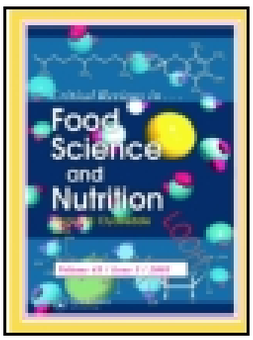

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REVIEW

Targeting epigenetics in cancer: therapeutic potential of flavonoids

Haroon Khan[a], Tarun Belwal[b], Thomas Efferth[c], Ammad Ahmad Farooqi[d], Ana Sanches-Silva[e,f], Rosa Anna Vacca[g], Seyed Fazel Nabavi[h], Fazlullah Khan[i], Hari Prasad Devkota[j], Davide Barreca[k], Antoni Sureda[l], Silvia Tejada[m], Marco Dacrema[n], Maria Daglia[n]*, İpek Suntar[o], Suowen Xu[p§], Hammad Ullah[a], Maurizio Battino[q,r,s], Francesca Giampieri[q,r,t], and Seyed Mohammad Nabavi[h]

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ABSTRACT

Irrespective of sex and age, cancer is the leading cause of mortality around the globe. Therapeutic incompliance, unwanted effects, and economic burdens imparted by cancer treatments, are primary health challenges. The heritable features in gene expression that are propagated through cell division and contribute to cellular identity without a change in DNA sequence are considered epigenetic characteristics and agents that could interfere with these features and are regarded as potential therapeutic targets. The genetic modification accounts for the recurrence and uncontrolled changes in the physiology of cancer cells. This review focuses on plant-derived flavonoids as a therapeutic tool for cancer, attributed to their ability for epigenetic regulation of cancer pathogenesis. The epigenetic mechanisms of various classes of flavonoids including flavonols, flavones, isoflavones, flavanones, flavan-3-ols, and anthocyanidins, such as cyanidin, delphinidin, and pelargonidin, are discussed. The outstanding results of preclinical studies encourage researchers to design several clinical trials on various flavonoids to ascertain their clinical strength in the treatment of different cancers. The results of such studies will define the clinical fate of these agents in future.

KEYWORDS

Anticancer; cancer therapy; epigenetic; flavonoids

Introduction

Cancer is the second leading cause of mortality, only behind cardiovascular disorders. In 2018 as reported by World Health Organization (https://www.who.int/news-room/fact-sheets/detail/cancer), cancer was the cause of 9.6 million deaths worldwide. Colorectal, lung and stomach are common in both sexes, but some cancers are more common in men (e.g., liver and prostate cancer) and other in women (e.g., breast and cervix cancer). Due to the incidence of cancers worldwide, there is growing interest in using epigenetic therapies to reprogram cancer cells toward a normal state (Ahuja, Sharma, and Baylin 2016; Shukla and Meeran 2014).

The heritable features in gene expression, that are propagated through cell division and contribute to cellular identity without change in DNA sequence, are considered epigenetic characteristics (Berger 2016). These mechanisms include DNA methylation, non-coding RNA-dependent gene

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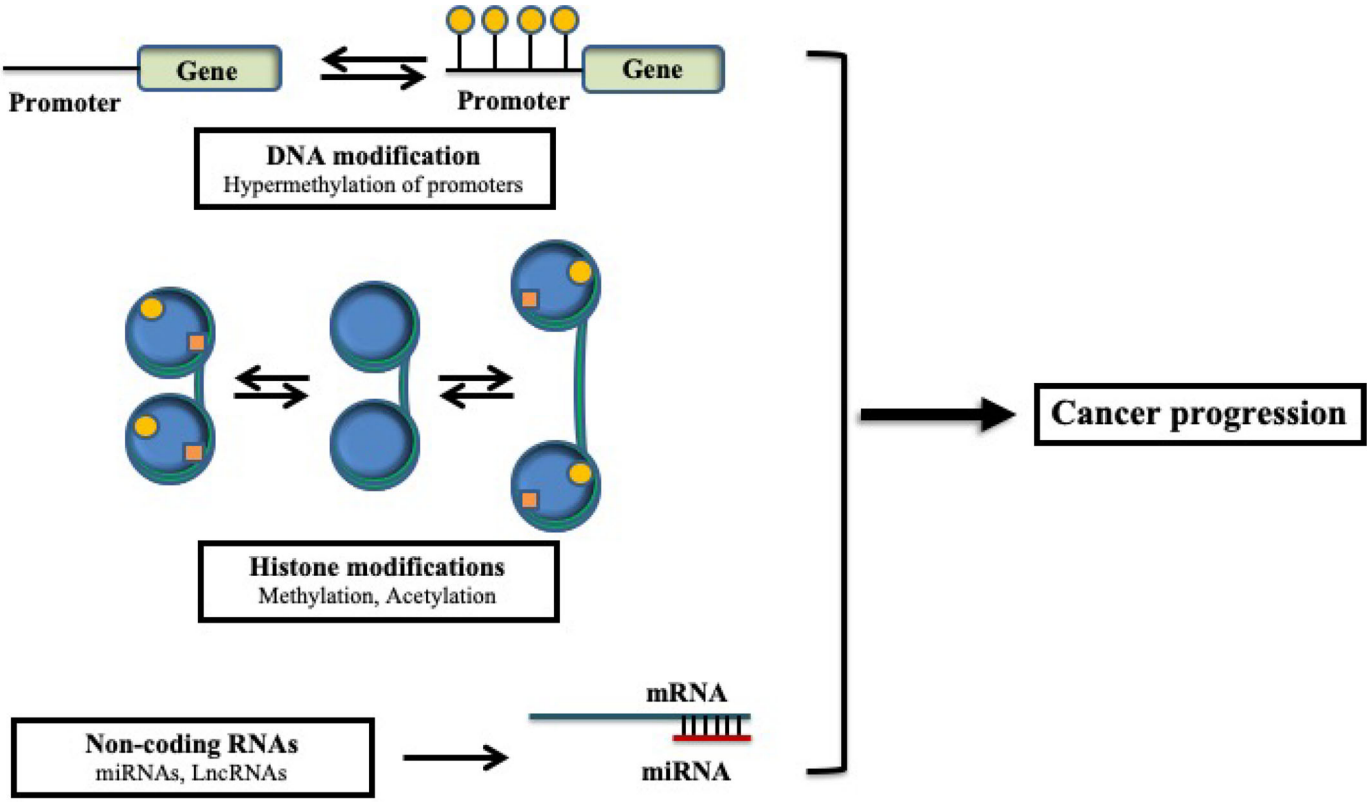

Figure 1. Targeting epigenetic regulation in cancer *via* DNA modifications, histone modifications and Non-coding RNAs (miRNAs and lncRNAs).

regulation and covalent histone modifications (Wainwright and Scaffidi 2017). DNA methyltransferases catalyze DNA methylation, histone acethyltransferases regulate histone acetylation, while histone methyltransferases as well as histone demethylases are responsible for histone methylation (Busch et al. 2015). MicroRNAs (miRNAs) are further regulators of epigenetic changes and regulate gene expression and, at the same time, are important for RNA-silencing (Busch et al. 2015) (Figure 1). The epigenetic changes in cancer are recognized as contributors to malignant transformation, but they are also potentially reversible in somatic cells, allowing tailoring cancer strategies (Link, Balaguer, and Goel 2010). Some agents targeting epigenetic regulation have been approved by the FDA for cancer treatment or are under study (Berger 2016; Byrne, Murphy, and Ryan 2014).

Nowadays, diets rich in fruits and vegetables are recommended for their association with health-promoting effects due to their content on bioactive compounds such as phenolics. So far, more than 8000 phenolic compounds have been identified (Pan et al. 2015). The preventive cancer effects of polyphenols are often related with their antioxidant and anti-inflammatory activities but according to Pan et al. (2015) polyphenols are also multifunctional autocrine-paracrine disruptors. Therefore, polyphenols can exert beneficial effects in cancer chemoprevention, due to their capability of interfering with epigenetic signaling cascades responsible for tumorigenesis and metastasis. Flavonoids are a class of polyphenols that has been associated with numerous cell-regulatory activities in cancer cells (Berghe 2012; Lee et al. 2013; Link, Balaguer, and Goel 2010; Schnekenburger, Dicato, and Diederich 2014; Shankar et al. 2016; Afrin et al. 2020). For example, genistein and daidzein, which are abundant flavonoids found in soybean and fava beans, as well as hesperetin and naringenin, which are found in citrus peels, have been recognized as inhibitors of DNA methyltransferases (Fang, Chen, and Yang 2007; Fang et al. 2005). The most abundant flavonoid of green tea (*Camelia sinensis* L.), epigallocatechin-3-gallate (EGCG), has shown to modulate DNA methyltransferase and histone acetyltransferase activities (Gilbert and Liu 2010).

This review highlights the potential of flavonoids as a therapeutic tool for cancer due to their ability for epigenetic regulation of cancer pathogenesis. Main epigenetic regulation mechanisms of flavanones (hesperetin, naringenin, silibinin), flavones (luteolin, apigenin), isoflavones (genistein, daidzein), flavonols (fisetin, quercetin, kaempferol, myricetin), flavan-3-ols (EGCG), and anthocyanidins (cyanidin, delphinidin, malvidin, and pelargonidin) are discussed. Clinical trials focused on flavonoids with the capacity of treating cancer are also addressed. Finally, future directions on the impact of epigenetic of flavonoids in the prevention and treatment of cancer are pointed.

Targeting epigenetic modifications in cancer

The word epigenetics, "above genetics," was coined for the first time by Conrad Hal Waddington in 1942 to explain "the causal interactions between genes and their products, which bring the phenotype into being." The Waddington's theory was brilliant and after the conclusion of his experiment on fruit flies, he realized that the adult phenotype could be influenced by environmental stimuli, while

respecting the Neo-Darwinian's law. According to Waddington's theory, every organism could exert its plasticity, which is already contained in genetic heredity. Following his theory, the developmental process is a landscape, which contains valleys and forks and the organism can be accompanied toward a specific phenotype by the environment, while maintaining the same genotype (Waddington 1942). Waddington's discovery laid the groundwork to the most important discoveries of epigenetics, such as DNA methylation, histone modification, long non-coding RNA (lncRNA) and microRNA, creating an interim step between genotype and phenotype for the first time.

DNA methylation/demethylation

One of the most important mechanisms involved in the epigenetic regulation is the DNA methylation, which consists in the addition of one methyl group at 5′ cytosine of 5′—C—phosphate—G—3′ (CpG) dinucleotides. The methylation can regulate different key processes, such as genomic imprinting, inactivation of X chromosome, silencing of target gene, regulation of transcription events. There are three main enzymes involved in the methylation processes, called DNA methyltransferases (DNMTs). They can be subdivided according to their task (Rodríguez-Paredes and Esteller 2011). In fact, DNMT1 have the role to maintain the methylation pattern, especially during the replication of DNA. On the contrary DNMT3A and DMT3B are *de novo* DNA methylases, which are also involved in the methylation of CpGs target during the genomic imprinting after the fecundation of the oocyte (Friedman et al. 2008). The DNA methylation was discovered in the 1948 (Bogdanović and Veenstra 2009), but only in the 1980 Razin and Riggs described the possible correlation between gene expression and an epigenetic modification (Razin and Riggs 1980). The silencing of one specific DNA region can occur in two different ways. The first one is the interference between the proteins involved during the transcription phase and the methylated sequence. The other one is the intervention of methyl-CpG-binding protein (MBD), which can determine the recruitment of complexes to induce a remodeling of DNA condensations. In mammals, the known to date methyl-CpG-binding domains (MBDs) are MBD1, MBD2, MBD3, MBD4, methylcytosine binding protein 2 (MECP2) and Kaiso (ZBTB33) (Bots and Johnstone 2009). Their correct function is essential to avoid the occurrence of tumors. In fact, the up-regulation of these proteins can lead to the silencing of tumor suppressor gene (Mahmood and Rabbani 2019). Hypermethylation of DNA bases, especially in the promoter regions, allow the binding of methyl DNA binding proteins, which down-regulate the expression of tumor suppressor and other genes. The most frequent epigenetic alteration is increased methylation of phosphorylated cytosine-guanine (CpG) in promoter sequences (CpG islands) (Pfeifer 2018). On a global level, DNA hypomethylation is linked with genetic stability (You and Jones 2012). DNA hypomethylation can be frequently found in heterochromatic DNA repeats and dispersed retrotransposons (Ehrlich and Lacey 2013). Hence, both events, hyper- and hypomethylation, represent carcinogenic events.

Although heritable, epigenetic changes are reversible. This opens avenues for drug development to prevent or reverse malignant transformation of cells based on epigenetic changes. DNA methylation changes take part not only in the early steps of carcinogenesis, but also in the more progressive events in the carcinogenic cascade such as proliferation, invasion, metastasis, neo-angiogenesis, apoptosis etc. (Kanwal and Gupta 2012; Lee and Kong 2016; Thomas and Marcato 2018).

While a majority of CpG islands resist *de novo* methylation, tumor suppressor and other genes are prone to DNA methylation changes (Long, Smiraglia, and Campbell 2017). Aberrant DNA methylation is characteristic for cancer and some other diseases (e.g., cardiovascular diseases, neurodegenerative diseases, dementia, diabetes mellitus, depression) (Smith and Ryckman 2015; Thomas and Marcato 2018).

Therapeutic intervention focusing on the inhibition of DNMTs attempts to alter erroneously hypermethylated tumor suppressor genes in tumor cells, although it has to be considered that demethylation is not-target-specific and other genes, in addition to tumor suppressor genes, may also be demethylated (Subramaniam et al. 2014; Yoo and Jones 2006). Several DNMT inhibitors are already used in clinical pratice or are under clinical investigation (e.g., 5-azacytidine, 2-deoxycytidine, decitabine (=5-aza-2′-deoxycytidine)). Their clinical utility is still hampered by high toxicities, low bioavailability, and rapid elimination (Subramaniam et al. 2014). Hence, the quest for novel DNMT inhibitors continues. Natural products from marine sources (e.g., psammaplin A from the spongue *Pseudocarina purpurea*) or polyphenols from terrestrian plants have been described as DNMT inhibitors (Busch et al. 2015; Schneider-Stock et al. 2012; Schnekenburger, Dicato, and Diederich 2014; Thakur et al. 2014). Importantly, blood concentrations of flavonoids were high enough to be achievable (8 mmol/L). This gives reason to hope that i.v. administration are high enough to exert anti-DNMT inhibitory activity (Venturelli et al. 2014), showing that the search for novel DNMT inhibitors from natural resources is not only of academic interest, but is also clinically reachable.

Histone methylation/demethylation

As regards histones modification, it is well known that DNA presents different levels of organization. Chromatin is the structured form in which DNA is present in the cell nucleus. The basic units of chromatin are the nucleosomes that allow a first stage of compaction of the genetic material. Nucleosomes are constituted by approximately 146 base-pairs associated with a complex of eight histone proteins. This octamer forms a protein core, around which the DNA helix is wound. Nucleosomes are separated by a section of free DNA of variable length called spacer DNA. At a second level of higher order organization, several groups of nucleosomes are packaged by histone H1 binding. Epigenetic

modulation of this chromatin structure allows the modulation of the accessibility of nuclear proteins to specific sections of DNA. The covalent modifications of histones include phosphorylation, acetylation, ubiquitination, proline isomerization, ADP ribosylation and sumoylation (Bannister and Kouzarides 2011; Cohen et al. 2011; Kouzarides 2007). All these modifications are regulated by different proteins. For instance, the methylation and acetylation are controlled respectively by methyltransferases (HMTs) and acetyltransfereses (HATs). At the same time, these modifications can be removed by demethylases (HDMs) and deacetylases (HDACs) underlying the plasticity of the chromatin remodeling system (Kouzarides 2007). Indeed, the different conformation of the chromatin in its two main states is driven also by the acetylation and methylation levels of the histones. Histone acetylation is a good example of direct mechanism of chromatin modification; in fact HATs induce a reduction of histones positive charge, promoting the access to the DNA by the protein involved in the transcription machinery (Xhemalce, Dawson, and Bannister 2011). The methylation process of histone protein, which consists in the addition of methyl groups on lysine or arginine residues, without inducing a change in a charge of nucleosomes, is a different modification. In this case, HMTs can add one, two or three methyl groups on lysine residues or only one methyl or arginine residues (Lan and Shi 2009; Ng et al. 2009). It is well known that the deregulation in the methylation pattern can also drive to carcinogenesis. The hyper or hypomethylation of specific regions are related to the silencing or expression of the altered gene (Li, Carey, and Workman 2007; Portela and Esteller 2010).

One important post-translational modification of histones is the methylation of lysine and arginine residues. In this sense, lysine can be found in mono-, di-, or trimethylated forms, whereas arginine residues can be mono- or demethylated by HMT enzymes using S-adenosyl methionine (SAM) as the methyl group donor (Martin and Zhang 2005). The methylation of histones is dynamic and can be reversed by the action of HDMs. This process can result in both transcription repression and activation depending on the methylated residue and degree of methylation (Martin and Zhang 2005). For instance, this dual effect is evident in the fact that the methylation of histone H3 at lysine residues 4 or 36 (H3K4 or H3K36) results in chromatin activation, while methylation at H3K9, H3K27 or histone H4 at lysine 20 (H4K20) leads to gene silencing donor (Martin and Zhang 2005). Although methylation is mainly found in H3 followed by H4, methylated residues have also been found in H1, H2A and H2B. Unlike the process of acetylation of lysine where the positive charge of the amino acid disappears, favoring the formation of euchromatin by eliminating the electrostatic bond between histones and DNA, methylation of lysines and arginines does not modify the charge (Copeland, Solomon, and Richon 2009). However, these modifications modify the interaction with various proteins associated with chromatin and this change can be recognized by different protein modules termed effectors, which specifically recognize these modifications (Taverna et al. 2007). The action of these protein modules facilitates specific downstream events through the stabilization or recruitment of module-associated chromatin-templated machinery (Seet et al. 2006).

