Abstract. Epidemiological and clinical studies support the association between nutrition and development or progression of different malignancies such as colon, breast, and prostate cancer, defining these tumors as diet-associated cancer. The Mediterranean diet shows inverse associations with metabolic diseases, cardiovascular pathologies and various types of cancer. Many bioactive nutrients of the Mediterranean diet have been identified as factors protective against these types of pathologies. The epigenome has been identified as the primary goal of modulations in gene expression related to these molecular nutrients. In fact, they can modify the epigenome and can be incorporated into the ‘epigenetic diet’, which translates into a diet regimen that can be used therapeutically for health or preventative purposes. Most epigenetic changes are influenced by lifestyle and nutrition. Epigenetic therapy is a new area for the development of nutraceuticals whose absence of toxicity can represent a valid asset in cancer prevention strategies. Recent advances in understanding the mechanisms of nutrigenomics, nutrigenetics and nutraceuticals have led to the identification of superfoods capable of favorably conditioning gene expression. In this review, we highlight the importance of nutraceuticals present in the Mediterranean diet as epigenetic modifiers both in the mechanisms of tumor onset and as protective agents.

The Mediterranean diet constitutes a food model that characterizes not only a lifestyle, but also a culture, and has been indicated as a hub for improving health, quality of life and life span (1). Numerous studies have highlighted the positive correlation between the Mediterranean diet and longevity; individuals who adhere to a nutritional style like this have a longer life expectancy (2-4). Moreover, the Mediterranean diet prevents many metabolic, cardiovascular and neurodegenerative diseases, insulin resistance and different types of cancer (5-7). Today cancer represents the second leading cause of death in the world, immediately after cardiovascular diseases, but its onset curve has lowered in parallel with other chronic degenerative diseases, such as diabetes and obesity. In this context, diet plays a very important role. Epidemiological and clinical studies support the association between nutrition and development or progression of different cancer malignancies such as of the colon, breast, prostate and others, defining these tumors as diet-associated cancer (8-11). Over the years, many bioactive nutrients have been identified, on the one hand because they are involved in the development of tumors, on the other hand as protective factors. Among these are polyphenols, selenium, donors of methyl groups, retinoids, isothiocyanates and some allyl compounds (12, 13). These are molecules capable of intervening in the hepatic detoxification phases of type 1 and 2, DNA repair mechanisms, cell growth and differentiation, apoptosis, oxidative stress and in modulation of inflammation (14). However, in recent years, the epigenome has been identified as the primary goal of modulating gene expression related to these nutrients. The term ‘epigenetic diet’ has been introduced to indicate the consumption of foods such as soy, cruciferous vegetables and green tea, which influence epigenetic mechanisms capable of protecting against cancer and the aging process (15, 16). Proven bioactive nutritional factors are therefore able to modify the epigenome and can be incorporated into...
this epigenetic diet, which translates into a diet regimen that can be used therapeutically for health or preventative purposes (17, 18).

In this context, the Mediterranean diet as an epigenetic diet is characterized by a high consumption of whole grains (about 50-60% of the total caloric intake), and a high consumption of vegetables, fruit and legumes; use of extra virgin olive oil to cover about 70% of the lipid supply; regular consumption of fresh fish (especially blue fish); a regular but moderate consumption of red wine during main meals; with an optimal supply of omega-3 both of animal and vegetable origin. This type of diet is associated with low mortality from all causes (19-21). For example, a high adherence to the Mediterranean diet is associated with a significant reduction in the risk of general mortality from cancer (10%), with particular epidemiological relevance towards colorectal (14%), prostate (4%) and gastrointestinal tract (56%) cancer (22-24). In 2003, the PREDIMED study confirmed that the Mediterranean diet, implemented with extra virgin olive oil or the consumption of three walnuts per day, was able to prevent cardiovascular disease (25). Between 2005 and 2010, the MOLI-SANI Study showed greater adherence to the Mediterranean diet to be associated with a reduction in leukocytes and platelets suggesting that the set of foods that make up the Mediterranean diet has anti-inflammatory activity and a protective effect against many pathologies (primarily arteriosclerosis) with inflammatory pathogenesis (26). These and other studies demonstrate the existence of an inverse association between the Mediterranean diet and total mortality, incidence of coronary heart disease, thrombotic infarction and numerous neoplasms (27). Starting from this basis, the international scientific community has taken seriously the important role of the Mediterranean Diet, and the lifestyle it is inspired by, in increasing longevity and improving public health.

