

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Effect of Bioactive Nutriment in Health and Disease: The Role of Epigenetic Modifications

---

Pablo Bautista-García, Lorena González-López,  
Berenice González-Esparza and  
Camila Del Castillo-Rosas

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.68789>

---

## Abstract

Recently, a list of clinical, physiopathological, and epidemiological studies has underlined the detrimental or beneficial role of nutritional factors in some chronic diseases such as obesity, type 2 diabetes, cardiovascular disease, and cancer. It has been described that lifestyle, environmental conditions, and nutritional compounds influence gene expression. In the last instance, it has been demonstrated that bioactive nutrimental components are important signal molecules that carry information from the external environment and could affect in biological terms, processes related to gene expression. Bioactive nutrients can work in different ways: regulating the chromatin structure or factors that directly regulate the activity of nuclear receptors. The relevance of the changes in the chromatin structure has been demonstrated by the fact that many chronic diseases and metabolic disorders are related with changes in DNA methylation patterns. For this reason, recently, the bioactive food nutrients have been investigated to characterize the molecular mechanism involved in changes of the chromatin structure, such as acetylation and methylation, and their potential benefit on chronic diseases. The dietary compounds intake involved in the regulation of epigenetic modifications can provide significant health effects and may prevent various pathological processes involved in the development of cancer and other serious diseases.

**Keywords:** bioactive nutrients, epigenomic changes, obesity, diabetes mellitus, carcinogenesis

---

## 1. Introduction

Bioactive food nutriment are constituents provided in food or dietary supplements; those have been characterized as biomolecules and have the capacity to regulate a myriad of metabolic processes in the body resulting in health benefits. In contrast, overload intake of bioactive nutriment can either be involved in the development of various stages of disease or may change the natural history of a disease. For this reason, the knowledge of these biological functional features can be applied in the treatment and prevention of human diseases.

Currently, advancements in biological and medical science have allowed a better understanding of physiopathological bases of disease, as well as identify the role of several bioactive components in food under metabolic processes. The development of new technologies have provided analytical and molecular tools for discerning the intricate relationship between a myriad of signaling pathways linked to pathological processes. The results have been useful to evaluate a vast numbers of food components and their role in disease prevention and health promotion.

Bioactive food nutriment can be provided in daily diet in many forms. Some of them can be found in conventional foods and others can be added to fortified foods, these kinds of supplements have been designed to reduce disease risk in special human groups with nutrimental deficiencies [1].

During decades, physicians and nutritionists have adopted nutritional guides, where they can find punctual information about nutritional recommendation for a large list of nutriment. However, the availability of nutritional guides for bioactive nutriment compounds is restricted because; these need more elements to evaluate dietary recommendation. One of the most important requirements to recommend a bioactive nutriment compound is based on the result obtained in clinical and experimental studies; this data must contain scientific evidence that shows a relationship between the bioactive nutriment compound and a beneficial health impact. In the same sense, other element that must be considered to choose a bioactive nutriment compound is whether the bioactive product exhibit side effects upon exposition.

For this purpose, researches must develop accurate biochemical markers to validate either the safety or hazardous effects of food intake for human, and finally physicians and nutritionist will decide the correct doses for each bioactive nutriment component, depending on many factors, such as sex, age, pregnancy, health, or pathological condition [2].

## 2. Bioactive nutriment in health: the role of epigenetic modifications

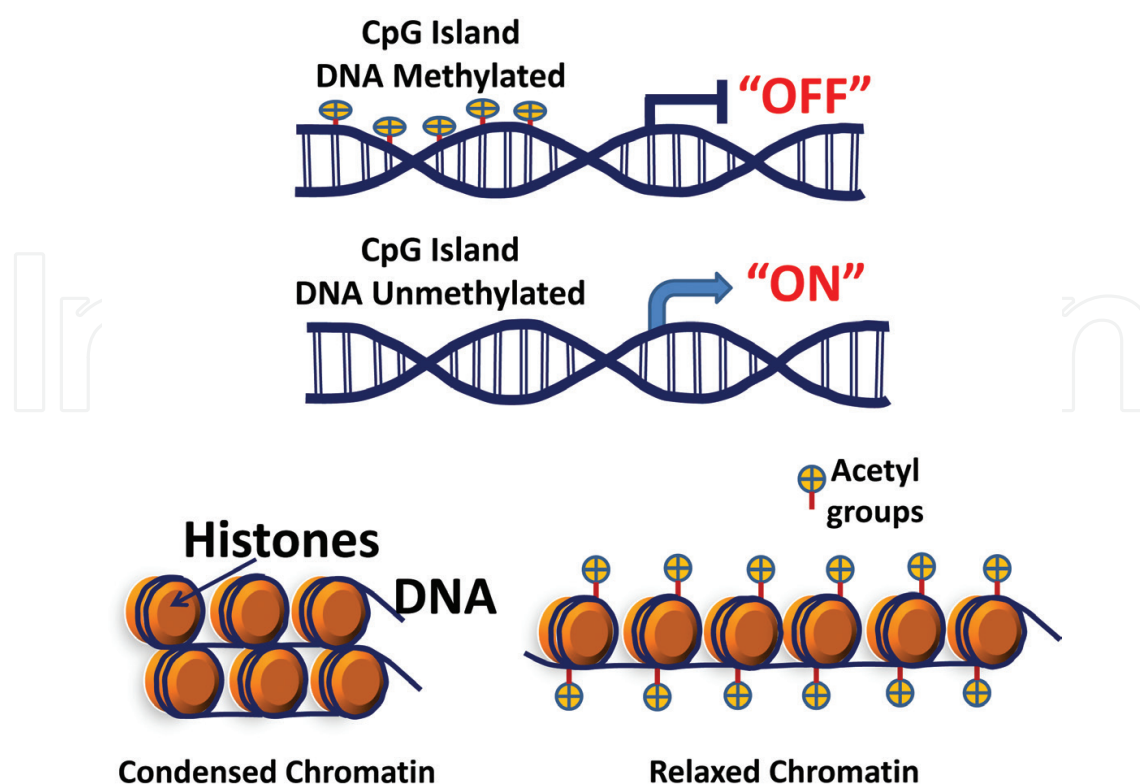
Human homeostasis is influenced by molecular signal pathways, exogenous factors, and diet habits. It has been demonstrated that bioactive nutriment have substantive impact on health and disease. A biological area that describes the molecular effect of certain nutriment on DNA expression is "Epigenomics," which can be defined as the study of the complete set of epigenetic modifications in a cell or in a tissue at a given time. The epigenome consists of chemical compounds that modify or mark the genome in such a way that can indicate how

and when a specific set of genes are expressed in a cell or in a tissue, enhancing or inhibiting the production of a specific protein in a cell. These chemical modifications on DNA or histones have been characterized as “epigenetic marks” [3].

The epigenetic modifications are targeted to DNA or histones (DNA associated proteins), which induce modifications in chromatin without affecting the nucleotide sequence; these structural changes could modify the expression patterns of gene expression; however, these molecular modifications can be slow but progressive and potentially reversible. When epigenomic compounds attach to DNA and modify its structure and its transcriptional activity, they “marked” the genome. The biological transcendence of these marks is not to change the sequence of the DNA, conversely they change the way cells use the DNA’s instructions. The marks are sometimes passed on from cell to cell as cells divide. They also can be passed down from one generation to the next.