The type and degree of histone modifications is different between cell types but also diverse tumor types present alterations in the general profile of histone modifications (Morera, Lübbert, and Jung 2016; Varier and Timmers 2011). Alterations in histone methyltransferases, including mutational inactivation or reduced/increased expression, have been associated with the pathogenesis of a wide number of cancers (Hess 2004; Michalak and Visvader 2016; Nishikawaji et al. 2016). In this sense, an anomalous histone modification pattern, which can lead to a dysregulated expression of oncogenes and/or tumor suppressor genes, is frequently linked to cancer (McGrath and Trojer 2015). Consequently, histone methylation/demethylation is a promising new target for the development of novel anti-cancer agents, being some of them in first stages of clinical trials as potential cancer therapy (Morera, Lübbert, and Jung 2016).

miRNAs and lncRNAs

mRNAs are small non-coding RNA long 22 nucleotides involved in the post-transcriptional silencing and mRNA decay (Huntzinger and Izaurralde 2011). The transcription process starts in the nucleus thanks to RNA polymerases II, although some miRNAs can also be transcribed by the RNA polymerases III (Babiarz et al. 2008). The transcription of miRNAs is under fine control. In fact, histone modification and DNA methylation, previously described, play a main role in the regulation of miRNA expression (Davis-Dusenbery and Hata 2010). The transcription process generates a primary RNA, also called pri-miRNA. This transcript is generally long 1 kb and presents a stem of 33–35 pb with a terminal single strand segment to the 5′ and 3′ extremities. The next step includes the intervention of Drosha, a RNase III protein, and the DGCR8 (Di George syndrome Critical Region 8 protein) to induce the assembling of microprocessor (Goldberg et al. 1993; Shiohama et al. 2003). The respective functions of DGCR8 and Drosha are first to recognize the pri-miRNA target and then to process the pri-miRNA generating a pre-miRNA. Exportin 5 (EXP5) with a RAN-GTP binding protein mediates the translocation of pre-miRNA from nucleus to cytoplasm (Bohnsack, Czaplinski, and Görlich 2004; Lund et al. 2004; Yi et al. 2003): together they induce the formation of a pre-miRNA/EXP-5 complex and then the release of the pri-miRNA into cytoplasm after the hydrolisation of the RAN-GTP binding protein. In the cytoplasm another RNase III, called Dicer, promotes the maturation of pre-miRNA through its interaction with the TAR RNA binding protein, which contains specific dsRBD, i.e., double-stranded RNA binding domain (MacRae, Zhou, and Doudna 2007). In fact, Dicer cleaves the pre-miRNA near the terminal loop to generate a small double strand RNA (Bernstein et al. 2001; Grishok et al. 2001; Hutvágner et al. 2001; Ketting et al. 2001; Knight and Bass 2001), which is loaded on the RISC (RNA-induced

silencing complex) (Hammond et al. 2001; Tabara et al. 1999) by the argonaute proteins 1-4 (AGO 1-4) to generate the pre-RISC complex. One strand of the RNA is now called passenger strand, while the other is the guide strand. Generally, the selection of the passenger strand, which is unstable at the 5′ and contains a U as first nucleotide, is operated by AGO 1-4 (Lau et al. 2001; Okamura, Liu, and Lai 2009; Wang et al. 2008). The final step for the maturation of miRNAs is the unwinding of the RNA duplex by the pre-RISC complex, which promotes the degradation of the passenger strands. Nowadays is well known that also the passenger strand could mature instead of the guide one, even if the first is generally less active in silencing than the latter one. This is called the canonical pathway, but also the Drosha/DCR8-indipendend, TUTase-dependent and Dicer-independent pathways are very important for the maintenance of the organism's homeostasis. The dysregulation of this pathways could induce cancer or neuro-developmental diseases (Im and Kenny 2012; Lujambio and Lowe 2012).

Nowadays, it is believed that more than 90% of the human genome can be transcribed into RNA, although of this percentage only 2% of transcribed RNAs is translated into proteins, while the rest, named non-coding RNAs (ncRNAs), is not frequently transcribed (Guglas et al. 2017; Wahlestedt 2013). lncRNAs are a type of regulatory RNAs constituted by more than 200 nucleotides in length and without the capability of encoding proteins (Pauli et al. 2012). The number of lncRNAs identified is growing constantly and derives from genome-wide human transcriptional studies, although the majority remains to be characterized and functionally validated (ENCODE Project Consortium 2012). lncRNAs can be classified depending on the genomic location into intergenic, intragenic (intronic, exonic), overlapping and antisense (Derrien, Guigó, and Johnson 2012). Unlike shorter RNAs, the greater length of the lncRNAs allows the formation of secondary and tertiary structures. This complex structure permits these RNAs to regulate various cellular processes including cell development and cell differentiation, due to their ability to bind to proteins, RNA and/or DNA (Rinn and Chang 2012). In this sense, lncRNAs can be involved in the regulation at different levels: chromatin organization, transcriptional, and post-transcriptional regulation (Yang et al. 2014). In addition, each lncRNA has its own specific location in different tissue and cell types which in turn can determine the context of the lncRNA function (Li, Wu, et al. 2014).

Despite the fact that the function of most of the lncRNAs is still unknown, their deregulated expression has been related with different diseases including diabetes, endometriosis or diverse types of cancers (Wang et al. 2016; Yarmishyn and Kurochkin 2015). Specifically, lncRNAs have a role in cancer cell proliferation, migration, invasion, and also favor drug resistance. For example, it has been evidenced that the lncRNA small nucleolar RNA host gene 16 (SNHG16) is overexpressed in colorectal, bladder and lung cancer, whereas prostate cancer antigen 3 (PCA3) can be used as an early cancer-type specific biomarker since is only expressed in prostate tissue (Bussemakers et al. 1999; Gao and Wei 2017; Guglas et al. 2017). The fact that some LncRNAs are directly related to some types of cancer opens the door to the advance in novel strategies for cancer therapy. One interesting approach reported that the depletion of HOX Antisense Intergenic RNA (HOTAIR), a highly expressed lncRNA in primary breast tumors and breast metastases, significantly inhibits cancer invasiveness (Gupta et al. 2010).

Epigenetic regulation of cancer pathogenesis by flavonoids

An increasing number of articles reports the importance of polyphenols in the prevention of different diseases, although the molecular mechanism of action remains unclear for most of them (Duthie and Brown 1994; Goldberg 1994). Polyphenols can be classified based on their chemical structure, function, bioavailability and stability. Nowadays, more than 8000 polyphenols have been discovered and the halves of these are flavonoids. Though, a lot of studies achieved results difficult to apply in practice because the studies have been performed using often too much high polyphenols concentration, without considering the daily intake and the bioavailability (Dong and Surh 2008; Williams, Spencer, and Rice-Evans 2004). In fact, in most cases only the metabolized polyphenols reach the tissues after the digestion process.

Naringenin

Naringenin (Figure 2) belongs to flavanone class of flavonoid. It occurs in many plant foods such as tomatoes, grapefruits and oranges. Several pharmacological activities of Naringenin are antioxidant and anti-inflammatory, hepatoprotective, cardioprotective, anti-mutagenic and anticancer activities (Orhan et al. 2015). As regards the influence of naringenin on the expression levels of miRNAs, Curti et al. analyzed the effect of racemic and enantiomeric naringenin on the expression of two miRNAs (i.e., miR-25-5p and miR-17-3p) concerned with the anti-inflammatory and antioxidant processes on human colon adenocarcinoma cells using 1, 10 and 100 μM/ml concentrations of racemic and enantiomeric Naringenin. The results showed that racemic naringenin exerted epigenetic activity being able to downregulate miR-17-3p at the concentration of 100 μg/ml and determining the up-regulation of mRNA coding for Mn-Superoxide dismutase (MnSOD) and glutathione peroxidase 2 (GPx2). Both enantiomeric naringenin exerted the downregulation of miR-17-3p at the concentration of 10 and 100 μg/ml. Also, in this case the suppression of miR-17-3p induced the up-regulation of MnSOD and GPx2 mRNA. Interesting results were achieved also for miR-25-5p using both enantiomeric naringenins, whose expression level was downregulated at the concentration of 10 and 100 μg/ml. However, in this case the miR-25-5p targets (TNF-α and IL-6 mRNAs) were not downregulated, underlying the complex regulation of epigenetic mechanisms (Curti et al. 2017). Shi et al. (2016) studied the neuroprotective action of naringenin after a

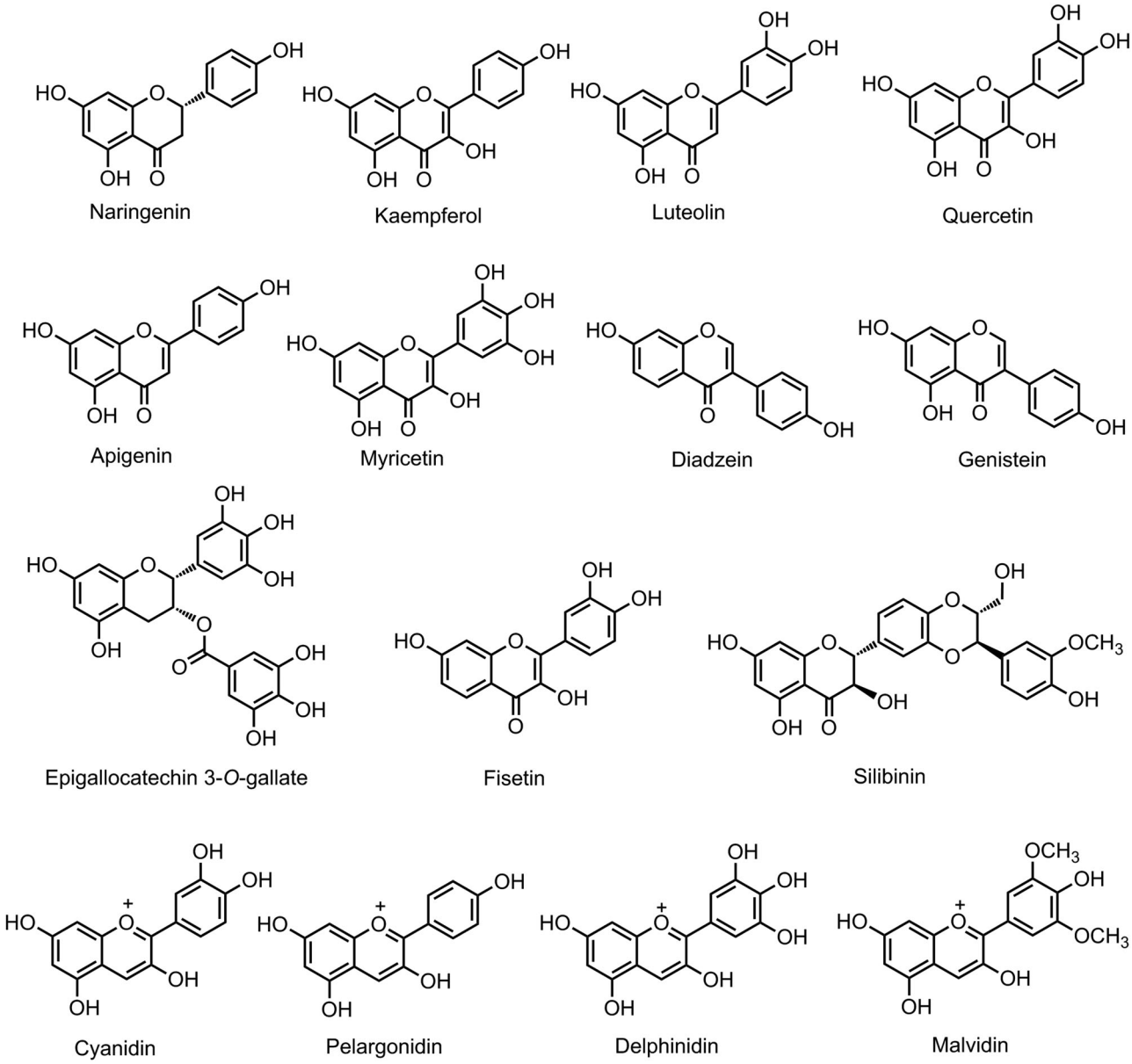

Figure 2. Some major flavonoid compounds involved in chemoprevention and treatment.

laminectomy at T9-T11 and compression using a vascular clip on five different groups of Sprague-Dawley rats treated for 11 consecutive days. The groups were subdivided into control group, sham group (treated with saline injection by intraspinal injection), SCI group (Spinal Cord Injury) treated with saline, and two SCI groups treated with naringenin at the concentrations of 50 and 100 mg/kg, p.o. The study showed that miR-223 played an important role in the granulocyte production (Shi et al. 2016). In fact, the authors reported that naringenin induced an up-regulation of this miRNA in the L4-L6 spinal cord. Moreover, they confirmed the presence of the miR-223 in the cytoplasm using in situ hybridization. Another *in vivo* research on naringenin was performed by Yan et al. (2016) that studied the reduction of blood glucose level in Sprague Dawley rats. The animals were subdivided into two different groups, the control group (n = 5) and the DN (Diabetic Nephropathy) group (n = 20). The DN group was further subdivided into two other groups, the first one was treated with saline (DN group) (n = 8), while the other one was treated with naringenin (NAR group) at the dose of 50 mg/kg/day with gavage for six weeks (n = 10). Generally, the DN patients present a downregulation of let-7a, which is important for the control of the glucose metabolism and insulin synthesis/secretion. The results showed that naringenin is responsible for the increase of the expression levels of let-7a in the NAR group compared with the DN group, underlying the possible use of naringenin against the DN.

Kaempferol

Kaempferol (Figure 2) is a flavonol that has been isolated from a number of commonly used vegetables and fruits (Lin, Luo, et al. 2015; Mandery et al. 2010; Palacz-Wrobel et al. 2017) and medicinal plants (Grosso et al. 2015; Han

et al. 2007). This plant derived flavanol has shown outstanding diverse pharmacological effects (Che et al. 2017; Choi et al. 2015; Dasgupta and Klein 2014; Devi et al. 2015). The flavanol intake, especially kaempferol, has shown strong anticancer properties against various cancers, such as potential reduction in the risk of pancreatic cancer as reported by Nothlings and coworker (Nothlings et al. 2007). Similarly, multiple studies have supported the significant protective role of this compound in the risk assessment of ovarian cancer alone as well as in combination with other flavanol (Cassidy et al. 2014; Gates et al. 2007).

A German research group of Berger et al. (2013) found that kaempferol had a marked inhibition of HDACs (Berger et al. 2013). As the HDACs inhibitors have current clinical interest in the treatment of cancer treatment (McClure, Li, and Chou 2018), the same study was extended to evaluate the action of HCT-116 colon cancer cells as well as human-derived hepatoma cell lines HepG2 and Hep3B. The results indicated that the various concentrations of kaempferol antagonized the various classes of HDAC including I, II, and IV enzymes. Similarly, the study showed downstream regulation of cellular viability and proliferation against various cell lines (Berger et al. 2013).

Similarly, regulation of disheveled binding antagonist of beta catenin 2 (DACT2) has been challenged by kaempferol treatment experimental model in which type of cells? (Lu et al. 2018). DACT2 modulation by DNA hypermethylation is reported in numerous cancer cell lines (Xiang et al. 2016; Zhang et al. 2016). It binds with β-catenin, suppresses the formation of the β-catenin/LEF1 complex and thus causes downstream regulation of tumor growth, invasion and metastasis in nucleus (Wang, Dong, et al. 2015), explaining its crucial role in cancer (Damsky et al. 2011; Oloumi, McPhee, and Dedhar 2004). In 2018, the study of Lu et al. demonstrated that kaempferol treatment in colorectal cancer cells causes marked over expression of DACT2 with strong reduction in the DACT2 demethylation. In the same study, it bonded to DNA methyltransferases DNMT1 and produced unmethylated DACT2 effect. The epigenetic effect of kaempferol was induced through nuclear β-catenin expression to inactivate Wnt/β-catenin modulation and thus the epigenetic stimulation of the compound that occurred though DACT2 expression, significantly interfered with the proliferation and treatment of colorectal cancer (Lu et al. 2018).

Luteolin

Luteolin (Figure 2) is a well-known flavone that has been isolated from a number of fruits and vegetables (Hertog, Hollman, and Katan 1992; Prior and Cao 2000) as well as medicinal plants (Seelinger, Merfort, and Schempp 2008; Srinivasa et al. 2004). Since long time, this natural compound has shown an outstanding therapeutic potential in the treatment of a variety of ailments (Kwon 2017; Liu et al. 2018; Wang et al. 2017). Similarly, this natural compound possesses strong anticancer effects in different types of human cancer cell lines including breast cancer (Hasanpourghadi, Pandurangan, and Mustafa 2018), cervical cancer (Lin, Lai, et al. 2015), gastric cancer (Zhou et al. 2018), colon cancer (Xavier and Pereira-Wilson 2016) and lung cancer (Kasala et al. 2016). Attoub et al. (2011) have shown strong anticancer, antitumor effects as well as preventative actions of luteolin (Attoub et al. 2011), while Yoo et al. (2009) have demonstrated that various proteins, peroxiredoxin 6 (PRDX6) and prohibitin (PHB) are involved in the anticancer role of luteolin (Yoo et al. 2009).

DNA methyltransferase (DNMT) regulates DNA methylation and the over expression of this enzyme has been documented in a number of cancers (Chen et al. 2018; Tse et al. 2017; Wirbisky-Hershberger et al. 2017). Interestingly, DNMT modulation is a potential target for the cancer treatment as DNA methylation is a reversible biochemical process (Kim et al. 2012; Tse et al. 2017). Luteolin caused marked attenuation of DNMT enzyme at various test concentrations (20 and 50 µmol/L) with overall >50% inhibition at 50 µmol/L (Fang, Chen, and Yang 2007). Similarly, Kanwal et al. (2016) studied the effect of luteolin against DNMTs and HMTs *in vitro* (Kanwal et al. 2016). The results showed that the inhibitory profile of luteolin was the best among the tested flavonoids. The effects were further supported by the molecular docking studies and the OH group was involved in hydrogen bonding. The luteolin binding with DNMT residues was supported by at least six different hydrogen bond interactions and, thus, the relative binding strength for luteolin was also high with high docking score. Luteolin also showed marked concentration dependent effect on H3K27me3 activity and the protein expression of EZH2. However, DNA interaction with luteolin has been reported as a complex process and might have some additional binding phenomena (Zhang et al. 2012).

Quercetin

Quercetin (Figure 2) has emerged as a premium phytochemical because of its ability to pleiotropically modulate myriad of proteins. Quercetin was observed to be very effective against prostate cancer cells, as it reversed epigenetic inactivation of androgen receptor (AR) (Baruah, Khandwekar, and Sharma 2016). Quercetin worked synergistically with curcumin and induced re-expression of epigenetically silenced AR in cancer cells of prostate origin (Baruah, Khandwekar, and Sharma 2016). Expectedly, treatment of AR expressing prostate cancer cells with an AR-antagonist (bicalutamide) induced apoptosis (Baruah, Khandwekar, and Sharma 2016). These findings provided clues that restoration of AR in androgen refractory PCa cells is necessary to maximize bicalutamide-mediated apoptotic response.

Mechanistically it was shown that extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinases (JNK) played central role in quercetin-induced activation of HAT (Lee, Chen, and Tseng 2011). It had been experimentally verified that quercetin-induced activation of HAT was severely impaired in cancer cells pretreated with ERK and JNK inhibitors. Quercetin promoted histone H3 acetylation through HAT that consequently resulted in transcriptional

upregulation of FasL gene in leukemic HL-60 cells (Lee, Chen, and Tseng 2011). Rapidly emerging scientific findings are also informing us about different strategies to improve bioavailability of quercetin. In accordance with this concept, PLGA-loaded gold-nanoparticles precipitated with quercetin have shown excellent promise. Quercetin loaded nanoparticles markedly reduced HDAC1 and HDAC2 in HepG2 cells (Bishayee, Khuda-Bukhsh, and Huh 2015).

Quercetin belongs to the flavanol class of flavonoids. It is commonly found in many plants foods and is known as excellent natural antioxidant and radical scavenger of ROS i.e., reactive oxygen and RNS i.e., reactive nitrogen species under both *in vitro* and *in vivo* conditions.

Many physiological effects are ascribed to quercetin such as anti-inflammatory, anti-apoptotic, neuroprotective, hepatoprotective, and antiobesity activities (Barreca et al. 2016; Miltonprabu et al. 2017; Nabavi et al. 2015). As far as the epigenetic activity of quercetin is concerned, Mahesh et al. investigated quercetin role in pancreatic cancer studying the expression level of miR-let-7. Different cell lines of pancreatic ductal adenocarcinoma (PDA) were used such as BxPc-3, MIA-PaCa2, CRL-1097 (h-TERT-HPNE immortalized pancreatic duct cell), and PaCaDD-183 (primary cells obtained from patients). All cell lines were treated with quercetin and other polyphenols (i.e., catechin gallate [CG], epicatechin gallate [ECG], epigallocatechin gallate EGCG] or polyphenol rich extract (green tea extract), or bioactive compounds such as DL-sulforaphane). One of the aims of this study was to observe the upregulation of miR-let-7, which is able to suppress the growth of pancreatic cancer. Some evidence suggests, in fact, that a poor prognosis in many cancer types is determined by the downregulation of KRAs and upregulation of miR-let-7. To understand if the treatments with the selected bioactive substances, alone or in combination, were able to induce the upregulation of the selected miRNA, all cell lines were analyzed after the inhibition of KRAs. The results showed that quercetin could mediate the upregulation of miR-let-7 at the concentration of 200 mM (Appari et al. 2014).