The Mediterranean diet can therefore be considered as a nutritional pool comprising various nutraceuticals, bioactive components present and carried by food, capable of favorably influencing health, both directly and through its own epigenetic mechanisms (Figure 1). The low animal protein content and the low glycemic index of the Mediterranean diet directly modulate the mammalian target of rapamycin (mTOR) pathway and the level of insulin-like growth factor-1 (IGF1), known to be involved in the aging process and in the regulation of forkhead box O3 (FOXO3A) and consequently to the transcription of homeostatic genes that promote longevity (28). Low-grade chronic inflammation due to poor nutrition in obesity, metabolic syndrome and diabetes mellitus 2 increases the risk of cancer and affects all its various stages, both by triggering the initial genetic mutation or epigenetic mechanism, and by promoting the onset of cancer and its progression and metastatic spread (29). Epidemiological studies have shown that the Mediterranean diet reduces the risk of the onset of various types of cancer. Bioactive nutrients in the Mediterranean diet not only modulate multiple interconnected processes involved in carcinogenesis, in the inflammatory response and in the production of free radicals, but also highlight the ability to promote the restoration of the inflammatory balance due to the maintenance of intestinal microbiota and the epigenetic modulation of oncogenetic and oncosuppressive factors (30-32).

In this review, we highlight the importance of nutraceuticals present in the Mediterranean diet as epigenetic modifiers both in the mechanisms of tumor onset and as protective agents.

**Nutraceuticals and Gene Expression**

Epigenetic therapy is a new area for the development of nutraceuticals whose absence of toxicity can represent a valid asset in the cancer prevention strategy. Recent advances in understanding the mechanisms of nutrigenomics, nutrigenetics and nutraceuticals have led to the identification of superfoods capable of favorably conditioning gene expression (33, 34). In the past, it was said, "you are what you eat". Today a new notion reflecting the interaction between genomic structure and nutrition is introduced: "eat correctly in relation to your genotype". However, the diet cannot always ensure an adequate supply of those nutrients and phyto derivatives able to actively condition gene expression, trying to optimize the positive aspects inherent in each individual’s DNA and to limit the consequences of unfavorable genomic susceptibility. Thus, was born the concept of nutraceuticals, a mix of substances able to interact with the individual genotypic structure in function with the environmental one (phenotype) (35, 36). Nutraceuticals therefore take on the role of cellular and functional modulators, capable of ensuring the optimization of physiological processes (37). Most epigenetic changes are influenced by lifestyle and nutrition (38). Some nutraceuticals have emerged in the context of the scientific literature as a source of molecules capable of reversing epigenetic alterations and actively regulating gene and molecular expression, also preventing chronic degenerative diseases due to epigenetic modulation (39-41). Cancer, for example, represents a heterogeneous multi-stage disease, driven by progressive genetic and epigenetic anomalies. The epigenetic component is influenced by various exogenous and endogenous factors, including nutrition, the environment, ethnicity, lifestyle, medications, exposure to xenobiotics and toxins, physical activity, age, gender and family genetic heritage (42). Epigenetic therapy is a new
area for the development of nutraceuticals whose absence of toxicity can represent a valid asset in the cancer prevention strategy. Recent advances in understanding the mechanisms of nutrigenomics, nutrigenetics and nutraceuticals have led to the identification of superfoods capable of favorably conditioning gene expression (Figure 2) (43).

Curcuma longa. Curcuma longa is a perennial rhizomatous plant belonging to the Zingiberaceae family. The root is the component of greatest nutritional and phytotherapeutic interest. The use of the spice in herbal medicine requires the consumption of at least one tablespoon of turmeric per day, with the addition of a modest amount of pepper, which improves its absorption (44). Among the main constituents of the root of turmeric are the curcuminoïds, of which the most represented is curcumin (45). Curcumin is a polyphenolic compound with anti-inflammatory, antioxidant and antilipidemic actions; its ability to modulate various pathologies has been recently demonstrated through modulation mechanisms and epigenetic regulation (46). In

Figure 1. Diet may influence genetic and epigenetic events associated with several cancer process.

