Review

A Benefaction of Flavonoids as Epigenetic Modulators for Effective Cancer Treatment

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A Benefaction of Flavonoids as Epigenetic Modulators for Effective Cancer Treatment

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Simple Summary: Flavonoids are a diverse group of phytocompounds or plant chemicals found in plants and vegetables. It has many potential health benefits. This manuscript mainly focuses on the benefits of flavonoids in epigenetics regulation in cancer. Epigenetics is a study of how cells control their gene activity without modifications in DNA sequence. It mainly involves histone modifications, DNA methylation, and the role of RNA in cancer epigenetics. Then, applications of flavonoids-based compounds and their efficacy in preventing tumor growth and progression by involving many pathways in it. There is a low availability of clinical trials, especially for flavonoids in cancer, but the current status is described in this manuscript.

Abstract: Histone changes that are adjustable and transmitted without altering the DNA sequence are part of epigenetic control. In many disorders, most famously malignancy, abnormal genetic information is seen as a result of mismanagement of typical epigenetic mechanisms. A paradigm change in the diagnosis and treatment of cancer has been brought about by recent discoveries about the processes of epigenetic modifications, chromatin remodeling, and noncoding RNAs implicated in the changed expression patterns of tumor cells. There is a significant increase in the search for drugs that could alter the epigenetic environment altered by tumor cells and benefit from their therapeutic potential. Phytochemicals with a high concentration of naturally produced phenol molecules known as flavonoids can regulate genomic processes. Understanding the precise epigenetic alterations brought on by flavonoid-mediated mechanisms is necessary to develop combination therapy techniques and genomic therapies for cancer. This article aims to thoroughly examine the epigenetic modifications of flavonoids, including their anticancer properties.

Keywords: Cancer; Chemotherapy; DNA methylation; Epigenetic; Flavonoids

1. Introduction

Epigenetics studies how cells control gene activity without changing the DNA sequence itself. Various factors, including environment, behavior, and age, can influence these modifications. With no alterations to the base DNA code, epigenetic modifications are created even during the initial phases of cell diversification. They are permanently inherited across successive dividing cells to produce diverse cellular characteristics [1,2]. As depicted in many studies, chromatin remodeling is

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a component of the genomic control of gene expression. It, therefore, is controlled by processes including gene methylation, histone changes, and the actions of noncoding RNA. Although these epigenetic alterations are necessary for organisms to mature normally, their dysregulation can result in some pathological conditions, such as malignancy [3]. The epigenetics in cancer is presented in Figure 1.

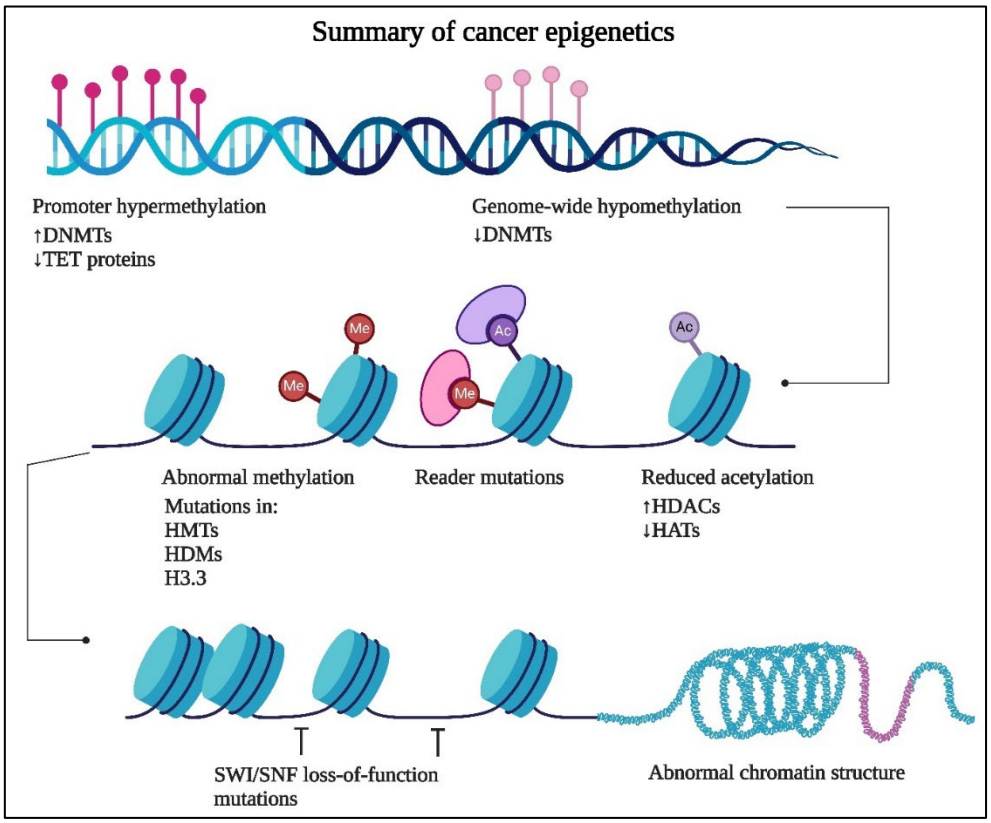

Figure 1. Summary of cancer epigenetics involving promoter hypermethylation, genome-wide hypomethylation resulted into the abnormal methylation which induces abnormal chromatin structure due to loss of function mutation of switch/sucrose nonfermenting (SWI/SNF).

Biologists generally agree that disease can be viewed as just a genetic inevitable. As humans grow, genetic mutations increase in our cells. The changes may occur naturally as a result of mistakes in the replication of DNA, or either chemicals or mechanical gene mutations may bring them on. Thus, the ecological or exogenous variables produce alterations in 90–95% of total cancers, while in the other 10% of the overall cases, the genetic component of malignancy is endogenous [4]. It is fascinating to consider that several gene abnormalities in malignancies are caused by epigenetic modifications that alter the expression pattern of these genes rather than changes in their sequence [5,6]. New advances in epigenetics have brought attention to widespread epigenetic aberrations that can emerge in cancerous cells in the initial phases of cell cycle growth. Epigenetic alterations can be used as new pharmacological targets for such cancer therapy because they are programmable and appear at the onset of cancer development in healthy cells [7,8]. At the same time, the number of new instances of cancer worldwide is 2 million in the year 2024. with approximately 10 million fatalities as a consequence, the number of cancer-related fatalities has been falling since 1991, and the mortality rate has decreased since 2021 [9,10]. The development of targeted therapies is responsible for increased patient survival rates. Chemotherapy drugs, radiation treatment, and immunotherapy are frequently employed for cancer treatment, so these therapies demonstrate great potential [11]. Histone deacetylase antagonists, other epigenetic stimulators, and specific cutting-edge techniques, such as chimeric antigen receptor-engineered immune cells (CART cells), have already been utilized to treat cancers with abnormal epigenetic changes [12]. Unfortunately, the

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majority of cancer treatments, including immune therapeutics, are linked to a variety of adverse reactions [13].

The search for alternative medicines with minimal side effects has, therefore, grown in light of the negative impact that radiotherapy and chemotherapy drugs have on patients. The antitumor activities of phytonutrients are investigated because they best meet this requirement. Anti-carcinogenic components in plant-based products have been shown to prevent cancer through several methods, including immunomodulatory and antioxidant actions. Fascinating reports suggest that phytonutrients can influence how histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) regulate epigenetic activities [14]. An essential family of phytonutrients called flavonoids is linked to altering cancer-related gene expression patterns, as presented in Figure 1 [15]. The role of epigenetic abnormalities in malignancy is first covered in this paper, after which a summary of the potential of flavonoids as chemotherapy and anti-carcinogenic agents is provided. The statistics of epigenetic modulators are presented in Figure 2.

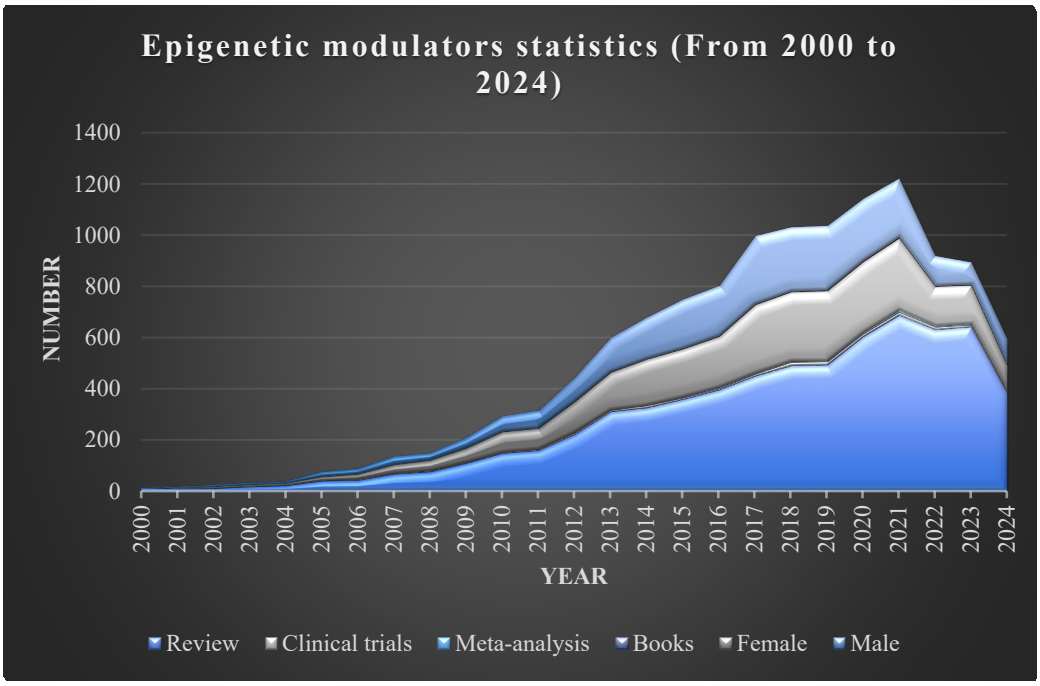

Figure 2. Summary of statistics for epigenetic modulators from the year 2000 to 2024 including number of review articles and books published, number of clinical trials and meta-analysis conducted and gender vise available data.

