetic changes, such as DNA methylation, histone modifications and post transcriptional gene regulation by non-coding microRNAs (miRNAs) are easily influenced by dietary and environmental factors. These processes affect transcript stability, DNA folding, nucleosome positioning, chromatin compaction, and complete nuclear organization of the genetic material. Synergistically and cooperatively they determine whether a gene is silenced or expressed, as well as the timing and tissue-specificity of the expression of these genes. Disruption of the epigenome certainly underlies disease development [12].

DNA methylation is probably the most well researched epigenetic mark that differs between normal cells and tumor cells in humans. In normal cells, CpG islands preceding gene promoters are generally unmethylated, while other individual CpG dinucleotides throughout the genome tend to be methylated. However, in cancer cells,these islands preceding tumor suppressor gene promoters are often hypermethylated, while CpG methylation of oncogene promoter regions and parasitic repeat sequences is often decreased [13].

In comparison to healthy cells, cancer cells have been seen to exhibit decreased monoacetylated and trimethylated forms of histone H4. In mouse models, many have noticed that the loss of histone H4 acetylation and trimethylation actually increases as tumor growth continues [14]. Loss of histone H4 Lysine 16 acetylation (H4K-16ac), that is a mark of aging at the telomeres, specifically loses its acetylation and this histone acetylation loss might be battled with a histone deacetylase (HDAC) inhibitor specific for SIRT1, an HDAC specific for H4K16 [15].

In mammals, miRNAs, a potential cancer biomarker, regulate around 60% of the transcriptional activity of protein-encoding genes. Some miRNAs have also been found to undergo methylation-associated silencing in cancer cells [16,17].

Dietary polyphenols can potentially impact all of the above mentioned epigenetic modifications, which in turn contribute towards their chemopreventive activities. Although epigenetic changes are heritable in somatic cells, these modifications are also potentially reversible, which makes them attractive and promising avenues for cancer preventive and therapeutic strategies. Dietary polyphenols from green tea, turmeric, soybeans, broccoli and others have shown to possess multiple cell-regulatory activities within cancer cells [18].

From a clinical point of view, epigenetics seem to offer a very promising and attractive fact, in contrast to genetic changes such mutations, gene deletions and DNA binding [19]. Unlike mutations, which exist for lifetime, epigenetically modified genes can be restored. Methylation silenced genes can be demethylated, and histone complexes can be rendered transcriptionally active by modification of acetylation and methylation of various histones via nutrients, drugs and other dietary interventions [20].

An ideal chemopreventive agent should have: 1) little or no toxicity; 2) high efficacy in multiple sites; 3) capability of oral consumption; 4) known mechanisms of action; 5) low cost, and human acceptance. A variety of grains, cereals, nuts, soy products, olives, beverages confer a protective effect against cancer [21]. In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen, containing as well as organosulfur compounds, which have been shown to suppress early and late stages of carcinogenesis [22]. Chemopreventing agents and their sources inducing epigenetic mechamisms are given in Table 1.

Table 1. Polyphenols acting as epigenetics via specific mechanisms

Polyphenols/ Flavonoids	*Plant sources*	*DNMTs inhibition*	*HDACs inhibition*	*Tumor suppressors*
Coffee polyphenols	coffee	*ISM*		
Curcumin	turmeric	*ISM*	*ISM*	*ISM*
Dihydro-coumarin	sweet glover		*ISM*	
Epigallocatechin-3-Gallate, Catechin	green tea	*ISM*	*ISM*	*ISM*
Garcinol	garcinia		*ISM*	
Genistein	soya	*ISM*		
Lycopene	tomatoes	*ISM*		
Quercetin, Kaempherol	plant food	*ISM*		
Resveratrol	red wine	*ISM*	*ISM*	
Rosmarinic acid	oregano	*ISM*		
Sanguinarine	blood root		*ISM*	

DNMTs: methyltranferases, HDACs: histone deacetylates, Tumor suppressors: gene regulation by non-coding microRNAs, ISM: involved specific mechanism

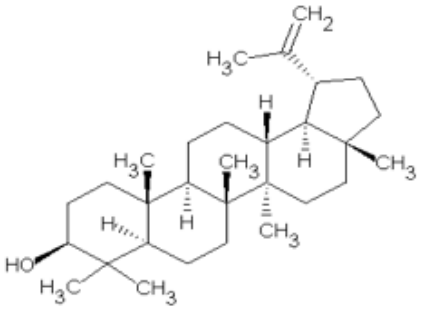

Figure 1. Lupeol structure.