Figure 2. Different mechanisms of action induced by nutrients in the pathways of activation of protective mechanisms and promotion of tumor cell growth. HDAC: Histone deacetylases; p53: protein p53; p21: protein p21; INS/IGF: insulin/insulin-like growth factor; GH: growth hormone; RAS: rat sarcoma; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinases; AKT: protein-chinasi B; FOXO: forkhead box O; PKA: protein-chinasi A; VEGF: vascular endothelial growth factor; IL-1: interleukin -1, IL-6: interleukin-6; TNF-α: tumor necrosis alfa.
fact, numerous studies have shown its role as ‘epigenetic inactivator’ of key genes that regulate important pathologies such as neurodegenerative diseases and cancer (47-52). Epigenetic changes imply changes in DNA methylation, modifications of histones or microRNA expression patterns. These are mechanisms known to be interconnected with each other and for the key role they play in the progression of tumor, as well as in the failure of conventional chemotherapy (53). Taken together, the epigenetic mechanisms of the action of curcumin include (54-59):

- Inhibition of DNA methyltransferase (DNMT), a hypomethylating agent.
- Histone modification through regulation of both histone acetyltransferase (HAT) and histone deacetylase (HDAC).
- MicroRNA modulation (miR-15a, miR-16, miR-21-22-26).
- Activation of transcription factors, chemokines, cytokines, and tumor-suppressor genes.

Turmeric can be considered a molecule capable of interacting with numerous molecular targets involved in the inflammatory process. Its use in the oncology field has been shown to inhibit angiogenesis implicated in the development of tumor and its progression (60, 61). It is a potent inhibitor of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), thus promoting a cell apoptotic response (62). Recent studies that have demonstrated the anticancer effects of turmeric have confirmed the beneficial effects of curcumin combined with various antineoplastic drugs in order to improve their clinical effects and reduce toxicity (63, 64). Curcumin can also exert an anticancer and chemopreventative activity on breast cancer. In this context, curcumin exerts its antitumor effect not only through its specific mechanisms of action already described, but also thanks to a complex molecular signaling network that involves the mechanisms underlying the cell proliferative processes, the receptors of estrogen (ER) and human epidermal growth factor receptor 2 (HER2) (65, 66).

**Resveratrol.** Resveratrol is another polyphenolic compound and is present in grapes, in wine, in some berries and oil seeds (peanuts), and in particular plants. In grapes, it is found only in the peel, while its content in wine depends on the vine plant, on the geographical location of the cultivation and on the fermentation time (67). Resveratrol is one of the phytoalexins naturally produced by numerous plants defending against pathogens such as bacteria and fungi. Resveratrol is capable of exerting a powerful antioxidant and anti-inflammatory action (68). Its role as a modulator of cell apoptosis is fundamental (69). The cellular apoptosis promoted by this stilbene, in fact, can be mediated by multiple mechanisms (70, 71):

- Activation of mitochondria and caspase cascade.
- Up-regulation of cyclin dependent kinase inhibitors, apoptosis-inducing cytokines and related receptors.
- Down-regulation of cell survival proteins, such as survivin, B-cell lymphoma 2 (BCL2), B-cell lymphoma-extra large (BCL-XL).
- Inhibition of cell kinases that promote survival [mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinases (PI3K), protein kinase C (PKC), epidermal growth factor receptor (EGFR) kinases] and factors that promote transcription, such as NF-κB, activator protein 1 (AP1) and early growth response protein 1 (ERG1).

Several studies have demonstrated the action of resveratrol in modulating DNA methylation in several genes involved in cancer (72). In a recent study, resveratrol was shown to restore the hypomethylated and hypermethylated state of key tumor-suppressor and oncogenic genes, respectively (73). In that study, methylation alterations were consistent with changes in mRNA expression. Therefore, the impact of resveratrol on the epigenetic methylation processes of breast cancer cells is significant and might allow potential new therapeutic targets for effective epigenetic therapy to be identified (74). In light of the above, resveratrol can be considered an epigenetic drug capable of exerting its anticancer activity by modifying the methylation status of genes related to various types of cancer and therefore represents a valid potential chemopreventative agent (75).