2. Cancer Epigenetics

Nucleosomes are formed in eukaryotes by wrapping DNA around the core of histones. These nucleosomes can either disappear or permanently assume a compressed state by wrapping themselves over. Various genetic regulation processes regulate how much a gene is transcribed within every cell, most of which disrupt chromatin structure. Refer Figure 3.

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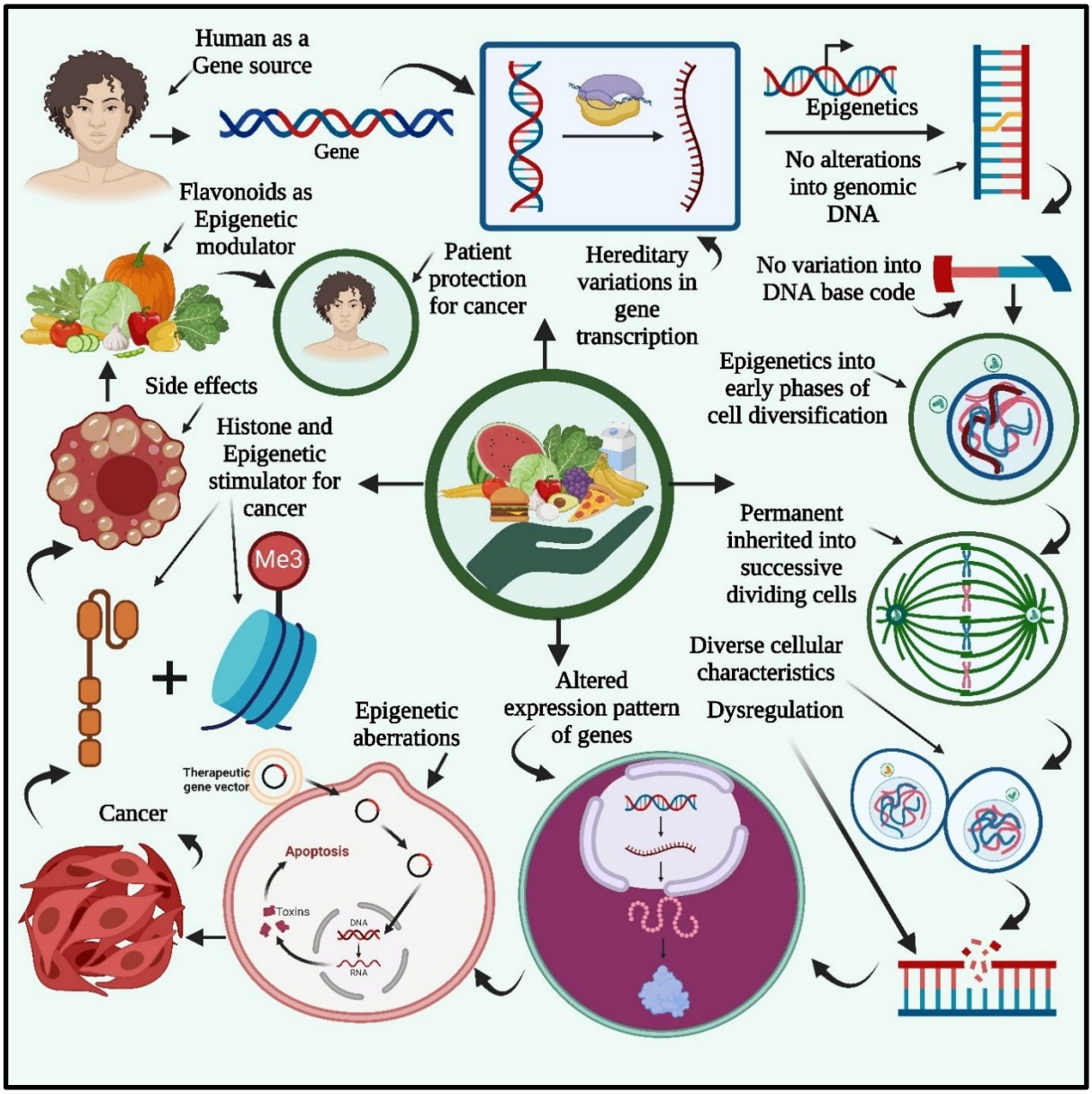

Figure 3. Epigenetic variation of genomic DNA. Genes from cells undergo hereditary variations in gene transcription with no alteration in genomic DNA called epigenetics. These epigenetic modifications provide no variations in the DNA base code and can be present in the early phase of cell diversification. Such events indicate permanently inherited successive dividing cells, resulting in diverse cellular characteristics. The dysregulation induces an altered expression pattern of the genes, which results in epigenetic aberrations. These aberrations generate cancer, which is treated with conventional chemotherapy and advanced drug treatment containing histone deacetylase antagonists, epigenetic stimulators, and CAR-T cells. Such therapy contributes more side effects, and hence, these are addressed by flavonoid formulations for better protection against cancer cells. (Created using Biorender.com).

Genes become hetero-chromatinized and dormant due to the tight packaging of nucleosomes that occurs during nuclear condensation. In contrast, chromatin de-condensation results in nucleosome opening and enhanced gene function. Normal cell transition into cancerous cells includes epigenetic changes and is typically accompanied by genetic variations. DNA changes (such as methylation), histone changes (such as phosphorylation, ubiquitination, and deacetylation), chromatin position, and noncoding RNAs (such as siRNA, lncRNA, and miRNA) are a few of the significant systems occurring in epigenetic control, as presented in **Figure 2**. Cell equilibrium is significantly impacted by these pathways [16,17]. These changes are often implicated in human

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pathologies, including solid tumors and hematological neoplasms [18]. The epigenetic deregulation in cancer resulted into the alteration of transcription along with the translation of oncogenic gene targets as presented in Figure 4.

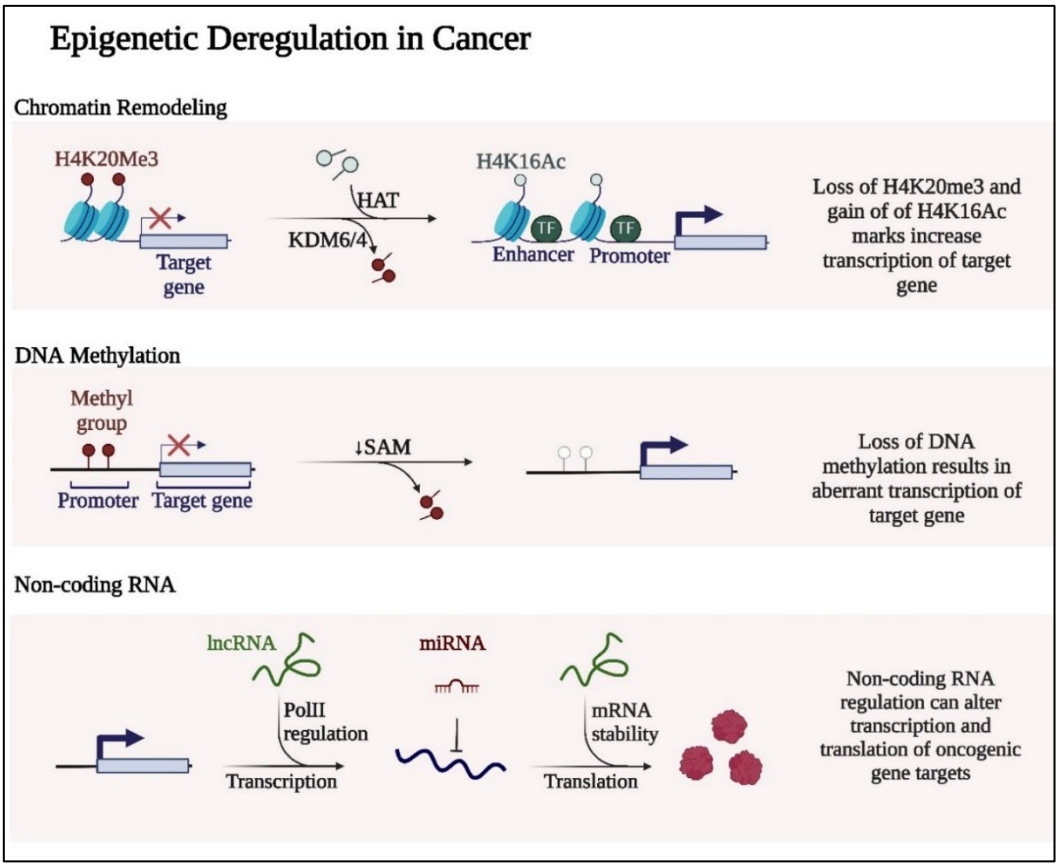

Figure 4. The summary of epigenetic deregulation in cancer including chromatin remodeling, DNA methylation and non-coding RNA resulted into alteration in transcription as well as translation of the oncogenic gene targets.