Epigenetics from nature

Terpenes

The bioactive triterpene, lupeol (Figure 1) commonly found in fruits like fig, mango, etc, has recently attracted interest in the context of chemoprevention attributable in large part to its antioxidant[23], apoptosis-inducing and antiproliferative, antimutagenic, and antiinflammatory properties as well as its efficacy in inhibiting cancer growth both *in vivo* and *in vitro* [24].

Triterpenes represent a varied class of natural products, which occur commonly and are found in fruits, vegetables and other parts of several medicinal plants e.g *Arbutus unedo, Tipuana tipu*, etc [25]. Tremendous efforts have been performed by researchers worldwide to develop this interesting molecule for clinical use for the treatment of a variety of disorders. Studies in the last 15 years provide insight into the mechanism of action of lupeol and suggest that it is a multitarget agent with immense antiinflammatory potential, targeting key molecular pathways which involve NF-kB, cFLIP, Fas, Kras, phosphatidylinositol-3-kinase (PI3 K)/Akt and Wnt/β-catenin in a variety of cells. It is noteworthy that lupeol at its effective therapeutic doses exhibits no toxicity to normal cells and tissues [26]. NF-kB, a transcription factor, is now known to be closely connected to the process of tumorigenesis, based on a multiplicity of evidence. NF-kB is activated in response to tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli that account for as much as 95% of all cancers. NF-kB a): regulates the expression of most antiapoptotic gene products associated with the survival of the tumor; b): regulates the gene products linked with proliferation of tumors; c): controls the expression of gene products linked with invasion, angiogenesis, and metastasis. While most carcinogens activate NF-kB, most chemopreventive agents suppress its activation. These observations suggest that NF-kB is intimately intertwined with cancer growth and metastasis. AP1 is another transcription factor that regulates the expression of genes that are involved in cellular adaptation, differentiation and proliferation. Functional activation of AP1 is associated with malignant transformation as well as tumor promotion [27]. In the same chemical class, carotenoids are naturally occurring pigments, some of which can be converted by the body into vitamin A, e.g. β-carotene which is found in carrots, red palm oil and pumkin. *Lycopene* (Figure 2) is another example of pigmented terpene found in tomatoes, watermelons, papaya, appricots and citrus fruit. They have been found

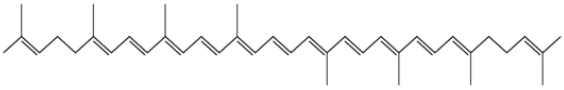

Figure 2. Lycopene structure.

to exhibit antioxidant, antiproliferative and antiinflammatory properties [28-30].

Phenolics-Flavonoids

Curcumin, (Figure 3) a spice widely used in Indian cuisine, has been identified to show considerable antitumor effects. It is a yellow pigment that is present in the rhizome of turmeric (*Curcuma longa L.*) and related species and is one of the most extensively investigated phytochemicals [31].

The mechanisms implicated in the inhibition of tumorigenesis by curcumin are diverse and appear to involve a combination of antiinflammatory, antioxidant, immunomodulatory, proapoptotic, and antiangiogenic properties via pleiotropic effects on genes and cell-signaling pathways at multiple levels. When curcumin is combined with some cytotoxic drugs or certain other diet-derived polyphenols, synergistic effects have been demonstrated [32].

A recent finding is that curcumin binds directly to and activates VDR (the nuclear vitamin D

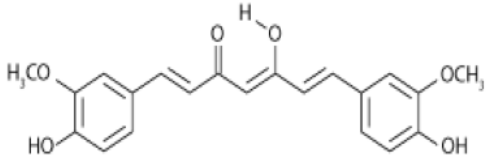

Figure 3. Curcumin structure.

receptor), inducing the VDR target genes CYP3A4, CYP24, p21 and TRPV6. Despite our increasing knowledge on this substance there still remain

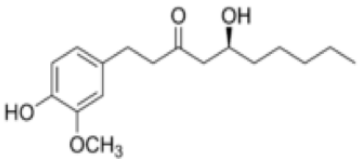

Figure 4. Gingerol structure.

many unknown effects that deserve intense investigation [33].