The first type of mark, called DNA methylation, directly affects the DNA in a genome. In this process, a set of proteins chemically tag with methyl groups the DNA bases in specific places. The methyl groups can make DNA either more or less accessible to transcriptional apparatus, thus changing the expression patterns of specific genes.

The second kind of mark, characterized as histone modification, affects DNA indirectly because in this case DNA remains intact but the chemical modifications in histones affect the way in which DNA is wrapped around histone proteins, thus affecting the DNA structures and in consequence, the transcriptional activity of many proteins (Figure 1) [4].



**Figure 1.** Activation/repression of DNA induced by epigenomic changes.

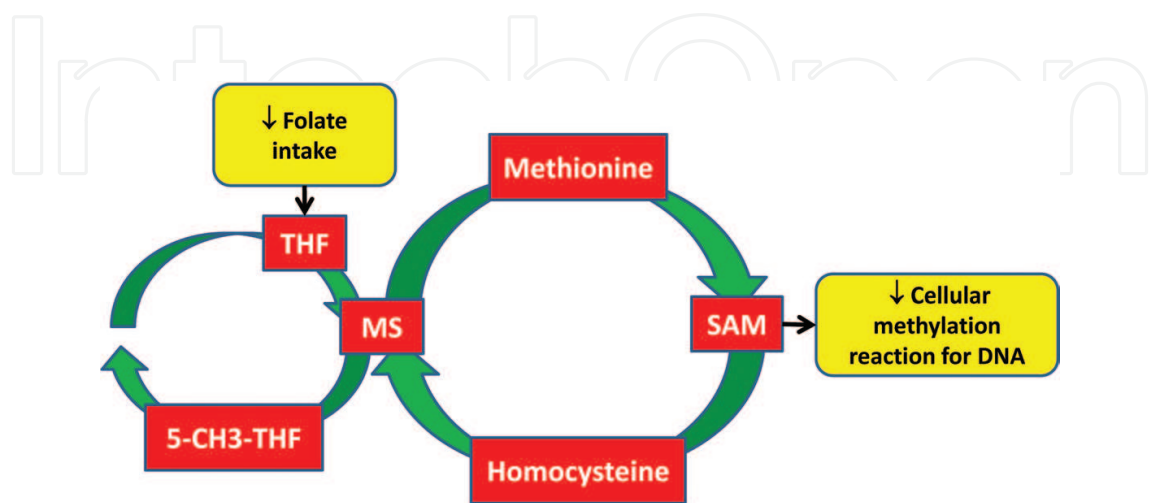
In the following paragraphs, we describe an increasing number of evidences that show how bioactive nutriment compounds can modify methylation patterns by interacting with enzymes that are able to place epigenetic marks on DNA or enhance the expression of specific proteins implicated in the formation of the epigenetic machinery.

2.1. Folates

Folate and folic acid are the forms of a water-soluble vitamin B; this can be obtained naturally in daily diet or in fortified foods and supplements. Sources include cereals, baked goods, spinach, broccoli, lettuce, asparagus, bananas, melons, lemons, legumes, yeast, mushrooms, beef liver, kidney, orange juice, and tomato juice. Folic acid supplements are effective for increasing folate levels in blood and decreasing symptoms associated with low folate levels. These kinds of supplements are prescribed for use in pregnancy women in order to prevent neural tube defects.

Folate is involved in DNA synthesis, repair, and methylation. After dietary ingestion, this compound undergoes many chemical reactions and is primary converted to tetrahydrofolate which is involved in the remethylation of homocysteine to methionine [5]. The relevance of this chemical reaction is that methionine is a precursor of SAM (S-adenosyl-L-methionine), the primary methyl donor group for most methylation reactions [6]. After transferring a methyl group, SAM is converted to S-adenosyl-L-homocysteine (SAH), an inhibitor of the methylation reactions.

This chemical event seems to be of particular relevance, because in the development of digestive neoplastic lesions related to folate deficiency may be involved in changes of the DNA methylation pattern in specific proto-oncogenes, such as c-myc, c-fos, and c-Ha-ras [7]. In all cases the malignant transformation was related to a significant decrease of SAM and global DNA hypomethylation, especially in DNA sequences where oncogenes are codified. In contrast, folic acid supplementation improved folate-related DNA biomarkers of cancer risk in colonic tissues adjacent to the former polyp site (Figure 2) [8].



**Figure 2.** Association between folate deficiency and DNA methylation process. THF, tetrahydrofolate; MS, methionine synthase; 5-CH<sub>3</sub>-THF, 5-methyltetrahydrofolate; SAM, S-adenosyl-L-.



Paradoxically, hypermethylation was induced in DNA sequences coding for tumor suppressor genes. The changes in the methylation processes exerted by an increase in DNMTs (DNA methyltransferases) activity may explain the hypermethylation observed in these experimental models, whereas the stimulation of MBD2 and MBD4 (methyl-CpG-binding domain proteins) may explain the decrease on DNA methylation favoring the expression of oncogenes and pro-metastatic genes [9, 10].

The above mentioned data indicates that current nutritional recommendations of folate in daily diet must be considered more than a simple nutriment; it must be also considered an indispensable bioactive compound to avoid at least in some degree the aberrant expression of proto-oncogenes in many cellular contexts, thus decreasing the incidence of neoplastic process.

## 2.2. Vitamin A

Vitamin A is the name of a group of fat-soluble retinoids, including retinol, retinal, and retinyl esters. It is involved in many physiological functions, including: immune function, vision, reproduction, and cellular communication processes. Vitamin A also supports cell growth and differentiation, playing a critical role in the normal organogenesis and maintenance of heart, lungs, and kidneys functions. Preformed vitamin A is found in dark green and yellow vegetables, and yellow fruits, such as broccoli spinach, turnip greens, carrots, squash, sweet potatoes, pumpkin, cantaloupe, apricots, and food animal sources, including fish and meat. It must be metabolized intracellularly into retinal and retinoic acid, the active forms of vitamin A, to support the vitamin's physiological functions [11].

Once absorbed, these bioactive compounds are translocated to the nucleus where they bind to specific nuclear Retinoic Acid Receptors (RARs), which have been characterized as RAR $\alpha$ ,  $\beta$ , and  $\gamma$  that heterodimerize with Retinoid X Receptors (RXRs). The molecular complex binds to specific response elements and downregulates transcriptional activity of many genes, which includes AP-1 gene. This gene is involved in mediating transcriptional responses to many biological, pharmacological, or stress stimuli. Even more, AP-1 regulates the expression of several molecular mediators involved in oncogenic transformation and cellular proliferation and plays a regulatory role in S phase DNA replication and DNA damage repair [12].

Once p21 and AP-1 are activated by retinoids, the proteins encoded by these genes can interact with many proteins involved in DNA methylation changes, for example, p21 is able to compete with DNMT1 substrates for the same binding site on Proliferating Cell nuclear Antigen (PCNA), then affecting DNMT1 activity and its DNA methylation efficiency (see **Figure 4**) [13, 14]. Meanwhile, the mechanism for AP-1 involved its binding to the promoter of the DNMT1 regulatory region inducing the expression of DNMT1, favoring DNA methylation [15].