Nwaeburu et al. (2017) studied the activity of quercetin on the expression levels of miRNAs after 12 h of treatment of AsPC1 human pancreatic adenocarcinoma cells. The results highlighted 11 different miRNAs implicated in the Notch signaling, which regulate neurovascular development and progression of pancreatic cancer (Büchler et al. 2005). Subsequent *in vitro* studies determined the significance of miR-200-3p in the cell fate determination in this type of cancer. Besides the cell line AsPC1, PANC1 and ASANPaCa, treated with 50 μM quercetin or trasfected with 50 nM mimic miRNA-200b-3p, were studied. To understand if this miRNA could regulate the Notch pathway, the authors performed a luciferase reporter assay, using Notch1 and Numb as targets. After 48 h from transfection they registered a reduction of luciferase Notch1 activity only in the cell lines used in this research in which the presence of the miR-200-3p was registered. Furthermore, miR-200-3p over expression after the treatments cited above, decreased the proliferation of cancer stem cell after three generation using a tumorsphere propagation assay (Tao, He, and Chen 2015).

In previous investigation, Li et al. (2015) investigated the downregulation of miRNA-27a on 786-O renal cancer cell. The results showed that the combination of quercetin and hyperoside (QH) at 0 μM to 20 μM concentration, after the treatment of 24 hours, could decrease the level of miRNA-27a, an inhibitor of specificity protein (Sp) transcription factors, which are generally overexpressed in various types of cancers. Tao, He, and Chen (2015) studied the upregulation of miR-146a in human breast cancer cells (MCF-7 and MDA-MB-231 cell lines) after the treatment with quercetin. Previous studies showed the importance of this miRNA in the regulation of apoptosis through the activation of caspase-3. The experiment was conducted with or without transfection of mimic and anti-miR-146a treating cell with quercetin (at the concentrations of 25, 50, 80, and 100 μM/ml) for 48 hours. The efficiency of transfection was 80% for both cell lines at the concentration of 100 nmol/L; this procedure was used to verify the possible correlation between the proliferation of these malignant cell lines and miR-146a. After the treatment an up-regulation of this miRNA was registered, and this effect was respectively magnified or canceled after the transfection with mimic-miR146a or anti-miR-146a.

Another miRNA involved in the apoptosis process is miR-34a, which seems to be an important factor in the p53 pathway. HepG2 and Huh7 cell lines were treated with a concentration of quercetin of 31.25 µM for 48 hours. For HepG2 a significant difference between the control and the treated cells (3 h, 6 h, 12 h, 24 h and 48 h) were registered, supporting a time dependent action of quercetin. Moreover, no significant difference in the expression levels of miRNA-34a at time 0 and 24 h in HepG2 p-53 siRNA transfected cell after the treatment with quercetin at the concentration of 31.25 µM was registered (Lou et al. 2015).

Induction of apoptosis by quercetin was investigated also by Zhou et al. Expression levels of miR-145 in ovarian cancer cell lines was the main focus of their research (i.e., SKOV-3 and A2780) treated with quercetin at concentrations of 25, 50 and 100 µm/ml, for 24 h. The results showed that quercetin induced an over expression of miR-145 in a dose-depend manner, suggesting that quercetin could stimulate apoptosis in ovarian carcinoma through the expression of caspase-3. The use of anti-miR-145 in this specific cell lines induced a reversion of the quercetin effect confirming this miRNA as a main agent in the subsequent apoptotic event (Zhou et al. 2015).

Zhang et al. (2015) investigated the opportunity to use the quercetin with cisplatin to treat osteosarcoma through the modulation of microRNA-217, which targets the KRAS in osteosarcoma acting as tumor suppressor via the inhibition of cell proliferation and metastasis. Human osteosarcoma 143B cells were treated with quercetin (5 µM) and cisplatin (5 µM) for 24 h and 48 h. The results showed that the combination of quercetin and cisplatin increased miR-217 expression levels. Moreover, a downregulation of KRAS mRNA and protein expression was registered.

In 2015, Wang, Phan, et al. (2015) investigated the activity of quercetin (at concentrations of 5, 10 and 20 μM), arctigenin (at concentrations of 0.5, 0.1 and 0.2 μM) alone and in combination in LNCaP and LAPC-4 (human prostate cancer cell lines), to induce an anti-proliferative effect through the regulation of different miRNAs. Arctigenin, which belongs to the class of lignan and is considered an important anti-inflammatory molecule, derived from *Arctium lappa* seeds (Li, Carey, and Workman 2007), inhibited the expression of miR-19b, miR21, miR-148a in the LAPC-4 cell line but not for LNCap. However, the combination of arctigenin with quercetin induced a down-regulation of miR-21 by 40% and 70% for both miR-19b and miR-148a, while for the LNCaP cells induced a down-regulation of 20%–30% for all miRNAs (Wang, Phan, et al. 2015).

Pratheeshkumar et al. (2017) studied the expression of miR-21, which is increased in many human cancers, in lung cancer. In particular, immortalized (BEAS 2B) human bronchial epithelial cells were exposed to quercetin (at the concentrations of 1 and 2 μM) and a well known carcinogen, hexavalent chromium Cr(VI) (at the concentration of 0,5 μM), for two, four and six months to verify miR-21and PDCD4 (programmed cell death 4) expression levels. PDCD4 is considered a suppressor gene that indicates the tumor progression and is a direct target of the miR-21 (Gupta et al. 2010; Ji et al. 2003). In this study the treatment with Cr(VI) induced an over expression of miR-21 with a downregulation of PDCD4 after the performance of RT-PCR and western blot analysis. In the presence of quercetin, a dose-depend suppression of miR-21 and an increase of PDCD4 were registered. The stable knockdown of this miRNA after Cr(VI) treatment for six months did not determine the canonical malignant transformation, confirming the oncogenic role of this miRNA. However, in this case, the combination with quercetin did not exhibit the same effect registered for the qRT-PCR experiment. These results were confirmed *in vivo* after the injection of BEAS-2B cells treated with Cr(VI), alone or in combination with quercetin, in nude mice. In particular, the growth of the tumor was evident in mice injected with BEAS-2B cells, treated with Cr(VI). On the contrary, tumor size and progression were reduced when quercetin was added to the treatment of BEAS-2B cell. These results suggested that quercetin could delay and reduce the malignant transformation of BEAS-2B cell.

Recently, Su et al. (2017) studied the effect of lychee (*Litchi chinesis*) pulp extract rich in polyphenols on hepatic lipid accumulation. The main compounds of lychee are quercetin 3-O-rutinoside-7-O-α-L-rhamonisdase (quercetin 3-rut-7-rha), rutin and (-)-epicatechin. The main focus of study was to monitor the expression levels of different miRNAs related to lipid metabolism and obesity in dyslipidemic mice treated with lychee pulp extract. To induce dyslipidemia 30 mice were subdivided into 3 groups of 10 mice. The first one was the High Fat Diet group (HFD), the second one was the HFD + lychee pulp extract group, and the last one was the Control Diet (CD) group. All the groups were feed for 10 weeks and at the end blood was collected from the orbital sinus. The RT-PCR results showed an up-regulation of miR-122 and a down-regulation miR-33 in the HFD group if compared with control group. However, expression of both miRNAs decreased after the treatment with lychee pulp extract suggesting a possible hypolididemic mechanism of quercetin.

Apigenin

Apigenin (Figure 2) has attracted considerable appreciation because of its ability to target different HDACs in different cancers. It has recently been convincingly revealed that apigenin arrested MDA-MB-231 BCa cells in G2/M phase (Tseng et al. 2017). Detailed mechanistic insights revealed that apigenin considerably induced acetylation of Histone-3 and repressed HDAC activity. Chromatin immunoprecipitation analysis indicated that apigenin induced an increase in acetylation of Histone-H3 in the p21WAF1/CIP1 promoter region that consequently resulted in transcriptional upregulation of p21WAF1/CIP1 (Tseng et al. 2017). Furthermore, apigenin was also found to efficiently target HDAC1 and HDAC3 in prostate cancer cells. Apigenin-modulated inhibition of HDACs induced global acetylation of H-3 and H-4, as well as hyperacetylation of histone H3 on promoter region of p21/waf1 (Pandey et al. 2012).

Apigenin triggered super induction of activating transcription factor 3 (ATF3) mainly through increasing the association of HuR proteins to ATF3 transcript (Park et al. 2014). HuR are RNA-binding proteins which regulate stability and cytosolic-nuclear localization of mRNAs rich in AU-rich elements. Structural studies provided evidence of accumulation of ATF3 at the promoter region of early growth response protein 1 (EGR-1). DNA-binding basic leucine zipper domain of ATF3 interacted with cyclic AMP response element present in promoter region of EGR-1. More importantly ATF3 worked synchronously with HDAC to epigenetically inactivate EGR-1 in cancer cells (Park et al. 2014). Data clearly suggested that apigenin effectively repressed ER stress-induced chemokine expression mainly through epigenetic inactivation of EGR-1; however, EGR-1 over expression severely impaired apigenin-mediated suppressive effects on chemokine expression.

Myricetin

Dietary factors such as certain type of flavonoid compounds were reported to play beneficial role on human health by regulating the epigenome (Fang, Chen, and Yang 2007). Polyphenols including anthocyanins, stilbenoids, phenolic acids and flavonoids (especially epicatechin, quercetin and myricetin), which are abundant in vegetables, fruits, wine and tea, were found to induce autophagy and protein deacetylation by stimulating the SIRT1 deacetylase effect (Ratovitski 2017; Pietrocola et al. 2012). Myricetin was reported to increase endogenous SIRT1 level, and through SIRT1 activation, it displayed downregulatory activity on cMyc and beta-catenin and upregulatory effect on HIF-1

alpha (Ayissi, Ebrahimi, and Schluesenner 2014; Hong et al. 2012). In a previous study by Lee et al., inhibitory activity on DNA methylation was assessed for catechol containing flavonoids including myricetin. The tested bioflavonoids were found to concentration-dependently inhibit SssI DNA methyltransferase (DNMT) mediated DNA methylation. Myricetin demonstrated higher effect than quercetin and fisetin with the IC_{50} value of 0.7 µM. Without catechol-O-methyltransferase (COMT), myricetin exhibited 60% direct inhibitory effect on DNA methylation at 20 µM concentration. Myricetin inhibited DNMT1-mediated DNA methylation with the IC_{50} value of 1.2 µM in the presence of COMT (Lee, Shim, and Zhu 2005). It was also reported that myricetin inhibited or stimulated epigenetic effects, depending on the experimental conditions (Ayissi, Ebrahimi, and Schluesenner 2014). Strong DNMT inhibitory action of myricetin was attributed to its pyrogallol moiety (Gilbert and Liu 2010). In parallel to *in vitro* studies, clinical studies, which evaluated the relationship between the epithelial ovarian cancer risk and the flavonoid intake, revealed that consumption of quercetin, kaempferol, luteolin, apigenin and myricetin is correlated with a lower ovarian cancer risk (Cassidy et al. 2014; Gates et al. 2007). Onion, strawberry, green and black tea were reported to contain these flavonoids especially myricetin (Busch et al. 2015).

Daidzein and genistein

Daidzein and genistein (Figure 2) are two of the most representative and well-characterized isoflavones found in several legumes (especially, soy bean), vegetables, fruit, lentils, nuts and seeds, able to exert phyto-oestrogenic activity thanks to their similarity in structure with 17-β-estradiol (Busch et al. 2015; Hardy and Tollefsbol 2011; Rietjens et al. 2013; Rimbach et al. 2008). The effects of isoflavones have been tested both *in vitro* and *in vivo*, although attention may be taken in the use of the two isoflavones, especially in hormone dependent cancer pathologies in humans (Allred et al. 2001; Martínez-Montemayor et al. 2010). The role of daidzein and genistein in DNA methylation has been described by Vardi et al. (2010). They analyzed the effects of these isoflavones on 4 genes (glutathione S-transferase P1, ras association domain family-1, ephrin B2 and breastcancer-1) through methylation-specific-PCR in prostate cell lines. The cells treatment with 40 or 110 μM genistein and daidzein, respectively, resulted in a reversion of DNA hypermethylation, data confirmed also by immunohistochemistry analysis, that highlighted an increased expression of the corresponding proteins (Vardi et al. 2010).

Genistein (at a concentration of 2–20 μM) has inhibitory effect on DNA methyltransferase activity in both purified recombinant enzyme and nuclear extracts either alone or in combination with trichostatin, sulforaphane or 2′-deoxy-5-aza-cytidine, and its activity is superior to other isoflavones like daidzein and biochanin A (Fang et al. 2005). The inhibition of DNA methyltransferase activity in dose-dependent fashion is function of both substrate- and methyl donor-dependent inhibition processes. Quantitative real-time PCR and Methylation-specific PCR showed a reduction of genomic DNA hypermethylation and an increase in the protein amount of retinoic acid receptor β, p16INK4a, and O6-methylguanine DNA methyltransferase in human KYSE-510 cells (Fang et al. 2005). In KYSE-150 cells (esophageal squamous cells) carcinoma and in LNCaP and PC-3 (prostate cancer cells lines), genistein (20–50 μM) influenced the levels and availability of S-adenosyl methionine and subsequently brought to the inhibition of DNMT by competitive and noncompetitive mechanisms (Zhang and Chen 2011). Genistein influences also telomerase activity. The isoflavone brought to the inhibition of human telomerase reverse transcriptase (hTERT) in a time- and dose-dependent fashion, impacting on epigenetic pathways by the decrease in the DNMT1, 3a and 3 b activity i.e., activity of three major DNA methyltransferases (Li et al. 2009). In addition, the same authors (Li et al. 2009) described the remodeling of chromatin structures of the hTERT promoter by genistein following the increase in trimethyl-H3K9 but the decrease of dimethyl-H3K4. Moreover, the treatment of breast cancer cells (MDA-MB-231 and MCF7) with daidzein (78.5 μM) or genistein (18.5 µM) was able to increase histone acetylation and reduce histone trimethylation of six different genes. In fact, chromatin immunoprecipitation coupled with quantitative PCR showed modification of histone-lysine N-methyltransferase, breast cancer 1, early onset (BRCA1), nuclear receptor coactivator 3, estrogen receptor α and β, and P300, all genes involved in the production of proteins associated with breast cancer (Dagdemir et al. 2013). *In vivo* study on epigenetic effects of isoflavones has been reported by Zhang, Li, and Chen (2013). Purified or soy protein lysate genistein was given to rats and compared to a genistein-free control diet (Zhang, Li, and Chen 2013). The obtained results, after carcinogen azoxymethane injection, showed a dietary genistein modulation of wingless-related integration site genes by histone modifications and DNA methylation, highlighting the role of genistein not only in DNA methyltransferases inhibition, but also on sirtuin inhibition and histone acetyltransferase activation (Kikuno et al. 2008; Rajendran et al. 2011; Zhang, Li, and Chen 2013). Reported that genistein and daidzein (both administered at 1.0 mg per 30 g BW, single concentration, every 4 weeks) suppressed the estrogen-related endometrial carcinogenesis in mice, reducing the expression of internal cytokines (TNF-α and IL-lα), estrogen-induced estrogen-related genes c-fos and c-jun, and a system that involved both cytokine and estrogen receptor-mediated pathways.

EGCG

EGCG (Figure 2) is one of the most widely studied dietary flavan derivatives found in tea (*Camellia sinensis* (L.) Kuntze) and many other plant species (Wai Kan Yeung et al. 2018). EGCG has been reported as a potent antioxidant compound along with its various health promoting and disease promoting activities (Nagle, Ferreira, and Zhou 2006; Singh, Shankar, and Srivastava 2011). ECGC is also one of the phytochemicals studied widely for its epigenetic

modulatory activity. Berletch et al. (2008) evaluated the human telomerase reverse transcriptase (hTERT) inhibitory activity of EGCG in MCF-7 breast cancer cell lines and HL60 promyelocytic leukemia cell lines. EGCG reduced the cellular proliferation and induced apoptosis in both cells line through down regulation of hTERT gene expression through epigenetic alterations. Balasubramanian, Adhikary, and Eckert (2010) studied the role of EGCG on the function B-cell-specific Moloney murine leukemia virus integration site 1 (Bmi-1), key protein of epigenetic regulators for cell survival and enhancer ofzeste homolog 2 (Ezh2) in SCC-13 cells. ECGC treatment in these cells reduced the levels of both Bmi-1 and Ezh2. The reduction was associated with the reduction in histone H3 lysine 27 trimethylation. Pandey, Shukla, and Gupta (2010) studied the role of green tea polyphenols on gluthathione-S-transferase pi (GSTP1) re-expression. When treated with green tea polyphenols, re-expression of GSTP1 was observed in human cancer prostate cancer LNCap cells. Fang et al. (2007) reported the 5-cytosine DNA methyltransferase (DNMT) inhibitory and methylation-silenced genes reactivating activity of EGCG in human esophageal squamous cell carcinoma cell lines KYSE 510 and KYSE 150. Moseley et al. (2013) reported that EGCG treatment in HCT 116 human colon reduced the expression of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), through their degradation. Meeran et al. (2011) studied the effect of EGCG or its pro-drug on cell proliferation of human breast cancer MCF-7 and MDA-MB-231 cells and their activity on human telomerase reverse transcriptase (hTERT) expression. Both EGCG and its pro-drug inhibited the proliferation of these cells and inhibited the transcription of hTERT through epigenetic mechanisms.

Fisetin

Fisetin (Figure 2) is a flavonol derivative found in various fruits and vegetables including strawberries, apples, grapes, persimmons, kiwi fruits, onions, lotus roots, cucumbers, etc. (Kashyap et al. 2018; Khan et al. 2013). Various studies have reported the antioxidant, anti-inflammatory, neuroprotective, anticancer activities of fisetin (Ahmad et al. 2017; Donado, Sandoval, and Carrillo 2011; Khan et al. 2013; Park et al. 2007).

Fisetin has been reported to induce apoptosis and inhibit the growth in hepatic, colorectal and pancreatic cells lines i.e., HepG-2, Caco-2, and Suit-2, respectively by multiple signaling pathways which mainly included the activation of CDKN1A, SEMA3E, GADD45B and GADD45A genes and down-regulation of TOP2A, KIF20A, CCNB2 and CCNB1 genes (Youns and Hegazy 2017).

Lee, Shim, and Zhu (2005) evaluated the DNA methyltransferase (DNMT) inhibitory activity of fisetin and other flavonoids. Fisetin showed concentration-dependent of the prokaryotic SssI DNMT and human DNMT1-mediated DNA methylation. Recently, fisetin was reported to inhibit the ten eleven translocation protein, TET1 expression in renal cancer stem cells (HuRCSCs). Fisetin also reduced the 5-hydroxymethylcytosine (5hmC) modification in specific loci in the promoters of CpG islands in cyclin Y/cyclin dependent kinase (CCNY/CDK16) in these cells (Si et al. 2019).