Gingerol, (Figure 4) a phenolic substance that is responsible for the spicy taste of ginger (*Zingiber officinale*) was reported to inhibit tumor promotion and PMA-induced ornithine decarboxylase

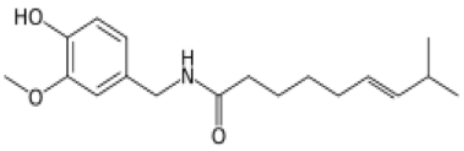

Figure 5. Capsaicin structure.

(ODC) activity and TNF-production in mouse skin [34].

Capsaicin, (Figure 5) a pungent component of hot chilli pepper (*Capsicum annuum* L.) has been suspected to act as a carcinogen or a co-carcinogen in experimental animals because of its irritant properties, but other studies indicate that this compound has chemopreventive and chemoprotective effects [35]. Capsaicin, more specific, inhibited the proliferation of CCRFCEM cells in a dose-dependent manner. Increased mRNA expressions of caspase gene family members, activated caspase-3 and decreased mRNA and protein expression of BCL-2 gene indicated apoptotic response to capsaicin. Moreover, capsaicin treatment suppressed significantly the expression of the key cell signaling pathways of KRAS, AKT, GAB2, PTPN11, BRAF, INPP5D, MAPK7 [36].

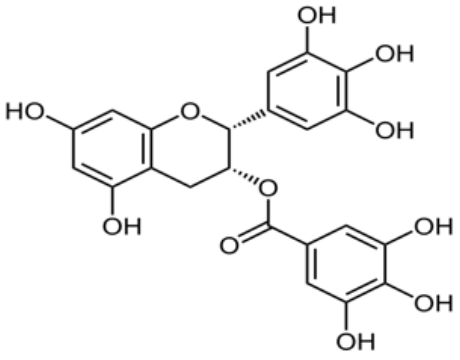

Figure 6. Epigallocatechin gallate structure.

Epigallocatechin gallate (EGCG, Figure 6) is an antioxidant and chemopreventive polyphenol that is found in green tea. It has been shown to suppress malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line, which

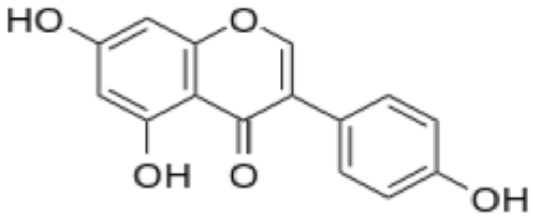

Figure 7. Genistein structure

seemed to be mediated by blocking activation of Ap1 [37].

Genistein (Figure 7) a soy-derived isoflavone, is believed to contribute to the putative breast- and prostate cancer preventive activity of soya [38]. Genistein inhibited PMA-induced AP1 activity, expression of c-FOS and ERK activity in certain human mammary cell lines. Genistein treatment abrogated NF-kB DNA binding in human hepatocarcinoma cells stimulated with hepatocyte growth factor [39].

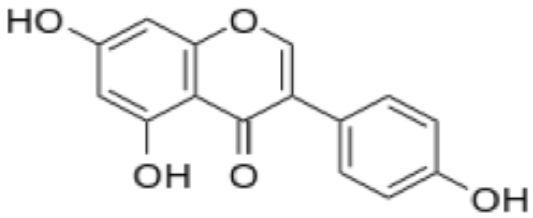

Figure 8. Resveratrol structure.

Resveratrol (3,4',5-trihydroxy-transstilbene, Figure 8) is a phytoalexin that is present in grapes (*Vitis vinifera*) and a key antioxidant ingredient of red wine. It is believed to be responsible for the so-called '*French paradox*', in which consumption of red wine has been shown to reduce the mortality rates from cardiovascular diseases and certain cancers [40,41]. Since only 70% of orally adminis-

tered resveratrol is absorbed, its oral bioavailability is approximately 0.5% due to extensive hepatic glucuronidation and sulfation [42] and the trace amounts of resveratrol reaching the blood seem insufficient to fully explain the French paradox. The beneficial effects of wine apparently could be explained by the effects of alcohol or the whole complex of substances wine contains, for example, the cardiovascular benefits of wine appear to correlate with the content of *procyanidins* [43].