The biological transcendence exhibited by p21 and AP-1 expression induced by retinoids is the downregulation of enzymes that enhance DNA methylation events, which may contribute to increase the expression patterns of genes involved in antiproliferative, differentiating, and proapoptotic actions reducing the incidence of many types of cancers [16, 17].

Indeed, recently it has been demonstrated the antitumoral effect exerted by derivative of all trans retinoic acid in cellular cultures of human gastric cancer, which is related to the ability of these compounds to induce cycle cell arrest and cellular differentiation [18].

### 2.3. Vitamin D3

Vitamin D is found in many foods, including fish, eggs, fortified milk, and cod liver oil. However, Vitamin D can be also obtained by few minutes of sun exposition. There are several different forms of vitamin D. Two forms are important in humans: vitamin D2, which is made by plants, and vitamin D3, which is made by human skin when exposed to sunlight [19].

Although for VitD3, one of the most known physiological effects is the preservation of the calcium homeostasis. Currently, it has been explored other mechanisms not linked to calcium metabolism. In this sense, once VitD3 is converted into its active form (calcitriol), the biological actions of this vitamin share similar mechanisms to RA, because it must bind to specific vitamin D receptors (VDR), establishing homodimers, or heterodimers with RXR or RAR, and affect gene transcription through VDR responsive elements (VDRE) in target genes, such as p21 and PTE; this protein specifically catalyzes the dephosphorylation of the 3' phosphate. This dephosphorylation is important because it results in inhibition of the AKT signaling pathway. Meanwhile, its weak protein phosphatase activity is also crucial for its role as a tumor suppressor, preventing cells from growing and dividing [20].

Bioactive nutriment	Natural sources	Antineoplastic effects	Epigenetic mechanisms of action
Folate,	spinach, asparagus, beans, peas, lentils, almonds	Anti-cancer, chemoprevention of malignant transformation	Regulation of SAM/SAH ratio, DNMT and MBD expression; regulation of tumor suppressor miRNAs and oncogenic miRNAs
Retinoic acid	Mango, papaya, carrots, spinach, sweet potatoes	Anti-cancer, differentiating, pro-apoptotic	Regulation of DNMTs expression and activity, regulation of miRNAs targeting DNMTs; regulation of tumour suppressor miRNAs and oncogenic miRNAs; GNMT regulation; histone acetylation
Vitamin D3	Sun exposure, fish, fish liver oils	Anti-cancer, differentiating, pro-apoptotic	Regulation of DNMTs expression and enzyme activity; regulation of histone acetylation; regulation of oncogenic miRNAs
Resveratrol	Grapes, mulberries, apricots, pineapples, peanuts	Anti-cancer, antioxidant, anti-angiogenesis, pro-apoptotic	Regulation of DNMTs expression and enzyme activity; activation of deacetylase SIRT1 and p300 HAT; down-regulation of UHRF1; regulation of miRNAs
EGCG	Green tea	Anti-cancer, antioxidant, anti-angiogenesis, pro-apoptotic	Regulation of SAM/SAH ratio by COMT-mediated reactions; direct inhibition of DNMTs by binding to catalytic domain of the enzyme; regulation of tumour suppressor miRNAs
Curcumin	Spice turmeric	Anti-cancer, antioxidant, protects against heart failure	Direct inhibition of DNMTs by binding to catalytic domain of the enzyme; inhibition of HDACs and p300 HAT; regulation of tumour suppressor miRNAs and oncogenic miRNAs

Table 1. Epigenomic roles of bioactive nutriment.

In a similar way as for retinoid, the biological effect of VitD3 in cancer is linked to the ability of p21 to downregulate the activity of DNMT1 enzymes, which can modify the DNA methylation patterns of certain protective genes conferring an antitumoral role as was demonstrated for colon cancer [21] and more recently for metastatic castration-resistant prostate cancer patients (**Table 1**) [22].

One important fact is that in industrialized countries VitD3 intake is generally linked to calcium homeostasis but its role in the prevention of cancer development by epigenetic mechanisms is commonly unknown.

The date mentioned above can represent a new challenge for physicians and nutritionists to develop new strategies to raise awareness about the biological properties provided by many bioactive nutriment in the daily diet of the general population. This may contribute to reduce the incidence of most common types of cancer.

### **3. Nutriment linked to disease: the role of epigenetic mechanism**

#### **3.1. High fat diet and induction of obesity**

As mentioned before, we showed the beneficial effects of bioactive nutriment in health. In contrast, it has been demonstrated that the overfeeding of many of these nutriment can also participate in the evolution of several diseases. In this sense, there are lines of evidence that had proved the existence of obesity-genes. These genes are critical for energy balance and can be regulated by epigenetic mechanisms depending on nutritional environment conditions [23, 24]. For example, it has been proved that a long-term exposition to high fat diet in mice, MC4R promoter gene undergoes a reduced methylation in the brain of mice, promoting the fat storage and obesity [25].

In addition, it has been demonstrated that other genes may potentiate the effect of MC4R. For example, it has been shown that under a high-fat diet the methylation state of the Proopiomelanocortin (POMC) promoter can be modified, thus changing the correct balance between energy taken from the food and energy spent by the body, favoring obesity. It has been shown that proopiomelanocortin (POMC) deficiency causes severe obesity that begins at an early age. Affected infants usually have a normal weight at birth, but they are constantly hungry. Affected individuals experience excessive hunger and remain obese for life. It is unclear if these individuals are prone to weight-related conditions like cardiovascular disease or type 2 diabetes. Thus, changing the correct balance between energy taken from the food and energy spent by the body, favoring obesity [26].

The methylation changes observed in gene promoters involved in energy balance induced by long-term exposition to a fat diet in western countries, may explain the high incidence of obesity and metabolic diseases, which may be potentially prevented by healthy diet habits and exercise. Thereby, the current treatment of obesity must also consider the epigenetic effects on



obesity genes exerted by overfeeding, more than considering surgery as first-line treatment, which only avoids the absorption of overcharged nutriment, but do not have any effect on the intrinsic mechanism of obesity.

#### 4. Epigenetic changes associated with diabetic complications

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [27].

One of the most frequent diabetes complications is diabetic vasculopathy, which is characterized by a vascular inflammation process. Recent studies have proposed that hyperglycemia may produce epigenetic modifications of specific genes involved in vascular inflammation. One of them is the transcription factor, Nuclear Factor- $\kappa$ B (NF- $\kappa$ B), which regulates the expression of a large list of genes who participate in inflammatory diseases, such as atherosclerosis and diabetic complications.

It has been demonstrated *in vitro* experiments that hyperglycemia increases NF- $\kappa$ B activity in monocytes thus enhancing gene expression of inflammatory cytokines. This step is the result of molecular interaction between the transcription factor (NF- $\kappa$ B) and histone acetyltransferases (HATs), resulting in hyperacetylation of target genes including the tumor necrosis factor (TNF)-and cyclooxygenase-2 promoters [28].