Silibilin

Silibinin (Figure 2) is a flavanolignan derivative isolated from milk thistle (*Silybum marianum* (L.) Gaertn.). Silibinin and its mixture with other stereoisomers, known as silymarin, are being used in the treatment of liver diseases and also reported to be a potent cancer chemopreventive agent (Bosch-Barrera and Menendez 2015; Lu et al. 2012; Ullah and Khan 2018). Anestopoulos et al. (2016) evaluated the pleiotropic effects of silibinin in DU145 and PC3 human prostate cancer cell lines. Silibinin reduced the gene expression levels of the Polycomb Repressive Complex 2 (PRC2) members such as Enhancer of Zeste Homolog 2 (EZH2), Suppressor of Zeste Homolog 12 (SUZ12), and Embryonic Ectoderm Development (EED). Silibinin was also found to decrease histone deacetylases 1-2 (HDACs1-2) expression level and increase in total DNA methyltransferase (DNMT) activity. Similarly, Kauntz et al. (2013) evaluated the epigenetic effects of silibinin in the primary adenocarcinoma cells SW480, a model for colon cancer cell progression and their metastatic cells SW620. Silibinin inhibited the DNMT activity in both of these cells lines; however, histone deacetylase (HDAC) activity was not affected. Silibinin also showed synergetic activity with suberoylanilide hydroxamic acid (SAHA), a HDAC inhibitor and trichostatin A (TSA), a broad spectrum HDAC inhibitor. In another study, Mateen et al. (2012) studied the combined effects of silibinin with TSA or SAHA against non-small cell lung cancer (NSCLC), where silibinin inhibited the HDAC activity and decreased HDAC1-3 levels. Silibinin also decreased the cytotoxic activity of HDCA inhibitors. Mateen et al. (2013) also evaluated the anticancer activity of silibinin against lung cancer through activity to modulate E-cadherin expression in NSCLC cell lines. Silibinin in combination with TSA or 5′-aza-deoxycytidine (Aza), a DNMT inhibitor, significantly restored the E-cadherin levels and also decreased the invasion or migration of these cells. Authors concluded that silibinin in combination with TSA or Aza is a potent inducer of E-cadherin expression and inhibitor of these cells' migration and invasion potential.

Anthocyanins

Anthocyanins (cyanidin, delphinidin, malvidin, and pelargonidin) (Figure 2), a class of flavonoid derivatives, are major chemical constituents responsible for the beautiful colors of many colorful flowers, fruits and vegetables (Iwashina 2015). Anthocyanins are reported to have strong antioxidant activity and to be responsible for the prevention and treatment of various diseases (de Pascual-Teresa and Sanchez-Ballesta 2008; Peiffer 2018).

Various plant/fruit extracts rich in anthocyanins and pure anthocyanins compounds have been evaluated for their

potential activity in modulating epigenetics. Black raspberries powder was administered to colorectal adenocarcinoma patients for 1–9 weeks and the expression of DNMT1 and genes associated with cell proliferation, angiogenesis and apoptosis. Administration of anthocyanins rich black raspberries powder was found to reduce the expression of DNMT1 (Wang et al. 2011). Wang et al. (2013) further purified the extract to obtain anthocyanins enriched extract containing cyanidin 3-O-glucoside, cyanidin 3-O-rutinoside, cyanidin 3-O-xylosylrutinoside and cyanidin 3-O-sambubioside and evaluated the activity of demethylation for anthocyanins. Treatment of anthocyanins rich extract was found to decrease the activity and protein expression of DNMT1 and DNMT3B in cancer cell lines, HCT116, Caco2 and SW480 cells.

Flavonoids and cancer risk

At the end of the last century there was increasing awareness that many chronic diseases and/or cancers can be prevented by proper nutrition. Almost 20 years ago, in 1999 World Cancer Research Fund and AICR (American Institute for Cancer Research) published report which focus mainly on the prevention of cancer, with clear emphasis on role of food and nutrition in reduction of the risk of specific cancers, and importance of dietary factors likely to increase risk (World Cancer Research Fund/American Institute for Cancer Research 2007). In this report, international experts concluded that intake of fruit and vegetables are inversely related to several cancers development. This report triggers studies dealing with the question of which phytochemicals in dietary sources may have cancer preventive properties. Groups of polyphenols- and flavonoids-exert powerful anticancer effects in various *in vitro* conditions (Table 1) and become under investigation for their putative chemoprotective properties. Their role in cancer prevention has been extensively studied and reviewed (Mohammadi et al. 2016; Neuhouser 2004; Romagnolo and Selmin 2012; Sak and Everaus 2015), but conclusions are inconsistent. Common way of studying the role of flavonoids in cancer risk has been epidemiological studies whose purpose is the determination of the factors associated with the onset of specific cancer and if flavonoid intake plays role in this process. For example, recently published study by Zamora-Ros et al. (2017) observed the relation between intakes of total flavonoids and risk of colorectal cancer development. In that study authors did not find relation of total flavonoid intake with risk of overall colorectal cancer or any subtype. This is just one example, but during the last couple of decades many similar epidemiological studies have been published with, unfortunately, inconsistent conclusions. Therefore, over the years, scientist performed meta-analysis and gain a more powerful conclusion from relevant studies. Some of the meta-analysis of epidemiologic studies related to the flavonoids and cancer risk published in the last 10 years are summarized in the Table 2.

Recently, comprehensive meta-analysis including 143 studies published focused on cancer risk and intake of lignan and dietary flavonoid (Grosso et al. 2017). Meta-analyses revealed that isoflavones significantly decreases risk of stomach and lung cancers and nearly significant colorectal and breast cancers, while non-significant reduction in risk of breast cancer were showed with intake of total flavonoids. At the end, Grosso et al. (2017) concluded that research on this topic is far from being decisive or even comprehensive and thus further research studies are needed to increase the quality and quantity of available data and to confirm current potential trends toward decreased risk.

Clinical trials of flavonoids in treating cancer

Flavonoid compounds have been examined against cancer patients under various clinical trials (Table 3) and some of them discussed in this section.

A semi-synthetic flavonoid (7-monohydroxyethylrutoside) was tested clinically in humans (age between 19 and 56 years) using a single blind randomized trial (Bast et al. 2007). At each dose level (from 100 to 1500 mg/m^2), six voluntaries were received flavonoid and three received placebos. The dose of 1500 mg/m^2 was found to be safe in phase I trial and could be further investigate for phase II trial against doxorubicin-induced cardiotoxicity in cancer patients (Bast et al. 2007). In another study, quercetin was examined for phase I clinical trial and administered i.v. dose (from 60 mg/m^2 to 1700 mg/m^2) at 3-week interval to patients diagnosed with cancer (Ferry et al. 1996). At 1400 mg/m^2 dose level, five patients were investigated at 3-week interval and 8 patients on a once weekly schedule and result revealed that two out of ten found to have renal toxicity. Moreover, at a dose of 945 mg/m^2, 3 out of 14 showed renal toxicity. In 9 out of 11 patients the lymphocytes protein tyrosine phosphorylation was inhibited. It was also seen that, at a dose of 420 mg/m^2, the CA125 was downregulated along with serum α fetoprotein concentration (Ferry et al. 1996).

Isoquercetin was evaluated for its venous thrombosis prevention activity in patients having pancreatic, lung or colorectal cancer under phase II/III clinical trial (NCT02195232) (Zwicker et al. 2018). In phase II trial the dose of isoquercetin was tested for its safety, while in phase III the study was conducted under double blinded randomized placebo controlled clinical trial in 618 patients (NCT02195232) (Zwicker et al. 2018). Similarly, a commercially available preparation named "Flavo-Natin" containing bioflavonoids (mixture of 200 mg chamomile and tea extract, vitamin and folic acid) was tested against recurrence of neoplasia in 382 patients in a randomized clinical trial (NCT00609310) (Kroonen et al. 2012).

Watercress extract containing flavonoids and carotenoids was tested for long term in breast cancer patients (200 no, 18–70 years of age) at a dose of 100 g daily during radiation therapy and found effective (NCT02468882) (Milisav, Poljšak, and Ribarič 2017). Similarly, quercetin was found effective in prevention and treatment of chemotherapy induced oral mucositis in 20 patients (15–40 years, randomized, all sex) when administered at a dose of 250 mg per (NCT01912820) (Zwergel, Valente, and Mai 2015).

Table 1. Effects of flavonoids on different types of cancer in *in vitro* conditions.

Compound	Cell cultures	Dose	Effects	References
Naringenin	Human colon adenocarcinoma (CaCo-2)-cells	1, 10, and 100 μM/ml concentrations	Downregulating miR-17-3p, miR-25-5p at the concentration of 10 and 100 μg/ml up-regulating mRNA coding for MnSOD and GPx2	Curti et al. (2017)
Naringenin	Rat model of spinal cord injury	50 and 100 mg/kg, p.o.	Downregulating miR-223 and inflammatory cytokines	Shi et al. (2016)
Naringenin	Mouse glomerular mesangial cell (MMC) line	50 mg/kg/day	Downregulating let-7a	Yan et al. (2016)
Kaempferol	HCT-116 colon cancer cells human-derived hepatoma cell lines HepG2 and Hep3B	5 μM, 10 μM, 20 μM, 50 μM, 100 μM	Inhibition of various classes of histone deacetylases (HDACs) including I, II and IV enzymes	Berger et al. (2013)
Luteolin	Human prostate cancer LNCaP and DU145 cells	10 μM, 20 μM	Dose dependent inhibition of DNMT activity	Kanwal et al. (2016)
Quercetin	Human leukemic HL-60 cells	0–100 μM	Dose and time dependent effect (histone acetylation through activation of HAT and inhibition of HADC)	Lee, Chen, and Tseng (2011)
Quercetin	HepG2 hepatocarcinoma cells	10 to 60 μg/ml	Marked reduction of HDAC1 and HDAC2	Bishayee, Khuda-Bukhsh, and Huh (2015)
Quercetin	human breast cancer cell lines MCF-7 and MDA-MB-231	25 μm/ml, 50 μm/ml, 80 μm/ml, 100 μm/ml	Upregulating miR-146a	Tao, He, and Chen (2015)
Combination of quercetin (Q), catechin gallate (CG), epicatechin gallate (ECG), epigallocatechin gallate (EGCG) and sulforaphane (SF)	Pancreatic ductal adenocarcinoma (PDA) cell lines (BxPc-3, MIA-PaCa2, CRL-1097, PaCaDD-183)	10 μM SF, 200 mM Q, 40 μM EGCG), 40 μM ECG), 40 μM CG	Upregulation of miR-let-7	Appari et al. (2014)
Quercetin and cisplatin	Human osteosarcoma 143B cell lines	Quercetin (5 μM), cisplatin (5 μM)	Increased miR-217 expression	Zhang et al. (2015)
Apigenin	Human prostate cancer cell lines 22Rv1 and PC-3	20–40 μM	Inhibiting HDACs activity	Pandey et al. (2012)
Catechol containing flavonoids including myricetin	Human breast cancer cell lines (MCF-7 and MDA-MB-231)	IC50 values ranges from 1.0 to 8.4 μM (IC50 for myricetin was 0.7 μM)	Inhibiteing DNMT mediated DNA methylation	Lee, Shim, and Zhu (2005)
Daidzein and Genistein	Prostate cell lines (PC-3, DU-145, LNCaP)	40 or 110 μM genistein and daidzein	Reversion of DNA hypermethylation	Vardi et al. (2010)
	Breast cancer cell lines (MDA-MB-231 and MCF7)	Daidzein (78.5 μM) and genistein (18.5 μM)	Increase histone acetylation and reduce histone trimethylation	Dagdemir et al. (2013)
Genistein	Esophageal squamous cell lines (KYSE-150) and Prostate cancer cells lines (LNCaP and PC-3)	20–50 μM	inhibition of DNMT activity	Zhang and Chen (2011)
EGCG	MCF-7 breast cancer cell lines and HL60 promyelocytic leukemia cell lines.	100 μM for treatment of MCF-7 cells and 50 μM for treatment of HL60 cells	Inhibition of human telomerase reverse transcriptase (hTERT) activity	Berletch et al. (2008)
	Human esophageal squamous cell carcinoma cell lines (KYSE 510 and KYSE 150)	2 μM, 10 μM, 50 μM	Inhibiting DNMT activity	Stresemann et al. (2006)
Fisetin	Hepatic cell lines (HepG-2), colorectal cell lines (Caco-2) and pancreatic cells lines (Suit-2)	HepG-2 (IC50: 3.2 μM), Caco-2 (IC50: 16.4 μM), Suit-2 (IC50: 8.1 μM)	Inhibiting cellular proliferation and viability of cancer cell lines. Activation of CDKN1A, SEMA3E, GADD45B and GADD45A genes and down-regulation of TOP2A, KIF20A, CCNB2 and CCNB1 genes	Youns and Hegazy (2017)
Silibilin	Human prostate cancer cell lines (DU145 and PC3)	25–75 μg/ml	Decrease HDACs1-2 expression level. Increase in total DNMT activity	Anestopoulos et al. (2016)
	Adenocarcinoma cell lines (SW480) and colon cancer cell lines (SW620)	300 μM	Inhibiting DNMT activity	Kauntz et al. (2013)
Anthocyanins	Colon cell lines (HCT116, Caco2 and SW480)	0.5 μg/ml, 5 μg/ml, 25 μg/ml	Inhibition of DNMT with strongest DNMT activity at 25 μg/ml	Wang et al. (2013)

Table 2. Meta-analysis of epidemiologic studies related to the flavonoids and cancer risk published in the last 10 years.

Type of cancer studied	Period covered with meta-analysis	No. of studies	Conclusions	Reference
Esophageal	January 1990 to April 2016	7 articles	Anthocyanidins flavanones and flavones were inversely associated with the risk of esophageal cancer. Total flavonoids showed marginal association with esophageal cancer risk.	Cui et al. (2016)
Ovarian	before April 25, 2015	5 cohort studies and 7 case-control studies	The ovarian cancer risk was decreased for isoflavone and flavonols, while there was no evidence that consumption of flavones could decrease risk.	Hua et al. (2016)
Brest	before July 1, 2012	6 prospective cohort and 6 case-control studies	Risk of breast cancer significantly decreased in women with high intake of flavonols and flavones while no significant association of flavan-3-ols, flavanones, anthocyanins or total flavonoids intake with breast cancer risk was observed	Hui et al. (2013)
smoking-related: aerodigestive tract and lung	before October 31, 2012	19 case-controls and 15 cohort studies	Total dietary flavonoids and most of the flavonoid subclasses were inversely associated with smoking-related cancer risk. Total dietary flavonoid intake was significantly associated with aerodigestive tract cancer risk and marginally associated with lung cancer risk. Aerodigestive tract cancer was inversely associated with most flavonoid subclasses.	Woo and Kim (2013)
Lung	before January 1, 2009	8 prospective studies and 4 case–control studies	Statistically significant association between highest flavonoids intake and reduced risk of developing lung cancer.	Tang et al. (2009)

Various clinical trials testing flavonoids against cancer are currently ongoing. For instance, one of the phase I randomized double blind placebo controlled two-arm clinical trial quercetin and green tea to enhance bioavailability of green tea polyphenolics in prostate tissue of patients undergone radial prostatectomy is currently ongoing (NCT01912820) (Zwergel, Valente, and Mai 2015). Similarly, isoquercetin tested as an adjunct therapy in patients with kidney cancer receiving first line sunitinib (Phase I and II trial) is under progress (NCT02446795) (Haque et al. 2017). Moreover, capsule with broccoli sprout grain containing a total of 90 mg sulforaphane and quercetin as active components is going to be tested against pancreatic cancer (NCT01879878) (Vendrely et al. 2017).

Investigating dietary natural supplements against cancer affecting hormones in breast cancer patients was also under trial (NCT00910884) (Manzo-Merino et al. 2014). Briefly, 300 breast cancer remission patients were provided oral natural supplements comprising indol-3-carbinol, perillyl alcohol, gluconic acid and flavonoids daily for 12 months (NCT00910884) (Kado et al. 2012; Manzo-Merino et al. 2014). In another randomized controlled double-blind crossover trial, 60 prostate cancer patients were provided 500 mg/day quercetin, vitamin C, folic acid and vitamin B3 and 100 mg/day genistein, vit C, folic acid and vit B3 over a period of 6 months (NCT01538316).

Purple grape juice was found to be effective in improving vascular health in childhood cancer survivors (NCT01043939) (Blair et al. 2014). Survivors of childhood cancer were likely to develop cardiovascular risk factors due to the cancer therapy. Purple grape juice rich in flavonoids was tested to find out its protective effect on cardiovascular risk in 24 patients under randomized clinical trial and found effective (NCT01043939) (Blair et al. 2014). In another randomized clinical trial, the effectiveness of sulindac, curcumin, rutin and quercetin was tested in 130 colon cancer patients (NCT00003365) (Hatcher, Torti, and Torti 2012). The patients received one of the following treatments, namely, nothing, oral sulindac twice daily, oral rutin at 1 of 3 doses twice daily, oral quercetin at 1 of 3 doses twice daily, oral curcumin at 3 doses twice daily. The treatment was found effective in colon cancer prevention (NCT00003365) (Hatcher, Torti, and Torti 2012).

Therapeutic potential of luteolin natural extract and its nanoparticle formulation was tested on tongue squamous cell carcinoma cell lines. The study revealed a preventive effect of luteoline and its nano formulation on inhibitory effect on tongue squamous cell carcinoma line by inducing apoptosis (NCT03288298) (Majumdar et al. 2014). In another clinical trial the use of quercetin for the treatment and prevention of chemotherapy induced neuropathic pain in cancer patients was examined (NCT02989129) (Sharma et al. 2018). Quercetin tablet administered at an oral dose of 500 mg twice per day for 12 weeks in 20 patients (18 years or older, all sex) under non-randomized clinical trial was found effective (NCT02989129) (Sharma et al. 2018).

In another randomized triple-blind controlled clinical trial, 56 breast cancer patients (age of 30–63 years) were

Table 3. Clinical trials of flavonoid compounds against cancer.