In molecular/cellular level, resveratrol treatment inhibited PMA-induced COX2 expression and catalytic activity, via the cyclic-AMP response element (CRE) in human mammary epithelial cells [44]. It also inhibited PKC activation, AP1 transcriptional activity and the induction of COX2-promoter activity in PMA-treated cells. Resveratrol induced apoptosis and reduced the constitutive activation of NF-kB in both rat and human pancreatic carcinoma cell lines [45]. Of particular interest is that resveratrol is capable of causing DNA breakage in cells such as human lymphocytes. Such cellular DNA breakage is inhibited by copper specific chelators but not by iron and zinc chelating agents [46]. Furthermore resveratrol has been also shown to inhibit metastasis by reducing hypoxia inducible factor-1α and MMP-9 expression in colonocytes as well as inhibiting Wnt signalling and β-catenin localisation [47]. In a recent paper, resveratrol inhibited the proliferation of SGC7901 cancer cells by inducing

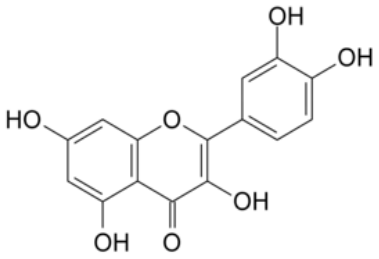

Figure 9. Quercetin structure.

cell apoptosis and down-regulating *survivin* expression [48].

In addition to the above polyphenolics, *quercetin* (Figure 9), a well-known flavonoid, is ubiquitously distributed in edible plant foods. With increasing dosage of quercetin, significant decrease in proliferation and increase in apoptosis was observed. Low concentrations of quercetin (10 μM) had no effects. Proliferation inhibition and apoptosis in MCF-7Ca/TAM-R cells increase with increasing dosage of quercetin. This suggests that quercetin can reverse tamoxifen resistance in breast cancer cells. The underlying mechanism likely involves upregulation of ERα combined with downregulation of Her-2. However, this effect is independent of whether quercetin and tamoxifen are administered simultaneously or sequentially [49].

More than 5000 natural flavonoids have been identified so far. Some representatives of the flavonoid group (such as *myricetin, fisetin, apigenin, luteolin, hesperetin, naringenin, daidzein* and the flavonoid-related class of flavonolignans such as *silibinin* have been reviewed above focusing on DNA methylation and histone acetylation [50,51] (Table 1). Epidemiological studies suggest that flavonoid ingestion reduces the risk of versatile cancer entities like pancreas, prostate, lung, colon, breast, and prostate cancer even though results are sometimes inconclusive [52].

In contrast, some other experimental data suggest that specific flavonoids could even promote tumor formation in certain subsets of patients. A randomized placebo-controlled study on female breast cancer patients illustrated that the supplementation of soy, which contains high amounts of isoflavones, may upregulate genes therefore could adversely affect breast carcinogenesis [53].

Caffeic acid phenethyl ester, sulphoraphane, silymarin, emodin and *anethole* have also been reported to suppress the activation of NF-kB and AP1, which might contribute to their chemopreventive and/or cytostatic effects [54]. The effects of doxorubicin, silymarin, and their combination on the proliferation of HepG2 cell line were recently tested by MTT assay, and Checkerboard micro plate method was applied to define the nature of doxorubicin and silymarin interactions on the cells. Doxorubicin-silymarin combination had shown indifferent antiproliferative effects on HepG2 cells. Telomerase activity of the cells incubated with IC_{50} of doxorubicin and silymarin decreased to 72% ($p<0.05$). IC_{50} combinations of doxorubicin and silymarin caused 70% ($p<0.05$) reduction [55].