The data may suggest that the uncontrolled hyperglycemia in diabetic patients may produce epigenetic changes in specific genomic region which control the expression of proinflammatory genes, and subsequently the development of vascular inflammation. However, the control of hyperglycemia in patient is not enough to reduce the risk of diabetic complication because in this patient the risk of diabetic vasculopathy was not modified. The mechanism involved is that persistent hyperglycemia may induce “epigenetic marks” in proinflammatory promoters, thus enhancing the persistent expression of proinflammatory genes despite diabetic control. This finding suggests that the epigenetic modifications induced by long-term hyperglycemia may persist for a long time. These data must be considered in the future for the design of new strategies to decrease persistent hyperglycemia in diabetic patients and avoid the appearance of “epigenetic marks,” which are associated with the development of diabetic complication [29, 30, 31].

#### 5. Epigenetic effects of bioactive compounds in evolution of cancer

Cancer is the result to prolonged exposure to many carcinogenic factors, such as radiations, chemical substances, and prolonged exposure to sun. In industrialized countries the higher prevalence of cancer diseases is major in elderly people [32].

It has been shown that cancer cells do not belong to a unique cellular lineage because into a malignant tumor or among the circulating cancerous cells, there can be a diversity of types of cells. Recently, it has been described a stem cell theory of cancer that proposes that among all cancerous cells, a few act as stem cells that reproduce themselves and sustain the cancer, much like normal stem cells that normally renew and sustain our organs and tissues. The idea that cancer is primarily driven by a smaller population of stem cells has important biological and clinical implications. Currently, many new anticancer therapies are evaluated based on their ability to decrease or eliminate tumors, but if the therapies are not killing the cancer stem cells, the tumor will soon grow back as well as the clinical symptoms. Therefore, if the special subpopulations of tumor cells characterized as “cancer stem cells” are destroyed, a full recovery is possible. Consequently, the new cancer therapy will be target to abolish or decrease the self-renewal capabilities of this subpopulation of cancer cells [33, 34].

The Wnt/ $\beta$ -catenin signaling pathway is one of the most conserved intercellular signaling cascades. Its pathway begins when a Wnt protein binds to the N-terminal extracellular cysteine-rich domain of a frizzled (Fz) family receptor. However, to facilitate Wnt signaling, coreceptors such as lipoprotein receptor-related protein-5/6 (LRP-5/6) may be required alongside the interaction between the Wnt protein and Fz receptor. Upon activation of the receptor, a signal is conducted to the phosphoprotein disheveled (Dsh), which is located in the cytoplasm. Cytoplasmic  $\beta$ -catenin levels are normally kept low through continuous proteasome complex-mediated degradation (adenomatous polyposis coli (APC)/glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ); however, when cells receive Wnt signals, the degradation of  $\beta$ -catenin is inhibited and levels of  $\beta$ -catenin build up in the cytoplasm and nucleus. Then, nuclear  $\beta$ -catenin interacts with transcription factors, such as T-cell factor/lymphoid enhancer-binding factor (Tcf/Lef) which is a transcription regulator for several genes that, in part, regulates tumor progression [35].

However, Wnt signaling is not only restricted to control self-renewal of stem cells in normal microenvironment, also this pathway is particularly active in a limited subpopulation of cells that display cancer stem properties.

The mechanism proposed for such effect is that once nuclear  $\beta$ -catenins are activated they could interact with transcription factors, such as T-cell factor/lymphoid enhancer-binding factor (Tcf/Lef) and increase the transcriptional activity of several genes involved in tumoral progression [36]. The biological significance of Wnt/ $\beta$ -catenin pathway in cancer was evidenced by the fact that in many neoplastic diseases (prostate, colon, and skin cancer) mutations have been detected in some Wnt-downstream effectors [37–39].

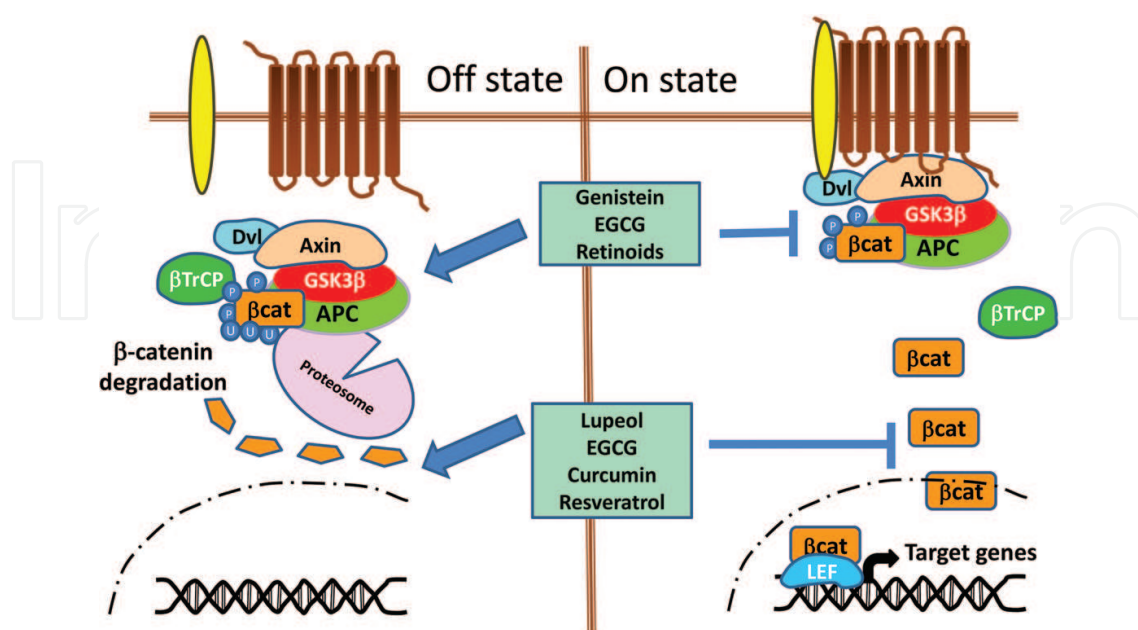
Currently, it has been explored many bioactive nutriment in cancer treatment due to their less toxic effects, as well as their property to exhibit less adverse effects compared to conventional antineoplastic drugs. The biological transcendence of many bioactive nutriment such as flavonoids, curcumin, green tea polyphenols, resveratrol, and lupeol lies in the fact that these compounds are able to disrupt  $\beta$ -catenin-mediated Wnt signaling (**Figure 3**). Their biological properties are mentioned below:

The flavonoids comprise a large class of low-molecular weight natural products of plant origin ubiquitously distributed in foods; many studies have demonstrated that these compounds

upregulate the expression and activity of GSK-3 $\beta$ , an essential component of the Wnt/ $\beta$ -catenin pathway. GSK-3 $\beta$  is a kinase that phosphorylates  $\beta$ -catenin for its eventual degradation in cytoplasm, thus inhibiting the signaling linked to Wnt receptor activation. Thereby, the use of flavonoids in cancer may potentially inactivate Wnt/ $\beta$ -catenin signaling reducing the proliferation index in prostate cancer cells [40]. Unlike flavonoids, curcumin (major component of turmeric and a member of the ginger *curcuma longa*) exhibits a different mechanism, which is based on constrain the transcriptional activity of Wnt target genes, such as c-myc, c-fos, c-jun, and iNOS, inhibiting cell proliferation and inducing apoptosis in human breast cancer cells [41].