S. No.	Flavonoid compound/extract	Study design	Dose	Mode and results	Reference/Clinical Trial No.
1	7-monohydroxyethylrutoside	Randomized single blind placebo-controlled trial on 19–56 years age cancer patients?	Study dose from 100 to 1500 mg/m^2 and at each dose 6 volunteer received the drug and 3 received the placebo	The dose of 1500 mg/m^2 was found to be safe.	Bast et al. (2007)
2	Quercetin	Human diagnosed with cancer	Dose level from 60 to 1700 mg/m^2	In 9 out of 11 patient the lymphocyte protein tyrosine phosphorylation inhibited. At a concentration of 420 mg/m^2, the CA125 downregulated along with serum α fetoprotein concentration. At 1400 mg/m^2 doe 2 out of 10 patients were found to have renal toxicity and at 945 mg/m^2 dose level 3 out of 14 showed renal toxicity	Ferry et al. (1996)
3	Isoquercetin	Patients having pancreas or non-small cell lung cancer or colorectal cancer, 618 patients were examined under randomized double blind placebo controlled	At a dose of 500 mg/day and 1000 mg/day for 28 days	Recruiting	NCT02195232
4	Flavo-Natin (mixture of 200 mg Chamomile and tea extract, vitamin, biflavonoids and folic acid	382 patients having recent surgical resection of colorectal cancer under randomized clinical trial	20 mg apigenin and 20 mg epigallocatechin gallate as tablet/day	Recruiting	NCT00609310
5	Watercress extract containing flavonoids and carrotenoids	Breast cancer patients 200 in number of 18–70 years	100 g of watercress daily during radiation therapy	Recruiting	NCT02468882
6	Quercetin	Chemotherapy induced oral mucositis in 20 patients of 15–40 years of age randomized?	250 mg quercetin capsule daily for 3 weeks	decrease in mucositis (Completed)	NCT01732393
7	Quercetin and green tea	40–45-year-age male undergoes radial prostatectomy, randomized double blind placebo controlled two-arm study	Patients receiving green tea extract and quercetin orally for 3–6 weeks before undergoing prostatectomy	Active	NCT01912820
8	Isoquercetin	Patients with kidney cancer receiving first line sunitinib drug. 104 patients of 18 year and older	Isoquercetin 225 mg twice and 450 mg twice a day	Recruiting	NCT02446795
9	Broccoli sprout grain (90 mg sulforaphane and quercetin)	40 patients having pancreatic cancer of age 18 year and older	Capsule containing broccoli sprout grain having a total of 90 mg sulforaphane and quercetin	Recruiting	NCT01879878
10	Natural supplements containing indol-3-carbinol, perillyl alcohol, gluconic acid and flavonoids	300 female patients of 18–70 years of age having breast cancer remission	Oral natural supplement for 12 months	Active	NCT00910884
11	Quercetin and Genistein	60 patients having prostate cancer, ramdomized placebo controlled double blind crossover trial	500 mg/day quercetin and 100 mg/day genistein along with vitamin C, folic acid and vitamin B3 for 6 months	Recruiting	NCT01538316
12	Purple grape juice rich in flavonoids	24 patients, 10–30 years and developed cardiovascular risk due to cancer therapy in childhood	After 4 weeks run-in period, 6 ounces of grape juice twice daily		NCT01043939
13	Sulindac, curcumin, rutin and quercetin	130 patients of 18 year and older having colon cancer	Patients receiving one of the following treatment: nothing, oral sulindace twice/day, oral	Prevent the development of colon cancer (Completed)	NCT00003365

(*continued*)

Table 3. Continued.

S. No.	Flavonoid compound/extract	Study design	Dose	Mode and results	Reference/Clinical Trial No.
			rutin 1 of 3 dose twice/day, oral quercetin at 1 of 3 doses twice/day, oral curcumin at 3 doses twice/day treatment for 6–10 weeks		
14	Quercetin	Chemotherapy induced neuropathic pain in 20 cancer patients of 18 and older age	Quercetin tablet at 500 mg twice per day for 12 weeks	Active	NCT02989129
16	Onion containing sulfur and flavonoids	Hyperglycemia and insulin resistance in breast cancer patient receiving doxorubicin based chemotherapy, randomized triple-blind placebo controlled	28 patients received 100–160 g/day of onion as high and 30–40 g/day as lower dose in 28 patients	Effective ameliorate hyperglycemia and insulin resistance in breast cancer patients	Jafarpour-Sadegh et al. (2017)
17	Dietary intake of flavonoids	Esophageal and gastric cancer patients	USA multicentre population based study (1993–1995)	57% reduction in the risk of esophageal squamous cell carcinoma and esophageal adenocarcinoma	Petrick et al. (2015)
18	Pomegranate juice (rich in flavonoids)	Simon two stage clinical trial for men with rising prostate specific antigen after surgery or radiotherapy	Patients treated with 8 ounces of pomegranate juice daily	12% reduction in cell proliferation and 17% increase in apoptosis with increase in serum nitric oxide and significant reduction in oxidative stress	Pantuck et al. (2006)
19	Curcumin	Patients with urinary bladder cancer, uterine cervical neoplasm, or intestinal metaplasia. Patients with advanced pancreatic cancer. Prospective phase I/II clinical trial. Nonrandomized open-label phase II trial	500 mg/day, orally, for 3 month. 8 g/day curcumin, orally, for one mouth	Histologic improvement in 1 out of 2 patients with bladder cancer, 1 out of 6 patients with intestinal metaplasia and 1 out of 4 patients with uterine cervical neoplasm. Among 21 patients, 1 had stable disease for >18 months and 1 had tumor regression	Hsieh (2001); Dhillon et al. (2008)
20	Green tea	Patients with high-grade prostate intraepithelial neoplasia, Patients with histologically confirmed adenocarcinoma of the prostate, Patients with esophageal cancer, Patients with colon, rectum and pancreas cancer, Patients with androgen independent metastatic prostate carcinoma	600 mg/day green tea catechins, orally, for one year. Usual tea consumption. Usual tea consumption. Regular, non-regular and high tea consumption. 6 g/day of green tea orally in 6 divided doses for 2 months	After 1 year, the incidence of tumor development was 3% and 30% in treated and control men, respectively; quality of life improved. The prostate cancer risk declined with increasing frequency, duration and quantity of green tea consumption green tea consumption was associated with reduced risk of esophageal cancer. An inverse association with each cancer was observed with increasing amount of green tea consumption. Decrease of PSA was seen only in 2% of patients	Bettuzzi et al. (2006); Jian et al. (2004); Gao et al. (1994); Ji et al. (1997); Jatoi et al. (2003)
21	Resveratrol	Patients with colorectal cancer and hepatic metastases. Phase I pilot study. Phase I randomized double-blind pilot study. Pre- and posttreatment	20–80 mg/day of resveratrol-containing grape powder for 14 days. 5 g/daily for 14 days. 0.5 or 1.0 g/day resveratrol for 8 days, before surgical resection	Resveratrol did not inhibit the Wnt pathway in colon cancer but inhibited the pathway in normal colonic mucosa. Apoptosis increased by 39% in malignant hepatic tissue. Decrease of tumor cell proliferation by 5% ($p = 0.05$)	Nguyen et al. (2009); Howells et al. (2011); Patel et al. (2010)

investigated (Jafarpour-Sadegh et al. 2017). Following the second cycle of chemotherapy, patients were received (28 no) 100–160 g/day of onions as high and 30–40 g/day small onions as low dose. The study showed positive effect of onions in ameliorating hyperglycemia and insulin resistance in breast cancer doxorubicin-based chemotherapy

(Jafarpour-Sadegh et al. 2017). In another study, dietary intake of flavonoids along with esophageal and gastric cancer incidence and survival in the United States of America was examined (Petrick et al. 2015). Multicenter population-based study was conducted, and participants (diagnosed during 1993–1995) with esophageal adenocarcinoma (OEA, n = 274), gastric cardia adenocarcinoma (GCA, n = 248), esophageal squamous cell carcinoma (OES, n = 191), other gastric adenocarcinoma (OGA, n = 341) were examined. It was found that the intake of flavonoids, especially anthocyanidins (in wine and fruit juice), was associated with 57% reduction in the risk of OEA and OES. Also, anthocyanidins were found to decrease risk of mortality in GCA patients. Moreover, in general, intake of dietary anthocyanidin reduced the incidences and improved survival for the cancer patients (Petrick et al. 2015). In a similar experiment, pomegranate juice (rich in flavonoids) were subjected to phase II two stage clinical trial for men with rising prostate specific antigen after surgery or radiotherapy (Pantuck et al. 2006). Patients treated with 8 ounces of pomegranate juice daily were found to have significantly increased PSA doubling time, 12% decrease in cell proliferation, 17% increase in apoptosis, 2.3% increase in serum nitric oxide and a significant reduction in oxidative stress, thus further preventing cancer proliferation and growth (Pantuck et al. 2006).

Conclusions and future directions

Strong evidences have been observed in literature data bases regarding the abnormal changes in epigenetics in various human tumors, therefore targeting epigenetic to regain normal physiology and thereby epigenome in cancer cells is an ideal approach for discovery of precision medicines. The FDA has already approved some of the epigenetic drugs for the effective treatment of cancer while few more are in different stages of clinical trial.

Enormous studies are available for the support of flavonoids that regulate epigenome. The epigenetic studies of various individual flavonols (quercetin, kaempferol myricetin), flavones (luteolin, apigenin), flavan-3-ols (fisetin, EGCG), isoflavones (genistein, daidzein), flavanones (silibinin, hesperetin, naringenin) and anthocyanidins (cyanidin, delphinidin, malvidin, and pelargonidin) showed strong preclinical potential. Similarly, initial clinical studies also revealed significant epigenetic effects of tested flavonoids. Large scale clinical studies would be required for the clinical applications of these flavonoids.

Abbreviations

AR	androgen receptor
ATF3	activating transcription factor 3
CG	catechin gallate
COMT	catechol-O-methyltransferase
CpG	cytosine-guanine
DACT2	disheveled binding antagonist of beta catenin 2
DNMT	DNA methyltransferase
dsRBD	double-stranded RNA binding domain
ECG	epicatechin gallate
EGCG	epigallocatechin-3-gallate
ERK	extracellular signal-regulated kinases
EXP5	Exportin 5
FDA	Food and Drug Administration
GSTP1	gluthathione-S-transferase pi
HAT	histone acetyltransferese
HDAC	histone deacetylase
HDM	histone demethylase
HMT	histone methyltransferase
hTERT	human telomerase reverse transcriptase
JNK	c-Jun N-terminal kinases
lncRNA	long non-coding RNA
MBD	methyl-CpG-binding domain
MECP2	methylcytosine binding protein 2
miRNA	microRNA
MnSOD	Mn-Superoxide dismutase
NSCLC	non-small cell lung cancer
PDA	pancreatic ductal adenocarcinoma
PHB	prohibitin
PRDX6	peroxiredoxin 6
RISC	RNA-induced silencing complex
SAHA	suberoylanilide hydroxamic acid
SAM	S-adenosyl methionine
TAR RNA	trans-activation response
TSA	trichostatin A

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References

Afrin, S., F. Giampieri, M. Gasparrini, T. Y. Forbes-Hernández, D. Cianciosi, P. Reboredo-Rodriguez, J. Zhang, P. P. Manna, M. Daglia, A. G. Atanasov, et al. 2020. Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. *Biotechnology Advances* 38:107322. doi: 10.1016/j.biotechadv.2018.11.011.

Ahmad, A., T. Ali, H. Y. Park, H. Badshah, S. U. Rehman, and M. O. Kim. 2017. Neuroprotective effect of fisetin against amyloid-beta-induced cognitive/synaptic dysfunction, neuroinflammation, and neurodegeneration in adult mice. *Molecular Neurobiology* 54 (3): 2269–85. doi: 10.1007/s12035-016-9795-4.

Ahuja, N., A. R. Sharma, and S. B. Baylin. 2016. Epigenetic therapeutics: A new weapon in the war against cancer. *Annual Review of Medicine* 67 (1):73–89. doi: 10.1146/annurev-med-111314-035900.

Allred, C. D., Y. H. Ju, K. F. Allred, J. Chang, and W. G. Helferich. 2001. Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. *Carcinogenesis* 22 (10):1667–73. doi: 10.1093/carcin/22.10.1667.

Anestopoulos, I., A. Sfakianos, R. Franco, K. Chlichlia, M. Panayiotidis, D. Kroll, and A. Pappa. 2016. A novel role of silibinin as a putative epigenetic modulator in human prostate carcinoma. *Molecules* 22 (1):62. doi: 10.3390/molecules22010062.

Appari, M., K. R. Babu, A. Kaczorowski, W. Gros, and I. Her. 2014. Sulforaphane, quercetin and catechins complement each other in elimination of advanced pancreatic cancer by miR-let-7 induction and K-ras inhibition. *International Journal of Oncology* 45 (4): 1391–400. doi: 10.3892/ijo.2014.2539.

Attoub, S., A. H. Hassan, B. Vanhoecke, R. Iratni, T. Takahashi, A.-M. Gaben, M. Bracke, S. Awad, A. John, H. A. Kamalboor, et al. 2011. Inhibition of cell survival, invasion, tumor growth and histone deacetylase activity by the dietary flavonoid luteolin in human epithelioid cancer cells. *European Journal of Pharmacology* 651 (1-3): 18–25. doi: 10.1016/j.ejphar.2010.10.063.

Ayissi, V. B. O., A. Ebrahimi, and H. Schluesenner. 2014. Epigenetic effects of natural polyphenols: A focus on SIRT1-mediated mechanisms. *Molecular Nutrition & Food Research* 58 (1):22–32. doi: 10.1002/mnfr.201300195.

Babiarz, J. E., J. G. Ruby, Y. Wang, D. P. Bartel, and R. Blelloch. 2008. Mouse ES cells express endogenous shRNAs, siRNAs, and other Microprocessor-independent, Dicer-dependent small RNAs. *Genes & Development* 22 (20):2773–85. doi: 10.1101/gad.1705308.

Balasubramanian, S., G. Adhikary, and R. L. Eckert. 2010. The Bmi-1 polycomb protein antagonizes the (−)-epigallocatechin-3-gallate-dependent suppression of skin cancer cell survival. *Carcinogenesis* 31 (3):496–503. doi: 10.1093/carcin/bgp314.

Bannister, A. J., and T. Kouzarides. 2011. Regulation of chromatin by histone modifications. *Cell Research* 21 (3):381–95. doi: 10.1038/cr.2011.22.

Barreca, D., E. Bellocco, G. D'Onofrio, S. Fazel Nabavi, M. Daglia, L. Rastrelli, and S. Mohammad Nabavi. 2016. Neuroprotective effects of quercetin: From chemistry to medicine. *CNS & Neurological Disorders - Drug Targets* 15 (8):964–75. doi: 10.2174/1871527315666160813175406.

Baruah, M. M., A. P. Khandwekar, and N. Sharma. 2016. Quercetin modulates Wnt signaling components in prostate cancer cell line by inhibiting cell viability, migration, and metastases. *Tumor Biology* 37 (10):14025–34. doi: 10.1007/s13277-016-5277-6.

Bast, A., G. R. Haenen, A. M. Bruynzeel, and W. J. Van der Vijgh. 2007. Protection by flavonoids against anthracycline cardiotoxicity: From chemistry to clinical trials. *Cardiovascular Toxicology* 7 (2): 154–9. doi: 10.1007/s12012-007-0018-0.

Berger, A., S. Venturelli, M. Kallnischkies, A. Böcker, C. Busch, T. Weiland, S. Noor, C. Leischner, T. S. Weiss, U. M. Lauer, et al. 2013. Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases. *The Journal of Nutritional Biochemistry* 24 (6): 977–85. doi: 10.1016/j.jnutbio.2012.07.001.

Berger, N. A. 2016. *Epigenetics, energy balance, and cancer*. Basel, Switzerland: Springer.

Berghe, W. V. 2012. Epigenetic impact of dietary polyphenols in cancer chemoprevention: Lifelong remodeling of our epigenomes. *Pharmacological Research* 65:565–76.

Berletch, J. B., C. Liu, W. K. Love, L. G. Andrews, S. K. Katiyar, and T. O. Tollefsbol. 2008. Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *Journal of Cellular Biochemistry* 103 (2):509–19. doi: 10.1002/jcb.21417.

Bernstein, E., A. A. Caudy, S. M. Hammond, and G. J. Hannon. 2001. Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature* 409 (6818):363–6. doi: 10.1038/35053110.

Bettuzzi, S., M. Brausi, F. Rizzi, G. Castagnetti, G. Peracchia, and A. Corti. 2006. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: A preliminary report from a one-year proof-of-principle study. *Cancer Research* 66 (2):1234–40. doi: 10.1158/0008-5472.CAN-05-1145.

Bishayee, K., A. R. Khuda-Bukhsh, and S. O. Huh. 2015. PLGA-loaded gold-nanoparticles precipitated with quercetin downregulate HDAC-Akt activities controlling proliferation and activate p53-ROS cross-talk to induce apoptosis in hepatocarcinoma cells. *Molecules and Cells* 38 (6):518–27. doi: 10.14348/molcells.2015.2339.

Blair, C. K., A. S. Kelly, J. Steinberger, L. E. Eberly, C. Napurski, K. Robien, J. P. Neglia, D. A. Mulrooney, and J. A. Ross. 2014. Feasibility and preliminary efficacy of the effects of flavanoid-rich purple grape juice on the vascular health of childhood cancer survivors: A randomized, controlled crossover trial. *Pediatric Blood & Cancer* 61 (12):2290–6. doi: 10.1002/pbc.25202.

Bogdanović, O., and G. J. C. Veenstra. 2009. DNA methylation and methyl-CpG binding proteins: Developmental requirements and function. *Chromosoma* 118 (5):549–65. doi: 10.1007/s00412-009-0221-9.

Bohnsack, M. T., K. Czaplinski, and D. Görlich. 2004. Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. *RNA* 10 (2):185–91. doi: 10.1261/rna.5167604.

Bosch-Barrera, J., and J. A. Menendez. 2015. Silibinin and STAT3: A natural way of targeting transcription factors for cancer therapy. *Cancer Treatment Reviews* 41 (6):540–6. doi: 10.1016/j.ctrv.2015.04.008.

Bots, M., and R. W. Johnstone. 2009. Rational combinations using HDAC inhibitors. *Clinical Cancer Research* 15 (12):3970–7. doi: 10.1158/1078-0432.CCR-08-2786.

Büchler, P., A. Gazdhar, M. Schubert, N. Giese, H. A. Reber, O. J. Hines, T. Giese, G. O. Ceyhan, M. Müller, M. W. Büchler, et al. 2005. The Notch signaling pathway is related to neurovascular progression of pancreatic cancer. *Annals of Surgery* 242:791.

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

Bussemakers, M. J., A. van Bokhoven, G. W. Verhaegh, F. P. Smit, H. F. Karthaus, J. A. Schalken, F. M. Debruyne, N. Ru, and W. B. Isaacs. 1999. DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Research* 59 (23):5975–9.

Byrne, M. M., R. T. Murphy, and A. W. Ryan. 2014. Epigenetic modulation in the treatment of atherosclerotic disease. *Frontiers in Genetics* 5:364. doi: 10.3389/fgene.2014.00364.

Cassidy, A., T. Huang, M. Rice, E. Rimm, and S. Tworoger. 2014. Intake of dietary flavonoids and risk of epithelial ovarian cancer. *The American Journal of Clinical Nutrition* 100 (5):1344–51. doi: 10.3945/ajcn.114.088708.

Che, J., B. Liang, Y. Zhang, Y. Wang, J. Tang, and G. Shi. 2017. Kaempferol alleviates ox-LDL-induced apoptosis by up-regulation of autophagy via inhibiting PI3K/Akt/mTOR pathway in human endothelial cells. *Cardiovascular Pathology* 31:57–62. doi: 10.1016/j.carpath.2017.08.001.

Chen, H.-Q., J. Zhao, Y. Li, L.-X. He, Y.-J. Huang, W.-Q. Shu, J. Cao, W.-B. Liu, and J.-Y. Liu. 2018. Gene expression network regulated by DNA methylation and microRNA during microcystin-leucine arginine induced malignant transformation in human hepatocyte L02 cells. *Toxicology Letters* 289:42–53. doi: 10.1016/j.toxlet.2018.03.003.

Choi, J. H., S. E. Park, S. J. Kim, and S. Kim. 2015. Kaempferol inhibits thrombosis and platelet activation. *Biochimie* 115:177–86. doi: 10.1016/j.biochi.2015.06.001.

Cohen, I., E. Poreba, K. Kamieniarz, and R. Schneider. 2011. Histone modifiers in cancer: Friends or foes? *Genes & Cancer* 2 (6):631–47. doi: 10.1177/1947601911417176.

Copeland, R. A., M. E. Solomon, and V. M. Richon. 2009. Protein methyltransferases as a target class for drug discovery. *Nature Reviews Drug Discovery* 8 (9):724–32. doi: 10.1038/nrd2974.