1.1. DNA Methylation

DNA methylation or hydroxy-methylation is a crucial epigenetic process for controlling the expression of genes in cells [19], and DNA methylation sequences help to create epigenetic recollection. A family of DNA methyltransferase catalysethe transfer of a methyl group from S-adenyl methionine (SAM) to the fifth carbon of cytosine residue to form 5-methylcytosine. So, SAM is a key donoe of methyl group in this process. [20]. However, the placement of modified bases regarding the coding sections of a protein being regulated affects the relationship between DNA methylation and gene function, which is often negatively associated [21].

Most frequently, cytosine methylation occurs at CpG sites and is found throughout the entire genomic DNA [22]. Whenever an area of a CpG site has a size of much more than 200 bp, a GC concentration of much more than 55%, and an identified CpG ratio of >60%, it is referred to as a CpG island [23]. Over 70% of mammalian promoter regions contain CpG islands, which are especially common there. When CpG locations are found in the enhancer or promoter parts of genes, their methylation suppresses the expression of genes; nevertheless, if CpG spots are found in the programming sections of genes, their methylation increases gene transcription [24]. In contrast to typical cells, cancerous cells have a different trend of CpG methylation [25]. Additionally, hypermethylation on their promotor gene is highly expressed in the case of human telomerase gene (hTERT) and TERT hypermethylated oncogenic region (THOR) associated with telomerase activation stable under various epigenetic drugs [26]. Whereas most CpG locations in the DNA stay methylated in healthy cells, the CpG islands that precede regulators are unmethylated, permitting

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effective transcription. CpG islands are often hypomethylated, and CpG dinucleotides exhibit approximately 50% lower methylation in cancerous cells than in healthy cells [27]. Typically, oncogene regulators in malignancy are hypomethylated and triggered, whereas those for tumor suppressors become hypermethylated, limiting their activity. Anomalous DNA methylation causes dysregulation of genes that regulate DNA repair, cell growth, motility, and death in tumor tissue [28]. DNMTs, made up of the three isoenzymes DNMT1, DNMT3, and DNMT3a, are responsible for this genetic DNA methylation activity. The enzyme Ten-elevan translocation (TET) catalyses the oxidation of 5-methylcytosine, leading to sequential removal of methyl group [29].

2.1. Histone Modifications

Positively charged molecules called histones are involved in the packing and compressing DNA to nucleosomes within the nuclei. Euchromatin, an open chromosome architecture, is linked to gene transcription, while heterochromatin, an enclosed nucleosome structure, is linked to transcriptional regulation. The methylation, acetylation, and phosphorylation of histones, in particular, could control chromatin conformational changes that affect the expression of genes[30,31]. The DNA methylation and histone modifications are presented in Figure 5. Acetyl CoA is synthesize within the cell mainly by glycolysis, fatty acid oxidation and amino acid catabolism pathways. Then Acetyl-CoA is transported from the cytoplasm into nucleus, and inside the nucleus, acetyl CoA serve as substrate for histone acetyltransferase (HAT), which add an acetyl group to lysine groups found in the histone tail at a time of histone acetyltransferase (HAT) process. The DNA-histone connection is weakened by this alteration, which ultimately causes chromatin to decondense and transcriptional expression to rise. Lactylation is Post translation modification of histons, which involves the addition of a lactyl group to lysine resudues. This modification has been identified as a significant factor in the regulation of gene expression, which causes supression of immune system, therapy resistance, and metastasis inhibition of antitumor immune response. As lactate is produced as a consequence of anaerobic glycolysis, lactylation starts. Because of the Warburg effect or hypoxia, cancer cells generate a lot of lactate. Lactyl-CoA, the donor molecule for the lactyl group, can be produced from lactate. The ε-amino group of lysine residues on histone proteins receives the lactyl group from lactyl-CoA. Gene expression and chromatin structure can be impacted by histone lactylation. Depending on the situation and the particular lysine residues involved, lactylation can either stimulate or repress the transcription of a certain gene by altering histones [32].

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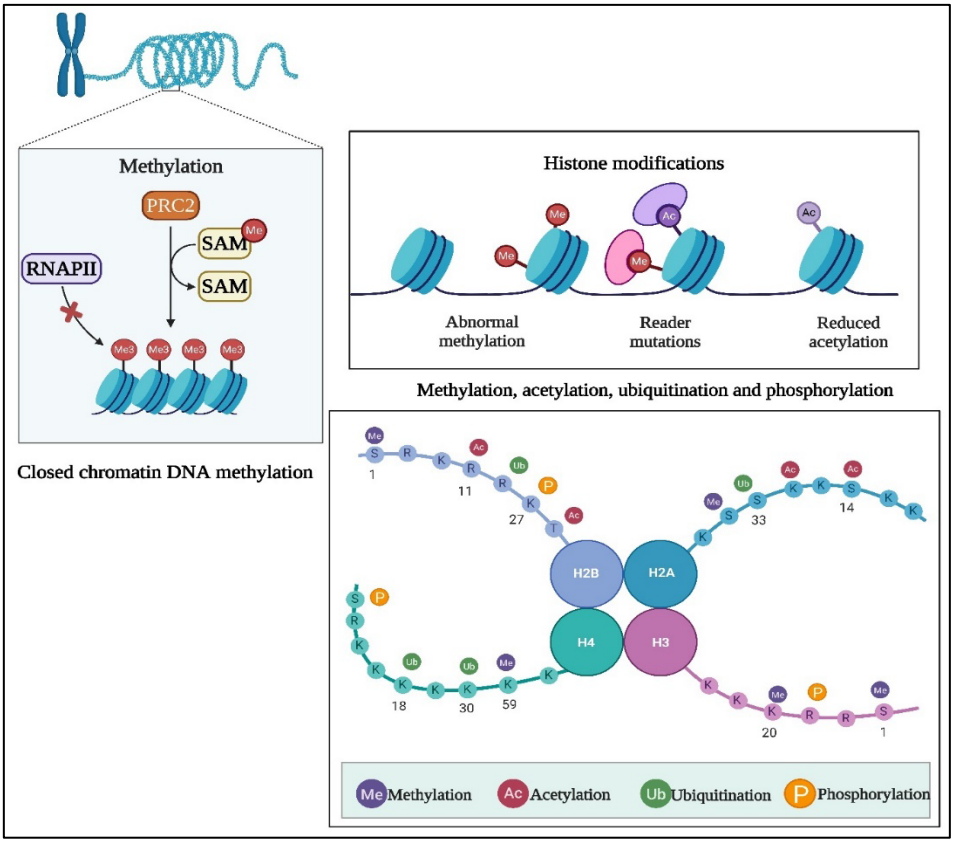

Figure 5. The DNA methylation in closed chromatin and histone modification involving acetylation, ubiquitination, and phosphorylation.

In contrast, HDACs are a significant type of enzyme that deacetylates e-amino compounds on lysine residues, which causes nucleosomes to condense and reduces the expression of genes. Researchers have discovered that benign and cancerous cells exhibit strikingly distinct patterns of histone acetylation [33]. Tumors have lower levels of monoacetylation of Lys20 and contain three methods of Lys16 on histone H4 [34]. Moreover, reduced acetylation of histone modifications H3 and H4 is associated with the development of cancer [35]. Another epigenetic alteration that controls the expression of genes in malignancy is histone methylation. Histone demethylases (HDMs) and histone methyltransferases (HMTs) of the appropriate amino acids in histone proteins catalyse these alterations. The control of histone methylation is frequently linked to the transcriptional patterns of particular cancer genes [36]. For example, a reduction in trimethylation on histone H3 lysine 4 (H3K4me3) linked to malignancy is accompanied by a rise in mono-methylation on lysine 9 of that same histone H3, which has an impact on the expression of genes [37]. Another histone posttranslational change caused by kinases relevant to a cell is activation [38]. Genomic instability eventually causes cancer due to the phosphorylation of serine at the C-terminus of the H2A histone close relative X (H2AX), a genome double-strand break indicator [39]. RNAs that do not encode noncoding RNAs, which have been demonstrated to impact gene transcription significantly, constitute the following critical epigenetic process determining how cells function [40,41]. MicroRNAs are small nucleotide molecules that often link with the 3' domain of the mRNA to alter mRNA stabilization and translation. Numerous miRNAs can impact the activity of a single gene, or just one miRNA might control the function of numerous genes [42].