Other important effect linked to curcumin administration is a dose-dependent decrease in expression of the nuclear p300 coactivator; p300 and CBP are thought to increase gene expression by relaxing the chromatin structure at the gene promoter through their intrinsic histone acetyltransferase (HAT) activity, recruiting the basal transcriptional machinery including RNA polymerase II to the promoter acting as adaptor molecules [42]. This is especially significant since nuclear beta-catenin forms a complex between Tcf4 and an important histone acetyltransferase mediator (p300 coactivator). This molecular interaction may change the DNA methylation patterns in Wnt target genes decreasing its transcriptional activity and consequently decreasing the tumoral progression [43].

Green tea polyphenols intake is linked to beneficial effects in many cancer cells, the mechanism involved is the ability of the polyphenols to downregulate  $\beta$ -catenin expression and consequently  $\beta$ -catenin/Tcf target genes (c-jun and cyclin D1). The clinical transcendence of these findings is that green tea intake may change the aberrant progression of many neoplastic during its early stages and consequently modify the clinical prognosis of the

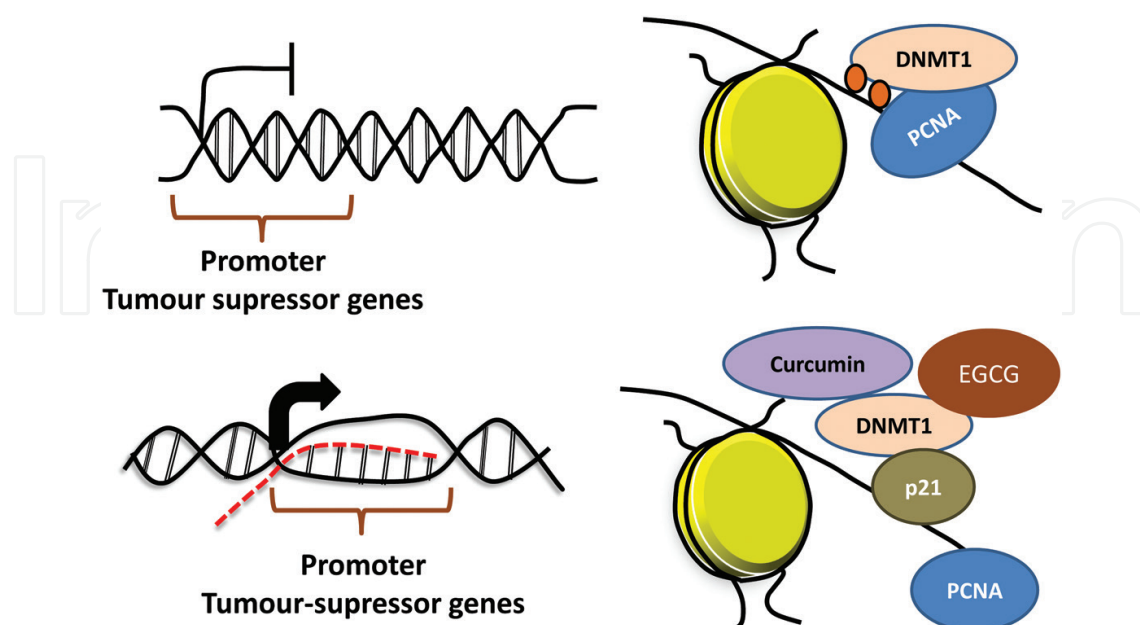


**Figure 3.** Effects of bioactive nutriment on Wnt/ $\beta$ -catenin pathway.

disease [44]. However, the beneficial effects of green tea are not restricted to bowel cancer; it has been shown that Wnt/ $\beta$ -catenin signaling can be inhibited by polyphenols in a dose-dependent manner in breast cancer cells [45]. The beneficial role of green tea compounds make them excellent candidates to bioactive antineoplastic drugs in many tumor contexts without the adverse effects exhibited by conventional drugs (**Figure 4**).

Resveratrol, a dietary polyphenol can be provided by roots of hellebore, grapes, mulberries, apricots, pineapples, and peanuts. Its role as antineoplastic agent is associated with the reduced expression of a long noncoding metastasis associated lung adenocarcinoma transcript 1 (RNA-MALAT1), thus decreasing the amount and proportion of  $\beta$ -catenin in the nucleus in colon cancer cells [46]. In addition, the role of resveratrol is not only restricted to solid tumor, but it can also inhibit proliferation and induce cell cycle arrest and apoptosis in Waldenstrom's macroglobulinemia cells. These effects of resveratrol were found to be mediated via the downregulation of Akt, mitogen-activated protein kinase (MAPK), and Wnt signaling pathways [47]. Meanwhile, lupeol, a well-studied dietary triterpene found in several fruits (olives, figs, mangoes, strawberries, and grapes) and vegetables (green peppers, white cabbage, and tomato) has shown a significant growth inhibition role on melanoma cells that exhibit constitutive Wnt/ $\beta$ -catenin signaling decreasing its neoplastic potential [48].

Further, Fan et al. demonstrated that lupeol inhibits the localization of  $\beta$ -catenin into the nucleus and decreases the phosphorylation status of  $\beta$ -catenin at important serine sites (ser 552 and ser 675), which are the signals for their translocation into the nucleus and induce transcription of various downstream targets linked to neoplastic processes [49].



**Figure 4.** Antineoplastic effects of bioactive nutriment.



## 6. Novelty technologies for obtaining and delivering bioactive compounds for health and medical therapy

After identifying a potential new bioactive component, it is necessary to evaluate many factors for its availability, such as the efficacy and safety of the product, select the appropriate food vehicle, ensure the bioavailability, and accuracy of health claims, and finally ensure that during the process of synthesis, stabilization, and processing the bioactive product does not lose its biological properties.

Recently, a great effort has been performed to develop novel procedures to synthesize new bioactive formulations that can overcome poor bioavailability, stability limitations, and rapid metabolism of bioactive compounds.

In this sense, novel technologies have been developed to improve the process to obtain biological compounds at low cost, as well as new procedures to deliver these bioactive products in tissues to enhance their biological effects.

One of these novel procedures is the delivery of bioactive compounds by microorganisms; these procedures take the ability of microbiota to deliver bioactive compounds contained in dairy diet, which cannot be processed by digestive human enzymes. These microorganisms produce a set of digestive enzymes that overcome the human ability to entirely digest the biocomponents encrypted in diverse food matrixes. Lactic acid bacteria (LAB) have been chosen due to their property to release, almost completely, the bioactive compounds from food matrix.