Cui, L., X. Liu, Y. Tian, C. Xie, Q. Li, H. Cui, and C. Sun. 2016. Flavonoids, flavonoid subclasses, and esophageal cancer risk: A

meta-analysis of epidemiologic studies. *Nutrients* 8 (6):350–65. doi: 10.3390/nu8060350.

Curti, V., A. D. Lorenzo, D. Rossi, E. Martino, E. Capelli, S. Collina, and M. Daglia. 2017. Enantioselective modulatory effects of naringenin enantiomers on the expression levels of miR-17-3p involved in endogenous antioxidant defenses. *Nutrients* 9 (3):215. doi: 10.3390/nu9030215.

Dagdemir, A., J. Durif, M. Ngollo, Y. J. Bignon, and D. Bernard-Gallon. 2013. Histone lysine trimethylation or acetylation can be modulated by phytoestrogen, estrogen or anti-HDAC in breast cancer cell lines. *Epigenomics* 5 (1):51–63. doi: 10.2217/epi.12.74.

Damsky, W. E., D. P. Curley, M. Santhanakrishnan, L. E. Rosenbaum, J. T. Platt, B. E. Gould Rothberg, M. M. Taketo, D. Dankort, D. L. Rimm, M. McMahon, et al. 2011. *β*-catenin signaling controls metastasis in Braf-activated Pten-deficient melanomas. *Cancer Cell* 20 (6):741–54. doi: 10.1016/j.ccr.2011.10.030.

Dasgupta, A., and K. Klein. 2014. Chapter 12: Fruits, vegetables, and nuts: Good sources of antioxidants. In *Antioxidants in food, vitamins and supplements*, 209–35. San Diego, CA: Elsevier.

Davis-Dusenbery, B. N., and A. Hata. 2010. Mechanisms of control of microRNA biogenesis. *The Journal of Biochemistry* 148:381–92.

de Pascual-Teresa, S., and M. T. Sanchez-Ballesta. 2008. Anthocyanins: From plant to health. *Phytochemistry Reviews* 7 (2):281–99. doi: 10.1007/s11101-007-9074-0.

Derrien, T., R. Guigó, and R. Johnson. 2012. The long non-coding RNAs: A new (p) layer in the "dark matter". *Frontiers in Genetics* 2: 107. doi: 10.3389/fgene.2011.00107.

Devi, K. P., D. S. Malar, S. F. Nabavi, A. Sureda, J. Xiao, S. M. Nabavi, and M. Daglia. 2015. Kaempferol and inflammation: From chemistry to medicine. *Pharmacological Research* 99:1–10. doi: 10.1016/j.phrs.2015.05.002.

Dhillon, N., B. B. Aggarwal, R. A. Newman, R. A. Wolff, A. B. Kunnumakkara, J. L. Abbruzzese, C. S. Ng, V. Badmaev, and R. Kurzrock. 2008. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clinical Cancer Research* 14 (14):4491–99. doi: 10.1158/1078-0432.CCR-08-0024.

Donado, F., U. Sandoval, and J. Carrillo. 2011. Viscosity enhancement in dilute magnetorheological fluids through magnetic perturbations. *Revista Mexicana de Física* 57:426–34.

Dong, Z., and Y. J. Surh. 2008. *Dietary modulation of cell signaling pathways*. Boca Raton, FL: CRC Press.

Duthie, G., and K. Brown. 1994. *Reducing the risk of cardiovascular disease, functional foods: Designer foods, pharma foods, nutraceuticals*, 19. Upper Saddle River, NJ: Chapman & Hall.

Ehrlich, M., and M. Lacey. 2013. DNA hypomethylation and hemimethylation in cancer. In *Epigenetic alterations in oncogenesis*, ed. A. Karpf, 31–56. New York, NY: Springer.

ENCODE Project Consortium. 2012. An integrated encyclopedia of DNA elements in the human genome. *Nature* 489:57.

Fang, M. Z., D. Chen, Y. Sun, Z. Jin, J. K. Christman, and C. S. Yang. 2005. Reversal of hypermethylation and reactivation of p16INK4a, RAR*β*, and MGMT genes by genistein and other isoflavones from soy. *Clinical Cancer Research* 11 (19):7033–41. doi: 10.1158/1078-0432.CCR-05-0406.

Fang, M., D. Chen, and C. S. Yang. 2007. Dietary polyphenols may affect DNA methylation. *The Journal of Nutrition* 137 (1):223S–8S. doi: 10.1093/jn/137.1.223S.

Ferry, D. R., A. Smith, J. Malkhandi, D. W. Fyfe, P. G. deTakats, D. Anderson, J. Baker, and D. J. Kerr. 1996. Phase I clinical trial of the flavonoid quercetin: Pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 2 (4):659–68.

Friedman, R. C., K. K. H. Farh, C. B. Burge, and D. P. Bartel. 2008. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Research* 19 (1):92–105. doi: 10.1101/gr.082701.108.

Gao, P., and G. H. Wei. 2017. Genomic insight into the role of lncRNAs in cancer susceptibility. *International Journal of Molecular Sciences* 18:1239.

Gao, Y. T., J. K. McLaughlin, W. J. Blot, B. T. Ji, Q. Dai, and J. F. Fraumeni. 1994. Reduced risk of esophageal cancer associated with green tea consumption. *JNCI: Journal of the National Cancer Institute* 86 (11):855–58. doi: 10.1093/jnci/86.11.855.

Gates, M., S. Tworoger, J. Hecht, I. De Vivo, B. Rosner, and S. Hankinson. 2007. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. *International Journal of Cancer* 121 (10):2225–32. doi: 10.1002/ijc.22790.

Gilbert, E., and D. Liu. 2010. Flavonoids influence epigenetic-modifying enzyme activity: Structure-function relationships and the therapeutic potential for cancer. *Current Medicinal Chemistry* 17 (17):1756–68. doi: 10.2174/092986710791111161.

Goldberg, I. 1994. *Functional foods: Designer foods, pharmafoods, nutraceuticals*. New York, NY: Springer.

Goldberg, R., B. Motzkin, R. Marion, P. J. Scambler, and R. J. Shprintzen. 1993. Velo-cardio-facial syndrome: A review of 120 patients. *American Journal of Medical Genetics* 45 (3):313–9. doi: 10.1002/ajmg.1320450307.

Grishok, A., A. E. Pasquinelli, D. Conte, N. Li, S. Parrish, I. Ha, D. L. Baillie, A. Fire, G. Ruvkun, C. C. Mello, et al. 2001. Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans developmental timing. *Cell* 106 (1):23–34. doi: 10.1016/S0092-8674(01)00431-7.

Grosso, C., P. Valentão, C. Andrade, and P. B. Andrade. 2015. HPLC–DAD analysis and in vitro enzyme inhibition: An integrated approach to predict herbal binary mixture behaviour employing median effect equation. *Microchemical Journal* 119:176–82. doi: 10.1016/j.microc.2014.12.006.

Grosso, G., J. Godos, R. Lamuela-Raventos, S. Ray, A. Micek, A. Pajak, S. Sciacca, N. D'Orazio, D. Del Rio, F. Galvano, et al. 2017. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. *Molecular Nutrition & Food Research* 61 (4):1600930. doi: 10.1002/mnfr.201600930.

Guglas, K., M. Bogaczyńska, T. Kolenda, M. Ryś, A. Teresiak, R. Bliźniak, I. Łasińska, J. Mackiewicz, and K. Lamperska. 2017. lncRNA in HNSCC: Challenges and potential. *Współczesna Onkologia* 21 (4):259–66. doi: 10.5114/wo.2017.72382.

Gupta, R. A., N. Shah, K. C. Wang, J. Kim, H. M. Horlings, D. J. Wong, M.-C. Tsai, T. Hung, P. Argani, J. L. Rinn, et al. 2010. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 464 (7291):1071–6. doi: 10.1038/nature08975.

Hammond, S. M., S. Boettcher, A. A. Caudy, R. Kobayashi, and G. J. Hannon. 2001. Argonaute2, a link between genetic and biochemical analyses of RNAi. *Science* 293 (5532):1146–50. doi: 10.1126/science.1064023.

Han, X. H., S. S. Hong, J. S. Hwang, M. K. Lee, B. Y. Hwang, and J. S. Ro. 2007. Monoamine oxidase inhibitory components from *Cayratia japonica*. *Archives of Pharmacal Research* 30 (1):13–7. doi: 10.1007/BF02977772.

Haque, I., A. Subramanian, C. Huang, A. Godwin, P. Van Veldhuizen, S. Banerjee, and S. Banerjee. 2017. The role of compounds derived from natural supplement as anticancer aagents in renal cell carcinoma: A review. *International Journal of Molecular Sciences* 19 (1): 107. doi: 10.3390/ijms19010107.

Hardy, T. M., and T. O. Tollefsbol. 2011. Epigenetic diet: Impact on the epigenome and cancer. *Epigenomics* 3 (4):503–18. doi: 10.2217/epi.11.71.

Hasanpourghadi, M., A. K. Pandurangan, and M. R. Mustafa. 2018. Modulation of oncogenic transcription factors by bioactive natural products in breast cancer. *Pharmacological Research* 128:376–88. doi: 10.1016/j.phrs.2017.09.009.

Hatcher, H. C., F. M. Torti, and S. V. Torti. 2012. Curcumin, oxidative stress, and cancer therapy. In *Oxidative stress in cancer biology and therapy*, eds. D. R. Spitz, K. J. Dornfeld, K. Krishnan, and D. Gius, 233–56. Totowa, NJ: Humana Press.

Hertog, M. G., P. C. Hollman, and M. B. Katan. 1992. Content of potentially anticarcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. *Journal of Agricultural and Food Chemistry* 40 (12):2379–83. doi: 10.1021/jf00024a011.

Hess, J. L. 2004. MLL: A histone methyltransferase disrupted in leukemia. *Trends in Molecular Medicine* 10 (10):500–7. doi: 10.1016/j.molmed.2004.08.005.

Hong, K.-S., J.-I. Park, M.-J. Kim, H.-B. Kim, J.-W. Lee, T. T. Dao, W. K. Oh, C.-D. Kang, and S.-H. Kim. 2012. Involvement of SIRT1 in hypoxic down-regulation of c-Myc and β-catenin and hypoxic preconditioning effect of polyphenols. *Toxicology and Applied Pharmacology* 259 (2):210–8. doi: 10.1016/j.taap.2011.12.025.

Howells, L. M., D. P. Berry, P. J. Elliott, E. W. Jacobson, E. Hoffmann, B. Hegarty, K. Brown, W. P. Steward, and A. J. Gescher. 2011. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—Safety, pharmacokinetics, and pharmacodynamics. *Cancer Prevention Research* 4 (9):1419–25. doi: 10.1158/1940-6207.CAPR-11-0148.

Hsieh, C. Y. 2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Research* 21 (2895):e2900.

Hua, X., L. Yu, R. You, Y. Yang, J. Liao, D. Chen, and L. Yu. 2016. Association among dietary flavonoids, flavonoid subclasses and ovarian cancer risk: A meta-analysis. *PLoS One* 11 (3):e0151134. doi: 10.1371/journal.pone.0151134.

Hui, C., X. Qi, Z. Qianyong, P. Xiaoli, Z. Jundong, and M. Mantian. 2013. Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. *PloS One* 8 (1):e54318. doi: 10.1371/journal.pone.0054318.

Huntzinger, E., and E. Izaurralde. 2011. Gene silencing by microRNAs: Contributions of translational repression and mRNA decay. *Nature Reviews Genetics* 12 (2):99–110. doi: 10.1038/nrg2936.

Hutvágner, G., J. McLachlan, A. E. Pasquinelli, É. Bálint, T. Tuschl, and P. D. Zamore. 2001. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science (New York, N.Y.)* 293 (5531):834–8. doi: 10.1126/science.1062961.

Im, H. I., and P. J. Kenny. 2012. MicroRNAs in neuronal function and dysfunction. *Trends in Neurosciences* 35 (5):325–34. doi: 10.1016/j.tins.2012.01.004.

Iwashina, T. 2015. Contribution to flower colors of flavonoids including anthocyanins: A review. *Natural Product Communications* 10 (3):1934578X1501000–44. doi: 10.1177/1934578X1501000335.

Jafarpour-Sadegh, F., V. Montazeri, A. Adili, A. Esfehani, M. R. Rashidi, and S. Pirouzpanah. 2017. Consumption of fresh yellow onion ameliorates hyperglycemia and insulin resistance in breast cancer patients during doxorubicin-based chemotherapy: A randomized controlled clinical trial. *Integrative Cancer Therapies* 16 (3):276–89. doi: 10.1177/1534735416656915.

Jatoi, A., N. Ellison, P. A. Burch, J. A Sloan, S. R. Dakhil, P. Novotny, W. Tan, T. R. Fitch, K. M. Rowland, C. Y. Young, et al. 2003. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer* 97 (6):1442–46. doi: 10.1002/cncr.11200.

Ji, P., S. Diederichs, W. Wang, S. Böing, R. Metzger, P. M. Schneider, N. Tidow, B. Brandt, H. Buerger, E. Bulk, et al. 2003. MALAT-1, a novel noncoding RNA, and thymosin β4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 22 (39):8031–41. doi: 10.1038/sj.onc.1206928.

Ji, B. T., W. H. Chow, A. W. Hsing, J. K. McLaughlin, Q. Dai, Y. T. Gao, W. J. Blot, and J. F. Fraumeni Jr. 1997. Green tea consumption and the risk of pancreatic and colorectal cancers. *International Journal of Cancer* 70 (3):255–58. doi: 10.1002/(SICI)1097-0215(19970127)70:3<255::AID-IJC1>3.0.CO;2-W.

Jian, L., L. P. Xie, A. H. Lee, and C. W. Binns. 2004. Protective effect of green tea against prostate cancer: A case-control study in southeast China. *International Journal of Cancer* 108 (1):130–35. doi: 10.1002/ijc.11550.

Kado, K., A. Forsyth, P. R. Patel, and J. A. Schwartz. 2012. Dietary supplements and natural products in breast cancer trials. *Frontiers in Bioscience* E4 (1):546–67. doi: 10.2741/e399.

Kanwal, R., M. Datt, X. Liu, and S. Gupta. 2016. Dietary flavones as dual inhibitors of DNA methyltransferases and histone methyltransferases. *PLoS One* 11 (9):e0162956. doi: 10.1371/journal.pone.0162956.

Kanwal, R., and S. Gupta. 2012. Epigenetic modifications in cancer. *Clinical Genetics* 81 (4):303–11. doi: 10.1111/j.1399-0004.2011.01809.x.

Kasala, E. R., L. N. Bodduluru, C. C. Barua, and R. Gogoi. 2016. Antioxidant and antitumor efficacy of Luteolin, a dietary flavone on benzo(a)pyrene-induced experimental lung carcinogenesis. *Biomedicine & Pharmacotherapy* 82:568–77. doi: 10.1016/j.biopha.2016.05.042.

Kashyap, D., A. Sharma, K. Sak, H. S. Tuli, H. S. Buttar, and A. Bishayee. 2018. Fisetin: A bioactive phytochemical with potential for cancer prevention and pharmacotherapy. *Life Sciences* 194:75–87. doi: 10.1016/j.lfs.2017.12.005.

Kauntz, H., S. Bousserouel, F. Gossé, and F. Raul. 2013. Epigenetic effects of the natural flavonolignan silibinin on colon adenocarcinoma cells and their derived metastatic cells. *Oncology Letters* 5 (4):1273–7. doi: 10.3892/ol.2013.1190.

Ketting, R. F., S. E. Fischer, E. Bernstein, T. Sijen, G. J. Hannon, and R. H. Plasterk. 2001. Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in C. elegans. *Genes & Development* 15 (20):2654–9. doi: 10.1101/gad.927801.

Khan, N., D. N. Syed, N. Ahmad, and H. Mukhtar. 2013. Fisetin: A dietary antioxidant for health promotion. *Antioxidants & Redox Signaling* 19 (2):151–62. doi: 10.1089/ars.2012.4901.

Kikuno, N., H. Shiina, S. Urakami, K. Kawamoto, H. Hirata, Y. Tanaka, S. Majid, M. Igawa, and R. Dahiya. 2008. Genistein mediated histone acetylation and demethylation activate tumor suppressor genes in prostate cancer. *International Journal of Cancer* 123 (3):552–60. doi: 10.1002/ijc.23590.

Kim, H. J., J. H. Kim, E. K. Chie, P. Da Young, I. A. Kim, and I. H. Kim. 2012. DNMT (DNA methyltransferase) inhibitors radiosensitize human cancer cells by suppressing DNA repair activity. *Radiation Oncology* 7 (1):39. doi: 10.1186/1748-717X-7-39.

Knight, S. W., and B. L. Bass. 2001. A role for the RNase III enzyme DCR-1 in RNA interference and germ line development in Caenorhabditis elegans. *Science* 293 (5538):2269–71. doi: 10.1126/science.1062039.

Kouzarides, T. 2007. Chromatin modifications and their function. *Cell* 128 (4):693–705. doi: 10.1016/j.cell.2007.02.005.

Kroonen, J., M. Artesi, V. Capraro, M.-T. Nguyen-Khac, M. Willems, A. Chakravarti, V. Bours, and P. A. Robe. 2012. Casein kinase 2 inhibition modulates the DNA damage response but fails to radiosensitize malignant glioma cells. *International Journal of Oncology* 41 (2):776–82. doi: 10.3892/ijo.2012.1489.

Kwon, Y. 2017. Luteolin as a potential preventive and therapeutic candidate for Alzheimer's disease. *Experimental Gerontology* 95:39–43. doi: 10.1016/j.exger.2017.05.014.

Lan, F., and Y. Shi. 2009. Epigenetic regulation: Methylation of histone and non-histone proteins. *Science in China Series C: Life Sciences* 52 (4):311–22. doi: 10.1007/s11427-009-0054-z.

Lau, N. C., L. P. Lim, E. G. Weinstein, and D. P. Bartel. 2001. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. *Science* 294 (5543):858–62. doi: 10.1126/science.1065062.

Lee, J. H., T. O. Khor, L. Shu, Z. Y. Su, F. Fuentes, and A. N. T. Kong. 2013. Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression. *Pharmacology & Therapeutics* 137 (2):153–71. doi: 10.1016/j.pharmthera.2012.09.008.

Lee, J. Y., and G. Kong. 2016. Roles and epigenetic regulation of epithelial–mesenchymal transition and its transcription factors in cancer initiation and progression. *Cellular and Molecular Life Sciences* 73 (24):4643–60. doi: 10.1007/s00018-016-2313-z.

Lee, W. J., Y. R. Chen, and T. H. Tseng. 2011. Quercetin induces FasL-related apoptosis, in part, through promotion of histone H3 acetylation in human leukemia HL-60 cells. *Oncology Reports* 25:583–91. doi: 10.3892/or.2010.1097.

Lee, W. J., J. Y. Shim, and B. T. Zhu. 2005. Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids.

Molecular Pharmacology 68 (4):1018–30. doi: 10.1124/mol.104.008367.

Li, B., M. Carey, and J. L. Workman. 2007. The role of chromatin during transcription. *Cell* 128 (4):707–19. doi: 10.1016/j.cell.2007.01.015.

Li, Q., Y. Shao, X. Zhang, T. Zheng, M. Miao, L. Qin, B. Wang, G. Ye, B. Xiao, J. Guo, et al. 2015. Plasma long noncoding RNA protected by exosomes as a potential stable biomarker for gastric cancer. *Tumor Biology* 36 (3):2007–12. doi: 10.1007/s13277-014-2807-y.