**Lycopene.** Lycopene is a natural antioxidant from the carotenoid family, present at high concentrations in ripe tomatoes and to a lesser extent in watermelon, apricot, grapes, pink grapefruit and papaya. The lycopene content in tomato is influenced by the ripening level; it has been calculated that 50 mg/kg of lycopene are present in ripe red tomatoes, while the concentration drops to 5 mg/kg in yellow varieties (76, 77). The bioavailability of the compound is higher in heat-treated products than in raw products thanks to the dissociation of the protein complexes in which it is incorporated and the dispersion of the crystalline aggregates of carotenoids (78). Several studies attribute the ability of lycopene to reduce prostate cancer risk to it modulating the expression of genes associated with inflammation, apoptosis and cancer progression (79). Carotenoids, as well as their metabolites and oxidation products, improve communication at the level of intercellular gap junctions, which are considered one of the cancer prevention mechanisms by playing a role in the regulation of cell growth, differentiation and apoptosis (80). Gap junction communication is in fact deficient in many forms of tumors and the restoration of this function is associated with a reduction in cell proliferation (81). Several studies have highlighted how lycopene has cytotoxic effects against different types of cancer (82, 83). It is commonly believed that a better understanding of the mechanisms underlying the anticancer effects of lycopene may provide new therapeutic targets for the treatment of cancer. In the case of prostate cancer, lycopene has been
observed to regulate the expression of serine/threonine kinase 2 (AKT2) and to regulate the expression of miRNA (84, 85). In this context, an important role in the inhibition of prostate cancer progression would be precisely correlated with these epigenetic mechanisms.

**Ellagic acid.** Ellagic acid is a phenolic compound that can be extracted from pomegranate peel and which is present in many red fruits, such as raspberries, strawberries and cranberries, as well as in walnuts. It is also present in goji berries (86). The anti-angiogenic activity of ellagic acid is mediated by the abolition of the hypoxia gate at the PI3K/AKT/mTOR, MAPK and VEGF/VEGFR2 pathways, which involve the suppression of the response towards HDAC6 and hypoxia-inducible factor 1 subunit alpha (HIF1α) (87). Molecular studies have confirmed the interaction of ellagic acid with the kinases that regulate the conduction of angiogenic signaling (88,89). Furthermore, ellagic acid was shown to reduce the expression of HDAC, thereby contributing to the inhibition of neovascularization processes (90). Ellagic acid is a natural anti-inflammatory and immunomodulating molecule; for example, it is able to modulate IL1β, IL6, IL8, IL10, C-C motif chemokine ligand 2 (CCL2) and the expression of the TNFA gene in HaCaT cells, after their irradiation with UVB (91). Combination of ellagic acid and curcumin at various concentrations demonstrated better anticancer properties than did the individual molecules (92). Furthermore, both curcumin and ellagic acid have been shown to restore the expression and action of p53, an important promoter of apoptosis. Recent in vivo and in vitro studies revealed that ellagic acid has evident epigenetic actions: Anticancer effects; inhibition of the proliferation of cancer cells; induction of apoptosis; breakdown of DNA binding by carcinogens; anti-inflammatory and antiangiogenic properties; reducing spread of metastases (93, 94).