2.2. Non-Coding RNAs

MiRNAs have been shown to regulate the transcription of approximately 60% of human genes that encode proteins [43]. Many miRNAs have indeed been linked to the control of oncogenes, implicating them in cancer development [44]. For example, miR-16Let-7 and miR-15 are the most prevalent onco-miRNAs (miRNAs linked to cancer) and are promising possibilities for the

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treatment of cancer [45]. A tumor suppressor gene role for miR-125b1 has additionally been demonstrated, and its decline has been linked to prostatic as well as ovarian tumors [46]. A large portion of the newly discovered information about cancers is influenced by microscopic RNAs' functions in tumor growth [47]. Generic changes, promoter hypermethylation, and other epigenetic alterations all control how miRNAs are expressed, which enhances community cell changes and the cancerous process [48–50]. Polyadenylated RNAs with a size exceeding 200 nucleotides are known as longer noncoding RNAs (lncRNAs), and they can attach to peptides, RNA, and DNA. One of the most prevalent techniques for controlling the expression of genes via lncRNAs is epigenetic modification, which is frequently linked to genetic suppression. According to research, lncRNAs could indeed behave as tumor suppressor genes or oncogenes through several processes, such as interacting with the polycomb repressive complex (PRC), which controls the manufacturing, stability, and transformation of transcripts; interacting with miRNAs, which are genomic boosters and regulatory proteins; and interacting with transcriptional regulators, which regulate the generation and transfer of transcripts [51–55]. Tumor patients have higher levels of lncRNAs, such as HOTAIR and MALAT1, which are linked to metastases, and lower levels of lncRNAs, such as MEG3 and PTENP1, which prevent the growth of cells and their movement [56]. Telomeric repeat-containing RNAs (TERRA) are small RNA molecules synthesized from telomeric regions, TERRA, naturally occurring ligands of telomerase and their genetic and epigenetic regulations in cancer aging-associated diseases. It plays a role in specific osteosarcomas and liposarcomas [57]. Long noncoding RNA (lncRNA) H19 leads to the progression of liver cancer by affecting biological processes, cell proliferation, apoptosis, invasion, and epigenetic modification [58]. Soy-isoflavone genistein mediated downregulation of miR-155 and inhibit mammary tumor growth and metastasis in highly metastatic MDA-MB-435 cancer cells in immunocompromised mice. Genistein produces its effect without affecting nonmetastatic MCF-7 breast cancer cell viability [59].

3. Flavonoids As Epigenetic Modulators

With a fundamental benzo-c-pyrone composition, flavonoids are a significant group of organically produced low-molecular-weight polyphenolic chemicals. Such secondary metabolites of plants are prevalently found in various vegetables, fruits, cereals, and nuts, especially in several drinks (tea and coffee). Various well-being products are associated with flavonoids, which also play a significant role in several pharmacological, nutritional, cosmetic, and medical uses. Flavonols, flavan-3-ols, flavanones, flavones, anthocyanidins, and isoflavones are some of the subclasses of flavonoids according to their biochemical compositions. In addition, flavonoids have various advantageous medicinal effects, such as hepatoprotective, antibacterial, antiviral, cytostatic, analgesic, antiestrogenic, estrogenic, anti-allergic, and apoptotic effects [60,61]. Suppression of kinases, modulation of transcriptional activation, effects on cell growth, and epigenetics are just a few of the molecular pathways believed to be linked to these diverse medicinal operations of flavones. New research indicates flavonoids may restore the typical epigenetic modifications altered during cancer [62–68]. Such phytochemical compounds typically stop the growth of tumors by attacking important signaling transducers, which restore tumor inhibitor genes and prevent the activation of oncogenes. These modifications and the ensuing antitumor effects are frequently caused by flavonoids' epigenetic stimulatory actions, which change epigenetic catalysts such as HDACs, DNMTs, and HATs.

Moreover, flavonoids are effective at modifying the transcription of lncRNAs and miRNAs, which are altered throughout the disease. Chemotherapy medicines can save lives when used to fight cancer, but one drawback of such medications is that they may have toxic effects on healthy cells. Therefore, it is crucial to have good options free of adverse reactions. Nevertheless, more extensive studies are required to assess their safety and side effects. Inside this area, flavonoids offer encouraging findings that many anti-carcinogenic flavonoids exhibit comparatively reduced cytotoxicity against healthy cells [64,68–71]. Additionally, when ingested at higher levels, they have been shown to have prooxidant effects on healthy cells, which can result in the generation of free radicals that are genetic mutations and inhibitory effects on necessary enzymes engaged in

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hormonal metabolic activities [72]. Nevertheless, flavonoids that alter gene expression, such as those used in combinational therapy, may be desirable for future cancer treatments.

4. Cancer Prevention And Therapy By Epigenetically Active Flavonoids

4.1. Flavan-3-Ols/Flavanols/Catechins

Green tea contains a potent polyphenolic component called epigallocatechin gallate (EGCG), a member of the catechin family of flavonoids. Epicatechin 3-gallate, epigallocatechin, and epicatechin make up the remaining ingredients in herbal tea. Several *in vitro*, *in vivo*, and human-based studies have suggested that EGCG may have proapoptotic, antiproliferative, anti-invasive, and antiangiogenic characteristics. A wealth of research reveals how green tea determines cancer epigenetic regulation. For the first time, the ability of EGG to suppress DNA hypermethylation of CpG islands by interfering with DNMTs was discovered by Fang et al. [67,73–76]. The potential actions of EGCG on adult cells with prostate cancer have been demonstrated in another investigation. In patients with prostate cancer, drinking green tea increases the amount of acetylated histone H3 in the total cellular nucleus, which induces epigenetic changes in p21/waf1 and Bax reactivation, causing arrest of the cell cycle and apoptotic cell death. In androgen-dependent cancer cells of the prostate stimulated with green tea catechins, Lee et al. measured the activities of histone acetyltransferase to investigate the control of adrenoceptor acetylation (epigallocatechin-3-gallate, epigallocatechin and epicatechin). These catechins result in the suppression of agonist-dependent androgen receptor (AR) excitation as well as AR-regulated transcriptional regulation in prostate cancer cells [77,78]. In a separate study, the combination of clofarabine as well as EGCG or genistein was reported to inhibit the development of breast tumor cells (MCF7 and MDA-MB231) and cause cell death, which was accompanied by RARB hypomethylation, leading to a massive rise in the concentrations of the transcripts for CDKN1A, PTEN, and RARB. In breast cancer cells from humans, this mixture of flavonoids as epigenetic modulation techniques induces death. It restores tumor suppressor genes repressed by DNA methylation with unusually aggressive potential. Negatively affecting histone deacetylases and DNA methyltransferases causes EGCG to change the transcription of several cancer genes found in human cervical carcinoma cell lines. Additionally, due to noticeable changes in the methylation of a gene promoter of these genes, time-dependent treatment with EGCG caused the stimulation of very well cancer genes (TSGs) in such cells. Recently, Ciesielski *et al* investigated how EGCG affected human endothelial cell nucleosome remodeling and the histone posttranslational alteration mechanism (HMEC-1 and HUVEC origin). The findings demonstrated that EGCG enhances histone acetylation (H3K9/14ac, H3ac) and modification, including both functional (H3K4me3) and inhibitory (H3K9me3) histone marks. These findings demonstrated the extensive epigenetic capability of EGCG concerning the regulation and activity of epigenome stimulators such as HDAC7, HDAC5, KMT2A, CREBP, LSD1, and p300 [79–81]. Additional research demonstrates that EGCG's anticancer activity was achieved in HeLa cells via synchronized transcription alteration of various biological targets via various signaling pathways. Many chromatin modifiers, particularly histone substitutions as well as DNA methyltransferases (DNMT3A, DNMT3B, AURKA, DNMT1, AURKC, PRMT6, PRMT7, KDM4A, HDAC5, KDM5C, HDAC7, HDAC6, UBE2B and HDAC11), were shown to have their transcriptional activity modulated in this work. Several pro-inflammatory molecules, such as CCNB2, CCNB1, PIK3C2B, TERT, IL6, MMP7, MMP2, MAPK8, and PIK3CA, as well as essential signaling molecules of the Wnt, PI3K, and MAPK networks, were also downregulated. Kang et al. demonstrated that EGCG may effectively prevent IR-induced damage to mice healthy hepatocytes (AML-12) but significantly increase the radiosensitivity of mice hepatic tissue H22 to 60Co. Researchers have also demonstrated that EGCG promotes the miR34a/Sirt1/p53 signaling mechanism, essential for the radiosensitization of H22 cells. According to Deb *et al.*, exposure to green tea polyphenols (GTPs) and their primary component, epigallocatechin-3-gallate (EGCG), promoted the transcription of TIMP3 through epigenetic pathways in adult cells with prostate cancer (DUPro and LNCaP). Additionally, clinical research on EGCG-consuming prostatectomy patients revealed increased plasma TIMP3 concentrations. Nutritional flavonoids

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may influence miRNAs and other noncoding RNAs in malignancy. Oral treatment with EGCG reduces the miR483-3p-induced metastases of hepatic cancer, according to a current in vivo model by Kang et al. [82–88]. When used to treat stomach cancer, EGCG targets the LINC00511/miR-29b/KDM2A axis to modify noncoding RNAs and slow tumor development. Transcription of the tumor suppressor miRNAs miR-34a and let-7a was dramatically enhanced by EGCG-capped metal nanoparticles [89,90].

