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Epigenetics of dietary phytochemicals in cancer prevention: fact or fiction Invited Review

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Abstract

Cancer development takes 10–50 years and epigenetics plays an important role. Recent evidence suggests that ~80% of human cancers are linked to environmental factors impinging upon genetics/epigenetics. Since advanced metastasized cancers are resistant to radiation/chemotherapeutic drugs, cancer prevention by relatively non-toxic “epigenetic modifiers” will be logical. Many dietary phytochemicals possess powerful antioxidant and anti-inflammatory properties that are hallmarks of cancer prevention. Dietary phytochemicals can regulate gene expression of the cellular genome via epigenetic mechanisms. In this review, we will summarize preclinical studies that demonstrate epigenetic mechanisms of dietary phytochemicals in skin, colorectal, and prostate cancer prevention. Key examples of the importance of epigenetic regulation in carcinogenesis include hypermethylation of the NRF2 promoter region in cancer cells, resulting in inhibition of NRF2-ARE signaling. Many dietary phytochemicals demethylate NRF2 promoter region and restore NRF2 signaling. Phytochemicals can also inhibit inflammatory responses via hyper-methylation of inflammation-relevant genes to block gene expression. Altogether, dietary phytochemicals are excellent candidates for cancer prevention due to their low toxicity, potent antioxidant and anti-inflammatory properties, and powerful epigenetic effects in reversing pro-carcinogenic events.

Keywords

Skin cancer; colorectal cancer; prostate cancer; dietary phytochemicals; epigenetic modulation; anti-oxidation; anti-inflammation

Introduction

Is cancer a preventable disease? Cancer is a complex chronic disease and cancer development comprises multistep processes [1, 2], involving initiation, promotion, progression, and metastasis [3, 4]. Recent evidence suggests that ~80% of human cancers are linked to

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environmental factors impinging upon the fidelity of the underlying genetic information [4–7]. Cancer development is a long process that typically takes 10–50 years (depending on the tissue/organ), and excessive oxidative stress and inflammation are regarded as vital determinants driving cancer development [8–10]. Since advanced metastasized cancers are resistant to radiation and chemotherapeutic drugs, prevention of early stages of cancer by relatively non-toxic, potent antioxidative and anti-inflammatory dietary phytochemicals would be logical.

During cancer development, particularly during the “promotion” stage, epigenetics has been postulated to play a vital role in driving cellular transformation such as stem cells forming benign microscopic tumors [11]. Feinberg et al. in the 1980s reported that most if not all tumors could be associated with widespread losses and some gains of DNA methylation throughout the genome [12, 13]. This concept was reviewed recently [6, 14] and implicated the role of epigenetics during cancer development.

Epigenetics influences many cellular activities, including cell growth and disease development [15]. Epigenetic mechanisms mediate gene activation/inhibition in response to environmental cues driving three major processes: DNA methylation, histone modification, and noncoding RNA expression[16, 17]. DNA methylation is a chemical modification via DNA methyltransferases (DNMTs) that add methyl groups to DNA molecules to modulate gene expression. Abnormal DNA methylation, such as hypermethylation and hypomethylation is considered a hallmark of cancer development. Hypermethylation of key tumor suppressor genes results in the “silencing” of the genes which drive cancer development[18, 19]. Histone modifications play the role of the “switch” and are post-translational modifications (acetylation/deacetylation and methylation/ demethylation) of histones by which the linkage between DNA molecules and histone proteins changes to either tighten or loosen the interaction, further affecting the gene expression[20]. MicroRNAs (miRNAs) are one of the noncoding RNAs involved in epigenetics and can be classified into tumor-promoting and tumor-suppressing miRNAs, which are upregulated and downregulated during cancer development[21, 22]. The interwind of cellular signaling pathways and epigenetics can also affect genomic alteration in cells[23]. For instance, the KEAP1-NRF2 signaling pathway is associated with the cellular defense system against oxidative stress. Hypermethylation of the NRF2 promoter is observed in several types of tumors and causes cancer progression[24].

Phytochemicals are bioactive ingredients derived from various plants and herbs [25]. Dietary phytochemicals stem from vegetables, fruits, grains, and culinary herbs; therefore, phytochemicals in general have low toxicity when consumed long term [26, 27]. They can exert antioxidant, anti-inflammatory, and anti-angiogenic properties, as well as function against cancer development via regulating receptors, ion channels, ion pumps, cytoskeletons, and transcriptional machinery in cells[28–30]. Additionally, recent research reveals that many dietary phytochemicals would possess epigenetic-modifying abilities [31]. This review aims to summarize preclinical evidence of cancer prevention elicited by dietary phytochemicals via epigenetic mechanisms in skin, colorectal, and prostate cancers.

Natural sources of dietary phytochemicals

Dietary phytochemicals are derived from natural sources, for example, vegetables, fruits, and medical herbs. Phytochemicals are divided into primary and secondary metabolites produced by plant metabolism and they can perform bioactive activities upon oral ingestion and they play a vital role in disease prevention and reduction in risk factors via their innate attribution [32]. In general, phytochemicals can be classified into five main categories: (1) phenolic phytochemicals; (2) terpenoids; (3) glucosinolates; (4) polyacetylene; (5) phytosterols and phytostanols[33].