LABs are ancient microorganisms adapted to anoxic conditions, but their functional capabilities to synthesize micronutrients are almost absent. Therefore, LAB evolved a very efficient proteolytic system, which allows them to release encrypted biomolecules present in different food matrices (alpha- and beta-caseins, albumin, and globulin from milk, rubisco from spinach, beta-conglycinin from soy, and gluten from cereals), which are linked to a myriad of physiological functions, such as mineral absorption, adaptive response to oxidative stress, hypoglycemic actions, cholesterol lowering, cardiovascular functions, and a highlight effect related to the control of food intake [50]. The bioenzymatic properties exhibited by LAB rise them as excellent candidates to be added to processed food to ensure the delivery of bioactive molecules encrypted in food matrix, which in normal conditions are not accessible to human proteolytic enzymes.

On the other hand, the potential benefits of nano-technology have been recognized by food industry sectors by its potential application, which include the development of nano-sensors, smart packaging, nano-encapsulation, and delivery of food compounds. However, nano-technology can also be used to encapsulate in nano-emulsions many bioactive compounds to increase their bioavailability, stability, and reduce their biodegradation. Examples of ingredients encapsulated in nano-emulsion are: minerals, vitamins, enzymes, and bioactive ingredients. In this sense, currently it has been explored the use of an ROS-responsive polymeric nano-particles for efficient Cur delivery into cancer cells. This nano-system improves



Cur stability at physiological environment and enhances the Cur release in response to hydrogen peroxide. Both mechanisms displayed an antitumoral effect in a cellular culture of lung cancer. Thereby, the use of nano-technology to deliver bioactive compounds may have a potential application in medicine to improve the cancer treatment without the adverse effect observed in conventional drugs currently available [51].

Quercetin is a major constituent of various dietary products and recently its anticancer potential has been extensively explored, revealing its antiproliferative effect on different cancer cell lines. However, its medical applications are limited due to its low oral bioavailability, rapid clearance from body, high metabolic rate, and poor aqueous solubility.

Therefore, to overcome these biological disadvantages, novel quercetin-based nano-formulations are being developed due to their properties of bioavailability, gut absorption, and their capability to increase quercetin biological half-time in serum. The pharmacological effect of quercetin loaded/conjugated nano-particles majorly depends on the drug carriers used and the physicochemical properties of the nano-particulate system. These characteristics can increase the stability of quercetin, its bioavailability, and target specificity [52, 53]. However, the medical application of quercetin nano-particles is still under investigation likely due to the necessity of more stable and target-specific nano-particles.

Indeed, it has been explored other delivery system based on different matrix where bioactive compounds are encapsulated within PLGA (poly lactic-co-glycolic acid) and PLA (poly D,L-lactic acid) nano-particles. For example, it was observed a significant cytotoxic effect of quercetin encapsulated PLGA nano-particles in combination with ectopside-loaded PLGA nano-particles in a human lung adenocarcinoma epithelial cell line. Similarly, a significant reduction of breast cancer cells upon treatment with PLA-quercetin was shown, which support the clinical use of these novel technologies for cancer treatment [54]. Thereby, the nano-technology can be used as a powerful tool to overcome the biochemical and physiological limitations of bioactive compounds, improve many pharmacodynamics parameters, and potentiate the pharmacological and functional effects exhibited by these compounds.

## 7. Conclusions

Although bioactive nutriment compounds have shown potential health benefits, currently, there are no nutritional guidelines to recommend intake levels as there are for other nutriment. The challenge for the future will be the establishment of nutritional recommendations for each bioactive food components. These kinds of products should not be only taken as vital nutriment, but also, they should be considered important molecules that depending on the nutritional conditions or cellular environments can modify the DNA methylation patterns and change the way that DNA is transcribed. The data provided show that the intake of bioactive products, provided in daily diet, may have a dual role depending on the load ingest, maintaining homeostasis at recommended levels, or induce the appearance of disease when are taken to overdoses. However, the most important role exhibited by bioactive nutriment is

their antineoplastic effect, which depends on their molecular interactions with enzymes that modify the DNA structure or as methyl or acetyl donors to DNA or histones.

The clinical transcendence of the molecular effects displayed by bioactive nutriment is that they are exempt of the adverse effects of conventional antineoplastic drugs, which make them excellent candidates for cancer treatment in the future. Thereby, food companies must direct their effort to the development of novel and low cost processes to ensure an adequate bioactive concentration in the diverse food presentations of industrialized food, or these food preparations may be added with a special set of microorganisms to enhance the delivery of bioactive compounds encrypted in food matrixes.

Currently, novel nano-particles systems to carry bioactive compounds have been evaluated. These systems were designed to avoid the accelerated metabolism that bio compounds undergo along the gastrointestinal tract. Thereby, pharmaceutical industries must direct their efforts to design novel technologies to ensure the bioavailability of many bioactive compounds linked to antitumoral activity, preserving their biological activity in the affected tissue. Both strategies may have an enormous economic impact on pharmaceutical and food industries, lowering the production cost of antineoplastic drugs, and decrease the cytotoxic effect displayed by the actual antineoplastic conventional drugs. These novel technologies may also be useful to prevent the high incidence of cancer in general population providing an accurate concentration of bioactive compounds in industrialized food with the corresponding impact on social medical security, decreasing the economical inversion to cancer treatment in affected population.

## Acknowledgements

This review was supported by the Centro de Investigación en Ciencias de la Salud (CICSA), Facultad de Ciencias de la Salud, Universidad Anáhuac México Campus Norte, Huixquilucan, Edo. de México, Mexico.

## Author details

Pablo Bautista-García<sup>1\*</sup>, Lorena González-López<sup>2</sup>, Berenice González-Esparza<sup>3</sup> and Camila Del Castillo-Rosas<sup>1</sup>

\*Address all correspondence to: pablobautista1973@hotmail.com

1 Center for Research in Health Science (CICSA), Faculty of Science Health, Anáhuac University North Campus, Huixquilucan, Mexico