4.2. Flavonols

The most common flavonoids within the diet are called flavonols (3-hydroxyflavones). One of the most prevalent plant flavonols in a wide range of vegetables and fruits, including apples, onions, and strawberries, includes myricetin, quercetin, fisetin, and kaempferol. From an epigenetic standpoint, quercetin's protective advantages for human wellness are assisted by its multifaceted, pleiotropic action. In cervical cancer cell carcinoma (HeLa) cells, quercetin modifies the transcription of several chromatin moderators and decreases the expression of HMTs, DNMTs, and HDACs dose-dependently. Additionally, it reduced the promoter methylation levels for the evaluated tumor suppressor in a sharp dose-dependent manner with recovery of its expression. This effect was shown in both a time-based and dose-dependent manner. Together with BET blockers, quercetin increases death and reduces pancreatic cancer cells' capacity for cell division and spherical formation [91–96]. Additionally, it was demonstrated that quercetin exerts certain antitumor activities with the aid of hnRNPA1, a nuclear protein recognized for regulating antiapoptotic gene mRNA synthesis and mRNA exportation [97–99]. Nwaeburu et al. found that quercetin also increased let-7c, inhibiting pancreatic cancer growth by indirectly inhibiting Notch and posttranscriptionally activating Numbl. Zheng et al. found that quercetin nanoliposomes, in combination with butyric acid, tunable aberrant epigenetic changes in Eca9706 molecules through epigenetic-NF-B signaling. In this research, p16INK4 and caspase-3 translations were ready, while opposite expression of global HDAC1, NF-B p65, Cyclin D1, and DNMT1 was downregulated. Moreover, quercetin modulates miR-197/IGFBP5, miR-16-5p/WEE1, miR-1-3p/TAGLN2, miR-16/HOXA10, miR-22/WNT1/β-catenin, miR15a/16, TP53/miR-15/miR-16, miR-145, miR-146a and miR-200b-3p in different types of cancer. Possible HDAC blockers and the anticancer drug kaempferol (3,4′,5,7-tetrahydroxyflavone) are effective against various malignancies. The unique epigenetic action of kaempferol, which HDACs inhibit, was originally described by Berger et al. Kaempferol falls into ligand binding of HDAC2, 4, 7, or 8, and in vitro screening among all preserved adult HDACs of categories I, II, and IV showed that this truly suppressed every HDAC that has been tested.

Moreover, HepG2 and Hep3B (hepatocellular carcinoma cell types) and HCT-116 (intestinal carcinoma carcinoma cells) exhibit hyperacetylation of histones in response to kaempferol. In gastric cancer cells, kaempferol causes the death of autophagic cells by blocking the HDAC/G9a axis, including IRE1-JNK-CHOP signaling. Kaempferol promotes the miR-340 production in lung A549 cells, which is associated with death and limits cell growth in NSCLC. Fisetin, a flavonol, is a potent antitumor drug used to block the activities of the Bcl-2 protein family in numerous cancerous cell lines, promote death, slow cellular proliferation, stop the advancement of cell growth, and suppress different phases of cancerous cells. Additionally, it decreases the amount of the oncogene securin, blocks the stimulation of ROS/PKC/p38 MAPK and ERK1/2 signal transduction, and activates NF-B less. Fisetin suppresses pancreatic cancer growth by causing damage to DNA through RFXAP/KDM4A-dependent histone H3K36 demethylation, according to research published earlier by Ding et al. [100–112].

4.3. Flavones

Flavones, a subgroup of flavonoids with the chemical formula 2-phenyl chromen-4-one (2-phenyl-1-benzopyran-4-one), were frequently discovered in plants such as celery as well as parsley as well as in practically every kind of nutritious grain. Some popular flavones are luteolin, tangeretin, apigenin, chrysin, baicalein, tricin, 6-hydroxy flavone, and rhoifolin. According to

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Pandey *et al.,* apigenin suppresses class I HDACs, specifically HDAC1 and HDAC3, altering chromatin to cause inhibition and death in adult cancer cells from the prostate. Apigenin reduced MDA-MB-231 cancer cellular growth and tumor formation by inducing G2/M pause and histone H3 acetylation-mediated p21 transcription. By regulating the miR-520b/ATG7 axis, apigenin increases the levels of miR-16 and miRNA215-5p, which suppresses the growth of gliomas and intestinal cancers, respectively, and chemosensitizes doxorubicin-resistant hepatic cancerous cells [113–117]. Wu et al. recently discovered that luteolin hindered triple-negative breast cancer cells with adrenoceptor positivity in their ability to proliferate and metastasize by altering the genomic regulation of MMP9 transcription by decreasing the concentrations of the histone modifications and H3K27Ac and H3K56Ac that stimulate AKT/mTOR.

Additionally, it was previously discovered that luteolin inhibits the spread of triple-negative cancer and reduces the production of ß-catenin to reverse epithelial-to-mesenchymal transitions. Luteolin causes death in colorectal cancer cells by suppressing the expression of calpain, DNMT1, and UHRF1. By controlling the chromatin regulator UHRF1, this study also implies that calpain may be engaged in genomic code inheritance. Via a cooperative method involving EGFR-associated kinase activity, gefitinib and luteolin control the cell growth cycle genes (CCNE2, CDC25A, CCNA2, PLK-1, and CDKN1B) in human prostate (PC-3) cells. The author's group previously demonstrated the interaction of luteolin with type II complex formation on histone H4 and how these phytonutrients likely impact the epigenetic expression of genes.

Furthermore, Farooqi et al. and Mishan et al. carefully analyzed how effectively luteolin can alter the transcription of miRNA in different malignancies. A tangeretin derivative suppresses the growth of tumor stem-like cells and stops the progression of biological cells with prostate cancer by epigenetic changes repairing p21 gene transcription. Breast, human prostate, myeloma, and T24 bladder cancer cells are affected by baicalein (5,6,7-trihydroxyflavone), which inhibits the growth of cancer cells, arrests the replication process, and triggers death. Baicalin hydrate suppresses the proliferation of NPC cells both in vivo and in vitro, according to research by Lai et al. on the genetic effect of this substance in nasopharyngeal cancer (NPC). Baicalin hydrate also boosted m6A RNA methylation rather than DNA methylation and facilitated Suv39H1 gene translation. Additionally, it has been shown that baicalin increases DNA methylation, inhibits apoptotic cell death, increases HSP70 transcription, and enhances mouse organogenesis in vitro. *Baicalein* modulates the transcription of miR-183, miR-139-3p, miR-25, and miR-196b-5p in multiple myeloma, according to many current studies [118–125].

4.4.. Flavanones

Citrus fruits mostly contain fragrant, colorless ketones called flavanones. Other major flavanones include isosakuranetin, hesperetin, naringenin, naringin, eriodictyol, iso-sakuranetin, and their specific glycosides. Frequent citrus flavanone hesperetin promotes DOT1L breakdown and reduces histone H3K79 activation to stop the spread of stomach cancer, demonstrating its epigenetic function. Silibinin, a native flavonolignan, is silymarin's (A milk thistle medicinal plant) most potent naturally occurring chemical [126]. It significantly inhibits the proliferation of many cancerous cells and is effective on its own or in conjunction with various chemotherapy and epigenetic treatments [127,128]. It induced the release of e-cadherin in concert with DNA methyltransferase and histone deacetylase blockers. It prevented the proliferation and spread of adult non-small cell cancer cells in the lungs. These findings are incredibly significant because the failure of E-cadherin, as well as the spread of the disease through epithelial-to-mesenchymal conversion, is linked to a poor outcome and high mortality rates in these tumor tissues.

EZH2 gene expression is decreased by silibinin in adult prostatic tumor (DU145 and PC3) cells, whereas H3K27me3 levels are elevated. Such reactions relied on lowered expression of activated EZH2 and Akt (ser21) (ser473). Other evidence that it alters the epigenome of human prostatic tumor tissues includes decreasing the transcription of histone deacetylases 1-2 (HDACs1-2) while increasing the action of complete DNA methyltransferase (DNMT). According to Hossainzadeh *et al.,* polymersome nanoparticles that contain silibinin suppress the production of carcinogenic miR-

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182 miRNAs and miR-125b. Citrus fruits contain naringin in the aglycone method known as naringenin (4,5,7 trihydroxyflavanone). It synergistically increased transamidation efficiency, and suberoylanilide hydroxamic acids (HDAC inhibitor) caused toxicity in neuroblastoma cells, although it had no cytotoxicity on healthy nonmalignant molecules. It suggests that naringenin has powerful histone deacetylase inhibiting action, but additional research is required to fully comprehend its possibility for altering epigenetic processes [129–133].