**Indole 3 carbinol (I3C), di-indoylmethane (DIM) and sulforaphane.** DIM and its precursor, I3C, are active nutrients derived from cruciferous vegetables, broccoli, cabbage, Brussels sprouts and savoy cabbage (95). These are natural substances derived from the degradation of glucosinolate glucobrassicin. Recent studies indicated the strong synergistic action of the association of I3C with DIM. Glucoraphanin is a glucosinate that is found at high concentrations in broccoli and other members of the brassicaceae family. Sulforaphane is its active form, which is obtained when glucorafanin is metabolized by the enzyme myrosinase, which is freed from the leaves of brassicaceae when they are chewed (96, 97). Cooking partially denatures myrosinase, leaving glucorafanin partially intact, but the bioavailability in this case is, however, guaranteed by the intestinal microflora, which can produce myrosinase (98). I3C induces the arrest of tumor cell growth in the G1 phase of the cell cycle. It is a potent inducer of cytochrome P450 enzymes, including CYP1A1, CYP1A2 and CYP1B1 (99). I3C and DIM modulate the metabolism of estrogens by increasing 2-hydroxylation, which leads to an increase in the 2-OH:16-OH ratio relative to the estrogen metabolites (100). In humans, these hormones are degraded into different metabolites, which can stimulate or inhibit the onset of a hormone-sensitive neoplasm (101, 102). The metabolites involved are estrone 2 (2OHE1), which tends to inhibit the growth of the neoplasm, and estrone 16 (16OHE1), which promotes tumor growth. Those who have a prevalence of estrone 2 are more protected than those who have a higher production of estrone 16. When the 2-OH:16-OH ratio is lower than unity, there are serious clinical implications, while when this ratio is higher than three, the consequences are more favorable (103). A metabolite of estradiol is 16-α-hydroxyestrone which, owing to its covalent bond with its receptor, induces a persistent biological response, which consists of stimulating tumor mitogenic growth (104). Other conversion products for estrone and estradiol are 2-hydroxylated estrogens, such as 2-hydroxyestrone and 2-hydroxyestradiol. Unlike 16-α-hydroxyestrone, these hydroxylated forms seem to inhibit mitogenic stimulation of neoplastic lesions, showing anticancer properties and target multiple aspects of cancer cell-cycle regulation and survival, including caspase activation, cyclin-dependent kinase activities, estrogen metabolism and estrogen receptor signaling (105-106). The positive effect that DIM and I3C have is related to the fact that they both modify the estradiol isoylation receptor site, reducing the production of 16-α-hydroxyestrone in favor of 2-hydroxyestrone. In addition, both I3C and DIM stimulate the liver production of detoxifying enzymes capable of neutralizing and degrading the harmful metabolites of both estrogens and xeno-estrogens taken up as environmental pollutants or in food (107). In experimental studies, the molecules have proven to be effective in reducing the growth of papillomavirus (108). They are also capable of stimulating the antitumor genes p21, p27 and p53 with nonspecific preventative effect and against herpes simplex and human papillomavirus (109, 110). Sulforaphane exhibits a well-known epigenetic action, being able to act for example as an inhibitor of HDAC, emerging as both a curative and preventive chemotherapy agent (111, 112). It has multiple effects including cell growth arrest, differentiation and apoptosis as recently demonstrated in the case of prostatic neoplasms (113, 114). Other benefits of sulforaphane come from its activities as an anticancer agent. For example, sporadic breast cancer is frequently associated with aberrant DNA methylation patterns that are reversible and sensitive to factors including diet (115). Sulforaphane affects the methylation and expression of tumor-suppressor genes phosphatase and tensin homolog...
(PTEN) and retinoic acid receptor-B (RARβ), as well as the expression of DNA methylation reaction regulators such as DNMT1, p53 and p21, silencing the tumor-suppressor genes in breast cancer cells, and representing a therapeutic opportunity to assist other conventional therapies (116, 117). Moreover, sulforaphane significantly inhibits the viability and proliferation of breast cancer cells in vitro, while it has negligible effects on normal cells. Telomerase inhibition has received considerable attention due to its high expression in tumor cells and its extremely low level of expression in normal cells (118). Sulforaphane treatment inhibits the catalytic subunit of human telomerase. Scientific studies have paralleled interferences in DNA methyltransferase activity, in particular DNMT1 and DNMT3A, which were found to decrease in breast cancer tumor cells treated with sulforaphane, suggesting how the latter may be able to repress telomerase through specific epigenetic precursors (119). Furthermore, the down-regulation of telomerase expression facilitates the induction of apoptosis of breast cancer neoplastic cells, opening a way for approaches aimed at sulforaphane-mediated prevention of this neoplasm. Diet is a known modifiable factor associated with the risk of several cancer types, especially breast cancer. The role of bioactive compounds of food origin, including those found in cruciferous vegetables, is an active field of research in terms of cancer chemoprevention (120-122). DIM, the main bioactive indole of cruciferous plants, has shown chemopreventative activity in all stages of breast cancer carcinogenesis. Oral intake of DIM has been associated with an increase in BRCA1 mRNA expression in women with an unfavorable BRCA1 mutation (123). The possibility of mitigating the effect of this hereditary mutation, increasing the physiological expression of the gene and thus normalizing the levels of DNA-repairing proteins, represents a clinically important additional tool in the prevention strategies available to women at high breast and ovarian cancer risk.

The epithelial–mesenchymal transition (EMT) plays a key role in tumor progression. The cells in EMT up-regulate the expression of proteins related to cell motility and show a greater propensity for migration and metastasis (124). Therefore, the prevention of EMT is an important tool for the inhibition of tumor metastases. Food phytoestrogens found in cruciferous vegetables are known to have biological efficacy including chemopreventative activity against tumors (125). In particular, it has been observed in tumor cell lines that DIM can induce not only antiproliferative action, apoptosis and cell-cycle arrest, but also anti-metastatic activity due to its ability to inhibit EMT, as well as associated processes (NOTCH1 and TGFβ) (126). A diet rich in fruit and vegetables provides phytochemicals such as I3C, sulforaphane and DIM, which may be jointly responsible for the prevention of many types of cancer, including hormone-dependent neoplasms such as those of the breast, ovary, uterus and prostate (127, 128). Attention should be paid to bioavailability, which is related to the cooking and storage methods. Both the cooking temperature and preservation even at 4°C can significantly alter the quantity of active components in foods containing these substances, compromising their efficacy of therapeutic action (129). In conclusion, glucosinolates present in cruciferous vegetables such as broccoli, cabbage, Brussels sprouts and cauliflower have beneficial effects on general health as potential anti-neoplastic effects due to their role in preventing the initial processes of carcinogenesis. This occurs, in particular, thanks to the induction of both anti-oxidant and detoxifying defense mechanisms and epigenetic mechanisms underlying them, including the modification of cytosine-phosphate-guanine (CpG) methylation, which occurs mainly in cancer-related genes, and the regulation of histone modification and changes in the expression of the miRNA (130).