Li, W., J. Zheng, J. Deng, Y. You, H. Wu, N. Li, J. Lu, and Y. Zhou. 2014. Increased levels of the long intergenic non–protein coding RNA POU3F3 promote DNA methylation in esophageal squamous cell carcinoma cells. *Gastroenterology* 146 (7):1714–26. doi: 10.1053/j.gastro.2014.03.002.

Li, W., M. Liu, Y. F. Xu, Y. Feng, J. P. Che, G. C. Wang, and J. H. Zheng. 2014. Combination of quercetin and hyperoside has anticancer effects on renal cancer cells through inhibition of oncogenic microRNA-27a. *Oncology Reports* 31 (1):117–24. doi: 10.3892/or.2013.2811.

Li, X., Z. Wu, X. Fu, and W. Han. 2014. lncRNAs: Insights into their function and mechanics in underlying disorders. *Mutation Research/Reviews in Mutation Research* 762:1–21. doi: 10.1016/j.mrrev.2014.04.002.

Li, Y., L. Liu, L. G. Andrews, and T. O. Tollefsbol. 2009. Genistein depletes telomerase activity through cross-talk between genetic and epigenetic mechanisms. *International Journal of Cancer* 125 (2):286–96. doi: 10.1002/ijc.24398.

Lin, C. W., G. M. Lai, K. C. Chen, T. H. Lin, J. J. Fan, R. L. Hsu, C. M. Chou, C. M. Lin, C. C. Kandaswami, M. T. Lee, et al. 2015. RPS12 increases the invasiveness in cervical cancer activated by c-Myc and inhibited by the dietary flavonoids luteolin and quercetin. *Journal of Functional Foods* 19:236–47. doi: 10.1016/j.jff.2015.09.030.

Lin, F., X. Luo, A. Tsun, Z. Li, D. Li, and B. Li. 2015. Kaempferol enhances the suppressive function of Treg cells by inhibiting FOXP3 phosphorylation. *International Immunopharmacology* 28 (2):859–65. doi: 10.1016/j.intimp.2015.03.044.

Link, A., F. Balaguer, and A. Goel. 2010. Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. *Biochemical Pharmacology* 80 (12):1771–92. doi: 10.1016/j.bcp.2010.06.036.

Liu, B., H. Yu, R. Baiyun, J. Lu, S. Li, Q. Bing, X. Zhang, and Z. Zhang. 2018. Protective effects of dietary luteolin against mercuric chloride-induced lung injury in mice: Involvement of AKT/Nrf2 and NF-κB pathways. *Food and Chemical Toxicology* 113:296–302. doi: 10.1016/j.fct.2018.02.003.

Long, M. D., D. J. Smiraglia, and M. J. Campbell. 2017. The genomic impact of DNA CpG methylation on gene expression; relationships in prostate cancer. *Biomolecules* 7 (4):15. doi: 10.3390/biom7010015.

Lou, G., Y. Liu, S. Wu, J. Xue, F. Yang, H. Fu, M. Zheng, and Z. Chen. 2015. The p53/miR-34a/SIRT1 positive feedback loop in quercetin-induced apoptosis. *Cellular Physiology and Biochemistry* 35 (6):2192–202. doi: 10.1159/000374024.

Lu, L., Y. Wang, R. Ou, Q. Feng, L. Ji, H. Zheng, Y. Guo, X. Qi, A.-N T. Kong, Z. Liu, et al. 2018. DACT2 epigenetic stimulator exerts dual efficacy for colorectal cancer prevention and treatment. *Pharmacological Research* 129:318–28. doi: 10.1016/j.phrs.2017.11.032.

Lu, W., C. Lin, T. D. King, H. Chen, R. C. Reynolds, and Y. Li. 2012. Silibinin inhibits Wnt/β-catenin signaling by suppressing Wnt co-receptor LRP6 expression in human prostate and breast cancer cells. *Cellular Signalling* 24 (12):2291–6. doi: 10.1016/j.cellsig.2012.07.009.

Lujambio, A., and S. W. Lowe. 2012. The microcosmos of cancer. *Nature* 482 (7385):347–55. doi: 10.1038/nature10888.

Lund, E., S. Güttinger, A. Calado, J. E. Dahlberg, and U. Kutay. 2004. Nuclear export of microRNA precursors. *Science* 303 (5654):95–8. doi: 10.1126/science.1090599.

MacRae, I. J., K. Zhou, and J. A. Doudna. 2007. Structural determinants of RNA recognition and cleavage by Dicer. *Nature Structural & Molecular Biology* 14 (10):934–40. doi: 10.1038/nsmb1293.

Mahmood, N., and S. A. Rabbani. 2019. DNA methylation readers and cancer: Mechanistic and therapeutic applications. *Frontiers in Oncology* 9:489. doi: 10.3389/fonc.2019.00489.

Majumdar, D., K.-H. Jung, H. Zhang, S. Nannapaneni, X. Wang, A. R. M. R. Amin, Z. Chen, Z. Chen, and D. M. Shin. 2014. Luteolin nanoparticle in chemoprevention: In vitro and in vivo anticancer activity. *Cancer Prevention Research* 7 (1):65–73. doi: 10.1158/1940-6207.CAPR-13-0230.

Mandery, K., K. Bujok, I. Schmidt, M. Keiser, W. Siegmund, B. Balk, J. König, M. F. Fromm, and H. Glaeser. 2010. Influence of the flavonoids apigenin, kaempferol, and quercetin on the function of organic anion transporting polypeptides 1A2 and 2B1. *Biochemical Pharmacology* 80 (11):1746–53. doi: 10.1016/j.bcp.2010.08.008.

Manzo-Merino, J., A. Contreras-Paredes, E. Vázquez-Ulloa, L. Rocha-Zavaleta, A. M. Fuentes-Gonzalez, and M. Lizano. 2014. The role of signaling pathways in cervical cancer and molecular therapeutic targets. *Archives of Medical Research* 45 (7):525–39. doi: 10.1016/j.arcmed.2014.10.008.

Martin, C., and Y. Zhang. 2005. The diverse functions of histone lysine methylation. *Nature Reviews Molecular Cell Biology* 6 (11):838–49. doi: 10.1038/nrm1761.

Martínez-Montemayor, M. M., E. Otero-Franqui, J. Martinez, A. De La Mota-Peynado, L. A. Cubano, and S. Dharmawardhane. 2010. Individual and combined soy isoflavones exert differential effects on metastatic cancer progression. *Clinical & Experimental Metastasis* 27 (7):465–80. doi: 10.1007/s10585-010-9336-x.

Mateen, S., K. Raina, C. Agarwal, D. Chan, and R. Agarwal. 2013. Silibinin synergizes with histone deacetylase and DNA methyltransferase inhibitors in upregulating E-cadherin expression together with inhibition of migration and invasion of human non-small cell lung cancer cells. *Journal of Pharmacology and Experimental Therapeutics* 345 (2):206–14. doi: 10.1124/jpet.113.203471.

Mateen, S., K. Raina, A. K. Jain, C. Agarwal, D. Chan, and R. Agarwal. 2012. Epigenetic modifications and p21-cyclin B1 nexus in anticancer effect of histone deacetylase inhibitors in combination with silibinin on non-small cell lung cancer cells. *Epigenetics* 7 (10):1161–72. doi: 10.4161/epi.22070.

McClure, J. J., X. Li, and C. J. Chou. 2018. Chapter six: Advances and challenges of HDAC inhibitors in cancer therapeutics. In *Advances in cancer research*, eds. K. D. Tew and P. B. Fisher, 183–211. Cambridge, MA: Academic Press.

McGrath, J., and P. Trojer. 2015. Targeting histone lysine methylation in cancer. *Pharmacology & Therapeutics* 150:1–22. doi: 10.1016/j.pharmthera.2015.01.002.

Meeran, S. M., S. N. Patel, T. H. Chan, and T. O. Tollefsbol. 2011. A novel prodrug of epigallocatechin-3-gallate: Differential epigenetic hTERT repression in human breast cancer cells. *Cancer Prevention Research* 4 (8):1243–54. doi: 10.1158/1940-6207.CAPR-11-0009.

Michalak, E. M., and J. E. Visvader. 2016. Dysregulation of histone methyltransferases in breast cancer–Opportunities for new targeted therapies? *Molecular Oncology* 10 (10):1497–515. doi: 10.1016/j.molonc.2016.09.003.

Milisav, I., B. Poljšak, and S. Ribarič. 2017. Reduced risk of apoptosis: Mechanisms of stress responses. *Apoptosis* 22 (2):265–83. doi: 10.1007/s10495-016-1317-3.

Miltonprabu, S., M. Tomczyk, K. Skalicka-Woźniak, L. Rastrelli, M. Daglia, S. F. Nabavi, S. M. Alavian, and S. M. Nabavi. 2017. Hepatoprotective effect of quercetin: From chemistry to medicine. *Food and Chemical Toxicology* 108:365–74. doi: 10.1016/j.fct.2016.08.034.

Mohammadi, V., S. Dehghani, B. Larijani, and L. Azadbakht. 2016. Ovarian cancer risk and nonisoflavone flavonoids intake: A systematic review of epidemiological studies. *Journal of Research in Medical Sciences* 21 (1):123. doi: 10.4103/1735-1995.196605.

Morera, L., M. Lübbert, and M. Jung. 2016. Targeting histone methyltransferases and demethylases in clinical trials for cancer therapy. *Clinical Epigenetics* 8 (1):57. doi: 10.1186/s13148-016-0223-4.

Moseley, V. R., J. Morris, R. W. Knackstedt, and M. J. Wargovich. 2013. Green tea polyphenol epigallocatechin 3-gallate, contributes to the degradation of DNMT3A and HDAC3 in HCT 116 human colon cancer cells. *Anticancer Research* 33:5325–33.

Nabavi, S. F., G. L. Russo, M. Daglia, and S. M. Nabavi. 2015. Role of quercetin as an alternative for obesity treatment: You are what you

eat! *Food Chemistry* 179:305–10. doi: 10.1016/j.foodchem.2015.02.006.

Nagle, D. G., D. Ferreira, and Y. D. Zhou. 2006. Epigallocatechin-3-gallate (EGCG): Chemical and biomedical perspectives. *Phytochemistry* 67 (17):1849–55. doi: 10.1016/j.phytochem.2006.06.020.

Neuhouser, M. L. 2004. Dietary flavonoids and cancer risk: Evidence from human population studies. *Nutrition and Cancer* 50 (1):1–7. doi: 10.1207/s15327914nc5001_1.

Ng, S., W. Yue, U. Oppermann, and R. Klose. 2009. Dynamic protein methylation in chromatin biology. *Cellular and Molecular Life Sciences* 66 (3):407–22. doi: 10.1007/s00018-008-8303-z.

Nguyen, A. V., M. Martinez, M. J. Stamos, M. P. Moyer, K. Planutis, C. Hope, and R. F. Holcombe. 2009. Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer. *Cancer Management and Research* 1 (25). doi: 10.2147/CMAR.S4544.

Nishikawaji, T., Y. Akiyama, S. Shimada, K. Kojima, T. Kawano, Y. Eishi, Y. Yuasa, and S. Tanaka. 2016. Oncogenic roles of the SETDB2 histone methyltransferase in gastric cancer. *Oncotarget* 7 (41):67251. doi: 10.18632/oncotarget.11625.

Nothlings, U., S. Murphy, L. Wilkens, B. Henderson, and L. Kolonel. 2007. Flavonols and pancreatic cancer risk: The multiethnic cohort study. *American Journal of Epidemiology* 166 (8):924–31. doi: 10.1093/aje/kwm172.

Nwaeburu, C. C., A. Abukiwan, Z. Zhao, and I. Herr. 2017. Quercetin-induced miR-200b-3p regulates the mode of self-renewing divisions in pancreatic cancer. *Molecular Cancer* 16 (1):23. doi: 10.1186/s12943-017-0589-8.

Okamura, K., N. Liu, and E. C. Lai. 2009. Distinct mechanisms for microRNA strand selection by Drosophila Argonautes. *Molecular Cell* 36 (3):431–44. doi: 10.1016/j.molcel.2009.09.027.

Oloumi, A., T. McPhee, and S. Dedhar. 2004. Regulation of E-cadherin expression and β-catenin/Tcf transcriptional activity by the integrin-linked kinase. *Biochimica et Biophysica Acta (Bba) - Molecular Cell Research* 1691 (1):1–15. doi: 10.1016/j.bbamcr.2003.12.002.

Orhan, I. E., S. F. Nabavi, M. Daglia, G. C. Tenore, K. Mansouri, and S. M. Nabavi. 2015. Naringenin and atherosclerosis: A review of literature. *Current Pharmaceutical Biotechnology* 16 (3):245–51. doi: 10.2174/1389201015666141202110216.

Palacz-Wrobel, M., P. Borkowska, M. Paul-Samojedny, M. Kowalczyk, A. Fila-Danilow, R. Suchanek-Raif, and J. Kowalski. 2017. Effect of apigenin, kaempferol and resveratrol on the gene expression and protein secretion of tumor necrosis factor alpha (TNF-α) and interleukin-10 (IL-10) in RAW-264.7 macrophages. *Biomedicine & Pharmacotherapy* 93:1205–12. doi: 10.1016/j.biopha.2017.07.054.

Pan, M. H., Y. S. Chiou, L. H. Chen, and C. T. Ho. 2015. Breast cancer chemoprevention by dietary natural phenolic compounds: Specific epigenetic related molecular targets. *Molecular Nutrition & Food Research* 59 (1):21–35. doi: 10.1002/mnfr.201400515.

Pandey, M., P. Kaur, S. Shukla, A. Abbas, P. Fu, and S. Gupta. 2012. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: In vitro and in vivo study. *Molecular Carcinogenesis* 51 (12):952–62. doi: 10.1002/mc.20866.

Pandey, M., S. Shukla, and S. Gupta. 2010. Promoter demethylation and chromatin remodeling by green tea polyphenols leads to re-expression of GSTP1 in human prostate cancer cells. *International Journal of Cancer* 126:2520–33. doi: 10.1002/ijc.24988.

Pantuck, A. J., J. T. Leppert, N. Zomorodian, W. Aronson, J. Hong, R. J. Barnard, N. Seeram, H. Liker, H. Wang, R. Elashoff, et al. 2006. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clinical Cancer Research* 12 (13):4018–26. doi: 10.1158/1078-0432.CCR-05-2290.

Park, H. H., S. Lee, J. M. Oh, M. S. Lee, K. H. Yoon, B. H. Park, J. W. Kim, H. Song, and S. H. Kim. 2007. Anti-inflammatory activity of fisetin in human mast cells (HMC-1). *Pharmacological Research* 55 (1):31–7. doi: 10.1016/j.phrs.2006.10.002.

Park, S. H., J. Kim, K. H. Do, J. Park, C. G. Oh, H. J. Choi, B. G. Song, S. J. Lee, Y. S. Kim, Y. Moon, et al. 2014. Activating transcription factor 3-mediated chemo-intervention with cancer chemokines in a non-canonical pathway under endoplasmic reticulum stress. *Journal of Biological Chemistry* 289 (39):27118–33. doi: 10.1074/jbc.M114.568717.

Patel, K. R., V. A. Brown, D. J. Jones, R. G. Britton, D. Hemingway, A. S. Miller, K. P. West, T. D. Booth, M. Perloff, et al. 2010. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer Research* 70 (19):7392–99. doi: 10.1158/0008-5472.CAN-10-2027.

Pauli, A., E. Valen, M. F. Lin, M. Garber, N. L. Vastenhouw, J. Z. Levin, L. Fan, A. Sandelin, J. L. Rinn, A. Regev, et al. 2012. Systematic identification of long noncoding RNAs expressed during zebrafish embryogenesis. *Genome Research* 22 (3):577–91. doi: 10.1101/gr.133009.111.

Petrick, J. L., S. E. Steck, P. T. Bradshaw, K. F. Trivers, P. E. Abrahamson, L. S. Engel, K. He, W. H. Chow, S. T. Mayne, H. A. Risch, et al. 2015. Dietary intake of flavonoids and oesophageal and gastric cancer: Incidence and survival in the United States of America (USA). *British Journal of Cancer* 112 (7):1291–300. doi: 10.1038/bjc.2015.25.

Peiffer, D. S. 2018. Preparing black raspberry components for their use as cancer therapeutics. *Journal of Berry Research* 8 (4):297–306. doi: 10.3233/JBR-180364.

Pfeifer, G. 2018. Defining driver DNA methylation changes in human cancer. *International Journal of Molecular Sciences* 19 (4):1166. doi: 10.3390/ijms19041166.

Pietrocola, F., G. Mariño, D. Lissa, E. Vacchelli, S. A. Malik, M. Niso-Santano, N. Zamzami, L. Galluzzi, M. C. Maiuri, G. Kroemer, et al. 2012. Pro-autophagic polyphenols reduce the acetylation of cytoplasmic proteins. *Cell Cycle* 11 (20):3851–60. [Mismatch] doi: 10.4161/cc.22027.

Portela, A., and M. Esteller. 2010. Epigenetic modifications and human disease. *Nature Biotechnology* 28 (10):1057–68. doi: 10.1038/nbt.1685.

Pratheeshkumar, P., Y.-O. Son, S. P. Divya, L. Wang, L. Turcios, R. V. Roy, J. A. Hitron, D. Kim, J. Dai, P. Asha, et al. 2017. Quercetin inhibits Cr (VI)-induced malignant cell transformation by targeting miR-21-PDCD4 signaling pathway. *Oncotarget* 8 (32):52118. doi: 10.18632/oncotarget.10130.

Prior, R. L., and G. Cao. 2000. Antioxidant phytochemicals in fruits and vegetables: Diet and health implications. *HortScience* 35 (4):588–92. doi: 10.21273/HORTSCI.35.4.588.

Rajendran, P., E. Ho, D. E. Williams, and R. H. Dashwood. 2011. Dietary phytochemicals, HDAC inhibition, and DNA damage/repair defects in cancer cells. *Clinical Epigenetics* 3 (1):4. doi: 10.1186/1868-7083-3-4.

Ratovitski, E. A. 2017. Anticancer natural compounds as epigenetic modulators of gene expression. *Current Genomics* 18 (2):175–205. doi: 10.2174/1389202917666160803165229.

Razin, A., and A. D. Riggs. 1980. DNA methylation and gene function. *Science* 210 (4470):604–10. doi: 10.1126/science.6254144.

Rietjens, I. M., A. M. Sotoca, J. Vervoort, and J. Louisse. 2013. Mechanisms underlying the dualistic mode of action of major soy isoflavones in relation to cell proliferation and cancer risks. *Molecular Nutrition & Food Research* 57 (1):100–13. doi: 10.1002/mnfr.201200439.

Rimbach, G., C. Boesch-Saadatmandi, J. Frank, D. Fuchs, U. Wenzel, H. Daniel, W. L. Hall, and P. D. Weinberg. 2008. Dietary isoflavones in the prevention of cardiovascular disease–A molecular perspective. *Food and Chemical Toxicology* 46 (4):1308–19. doi: 10.1016/j.fct.2007.06.029.

Rinn, J. L., and H. Y. Chang. 2012. Genome regulation by long noncoding RNAs. *Annual Review of Biochemistry* 81 (1):145–66. doi: 10.1146/annurev-biochem-051410-092902.