4.5. Isoflavones

Phytoestrogens are isoflavonoids that naturally occur and are primarily present in soybeans, legumes, and soy-based foods. They have a range of strong therapeutic actions, including anti-inflammatory, oxidative, antibacterial, and anticancer properties. These have clear evidence of having estrogenic and/or antiestrogenic effects. Isoflavones are utilized in a variety of complementary treatments for a broad range of menstrual irregularities, including many cancers, osteoporosis, menstrual issues, and heart disease. There seem to be conflicting claims that isoflavones interfere with endocrine function, although most adverse effects are modest and manifest in the digestive organs [134–137]. Isoflavones include substances such as genistein, daidzein, glycitein, and genistin. The strongest and most physiologically active isoflavone is genistein, which has shown various in vitro and in vivo antitumor and antiproliferative actions on various human malignancies. Soy phytoestrogens (daidzein and genistein) decrease DNA methylation at EPHB2, BRCA1, and GSTP1 promoters in prostatic cell cultures (DU-145 and PC-3). Genomic sequence DNA methylation conditions in prostatic malignancy are modulated by phytoestrogens (genistein and daidzein), according to research by Karsli-Cebioglu et al. In prostatic tumor DU-145 and LNCaP cell cultures, they discovered that daidzein and genistein treatments altered the methylation patterns of 58 genes. Genistein therapy significantly changed the MAD1L1, hTERT, TRAF7, and KDM4B gene modification rates. In cancer malignancy, genistein regulates the production of miRNAs. Genistein activates the miR-34a/RTCB axis in cancers of the head and neck, which causes ROS-associated apoptosis, a reduction in stemness, and inhibition of EMT. Imai-Sumida et al. [138–141] have discovered that genistein inhibits renal tumors by suppressing chromatin and HOTAIR modeling mechanisms. On the other hand, according to Allred *et al.*, nutritional genistin and genistein could boost the proliferation of estrogen-dependent breast cancer cells in situ. To fully comprehend the characterized nature of such nutritional chemicals, including their ability to influence epigenetics, toxicity, and antitumor qualities, in-depth molecular studies are required in light of such contradictory data [142–145].

4.6. Anthocyanidins

The sugar-free version of anthocyanins, known as anthocyanidins, is a group of water-soluble vital plant pigments. Delphinidin is a powerful and prevalent anthocyanin flavonoid in colored veggies and fruit, particularly blueberries. According to Kuo *et al*., delphinidin inhibits the malignant conversion of mouse epidermis JB6 P+ cells by epigenetically reactivating the Nrf2-ARE pathway. Inside the mouse Nrf2 gene promoter between nucleotides -1,226 and -863 from the start of transcription, 15 CpG spots were demethylated, and this action was linked to the stimulation of the Nrf2-ARE axis. In agreement with observed reductions in the protein production of DNA methyltransferase 1 (DNMT3a) and class I/II chromatin deacetylases (HDACs), the CpG activation percentage in the Nrf2 promoter region dropped. The primary anthocyanin molecule delphinidin was found by Jeong et al. to have epigenetic transceivers that cause adult prostatic tumor cells to undergo apoptosis [146–148]. Delphinidin was used to decreased the growth of cancerous cells, and a rise in the histone deacetylase function of caspase-3, -7, and -8 activity was observed. Delphinidin was the only substance that could prevent the function of HDAC3, the most prevalent class I HDAC.

Furthermore, the death induced by delphinidin depended on the breakdown of HDAC3 by caspases, which stabilized and acetylated p53. Researchers also noticed that anthocyanidin significantly downregulated many anti-apoptotic genes while efficiently upregulating pro-apoptotic

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genes controlled by p53. Han et al. found that delphinidin affects the HOT AIR/miR-34a pathway to reduce breast tumorigenesis and suppress colon cancer migration by upregulating the production of miR-204-3p [149,150]. For chemical structure of flavonoids refer Figure 6.

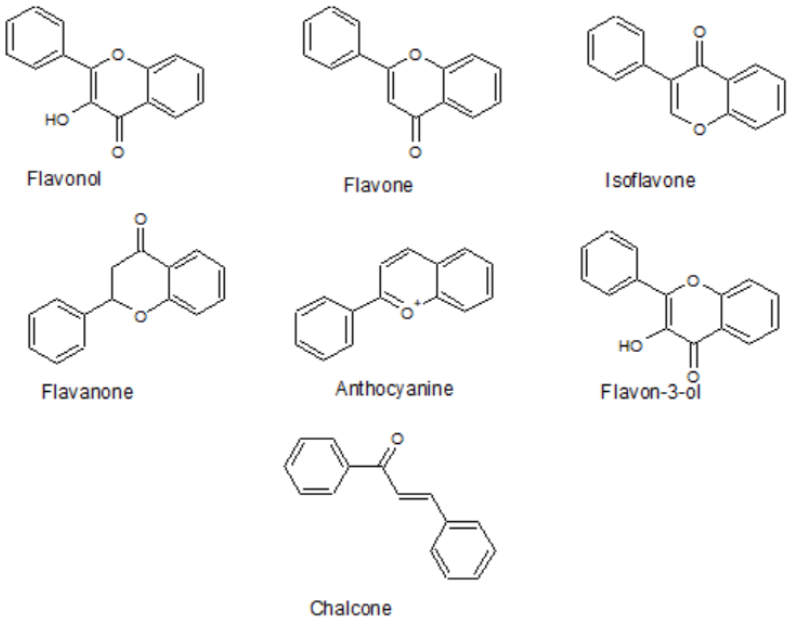

Figure 6. Chemical Structure of Flavonoids. *Created using Chemsketch.com*.

5. Applications of Flavanoids in Cancer

Flavonoids have been found to have a broad range of anticancer properties, including the ability to control reactive oxygen species (ROS)-scavenging enzyme activities, engage in cell cycle arrest, induce apoptosis and autophagy, and reduce cancer cell proliferation and invasiveness. Flavonoids have a dual activity regarding ROS homeostasis; under normal circumstances, they operate as antioxidants, but in cancer cells, they are potent pro-oxidants, activating apoptotic pathways and downregulating pro-inflammatory signaling pathways. Table 1 summarizes the application of various flavonoids in cancer management. Flavonoids exhibit anti-cancer effects by various mechanisms and pathways. It exhibits anti-oxidant activity and neutralizes free radicals, induces apoptosis in cancer cells, inhibits angiogenesis, and deprives tumors of the blood supply. It also induces cell cycle arrest and modulates enzyme activity. In this way, it exhibits effective anti-cancer effects [151].Table 1: Flavonoids in cancer management with their molecular targets.

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Name	Category	Source	Given with (in combination with)	Molecular target	Cancer type	Remarks	Epigenetic effect	Reference
Genistein	Isoflavonoids	Leguminosae species. It is found in *Scutellaria baicalensis*, *Morus alba*, and citrus species.	Genistein has synergistic action with tamoxifen and doxorubicin.	EGFR, CDK, KIF20A, PLK1, Erα/β, AR	It inhibits protooncogene HER-2 protein tyrosin phosphorylation in breast cancer cells. Studies have shown that genistein is effective in lymphoma, leukemia, cervical, neuroblastoma, ovarian, pancreatic, and prostate cancer.	• It inhibits topoisomerase 1 and 2, 5α reductase, and protein histidine kinase and has antiproliferative effects. • Polo-like-kinase 1 (PLK1), its overexpression led to severe carcinomas. • Genistein inhibits PLK1 and suppresses proliferation.	• Modifying the proteins that regulate the cell cycle leads to cell cycle arrest and the deactivation of the MAPK (ERK1/2) and PI3K/AKT signaling pathways. • Additionally, genistein influences epigenetic regulation, hinders angiogenesis, invasion, and cell migration, and alters the expression of various miRNAs. • By increasing the Bax/Bcl-2 ratio, genistein induces apoptosis via autophagy-dependent pathways and mitigates oxidative stress by changing the expression of antioxidant enzymes.	[152] [153] [154,155]
Baicalein	Flavone	Roots of *Scutellaria baicalensis*	It gives synergistic action with docetaxel and gemcitabine.	MAPKs, PI3K/AKT, Rb/E2f/cyclin-CDK4/p53	Pancreatic cancer	• Baicalein has been shown to induce cytochrome C release and caspase-9 activation and induced apoptosis. • In circulation, it forms a metabolite, O-glucuronide baicalin;	• Baicalin hydrate (BH) has been shown to inhibit the growth of nasopharyngeal carcinoma (NPC) cells both in vivo and in vitro by promoting apoptosis and causing cell cycle arrest.	[156,157]

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						some studies showed that it does not exert anti-tumour activity *in vivo*. • It inhibits the LOX pathway and inhibits cancer cell growth.	• BH influences genome stability through epigenetic mechanisms, leading to the up-regulation of satellite 2 (Sat2), alpha satellite (α-Sat), and major satellite (Major-Sat). • Additionally, BH enhances the levels of IKKα, Suv39H1, and H3K9me3 while reducing the expression of LSH.	
Apigenin	Flavones	Parsley, celery, celeriac, basil, chamomile tea, and other vegetables.	It gives synergistic action with paclitaxel to induce apoptosis.	JAK2/STST3, P53/p21, Nrf2	Apigenin exerts anti-invasion effects in lung cancer	• Apigenin is a dietary flavonoid; it possesses anticancer activity with low toxicity in normal cells. • It kills myeloma cells by triggering autophagy, leading to inhibiting gastric cancer.	• Apigenin was found to reduce the levels of cyclin A, cyclin B, and cyclin-dependent kinase-1 (CDK1), which are crucial for the G2-to-M phase transition in the cell cycle. • Additionally, apigenin increased the expression of p21WAF1/CIP1 and enhanced its interaction with proliferating cell nuclear antigen (PCNA), thereby hindering cell cycle progression. • Moreover, apigenin markedly reduced histone deacetylase (HDAC) activity and promoted acetylation of histone H3. • This increased acetylation of histone H3 at	[158] [159,160]