2 Center for Research and Advanced Studies (CINESTAV), Mexico City, Mexico

3 Technologic University of Mexico, Mexico City, Mexico

## References

- [1] Abuajah CI, Ogbonna AC, Osuji CM. Functional components and medicinal properties of food: A review. *Journal of Food Science and Technology*. 2015;**52**(5):2522-2529. DOI: 10.1007/s13197-014-1396-5
- [2] Balentine DA, Erdman J, Courtney GP, Dwyer JT, Ellwood KC, Hu FB, Russell RM. Are dietary bioactive ready for recommended intakes? *Advances in Nutrition*. 2013;**4**:539-541. DOI: 10.3945/an.113.004226
- [3] Mazzio EA, Soliman KF. Epigenetics and nutritional environmental signals. *Integrative and Comparative Biology*. 2014;**54**(1):21-30. DOI: 10.1093/icb/icu049
- [4] Ludwig AK, Zhang P, Cardoso MC. Modifiers and readers of DNA modifications and their impact on genome structure, expression, and stability in disease. *Frontiers in Genetics*. 2016;**7**:115. DOI: 10.3389/fgene.2016.00115
- [5] Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. *The Journal of Nutrition Health and Aging*. 2002;**6**:39-42. DOI: PMID 11813080
- [6] Shorter KR, Felder MR, Vrana PB. Consequences of dietary methyl donor supplements: Is more always better?. *Progress in Biophysics & Molecular Biology*. 2015;**118**(1-2):14-20. DOI: 10.1016/j.pbiomolbio.2015.03.007
- [7] Duthie SJ, Narayanan S, Sharp L, Little J, Basten G, Power H. Folate, DNA stability and colo-rectal neoplasia. *Proceedings of the Nutrition Society*. 2004;**63**:571-578. DOI: 10.1079/PNS2004387
- [8] O'Reilly SL, McGlynn AP, McNulty H, Reynolds J, Wasson GR, Molloy AM, Strain JJ, Weir DG, Ward M, McKerr G, Scott JM, Downes CS. Folic acid supplementation in post-polypectomy patients in a randomized controlled trial increases tissue folate concentrations and reduces aberrant DNA biomarkers in colonic tissues adjacent to the former polyp site. *Journal of Nutrition*. 2016;**146**(5):933-939. DOI: 10.3945/jn.115.222547
- [9] Wu X, Xu W, Zhou T, Cao N, Ni J, Zou T, Liang Z, Wang X, Fenech M. The role of genetic polymorphisms as related to one-carbon metabolism, Vitamin B6, and gene-nutrient interactions in maintaining genomic stability and cell viability in Chinese breast cancer patients. *International Journal of Molecular Sciences*. 2016;**17**(7):1-24. pii: E1003. DOI: 10.3390/ijms17071003
- [10] Detich N, Theberge J, Szyf M. Promoter-specific activation and demethylation by MBD2/demethylase. *Journal of Biological Chemistry*. 2002;**277**:35791-35794. DOI: 10.1074/jbc.C200408200
- [11] Ball GFM. Vitamin A: Retinoids and carotenoids. In: Blackwell Publishing Ltd, editor. *Vitamins: Their Role in the Human Body*. 1st ed. UK: Oxford; 2004:133-187. DOI: ISBN 0-632-06478-1

- [12] Benkoussa M, Braqund C, Delmontte MH, Formstecher P. Retinoic acid receptors inhibit AP1 activation by regulating extracellular signal-regulated kinase and CBP recruitment to an AP1-responsive promoter. *Molecular and Cellular Biology*. 2002;**22**:4522-4534. DOI: 10.1128/MCB.22.13.4522-4534.2002
- [13] Milutinovic S, Knox JD, Szyf M. DNA methyltransferase inhibition induces the transcription of tumour suppressor p21 (WAF1/CIP1/sdi1). *Journal of Biological Chemistry*. 2000;**275**:6353-6359. DOI: 10.1074/jbc.275.9.6353
- [14] Iida T, Suetake I, Tajima S, Morioka H, Ohta S, Obuse C. PCNA clamp facilitates action of DNA cytosine methyltransferase 1 on hemimethylated DNA. *Genes to Cells*. 2002;**7**:997-1007. DOI: 10.1046/j.1365-2443.2002.00584.x
- [15] Bigey P, Ramchandani S, Theberge J, Araujo FD, Szyf M. Transcriptional regulation of the human DNA methyltransferase (dnmt1) gene. *Gene*. 2000;**242**:407-418. DOI: 10.1016/S0378-1119(99)00501-6
- [16] Pitha-Rowe I, Petty WJ, Kitareewan S, Dmitrovsky E. Retinoid target gene in acute promyelocytic leukemia. *Leukemia*. 2003;**17**:1723-1730. DOI: 10.108/sj.leu.2403065
- [17] Kolb EA, Meshinchi S. Acute myeloid leukaemia in children and adolescents: Identification of new molecular targets brings promise of new therapies. *Haematology American Society of Hematology Education Program*. 2015;**2015**:507-513. DOI: 10.1182/asheducation-2015.1.507
- [18] Xia Q, Zhao Y, Wang J, Qiao W, Zhang D, Yin H, Xu D, Chen F. Proteomic analysis of cell cycle arrest and differentiation induction caused by ATPR, a derivative of all-trans retinoic acid, in human gastric cancer SGC-7901 cells. *Prot. Clin. Appl.* 2017, 1600099
- [19] Bouillon R, Suda T. Vitamin D: Calcium and bone homeostasis during evolution. *Bonekey Report*. 2014;**3**:480. DOI: 10.1038/bonekey.2013.214
- [20] Saramaki A, Diermeier S, Kellner R, Laitinen H, Vaisanen S, Calberg C. Cyclical chromatin looping and transcription factor association on the regulatory regions of p21 (CDKN1A) gene in response to 1  $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>. *Journal of Biological Chemistry*. 2009;**284**:8073-8082. DOI: 10.1074/jbc.M808090200
- [21] Picotto G, Liaudat AC, Bohl L, Tolosa de Talamoni N. Molecular aspects of Vitamin D anticancer activity. *Cancer Investigation*. 2012;**30**(8):604-614. DOI: 10.3109/0735907.2012.721039
- [22] Ben-Eltriki M, Deb S, Adomat H, Tomlinson Guns ES. Calcitriol and 20(S)-protopanaxadiol synergistically inhibit growth and induce apoptosis in human prostate cancer cells. *The Journal of Steroid Biochemistry and Molecular Biology*. 2016;**158**:207-219. DOI: 10.1016/j.jsbmb.2015.12.002
- [23] Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science*. 2007;**318**:1469-1472. DOI: 10.1126/science.1151710

- [24] Widiker S, Karst S, Wagener A, Brockmann GA. High-fat diet leads to a decreased methylation of the MC4R gene in the obese B6 and lean B6 mouse lines. *Journal of Applied Genetics*. 2010;**51**:193-197. DOI: 10.1007/BF03195727
- [25] Palou M, Pico C, McKay JA, Sánchez J, Priego T, Mathers JC, Palou A. Protective effects of leptin during the sucking period against later obesity may be associated with changes in promoter methylation of the hypothalamic pro-opiomelanocortin gene. *British Journal of Nutrition*. 2011;**106**:769-778. DOI: 10.1017/S000714511000973
- [26] Milagro FI, Campion J, García-Díaz DF, Goyenechea E, Paternain L, Martínez JA. High-fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. *Journal of Physiology and Biochemistry*. 2009;**65**:1-9. DOI: 10.1007/BF03165964
- [27] American Diabetes Association. Standards of medical care in Diabetes-2010. *Diabetes Care*. 2010;**33**(Suppl. 1):S1-S61. DOI: 10.2337/dc10.S011
- [28] Reddy MA, Natarajan R. Role of epigenetic mechanisms in the vascular complications of diabetes. *Subcellular Biochemistry*. 2013;**61**:435-454. DOI: 10.1007/978-94-007-4525-4\_19
- [29] Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: Implications for disease and therapy. *Nature Reviews Genetics*. 2009;**10**:32-34. DOI: 10.1038/nrg2485
- [30] Szyf M. Epigenetics, DNA methylation and chromatin modifying drugs. *Annual Review of Pharmacology and Toxicology*. 2009;**49**:243-263. DOI: 10.1146/annrev-pharmtox-061008-103102
- [31] Bieliasukas AV, Pflum MK. Isoforms-selective histone deacetylases inhibition. *Chemical Society Reviews*. 2008;**37**:1402-1413. DOI: 10.1039/b703830p
- [32] Gloeckler LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. *Oncologist*. 2003;**8**:541-552. DOI: 10.1634/theoncologist.8-6-541
- [33] Peitzsch C, Tyutyunnykova A, Pantel K, Dubrovskaya A. Cancer stem cells: The root of tumor recurrence and metastasis. *Seminars in Cancer Biology*. 2017. pii: S1044-579X(17)30031-7. DOI: 10.1016/j.semcancer.2017.02.011. [Epub ahead of print]
- [34] Kaur S, Singh G, Kaur K. Cancer stem cells: An insight and future perspective. *Journal of Cancer Research and Therapeutics*. 2014;**10**(4):846-852. DOI: 10.4103/0973-1482.139264
- [35] Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene* 2017; **36**, 1461-1473; doi:10.1038/onc.2016.304
- [36] Zhao C, Blum J, Chen A, Kwon HY, Jung SH, Cook JM, Lo A, Reya T. Loss of beta-catenin impairs then renewal of normal and CML stem cells in vivo. *Cancer Cell*. 2007;**12**:528-541. DOI: 10.1016/j.ccr.2007.11.003