Several dietary phytochemicals have been shown to downregulate the β-catenin-mediated signaling pathway as part of their molecular mechanism of chemoprevention. Curcumin and caffeic acid phenylethyl ester inhibited tumorigenesis and decreased β-catenin expression in the multiple intestinal neoplasia (Min/+) mouse model [56]. Moreover, curcumin reduced the cellular levels of β-catenin through caspase-mediated cleavage of the protein [57]. Downregulation of

β-catenin expression by resveratrol was observed

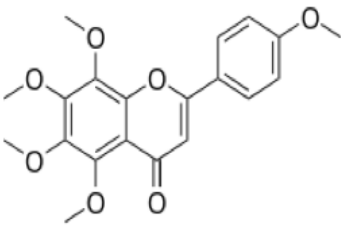

Figure 10. Tangeretin structure.

in a human colon cancer cell line [58].

Expression of a β-catenin-TCF4-binding reporter construct was reduced in HEK293 cells by epigallocatechin-3-gallate [59]. Indole-3-carbinol altered the pattern of β-catenin mutation in chemically-induced rat colon tumors [60], inhibited adhesion, migration and invasion of cultured human breast carcinoma cells, and upregulated E-cadherin and β-catenin [61]. A similar effect was observed with *tangeretin* (Figure 10) from citrus [62]. COX inhibitors have also been found to suppress β-catenin signalling and β-catenin–TCF/LEF transcriptional activity [63].

Omega-3 (n-3) PUFA

Epidemiological studies and populations consuming large numbers of polyunsaturated fish oils have been found to have lower rates of colon cancer [64]. This has led to the well-known hypothesis that diets high in n-3 fatty acids may reduce the risk of colorectal cancer. An inverse association between n-3 PUFA (omega-3) and colorectal cancer has been shown in case-control and prospective studies [65-68]. On the contrary, one of the major dietary sources of omega-3 fatty acids, alpha-linolenic acid, was associated with increased risk of colorectal cancer in women and that omega-6 intake was inversely related to colorectal cancer risk in men [69]. The above evidence that consumption of diets high in omega-3 PUFAs may prevent colorectal cancer is limited and in many cases contradictory. This includes n-3 fatty acids derived from fish and other sources such as α-Linolenic acid from food sources including rapeseed, soybeans, walnuts, flaxseed and olive oil. The evidence to propose any supplementation of omega-3 PUFAs with cod-liver oil is non-conclusive [70]. On the other hand, as many scientific work has shown, increased body mass index and obesity are associated with a significantly worse outcome for many cancers. Breast cancer risk in the postmenopausal setting and poor disease outcome for all patients is significantly augmented in overweight and obese persons. The expansion of fat involves a complex interaction of endocrine factors such as *adipokines* and *cytokines*. Many of the cytokines associated with a proinflammatory state are not only upregulated in obese adipose tissue but may also stimulate the self-renewal of cancer stem cells. Therefore, enhanced cytokine production in obese adipose tissue may serve both as a chemoattractant for invading cancers and to augment their malignant potential [71].

Alcohol

The mechanism by which alcohol might be linked to carcinogenesis is unknown, but proposed pathways include its ability to reduce folate, promote abnormal DNA methylation, delay DNA repair, alter the composition of bile salts or induce cytochrome p450 to activate carcinogens [72-74]. A large number of studies have suggested an association between alcohol intake and colonic adenoma as well as colorectal cancer risk [75-77]. Additionaly, diets high in n-3 fatty acids, dietary fibre, folate, vitamin D, calcium and polyphenols may protect against colorectal cancer and colorectal adenoma formation. The consumption of alcohol is not advocated. The role of probiotics and prebiotics is not completely clear but *in vitro* and *in vivo* studies have highlighted a possible protective role of gut microbiota in colorectal carcinogenesis [78].

Epigenetic analogs

A variety of compounds is considered as epigenetic carcinogens; they result in an increased incidence of tumors, but they do not show mutagenic activity. Examples include diethylstilbestrol, arsenite, hexachlorobenzene and nickel compounds. Many teratogens exert specific effects on the fetus by epigenetic mechanisms [79,80].

Epigenetic therapy, the use of drugs to correct epigenetic defects, is currently a new and promising area for drug development in the field of cancer prevention. Besides their promise as therapeutic agents, epigenetic drugs may also be used for prevention of various diseases, including cancer chemoprevention. Epigenetic therapy is a potentially novel form of therapy since epigenetic defects, in contrast to genetic defects, are quite reversible [81].

Additionally, there is growing trend that epi-

genetic drugs alone or in combination with conventional anticancer drugs may prove to be a significant advance over the conventional anticancer drugs, which inherently tend to be very toxic [82].