Silybum marianum. The milk thistle S. marianum is a biennial herbaceous plant of the Asteraceae family. The main phytochemical components to which its action and its therapeutic potential might be attributed go under the generic name of flavolignans (131). Its peculiar phytocomplex includes various active components such as:

- Silandrin, which interferes in the biosynthesis of triglycerides and the activity of cyclo-oxygenase, which show antioxidant activity (132).
- Silymarin, which modulates the action of liver enzymes capable of inactivating and eliminating pharmacological molecules, alcohol, and xenobiotics (133).
- Silibinin, which inhibits the biosynthesis of leukotrienes by acting on the inflammatory process and also shows antioxidant action (134).

Their generic action therefore is to stimulate the cellular elimination of toxins and the reduction of the inflammatory component (135). The most important flavonoid fraction is given by silymarin, which is a group of flavonoids characterized by an antioxidant and regenerative activity with a marked tropism towards hepatocytes (136). They have an anabolic action on the metabolic function of these cells and promote regeneration. In clinical practice, S. marianum is used in the treatment of liver diseases of any nature in which anatomo-functional damage has resulted. It exerts a regenerative action on hepatocytes making them more resistant to hepatotoxic agents (137). The damage caused by free radicals to cellular structures such as membranes causes a great release by lipolysis of fatty acids of the omega 6 series, such as arachidonic acid. This leads to an increase in the synthesis of the main inflammatory mediators, leukotrienes, produced by a reaction catalyzed by lipoygenase (138). Silymarin acts as a powerful inhibitor of this enzyme thereby stopping the pathological decomposition.
of membrane lipids and consequently the synthesis of prostaglandins during the inflammatory process. Silibinin exerts a strong anti-proliferative, anti-inflammatory and pro-apoptotic action (139, 140). Numerous studies have shown experimentally that through an epigenetic mechanism it inhibits the development of tumors induced in the liver, prostate, skin, colon and recently also in the breast, also promoting the inhibition of the proliferation of tumor cell lines in vitro by exercising anti-metastatic action (141-144). Furthermore, silymarin has found a role as a new therapy for the treatment of cancer in lung, colon, skin, prostate, breast, bladder and liver tumors, regulating neoplastic cells in the various stages of growth and proliferation, and influencing fundamental epigenetic and nutrigenomic processes, such as apoptosis and angiogenesis (145). Its synergistic combination with curcumin, quercetin, soy isoflavones and epigallocatechin-3-gallate (EGCG) is excellent in chemoprevention of aerodigestive and GI cancer (146).

Capsaicin. Capsaicin is a chemical compound present in different concentrations in plants of the Capsicum genus (e.g. in spicy chili), which gives them their characteristic irritating power. Chili pepper is the main source of capsaiacinoids in nature, which consist of capsaicin, di-hydrocapsaicin, nor-di-hydrocapsaicna, homo-di-hydrocapsaicin and homo-capsaicin which are capable of exerting multiple pharmacological and physiological effects (147). Therefore, capsaiacinoids might be used in the clinic to relieve pain, prevent cancer and lose weight (148). Capsaicin manifests anticancer activity through delicate molecular epigenetic mechanisms. On the one hand it facilitates apoptosis and on the other it inhibits the expression of VEGF responsible for the vascularization of the tumor mass, the angiogenic process that feeds it and its metastases (149, 150). In addition, capsaicin has been reported to preferentially inhibit the activity of tumor-associated NADH oxidase, which belongs to a family of hydroquinone oxidases implicated in the development and growth of cancer (151). Capsaicin exhibits antiproliferative actions on prostate cancer cells by inducing apoptosis. It reduces the expression of the androgenic receptor, inhibits the activity of the proteasome which suppresses the degradation of inhibitor of nuclear factor kappa B (IκBα), thereby preventing the activation of NF-xB (152). Such actions might play a role in the treatment of prostate cancer, even hormone-independent. The NF-xB signaling pathway is in fact constitutively activated in hormone-independent carcinomas (153, 154).