Rodríguez-Paredes, M., and M. Esteller. 2011. Cancer epigenetics reaches mainstream oncology. *Nature Medicine* 17 (3):330–9. doi: 10.1038/nm.2305.

Romagnolo, D. F., and O. I. Selmin. 2012. Flavonoids and cancer prevention: A review of the evidence. *Journal of Nutrition in Gerontology and Geriatrics* 31 (3):206–38. doi: 10.1080/21551197.2012.702534.

Sak, K., and H. Everaus. 2015. Epidemiological evidences on dietary flavonoids and breast cancer risk: A narrative review. *Asian Pacific Journal of Cancer Prevention* 16 (12):4843–7. doi: 10.7314/APJCP.2015.16.12.4843.

Schneider-Stock, R., A. Ghantous, K. Bajbouj, M. Saikali, and N. Darwiche. 2012. Epigenetic mechanisms of plant-derived anticancer drugs. *Frontiers in Bioscience* 17 (1):129–73. doi: 10.2741/3919.

Schnekenburger, M., M. Dicato, and M. Diederich. 2014. Plant-derived epigenetic modulators for cancer treatment and prevention. *Biotechnology Advances* 32 (6):1123–32. doi: 10.1016/j.biotechadv.2014.03.009.

Seelinger, G., I. Merfort, and C. M. Schempp. 2008. Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. *Planta Medica* 74 (14):1667–77. doi: 10.1055/s-0028-1088314.

Seet, B. T., I. Dikic, M. M. Zhou, and T. Pawson. 2006. Reading protein modifications with interaction domains. *Nature Reviews Molecular Cell Biology* 7 (7):473–83. doi: 10.1038/nrm1960.

Shankar, E., R. Kanwal, M. Candamo, and S. Gupta. 2016. Dietary phytochemicals as epigenetic modifiers in cancer: Promise and challenges. *Proceedings of the Seminars in Cancer Biology* 40-41:82–99. doi: 10.1016/j.semcancer.2016.04.002.

Sharma, A., D. Kashyap, K. Sak, H. S. Tuli, and A. K. Sharma. 2018. Therapeutic charm of quercetin and its derivatives: A review of research and patents. *Pharmaceutical Patent Analyst* 7 (1):15–32. doi: 10.4155/ppa-2017-0030.

Shi, L. B., P. F. Tang, W. Zhang, Y. P. Zhao, L. C. Zhang, and H. Zhang. 2016. Naringenin inhibits spinal cord injury-induced activation of neutrophils through miR-223. *Gene* 592 (1):128–33. doi: 10.1016/j.gene.2016.07.037.

Shiohama, A., T. Sasaki, S. Noda, S. Minoshima, and N. Shimizu. 2003. Molecular cloning and expression analysis of a novel gene DGCR8 located in the DiGeorge syndrome chromosomal region. *Biochemical and Biophysical Research Communications* 304 (1):184–90. doi: 10.1016/S0006-291X(03)00554-0.

Shukla, S., and S. M. Meeran. 2014. Epigenetics of cancer stem cells: Pathways and therapeutics. *Biochimica et Biophysica Acta (BBA) - General Subjects* 1840 (12):3494–502. doi: 10.1016/j.bbagen.2014.09.017.

Si, Y., J. Liu, H. Shen, C. Zhang, Y. Wu, Y. Huang, Z. Gong, J. Xue, and T. Liu. 2019. Fisetin decreases TET1 activity and CCNY/CDK16 promoter 5hmC levels to inhibit the proliferation and invasion of renal cancer stem cell. *Journal of Cellular and Molecular Medicine* 23 (2):1095–105. doi: 10.1111/jcmm.14010.

Singh, B. N., S. Shankar, and R. K. Srivastava. 2011. Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. *Biochemical Pharmacology* 82 (12):1807–21. doi: 10.1016/j.bcp.2011.07.093.

Smith, C. J., and K. K. Ryckman. 2015. Epigenetic and developmental influences on the risk of obesity, diabetes, and metabolic syndrome. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 8: 295.

Srinivasa, H., M. Bagul, H. Padh, and M. Rajani. 2004. A rapid densitometric method for the quantification of luteolin in medicinal plants using HPTLC. *Chromatographia* 60 (1–2):131–4. doi: 10.1365/s10337-004-0302-0.

Stresemann, C., B. Brueckner, T. Musch, H. Stopper, and F. Lyko. 2006. Functional diversity of DNA methyltransferase inhibitors in human cancer cell lines. *Cancer Research* 66 (5):2794–800. doi: 10.1158/0008-5472.CAN-05-2821.

Su, D., R. Zhang, F. Hou, J. Chi, F. Huang, S. Yan, L. Liu, Y. Deng, Z. Wei, and M. Zhang. 2017. Lychee pulp phenolics ameliorate hepatic lipid accumulation by reducing miR-33 and miR-122 expression in mice fed a high-fat diet. *Food & Function* 8 (2):808–15. doi: 10.1039/C6FO01507G.

Subramaniam, D., R. Thombre, A. Dhar, and S. Anant. 2014. DNA methyltransferases: A novel target for prevention and therapy. *Frontiers in Oncology* 4:80. doi: 10.3389/fonc.2014.00080.

Tabara, H., M. Sarkissian, W. G. Kelly, J. Fleenor, A. Grishok, L. Timmons, A. Fire, and C. C. Mello. 1999. The rde-1 gene, RNA interference, and transposon silencing in *C. elegans*. *Cell* 99 (2): 123–32. doi: 10.1016/S0092-8674(00)81644-X.

Tang, N. P., B. Zhou, B. Wang, R. B. Yu, and J. Ma. 2009. Flavonoids intake and risk of lung cancer: A meta-analysis. *Japanese Journal of Clinical Oncology* 39 (6):352–59. doi: 10.1093/jjco/hyp028.

Tao, S. F., H. F. He, and Q. Chen. 2015. Quercetin inhibits proliferation and invasion acts by up-regulating miR-146a in human breast cancer cells. *Molecular and Cellular Biochemistry* 402 (1–2):93–100. doi: 10.1007/s11010-014-2317-7.

Taverna, S. D., H. Li, A. J. Ruthenburg, C. D. Allis, and D. J. Patel. 2007. How chromatin-binding modules interpret histone modifications: Lessons from professional pocket pickers. *Nature Structural & Molecular Biology* 14 (11):1025–40. doi: 10.1038/nsmb1338.

Thakur, V. S., G. Deb, M. A. Babcook, and S. Gupta. 2014. Plant phytochemicals as epigenetic modulators: Role in cancer chemoprevention. *The AAPS Journal* 16 (1):151–63. doi: 10.1208/s12248-013-9548-5.

Thomas, M., and P. Marcato. 2018. Epigenetic modifications as biomarkers of tumor development, therapy response, and recurrence across the cancer care continuum. *Cancers* 10 (4):101. doi: 10.3390/cancers10040101.

Tse, J. W. T., L. J. Jenkins, F. Chionh, and J. M. Mariadason. 2017. Aberrant DNA methylation in colorectal cancer: What should we target? *Trends in Cancer* 3 (10):698–712. doi: 10.1016/j.trecan.2017.08.003.

Tseng, T.-H., M.-H. Chien, W.-L. Lin, Y.-C. Wen, J.-M. Chow, C.-K. Chen, T.-C. Kuo, and W.-J. Lee. 2017. Inhibition of MDA-MB-231 breast cancer cell proliferation and tumor growth by apigenin through induction of G2/M arrest and histone H3 acetylation-mediated p21WAF1/CIP1 expression. *Environmental Toxicology* 32 (2): 434–44. doi: 10.1002/tox.22247.

Ullah, H., and H. Khan. 2018. Anti-Parkinson potential of silymarin: Mechanistic insight and therapeutic standing. *Frontiers in Pharmacology* 9doi: 10.3389/fphar.2018.00422. [InsertedFromOnline

Vardi, A., R. Bosviel, N. Rabiau, M. Adjakly, S. Satih, P. Dechelotte, J.-P. Boiteux, L. Fontana, Y.-J. Bignon, L. Guy, et al. 2010. Soy phytoestrogens modify DNA methylation of GSTP1, RASSF1A, EPH2 and BRCA1 promoter in prostate cancer cells. *In Vivo (Athens, Greece)* 24 (4):393–400.

Varier, R. A., and H. M. Timmers. 2011. Histone lysine methylation and demethylation pathways in cancer. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* 1815 (1):75–89. doi: 10.1016/j.bbcan.2010.10.002.

Vendrely, V., E. Peuchant, E. Buscail, I. Moranvillier, B. Rousseau, A. Bedel, A. Brillac, H. de Verneuil, F. Moreau-Gaudry, S. Dabernat, et al. 2017. Resveratrol and capsaicin used together as food complements reduce tumor growth and rescue full efficiency of low dose gemcitabine in a pancreatic cancer model. *Cancer Letters* 390: 91–102. doi: 10.1016/j.canlet.2017.01.002.

Venturelli, S., T. W. Sinnberg, A. Berger, S. Noor, M. P. Levesque, A. BöCker, H. Niessner, U. M. Lauer, M. Bitzer, C. Garbe, et al. 2014. Epigenetic impacts of ascorbate on human metastatic melanoma cells. *Frontiers in Oncology* 4:227. doi: 10.3389/fonc.2014.00227.

Waddington, C. H. 1942. The epigenotype. *Endeavour* 1:18–20.

Wahlestedt, C. 2013. Targeting long non-coding RNA to therapeutically upregulate gene expression. *Nature Reviews Drug Discovery* 12 (6):433–46. doi: 10.1038/nrd4018.

Wai Kan Yeung, A., B. B. Aggarwal, D. Barreca, M. Battino, T. Belwal, O. K. Horbańczuk, I. Berindan-Neagoe, A. Bishayee, M. Daglia, H. P. Devkota, et al. 2018. Dietary natural products and their potential to influence health and disease including animal model studies. *Animal Science Papers & Reports* 36 (4):345–58.

Wainwright, E. N., and P. Scaffidi. 2017. Epigenetics and cancer stem cells: Unleashing, hijacking, and restricting cellular plasticity. *Trends in Cancer* 3 (5):372–86. doi: 10.1016/j.trecan.2017.04.004.

Wang, J., R. Ma, W. Ma, J. Chen, J. Yang, Y. Xi, and Q. Cui. 2016. LncDisease: A sequence based bioinformatics tool for predicting lncRNA-disease associations. *Nucleic Acids Research* 44 (9):e90. doi: 10.1093/nar/gkw093.

Wang, L.-S., C.-T. Kuo, S.-J. Cho, C. Seguin, J. Siddiqui, K. Stoner, Y.-I. Weng, T. H.-M. Huang, J. Tichelaar, M. Yearsley, et al. 2013. Black raspberry-derived anthocyanins demethylate tumor suppressor genes through the inhibition of DNMT1 and DNMT3B in colon cancer cells. *Nutrition and Cancer* 65 (1):118–25. doi: 10.1080/01635581.2013.741759.

Wang, L.-S., M. Arnold, Y.-W. Huang, C. Sardo, C. Seguin, E. Martin, T. H.-M. Huang, K. Riedl, S. Schwartz, W. Frankel, et al. 2011. Modulation of genetic and epigenetic biomarkers of colorectal cancer in humans by black raspberries: A phase I pilot study. *Clinical Cancer Research* 17 (3):598–610. doi: 10.1158/1078-0432.CCR-10-1260.

Wang, P., T. Phan, D. Gordon, S. Chung, S. M. Henning, and J. V. Vadgama. 2015. Arctigenin in combination with quercetin synergistically enhances the antiproliferative effect in prostate cancer cells. *Molecular Nutrition & Food Research* 59 (2):250–61. doi: 10.1002/mnfr.201400558.

Wang, S., M. Cao, S. Xu, J. Zhang, Z. Wang, X. Mao, X. Yao, and C. Liu. 2017. Effect of luteolin on inflammatory responses in RAW264.7 macrophages activated with LPS and IFN-γ. *Journal of Functional Foods* 32:123–30. doi: 10.1016/j.jff.2017.02.018.

Wang, S., Y. Dong, Y. Zhang, X. Wang, L. Xu, S. Yang, X. Li, H. Dong, L. Xu, L. Su, et al. 2015. DACT2 is a functional tumor suppressor through inhibiting Wnt/β-catenin pathway and associated with poor survival in colon cancer. *Oncogene* 34 (20):2575–85. doi: 10.1038/onc.2014.201.

Wang, Y., S. Juranek, H. Li, G. Sheng, T. Tuschl, and D. J. Patel. 2008. Structure of an argonaute silencing complex with a seed-containing guide DNA and target RNA duplex. *Nature* 456 (7224):921–6. doi: 10.1038/nature07666.

Williams, R. J., J. P. Spencer, and C. Rice-Evans. 2004. Flavonoids: Antioxidants or signalling molecules? *Free Radical Biology and Medicine* 36 (7):838–49. doi: 10.1016/j.freeradbiomed.2004.01.001.

Wirbisky-Hershberger, S. E., O. F. Sanchez, K. A. Horzmann, D. Thanki, C. Yuan, and J. L. Freeman. 2017. Atrazine exposure decreases the activity of DNMTs, global DNA methylation levels, and dnmt expression. *Food and Chemical Toxicology* 109:727–34. doi: 10.1016/j.fct.2017.08.041.

Woo, H. D., and J. Kim. 2013. Dietary flavonoid intake and smoking-related cancer risk: A meta-analysis. *PloS one* 8 (9):e75604. doi: 10.1371/journal.pone.0075604.

World Cancer Research Fund/American Institute for Cancer Research. 2007. *Food, nutrition, physical activity, and the prevention of cancer: A global perspective*. Washington, DC: American Institute for Cancer Research.

Xavier, C. P. R., and C. Pereira-Wilson. 2016. Medicinal plants of the genuses Salvia and Hypericum are sources of anticolon cancer compounds: Effects on PI3K/Akt and MAP kinases pathways. *PharmaNutrition* 4 (2):112–22. doi: 10.1016/j.phanu.2015.11.002.

Xhemalce, B., M. Dawson, and A. Bannister. 2011. Histone modifications. In *Encyclopedia of molecular cell biology and molecular medicine*, ed. R. Meyers. New York, NY: John Wiley and Sons.

Xiang, T., Y. Fan, C. Li, L. Li, Y. Ying, J. Mu, W. Peng, Y. Feng, M. Oberst, K. Kelly, et al. 2016. Dact2 silencing by promoter cpg methylation disrupts its regulation of epithelial-to-mesenchymal transition and cytoskeleton reorganization in breast cancer cells. *Oncotarget* 7 (43):70924–35. doi: 10.18632/oncotarget.12341.

Yan, N., L. Wen, R. Peng, H. Li, H. Liu, H. Peng, Y. Sun, T. Wu, L. Chen, Q. Duan, et al. 2016. Naringenin ameliorated kidney injury through let-7a/TGFBR1 signaling in diabetic nephropathy. *Journal of Diabetes Research* 2016:1–13. doi: 10.1155/2016/8738760.

Yang, X., L. Gao, X. Guo, X. Shi, H. Wu, F. Song, and B. Wang. 2014. A network based method for analysis of lncRNA-disease associations and prediction of lncRNAs implicated in diseases. *PLoS One* 9 (1):e87797. doi: 10.1371/journal.pone.0087797.

Yarmishyn, A. A., and I. V. Kurochkin. 2015. Long noncoding RNAs: A potential novel class of cancer biomarkers. *Frontiers in Genetics* 6:145. doi: 10.3389/fgene.2015.00145.

Yi, R., Y. Qin, I. G. Macara, and B. R. Cullen. 2003. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes & Development* 17 (24):3011–6. doi: 10.1101/gad.1158803.

Yoo, C. B., and P. A. Jones. 2006. Epigenetic therapy of cancer: Past, present and future. *Nature Reviews Drug Discovery* 5 (1):37–50. doi: 10.1038/nrd1930.

Yoo, D. R., Y. H. Jang, Y. K. Jeon, J. Y. Kim, W. Jeon, Y. J. Choi, and M. J. Nam. 2009. Proteomic identification of anti-cancer proteins in luteolin-treated human hepatoma Huh-7 cells. *Cancer Letters* 282 (1):48–54. doi: 10.1016/j.canlet.2009.02.051.

You, J. S., and P. A. Jones. 2012. Cancer genetics and epigenetics: Two sides of the same coin? *Cancer Cell* 22 (1):9–20. doi: 10.1016/j.ccr.2012.06.008.

Youns, M., and W. A. H. Hegazy. 2017. The natural flavonoid fisetin inhibits cellular proliferation of hepatic, colorectal, and pancreatic cancer cells through modulation of multiple signaling pathways. *PLoS One* 12 (1):e0169335. doi: 10.1371/journal.pone.0169335.

Zamora-Ros, R., D. K. Barupal, J. A. Rothwell, M. Jenab, V. Fedirko, I. Romieu, K. Aleksandrova, K. Overvad, C. Kyrø, A. Tjønneland, et al. 2017. Dietary flavonoid intake and colorectal cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort. *International Journal of Cancer* 140 (8):1836–44. doi: 10.1002/ijc.30582.

Zhang, M., E. Linghu, Q. Zhan, T. He, B. Cao, M. V. Brock, J. G. Herman, R. Xiang, and M. Guo. 2016. Methylation of DACT2 accelerates esophageal cancer development by activating Wnt signaling. *Development* 7:17957–69.

Zhang, S., B. Ling, F. Qu, and X. Sun. 2012. Investigation on the interaction between luteolin and calf thymus DNA by spectroscopic techniques. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 97:521–5. doi: 10.1016/j.saa.2012.06.040.

Zhang, X., Q. Guo, J. Chen, and Z. Chen. 2015. Quercetin enhances cisplatin sensitivity of human osteosarcoma cells by modulating microRNA-217-KRAS axis. *Molecules and Cells* 38 (7):638–42. doi: 10.14348/molcells.2015.0037.

Zhang, Y., and H. Chen. 2011. Genistein, an epigenome modifier during cancer prevention. *Epigenetics* 6 (7):888–91. doi: 10.4161/epi.6.7.16315.

Zhang, Y., Q. Li, and H. Chen. 2013. DNA methylation and histone modifications of Wnt genes by genistein during colon cancer development. *Carcinogenesis* 34 (8):1756–63. doi: 10.1093/carcin/bgt129.

Zhou, J., J. Gong, C. Ding, and G. Chen. 2015. Quercetin induces the apoptosis of human ovarian carcinoma cells by upregulating the expression of microRNA-145. *Molecular Medicine Reports* 12 (2):3127–31. doi: 10.3892/mmr.2015.3679.

Zhou, Y., B. Z. Ding, Y. P. Lin, and H. B. Wang. 2018. MiR-34a, as a suppressor, enhance the susceptibility of gastric cancer cell to luteolin by directly targeting HK1. *Gene* 644:56–65. doi: 10.1016/j.gene.2017.10.046.

Zwergel, C., S. Valente, and A. Mai. 2015. DNA methyltransferases inhibitors from natural sources. *Current Topics in Medicinal Chemistry* 16 (7):680–96. doi: 10.2174/1568026615666150825141505.

Zwicker, J. I., B. L. Schlechter, J. D. Stopa, H. A. Liebman, A. Aggarwal, M. Puligandla, T. Caughey, K. A. Bauer, N. Kuemmerle, E. Wong, et al. 2018. Targeting protein disulfide isomerase with the oral flavonoid isoquercetin 47 prevents venous thromboembolism in advanced cancer: Results of a multi-dose, multi-center, phase II clinical trial (CATIQ Study). *American Society of Hematology* 4 (4):125851.