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							the p21WAF1/CIP1 promoter region, leading to higher transcription of p21WAF1/CIP1.	
Luteolin	Flavones	Vegetables and fruits such as broccoli, celery, onion, carrots, peppers, cabbages	Luteolin synergistically acts with oxaliplatin to suppress HCT116 cells.	AKT, Nrf2, ROS/ER, VEGF, bFGF, MMP, HGF/ c-Met ,	Liver cancer, Lung cancer, gastric cancer	• It inhibits tumor proliferation of *in vitro* cell lines. • It induces cell arrest in G1, S, and G2 phases. • It inhibits VEGF and bFGF *in vitro*. • It is a potent inhibitor of human leukemic CEM-1 and CEM-C7 cell proliferation.	• Luteolin (LUT) has been shown to influence the mRNA and protein expression of Nrf2 and its downstream genes following treatment. • Bisulfite genomic sequencing demonstrated that LUT treatment reduces methylation in the Nrf2 promoter region, which is associated with an increase in Nrf2 mRNA expression. • Additionally, LUT-treated HCT116 cells exhibited decreased protein levels and enzymatic activities of epigenetic modifiers, such as DNMTs and HDACs. • This treatment also inhibited the proliferation and cellular transformation of HCT116 and HT29 cells in a dose-dependent manner.	[161] [162,163]
Nobiletin	Flavones	*Citrus sinensis*(orange),	It exerts synergistic action with atorvastatin on	-	Breast cancer, colon cancer	• Nobiletin is anti-proliferative against	• Nobiletin demonstrated a dose-dependent inhibition of	(11–13) [167,168]

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		Citrus aurantium(grapes)	colon carcinogenegenesis			human and rodent cell lines. • It induces apoptosis in human TMK-1 gastric cells, HepG2 hepatocellular cells, and Colo 320 colorectal cancer cell lines. • *The in vivo* effect is not yet clear; further study is required to determine the toxicity of this flavonoid. • Nobiletin concentration of 60-100 μM inhibits tumor cell line by 50-60 %.	breast cancer (BC) cell proliferation. • Additionally, the induction of pyroptosis in BC cells by miR-200b mimics was enhanced by nobiletin. • JAZF1 as a target of miR-200b. • Furthermore, nobiletin promoted both apoptosis and pyroptosis in BC cells through the miR-200b/JAZF1/NF-κB pathway.	
Quercetin	Flavanols	Berries, broccoli, citrus fruits, grapes and green leafy vegetables	It gives along with curcumin to induce anticancer activity against TNBC cells	BCL2/BAX, AMPK/COX-2, p53, β-catenin, EGFR/VEGFR2, mTOR	Gastric cancer	• It inhibits the proliferation of malignant glioma cells by inducing apoptosis, activating JNK, and upregulating p53. • Quercetin inhibits the cell cycle by activating p21 and decreasing the D1/Cd4 and E/Cdk2 ratio. • It inhibits microtubule polymerization and	• Arctigenin exhibited significantly greater anti-proliferative activity, being 10-20 times more potent than quercetin across both cell lines tested. • When combined, the compounds synergistically enhanced the anti-proliferative effects, particularly in androgen receptor (AR) wild-type LAPC-4 cells compared to AR-mutated LNCaP cells.	[169] [170,171]

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						arrests cells in the G1 phase.	• Arctigenin was notably effective at inhibiting AR protein expression in LAPC-4 cells. The combination treatment showed significant inhibition of both AR and PI3K/Akt pathways relative to control groups. • A protein array analysis indicated that the combination therapy affects multiple pathways, especially the Stat3 pathway in LAPC-4 cells. • Additionally, the mixture significantly reduced the expression of several oncogenic microRNAs, including miR-21, miR-19b, and miR-148a, when compared to controls.	
Kaempferol	Flavanols	Rhizomes of *Kaempferia galanga*	It is given alone or in combination with 5-fluorouracil	In gastric cancer, it acts by the IRE1-JNK-CHOP pathway. In lung cancer, it inhibits PTEN/PI3K/AKT pathway EGFR/ERK, ERRα/γ.	Colon cancer	• Kaempferol is a dietary flavanol mainly derived from the Rhizomes of *Kaempferia galanga.* • It induces autophagic cell death in human hepatic cancer cells by activating the AMPK signaling pathway.	• Kaempferol was found to enhance autophagy and induce cell death in gastric cancer (GC) cells. • This was evidenced by an increase in LC3-I to LC3-II conversion and a decrease in p62 levels. • The study also demonstrated that kaempferol triggers	[172–174]

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					• Induce cell death by activating IRE1-JNK-CHOP mediated ER stress in gastric cancer cells. • In lung cancer, it inhibits the PTEN/PI3K/AKT pathway and mediates autophagy.	autophagic cell death through the activation of the IRE1-JNK-CHOP signaling pathway, indicating an endoplasmic reticulum (ER) stress response. Inhibiting ER stress was shown to suppress kaempferol-induced autophagy a	
Myricetin	Flavanols	Vegetables, nuts, berries, fruits, and tea	Myricetin enhances the chemosensitivity of 5-FU.	NDPK mTOR/AKT, PIM1/CXCR4, BMMP-2/Smad, MAPKs	Colon cancer cells	• Myricetin promotes apoptosis by different regulating pathways. • It induces cell death by Bax and AIF expression. • It induces apoptosis in HCT-15 human colon cancer cell lines, increases the Bax/Bcl-2 ratio, and leads to cell death in HCT-15 cells.	• Myricetin effectively inhibits key anti-apoptotic signaling pathways, including extracellular signal-regulated kinase (ERK1/2) in lung cancer cell lines and phosphatidylinositol 3-kinase (PI3-K) in cervical and lung cancer cell lines. • By impacting these pathways, which influence the growth and survival of cancer cells, myricetin can lead to cell cycle progression and proliferation.	[175,176]
Hesperidin	Flavanones	Citrus fruits such as orange, lime, tangerines	It exhibits synergistic activity with doxorubicin, cytarabine, tamoxifen, and quercetin.	PI3K/AKT (liver), SDF-1/CXCR-4(lung), SDF-1/CXCR-4(lung), Nrf2/ARE/HO-1(liver)	Leukaemia, liver cancer, breast cancer, renal cancer, colon cancer, lung cancer	• Hesperidin acts with numerous targets and inhibits cancer cell proliferation by cell cycle arrest and apoptosis.	• Hesperidin, significantly decreased cell survival in the presence and absence of insulin over time compared to untreated cells. • Additionally, hesperidin notably	[177,178]

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					• Hesperidin induces apoptosis by accumulating ROS and regulating the kinase 1/ junN-terminal kinase pathway. • It arrests the cell cycle by downregulating cyclin D1, E1, and cyclin-dependent kinase 2. • Combined with fisetin, it inhibits cellular proliferation by triggering programmed cell death in myeloid leukemia cells.	increased apoptosis in NALM-6 cells, even under hyperinsulinemic conditions. • It also inhibited insulin-induced phosphorylation and activation of Akt, IκBα, and GSK-3β while reducing the expression of IKKα.	
Hesperetin	Flavanones	Citrus fruits	It is given in combination with luteolin to increase apoptosis. It produced synergistic effects with dextran, doxorubicin, and many chemotherapeutic drugs.	NF-Kβ, TNF-α, MAPK, COX-2, PCNA, BCL-xL	Lung cancer, breast cancer, liver cancer, prostate cancer	• It is an aglycon of hesperidin. • *In vivo* and *in vitro* studies have shown that it exhibits anticancer activity by apoptosis, inducing cell cycle arresting in the G0/G1 phase. • It induces apoptosis and reduces cell growth in MDA-MB-231 and SKBR3 breast cancer cells.	• Hesperetin promotes the degradation of DOT1L and reduces histone H3K79 methylation, thereby inhibiting the metastasis of gastric cancer through its epigenetic effects.	[179]

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Oroxylin A	Flavonoid	*Oroxylum indicum*, *Scutellaria baicalensis*, and *S. lateriflora*	It produces synergistic action with 5-fluoro uracil anti-cancer agent and is used in colon cancer	P53, Bcl-2, ERK/MAPK, CXCL12, STAT3	Breast cancer, Cervical cancer, colon cancer, glioma, hematological malignancies	• It inhibits the proliferation of human breast cancer cells. • It exerts an antitumor effect against hepatocellular carcinoma cells.	• Oroxylin A significantly reduced the TPA-induced rise in SHCBP1 expression. • The anti-inflammatory effect of oroxylin A was diminished by SHCBP1 overexpression. • Furthermore, TPA enhanced nuclear NF-κB p65 expression, while SHCBP1 siRNA notably lowered nuclear NF-κB p65 levels in JB6 P+ cells.	[180,181]
Wogonin	Isoflavones	Root of *Scutellaria baicalensis* Georgi	A combination with artesunate is used to exhibit an anti-hepatocellular carcinoma effect.	P53, PI3K-AKT, MMP-9, HIF-1α, cFLIPL and IAP, Nrf2/ARE	Bladder cancer, breast cancer, leukemia	• It inhibits PTK and reduces tumor progression. • It exerts a moderate effect on human bladder cancer cells	• Wogonin downregulated the expression of TXNRD2, a key antioxidant enzyme that regulates cellular ROS levels, by modifying histone acetylation at its regulatory region. • Furthermore, in senescent MDA-MB-231 cells induced by wogonin, there was an activation of NF-κB and inhibition of STAT3. • This treatment also suppressed tumor cell growth, promoted macrophage M1 polarization in vitro, and enhanced immune cell	[182,183]