Quercetin. Quercetin is a flavonol and is the aglyconic component of various glycosides including rutin and quercetrin. In foods it is found mainly in capers, in some vegetables such as red onion, cruciferous vegetables, celery, lettuce, asparagus, tomatoes and shallots (155, 156). Quercetin is also found in some fruits, such as berries, pomegranate, black uva and therefore also in red wine, citrus fruits, apples, nuts, pistachios, in green tea in propolis. The biosynthesis of quercetin is stimulated by light so that the compound accumulates mainly in the leaves and peel of fruit. A diet rich in vegetables and fruit with peel provides an intake of 200 to 500 mg per day of quercetin (157). The compound has antioxidant, anti-inflammatory, antiallergic, anti-aggregant and anti-thrombotic actions and has cardioprotective effects (158). The antioxidant activity is due to the reactivity of its phenolic group. There are several epigenetic mechanisms associated with quercetin such as the suppression of Janus kinase 2 (JAK2) capable of inhibiting the proliferation, invasion and migration of cancer cells with an associated effective stimulus towards the mechanisms of autophagy and apoptosis to promote the death of cancer cells (159). In vitro actions on cellular signaling pathways and anticancer effects have been detected. The actions of quercetin on signal pathways can be reproduced both with the use of food sources (simple onion soup) and with the contribution of dietary supplements (160). One of the main forms of quercetin present in the diet is quercetin-4-glucoside. This conjugate form occurs at high levels in onions and is preferentially absorbed in the intestine (161). Quercetin is eliminated rapidly (half-life of approximately 2 hours) and is present in the urine in conjugated form (162). Cell-culture studies show that the flavones quercetin and kaempferol inhibit inducible nitric oxide synthase, cyclooxygenase-2, and C-reactive protein (163). The inhibition of inflammatory factors is accomplished through the inhibition of the transcription factor NF-xB (164). The anti-inflammatory and antioxidant actions may be responsible for the favorable effects observed in patients with chronic prostatitis and interstitial cystitis (165). Quercetin inhibits the expression and function of the androgenic receptor in LNCaP prostate cancer cells and reduces regulation of androgen-inducible genes including PSA, and ornithine decarboxylase which play a role in tumor development and progression (166). Quercetin causes a decrease in IGF1 levels and an increase in IGFBP3 which is associated with an increase in pro-apoptotic protein and a decrease in anti-apoptotic proteins BCL2 and BCL-XL (167). Quercetin reduces HER2/neu protein level and inhibits the PI3K/AKT signaling pathway (168). Since activation is necessary for cell survival, its inhibition contributes to apoptosis (169). Quercetin activates caspase-3 and -9 and releases cytochrome c in leukemic cells. It blocks the G1 cell-cycle progression in numerous tumor cell lines, demonstrating antiproliferative effects (170). Quercetin significantly inhibited the growth of aggressive (PC3) and moderately aggressive (DU-145) prostate cancer cell lines, demonstrating that its effects are correlated with tumor aggression and that the mechanism of actions passes through
the hyper-regulation of tumor-suppressor genes and the decrease in regulation of oncogenes and cell cycle-controlling genes (171).

**Fisetin.** Fisetin is a flavonol found in various vegetables and some fruits, including strawberries, apples, persimmons, onions and cucumbers (172). Fisetin has been shown to inhibit or delay the growth of various cancer cells both in culture and in vivo. Its targets of action are multiple intracellular signaling pathways including cellular survival and apoptosis regulatory mechanisms, angiogenic and metastatic switches going upstream to modulate a distinct series of kinase transcription factors and their regulation modalities (173-175). Current scientific evidence supports the hypothesis that fisetin is a promising agent for the treatment of cancer and its epigenetic prevention (176). One of the epigenetic modulation pathways that characterizes the activity of fisetin is the inhibition of the mTOR and PI3K/AKT cascade, which is at the center of many studies concerning the mechanisms underlying the development and proliferation of neoplastic cells (177-179).