The current generation of epigenetic drugs primarily targets to inhibit the activity and expression of DNMTs and HDACs. Among the DNMT inhibitors, nucleic acid inhibitors, such as 5-azacytidine (VidazaR) and 5-aza-2-deoxycytidine (DacogenR) (Figure 11) are indicated for the treatment of myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes of refractory anaemia (with excess blasts, with excess blasts in transformation, and chronic myelomonocytic leukemia), being the most important and widely studied epige-

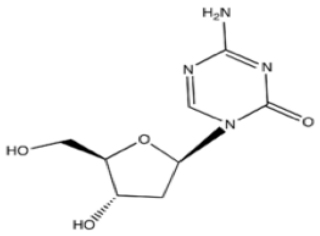

Figure 11. 5-aza-2-deoxycytidine structure.

netic drugs [83].

Both drugs, used also for diabetic retinopathy, have been approved by the FDA for the treatment of various forms of cancer and shown to reactivate the cellular antitumor systems repressed by cancer, enabling the body to weaken the tumor [84-86]. Dietary sources of cytidine include foods with high RNA content, such as organ meats, Brewer's yeast, as well as pyrimidine-rich foods such as beer. During digestion, RNA-rich foods are broken down into ribosyl pyrimidines, which are ab-

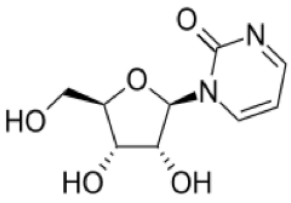

Figure 12. Zebularine structure

sorbed intact [87].

Zebularine (Figure 12), an analog of cytidine and activator of a demethylation enzyme, has also been used with some success. Because of their widely ranging effects throughout the entire organism, all of these drugs have major side effects, but survival rates are increased significantly when they are used for treatment [88].

In addition, certain non-nucleoside inhibitors such as procainamide, procaine and EGCG have also shown potent inhibition of DNMT activity in various experimental and clinical studies [89-92]. Concerning HDAC inhibitors, *trichostatin A* (TSA), *suberoylanilide hydroxamic acid, valproic acid and phenyl butyrate*, have been widely used with some success in various studies. Zhu et al. investigated the effects of HDACIs trichostatin A (TSA) and sodium valproate (VPA) on chondrosarcoma cells *in vitro* and *in vivo*. The cell proliferation and cell cycle were examined in two chondrosarcoma cell lines, SW1353 and JJ012, by MTS and flow cytometry assays, respectively. The *in vivo* effects of HDACIs were investigated by assessing the chondrosarcoma growth in a mouse xenograft model. TSA and VPA significantly repressed the proliferation of chondrosarcoma cells in a concentration-dependent manner. Flow cytometry indicated that TSA arrested the cell cycle in G2/M phase and VPA arrested the cell cycle in G1 phase. The tumor growth was markedly suppressed in mice

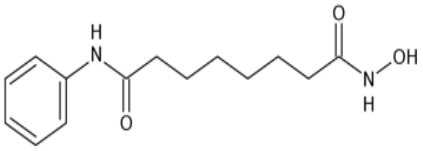

Figure 13. Suberoylanilide hydroxamic acid structure.

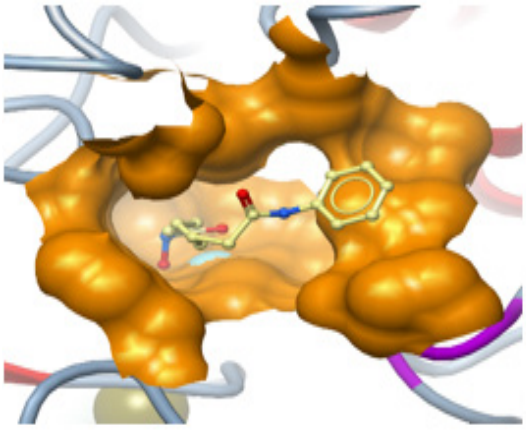

Figure 14. Vorinostat incorporation into HDAC enzymatic system (http://pharmaceuticalintelligence.com/author/sjwilliamspa/)

treated with TSA and VPA [93].