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							infiltration in xenografted tumors in vivo.	
Delphinidin	Anthocyanin	Maqui berry and other vegetables	It is given as a co-treatment with phorbol Myristate Acetate	AMPK/SIRT1, NF-κB, Bcl2, Ki67, MMP9 and PCNA	Colorectal cancer, Prostate cancer, breast cancer	• It induces apoptosis and inhibits cell growth of highly aggressive human PCa PC3 cells *in vitro.*	• Delphinidin has shown potential in cancer prevention and therapy by inhibiting the Wnt/β-catenin (canonical Wnt) signaling pathway. • It also promotes antioxidation by modulating the expression of phase II antioxidant enzymes through the Nrf2/ARE signaling pathway. • Furthermore, delphinidin can reduce inflammation by affecting the PI3K/Akt and NF-κB pathways, which lowers COX-2 levels and induces iNOS synthesis. • Additionally, delphinidin decreases receptor tyrosine kinase (RTK) activity and targets the MAPK pathway and the AP-1 factor, potentially preventing the early stages of cancer development.	[184,185]
Silibinin	Flavonoids	*Silybum marianum* seeds	It acts on CDLIs, decreases the level of cyclins and	CDKIs, VEGF, iNOS, EGFR, MAPKs, STATs,	Prostate cancer, colon cancer, lung cancer	• Silibinin is the main component of the silymarin complex and contains 50-60% of it.	• Silibinin is recognized for its ability to activate cellular checkpoints and cyclin-dependent kinase	[186]

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			CDKs, and induces cell cycle arrest.	PI3K/Akt, COX2, NF-κB		• Poor bioavailability due to its multi-ring structure. • Exhibit anti-angiogenic properties by inhibiting VEGF • It has an anti-migratory and anti-invasive effect on highly bone metastatic ARCaP cells.	inhibitors (CDKIs), lower the levels of both cyclins and CDKs, and induce significant cell cycle arrest in cancer cells. • Additionally, silibinin influences CDK-CDKI interactions, CDK kinase activity, Rb phosphorylation, and E2F activity in cancer cells. • It also promotes the activation of apoptotic pathways (both extrinsic and intrinsic), leading to apoptotic death in various cancer cell types. • Moreover, silibinin affects multiple cellular signaling pathways and molecules, including EGFR, MAPKs, AP1, HIF-1α, STATs, PI3K/Akt, β-catenin, IGF-IGFBP3, NF-κB, and COX2. • These molecular changes are largely responsible for silibinin's wide range of biological effects.	
Epigallocatechin gallate	Flavanols	Green tea	It has synergistic action with curcumin.	NF-κB, Bcl2, MMP-2, ERK1/2, MMP-9, TNF-α	Colon cancer, renal cancer, breast cancer, and leukemia	• The study reported that tea polyphenols decrease the HCT-116 cell cycle	• EGCG) triggers apoptosis through various mechanisms. It inhibits the PI3K/AKT/p-BAD cell	[187] [188,189]

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					at 40 μM concentration in the G1, S, and G2 phases. • It prevents mutagenesis by decreasing DNA damage, and it inhibits anchorage-independent growth and invasion by decreasing NOX1.	survival pathway, resulting in the downregulation of Bcl-2 and the upregulation of Bax, and activates the FASR/caspase-8 pathway. • Furthermore, EGCG influences additional factors involved in cell proliferation and death, such as the MAPK pathways (phosphoErk1/2) and growth factors (IGF1, IGF receptor, and IGFBP-3). • It also regulates the cell cycle by inhibiting class I histone deacetylase (HDAC) enzyme activity, which increases promoter region accessibility and enhances the expression of p21/waf1 and Bax.	
Chrysin	Flavones	Honey, propolis, and fruits	It has synergistic action with silibinin in breast cancer cells	MAPKs, p38, NF-κB	Leukemia cells, liver cancer, esophageal carcinoma, prostate cancer	• It inhibits the proliferation of MDA-MB-231 cells at 100μM concentration. • Chrysin and phosphorylated chrysin inhibit the growth of cervical cancer cells and HeLa cell lines and induce apoptosis.	• Chrysin induces G1 cell cycle arrest and inhibits HDAC-2 and HDAC-8. Cells treated with chrysin exhibit elevated levels of H3acK14, H4acK12, and H4acK16, along with reduced H3me2K9 methylation. • Notably, p21 induction by chrysin occurs independently of the p53 status. The chromatin	[190,191]

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						remodeling at the p21WAF1 promoter leads to increased p21 activity, heightened STAT-1 expression, and various epigenetic modifications, which collectively contribute to cell cycle arrest and apoptosis.	
Tangeretin	Flavones	*Citrus sinensis*(orange), *Citrus aurantium*(grapes)	It inhibits STAT-3 and decreases the proliferation of cancer cells	STAT-3	Breast cancer	• The study showed that tangeretin 54μM concentration given to hamsters in diet inhibits tumor cell growth 50-60% • *In vitro,* it suppresses the proliferation of MDA-MB-231 and MCF-7 cells • It arrests the cell cycle in the G1 phase.	• In human prostate cancer LNCaP cells, both compounds inhibited cell growth, but PMF2 demonstrated stronger effects and exhibited lower cytotoxicity to normal cells. PMF2 induced apoptosis by upregulating the expression of proapoptotic proteins Bad and Bax, downregulating the antiapoptotic protein Bcl2, and activating caspase-3 and PARP. • Furthermore, PMF2 was able to demethylate the p21 promoter and suppress the expression of DNMT3B, HDAC1, HDAC2, and HDAC4\5\6. • Additionally, PMF2 was found to interact with DNMTs in vitro, potentially leading to reduced DNMT catalytic activity.	[166,192,193]

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Genkwanin	Non-glycoside flavonoid	*Callicarpa americana*	It has synergistic action with PI3K/Akt inhibitor	PI3K/Akt	Breast cancer, lung cancer	• It exerts activity by inducing apoptosis and inhibiting angiogenesis. However, the actual mechanism is not yet clear.	• Genkwanin was found to significantly inhibit cell growth and proliferation. Mechanistic investigations revealed that genkwanin induced cell cycle arrest at the G2/M phase by reducing the expression levels of cyclin-dependent kinase 2 (Cdc2) and cyclin B1 proteins. • Additionally, genkwanin promoted apoptosis by downregulating poly [ADP-ribose] polymerase 1 (PARP1), B-cell lymphoma-2 (Bcl-2), and B-cell lymphoma-extra large (Bcl-xL) proteins, while increasing levels of cleaved caspase-3 through p53 activation in MDA-MB-231 cells. • Furthermore, genkwanin induced autophagy-mediated degradation of p62. • It also inhibited the expression of phosphoinositide 3-kinase (PI3K)γ-p110, phospho-PI3K, phospho-protein kinase B (AKT), phospho-	[194] [195]

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						p70S6K, phospho-mammalian target of rapamycin (mTOR), and phospho-ULK signaling pathways.	
Naringin	Flavonoid	Extracts of citrus fruits, sour orange, tart cherries, tomatoes and grapes.	The combination of doxorubicin and naringin is being explored as a potential alternative treatment for breast cancer. It is used in combination with cyclophosphamide to reduce its side effects	AKT/mTOR, HER2, MAPKs, ATF3, EGFR, NEU3, Zeb1, JAK2/STAT3	Breast cancer, liver cancer, lung cancer	• It is aglycon of naringnin • It inhibits cancer progression by cell cycle arrest, angiogenesis, and modification in signalling pathways	• The expression levels of miR-17-3p and miR-25-5p were decreased. The decrease in miR-17-3p corresponded with elevated levels of its target mRNAs, which encode the antioxidant enzymes manganese-dependent superoxide dismutase (MnSOD) and glutathione peroxidase 2 (GPx2). • In contrast, the reduced expression of miR-25-5p did not align with the expression levels of its target mRNAs, which encode the pro-inflammatory cytokines Tumor necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6).	[196,197]

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6. Conclusions

According to the body of research on the pathogenic mechanisms of malignancy, genes, and epigenetics are crucial to the development and spread of the disease. Epigenetic modifications are changeable and can be used to improve treatment plans. Naturally occurring substances such as phytochemicals can control or suppress epigenetic modifiers, including DNMTs, HDACs, HMTs, HATs, and others. Many flavonoids, including flavonols, flavanones, and flavones, were addressed in this overview, along with their ability to treat and fight diseases by altering epigenetic processes. It is common practice to fight cancer with a variety of plant-based medications, such as vinca alkaloids (such as vincristine and vinblastine), taxanes (such as paclitaxel as well as docetaxel), camptothecins, and many others. Many phytochemicals, such as flavonoids, have strong anticancer effects and are now through different preliminary research and clinical testing phases. Its poor bioavailability, poor water solubility, fast absorption by healthy cells, poor pharmacological index, and unfavorable impact on the hepatic system constitute a few of their drawbacks. These problems can be solved by creating unique techniques such as nanomedicines. The importance of phytonutrients is growing in the cure and avoidance of malignancy. They provide essential weapons in the fight against cancer because of their ability to reverse epigenetic changes made by cancerous cells. Combinatorial medicines that combine conventional chemotherapy and precision medicine with plant-based chromatin modifiers can improve treatment strategies and lessen adverse effects. Significant research is needed to identify and characterize anti-carcinogenic phytonutrients and their corresponding mechanisms of action. Given the rapid technical advancement, this looks like a viable endeavour in our effort to combat cancer.

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