**Epigallocatechin-3-gallate.** EGCG is a type of catechin which is especially abundant in green tea (180). It is a polyphenol with anti-inflammatory and antioxidant activity and can be found in other foods such as apples, blackberries, raspberries, walnuts and hazelnuts, pistachios, plums, peaches and avocados (181). Green tea catechins are able to reverse DNA methylation at the level of tumor-suppressor genes and increase their transcription (182). *In vivo* studies have shown that compared to a placebo group, high consumption of green tea, and therefore a high intake of EGCG, was able to reduce the methylation of cadal type homeobox 2 (*CDX2*) and bone morphogenetic protein 2 (*BMP2*) in gastric cancer, with effective epigenetic modulation (183). The polyphenols of green tea, including EGCG, are also able to mediate the epigenetic induction of metalloprotease inhibitors (*TIMP*), including TIMP3, whose levels play a key role in suppressing the invasiveness and gelatinolytic activity of MMP2 and MMP9, enzymatic activities promoting the metastatic process (184, 185).

**Anthocyanins.** Anthocyanins are among the most important groups of pigments found in vegetables, although they are found mainly in fruits and vegetables as potential chemopreventative agents (188, 189). In this context, isothiocyanates and anthocyanins, which are present in consumer vegetables, are two of the most important agents, especially thanks to their preventive efficacy both *in vitro* and in experimental models (190). At an epigenetic level, anthocyanins influence the cell cycle, allowing a better efficacy of the activation of DNA-repair mechanisms (191, 192).

*The polyphenols of extra virgin olive oil.* Extra virgin olive oil is obtained through a technological process that allows the preservation of compounds present in the olives which otherwise would be lost during the refining/rectification phases, as happens in the production of other vegetable oils (193). Extra virgin olive oil is composed of monounsaturated fatty acids (oleic acid) and omega-3. There is also a small percentage of saturated fats, linoleic acid and vitamin E. It is characterized by the presence of phenolic acids and alkalis, secoiridoids, flavonoids, lignans and hydroxy-isochromans (194). The phenolic fraction has the greatest protective action against oxidative processes and is responsible for shelf life of the product. The consumption of extra virgin olive oil is correlated with the low incidence of arteriosclerosis, diabetes, inflammatory and autoimmune diseases, skin diseases and aging, and tumor pathology (195). Laboratory experiments have shown that oleic acid, a powerful antioxidant, facilitates the repair of DNA damaged by excessive exposure to the sun. Oleic acid also exhibits favorable actions on the cardiovascular system (196). The polyphenol oleocantal, responsible for the pungent taste sensation of olive oil, has inhibitory actions on cyclooxygenases, so that the continuous consumption of olive oil may have preventative actions on inflammatory pathologies in a similar way to compounds such as ibuprofen (197). In the tumor field, polyphenols isolated from extra virgin olive oil inhibit the expression of the HER-2/neu protein (ERBB2), expression of which is correlated with aggressive breast carcinoma (198). Olive oil also enhances the inhibitory effects on tumor growth of the monoclonal antibody to HER2, trastuzumab (Herceptin™), in breast cancer (199).

**Conclusion**

Several bioactive components of the Mediterranean diet are of particular interest in the field of epigenetics. For many of these compounds, their anticancer properties have been highlighted and they can play an active role particularly in the prevention of cancer. Numerous studies suggest that a number of nutritional compounds have epigenetic targets on cancer cells, in both their formation and in their development and proliferation. It follows that today we can speak in all respects of an ‘epigenetic diet aimed at the integration of nutraceuticals capable of activating epigenetic modulation. However, in recent years, the epigenome has been identified...
as the primary goal of modulating gene expression related to these molecular nutrients. The latter can widely modulate epigenetic mechanisms that lead to a rapid and effective regulation of gene expression, precisely in response to nutritional changes. Considerable progress can be made with nutrigenomics and knowledge of the genome of plants which will allow the identification and selection of protective foods with more accuracy. In the near future, it will be possible to arrive at a sort of nutriprevention and nutritherapy based on the knowledge of the genome of individuals at risk or suffering from pathological events. The Mediterranean diet rich in fruit and vegetables and citrus fruits, cruciferous vegetables supplemented with food and phytotherapeutic compounds is probably the way forward for future studies.

Conflicts of Interest

No conflict of interest to declare.

Authors’ Contributions

Divella Rosa: Article writing. Daniele Antonella: References. Savino Eufemia: English language revision. Paradiso Angelo: Responsible for the BIOMIS project.

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