Vorinostat® (*suberoylanilide hydroxamic acid*, Figures 13 and 14) a highly potent histone deacetylase inhibitor, was recently approved by the FDA for the treatment of cutaneous T-cell lymphoma [94-96].

Vorinostat showed improved response rates and increased median progression free survival and overall survival in advanced non-small-cell lung cancer (NSCLC), although the survival improvements did not reach statistical significance [97].

HDAC inhibitors generally consist of three parts in their chemical structure:

1. a zinc-chelating group

2. a spacer group, which is generally hydrophobic

3. an "enzyme binding" group that confers specificity and is generally aromatic in character [98].

As for the common antiepileptic agent valproic acid it was suggested that impairs the liver function resulting in free radicals production. The latter seems to produce DNA oxidative damage in liver cells, not excluding neuronal cells, as evidenced by the measured remarkably increased 8-OHdG serum levels [99]. Interestigly, only recently, researchers have taken advantage of the high level of reactive oxygen species (ROS) in cancer cells, developing new therapeutic strategies to preferentially kill these cells. Strategies involving ROS activation may be used for development of new ROS-targeting prodrugs, which could lead to new approaches or technology for more effective cancer treatment. Several of these potentially useful epigenetic drugs are still undergoing preclinical and clinical drug trials. Although the current generation of epigenetic drugs has provided certain beneficial results, epigenetic therapy has its limitations. Some of these shortcomings include that both DNMT and HDAC inhibitors may activate oncogenes due to lack of specificity, resulting in accelerated tumor progression [100].

Furthermore, benefits and targets of phytochemicals mainly rely so far on cell and animal models. To safely apply phytochemicals as personalized cancer preventive agents, the effects of phytochemicals in humans will need to be assessed. Thus, personalized prevention methods using nutri-epigenetics could have a crucial role in cancer prevention, especially in high-risk populations. Extensive research in identifying molecular targets and conducting human studies with chemopreventing agents would provide a more orientated approach to personalized cancer prevention in the near future [101].

Conclusions

Epigenetic activity in general is influenced by several exogenous and endogenous factors including nutrition, environment, disease, ethnicity, life style, medication, toxins, physical activity, age, gender and family genetics.

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging nutritional hallmarks of potential generality to this list-reprogramming of energy metabolism and evading immune destruction [102]. A highly specific diet, of utilizing nutri-epigenomics termed an "EpiG diet," may be employed for an individual believed to be at higher risk of developing a metabolic disorder. These diets may include supplementation with methyl donors, such as folate [103].

As it was already stated, natural products consist of a wide variety of biologically active phytochemicals, including phenolics, flavonoids, terpenoids, alkaloids and nitrogen containing compounds, as well as organosulfur compounds that have been shown to suppress early and late stages of carcinogenesis. Effectiveness of natural chemopreventive agents reflects their ability to counteract certain upstream signals. All mechanisms described seem to be closely related to their well-known antioxidant effect. In addition, epigenetic drugs acting via similar mechanisms, alone or in combination with conventional anticancer drugs may prove to be a significant advance over the conventional anticancer drugs.

It has become obvious that chemoprevention in close relation to chemotherapy enforced by edible phytochemicals is now considered to be an inexpensive and promising approach to cancer control and management [104].

Despite the above promising results for diets rich in fruit and vegetables in terms of disease prevention, it remains unclear if additional supplementation with natural epigenetics would

have significant additional beneficial health effects in humans.

The huge accumulation of research laboratory data requires clinical studies in order to standardize the doses, routes of administration, organ specificity and bioavailability in humans, as well as therapeutic strategies for cancers of different organs/origins. At present, there are many challenges which remain to be solved, such as:

1. Full disclosure of multiple mechanisms regarding nutri-epigenetics .

2. Druggability, regarding that the epigenetic processes are quite reversible.

3. Their efficiency in monotherapy is variable among different cancers, thus, these compounds may not be a good choice for first-line cancer therapy. On the other hand, epigenetic therapy at later stages is not as effective, due to accumulation of multiple genomic alterations in the tumor cells.

Finally, well oriented receptor-targeted synthesized agents, along with the application of early diagnostic technology, regarding modern genomic methods, could also substantially create a more effective armamentarium towards the prevention and therapy of cancer via nutri-epigenetics and currently synthetic analogs [105].

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