- [37] Gerstein AV. APC/CTNNB1 (beta-catenin) pathway alteration in human prostate cancer. *Genes Chromosomes Cancer*. 2002;**34**:9-16. DOI: 10.1002/gcc.10037
- [38] Mir R, Pradhan SJ, Patil P, Mulherkar R, Galande S. Wnt/ $\beta$ -catenin signaling regulated SATB1 promotes colorectal cancer tumorigenesis and progression. *Oncogene*. 2016;**35**:1679-1691. DOI: 10.1038/onc.2015.232
- [39] Damsky WE, Curley DP, Santhanakrishnan M, rosenbaum LE, Platt JT, Gould BE, Taketo MM, Dankort D, Rimm DL, McMahon M, Boseberg M. Beta-catenin signaling controls metastasis in Braf-activated Pten-deficient melanomas. *Cancer Cell*. 2011;**20**(6):741-754. DOI: 10.1016/j.ccr.2011.10.030
- [40] Li Y, Wang Z, Kong D, Li R, Sarkar SH, Sarkar FH. Regulation of Akt/FOXO3a/GSK-3 $\beta$ /AR signaling network by isoflavone in prostate cancer cells. *Journal of Biological Chemistry*. 2008;**283**:27707-2776. DOI: 10.1074/jbcM802759200
- [41] Prasad CP, Rath G, Mathur S, Bhatnagar D, Ralhan R. Potent growth suppressive activity of curcumin in human breast cancer cells: Modulation of Wnt/beta-catenin signaling. *Chemico-Biological Interactions*. 2009;**181**:263-271. DOI: 10.1016/j.cbi.2009.06.012
- [42] Ryu MJ, Cho M, Song JY, Yun YS, Choi IW, Kim DE, Park BS, Oh S. Natural derivatives of curcumin attenuate the Wnt/beta-catenin pathway through down-regulation of the transcriptional coactivator p300. *Biochemical and Biophysical Research Communications*. 2008;**377**:1304-1308. DOI: 10.1016/j.bbr.2008.10.171
- [43] Gao Y, Teschendorff AE. Epigenetic and genetic deregulation in cancer target distinct signaling pathway domains. *Nucleic Acids Research*. 2017;**45**(2):583-596. DOI: 10.1093/nar/gkw1100
- [44] Niedzwiecki A, Roomi MW, Kalinovsky T, Rath M. Anticancer efficacy of polyphenols and their combinations. *Nutrients*. 2016;**8**(9). pii: E552. DOI: 10.3390/nu8090552
- [45] Kim J, Zhang X, Rieger-Christ KM, Summerhayes IC, Wazer DE, Paulson E, Yee AS. Suppression of Wnt signaling by the green tea compound epigallocatechin 3-gallate (EGCG) in invasive breast cancer cells. Requirements of transcriptional repressor HBP1. *Journal of Biological Chemistry*. 2006;**281**:10865. DOI: 10.1074/jbc.M513378200
- [46] Ji Q, Liu X, Fu X, Zhang L, Sui H, Zhou L, Sun J, Cai J, Qin J, Ren J, Li Q. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/ $\beta$ -catenin signal pathway. *PLoS One*. 2013;**8**(11):e78700. DOI: 10.1371/journal.pone.0078700
- [47] Roccaro AM, Leleu X, Sacco A, Moreau AS, Hatjiharissi E, Jia X, Xu L, Ciccarelli B, Patterson CJ, Ngo T, Russo D, Vacca A, Dammaco F, Anderson KC, Ghobrial IM, Treon SP. Resveratrol exerts antiproliferative activity and induces apoptosis in Waldenstrom's macroglobulinemia. *Clinical Cancer Research*. 2008;**14**:1849-1858. DOI: 10.1158/1078-0432.CCR-07-1750
- [48] Nitta M, Azuma K, Hata K, Takahashi S, Ogiwara K, Tsuka T, Imagawa T, Yokoe I, Osaki T, Minami S, Okamoto Y. Systemic and local injections of lupeol inhibit tumor growth in

a melanoma-bearing mouse model. *Biomedical Reports*. 2013;**1**(4):641-645. DOI: 10.3892/br.2013.116

- [49] Fang D, Hawke D, Zheng Y, Xia Y, Meisenhelder J, Nika H, Mills GB, Kobayashi R, Hunter T, Lu Z. Phosphorylation of beta-catenin by AKT promotes beta-catenin transcriptional activity. *Journal of Biological Chemistry*. 2007;**282**:11221-11229. DOI: 10.1074/jbcM611871200
- [50] Pessione E, Cirrincione S. Bioactive molecules released in food by lactic acid bacteria: Encrypted peptides and biogenic amines. *Frontiers in Microbiology*. 2016;**7**:876. DOI: 10.3389/fmicb.2016.00876
- [51] Luo C-Q, Xing L, Cui P-F, Qiao J-B, He Y-J, Chen B-A, Jin L, Jiang H-L. Curcumin-coordinated nanoparticles with improved stability for reactive oxygen species-responsive drug delivery in lung cancer therapy. *International Journal of Nanomedicine*. 2017;**12**:855-869. DOI: 10.2147/IJN.S122678
- [52] Nam J-S, Sharma AR, Nguyen LT, Chakraborty C, Sharma G, Lee S-S. Application of bioactive quercetin in oncotherapy: From nutrition to nanomedicine. *Molecules*. 2016;**21**:108. DOI: 10.3390/molecules21010108
- [53] Pimple S, Manjappa AS, Ukawala M, Murthy RS. PLGA nanoparticles loaded with etoposide and quercetin dihydrate individually: In vitro cell line study to ensure advantage of combination therapy. *Cancer Nanotechnology*. 2012;**3**:25-36. DOI: 10.1007/s12645-012-0027-y
- [54] Pandey SK, Patel DK, Thakur R, Mishra, DP, Maiti P, Halder C. Anti-cancer evaluation of quercetin embedded PLA nanoparticles synthesized by emulsified nanoprecipitation. *International Journal of Biological Macromolecules*. 2015;**75**:521-529. DOI: 10.1016/j.ijbiomac.2015.02.011