Phenolic phytochemicals account for 45% of known phytochemicals and are further classified as phenolic acids, flavonoids, stilbenes, and lignans [33]. Under flavonoids, there are two subgroups, anthocyanins and anthoxanthins. Anthoxanthins include flavonols, flavones, flavanones, flavanols, and isoflavones [34] and unlike anthocyanins that are responsible for the emission of red, blue, and purple colors in vegetables, anthoxanthins, covering fiver major subclasses, are colorless or white to yellow compounds [33, 35]. Flavonoids possess antioxidant and anti-inflammatory activities that contribute to, inhibition of carcinogenesis, involving induction of cell cycle arrest or apoptosis, regulation of the host immune system, and changes in cellular signaling pathways [36]. Examples of phenolic phytochemicals include curcumin, luteolin, resveratrol, pelargonidin, and more.

Terpenoids are bioactive compounds of essential oils that can be extracted from roots, seeds, and other parts of plants [37]. Biochemically, terpenoids are terpenes modified with various functional groups and they are secondary metabolites of aromatic and medicinal plants [38]. Terpenoids have important biological activities, such as antioxidant, anti-inflammatory, neuroprotective abilities, and anti-cancer effects, including induction of apoptosis, inhibiting proliferation, and inhibiting tumor growth [39]. Fucoxanthin, ursolic acid, and corosolic acid are examples of terpenoids.

Glucosinolates are sulfur-containing glucosides that are widely found in cruciferous vegetables and oilseeds [33]. The bioactive compounds, indole, allylic sulfur compounds, and isothiocyanates, are encompassed within glucosinolates [40]. The most common example is sulforaphane, which is a well-known activator of the NRF2-ARE signaling pathway and an HDAC modulator [41].

Phytosterols and phytostanols are plant sterols and the human body is unable to synthesize them; therefore, the only source is from dietary ingestion, such as vegetable oils, cereals, nuts, and seeds [42]. The health effects of phytosterols and phytostanols include lowering cholesterol levels, cancer prevention, and immunomodulation [33]. Polyacetylenes are emerging phytochemicals involved in cancer prevention and are found in apiaceous vegetables. Polyacetylenes have antioxidant and anti-inflammatory properties. The involving cellular mechanisms and molecular pathways of polyacetylene action are identified as the NF-κB pathway, antioxidant response elements, regulation of the cell cycle, and apoptosis [43].

Considering the overall strategy in cancer prevention, consuming vegetables and fruits is a convenient and logical way to ingest a wide range of phytochemicals that can provide cancer

prevention in the general population. For higher-risk individuals, pharmacological doses of a combination of bioactive phytochemicals with low toxicity would be a logical approach [44, 45].

Skin cancer prevention by dietary phytochemicals

The development of skin cancer is initiated by diverse drivers, such as DNA damage, chronic inflammation, suppression of the immune system, photoaging, and/or mutations. The process is accompanied by genetic and epigenetic changes, which further trigger multiple signaling pathways that drive skin carcinogenesis [46]. Non-melanomatous skin cancer (NMSC) is one of the most prevalent cancers in the world[47]. Basal cell carcinoma and squamous cell carcinoma are the two most commonly diagnosed types of NMSC accounting for 99% of all NMSC cases[48]. Exposure to ultraviolet (UV) radiation and environmental chemicals/pollutants, for example, arsenic and benzo[a]pyrene (B[a]P), are the most common known causes of NMSC[49]. Recently, our research revealed that exposures to UV or benzo[a]pyrene (B[a]P) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) led to DNA methylomic and transcriptomic changes at different stages of skin carcinogenesis[50, 51]. Additionally, increasing research supports alterations in cellular metabolism related to the epigenetic machinery is further linked to skin cancer development.

Polyphenols

Several polyphenols have activity against skin cancer. Tea catechins are known to re-activate silenced tumor suppressor genes, p16INK4a, and Cip1/p21 via epigenetic regulations including decreased global DNA methylation and increased histone acetylation (H3-Lys 9 and 14; H4-Lys 15,12 and 16) levels in A431 epidermoid carcinoma cells [52].

The topical application of apigenin has long been recognized as a potential chemoprevention strategy against skin carcinogenesis induced by TPA or UV irradiation in susceptible mouse strains [53, 54]. Later studies with apigenin have revealed a demethylation effect coupled with attenuated DNMT and HDAC activity at 15 CpG sites in the NRF2 promoter in JB6 P+ cells [55].

Pelargonidin has been shown to possess excellent potential in blocking TPA-induced cell transformation by reducing protein levels of genes encoding DNMTs and HDACs [56] and further decreasing DNA methylation in the NRF2 promoter region of JB6 P+ cells [56].

Isothiocyanates

Several isothiocyanates have demonstrated potential in restoring the epigenetic landscape that contributes to skin carcinogenesis [57, 58]. Sulforaphane (SFN), a well-studied anti-cancer phytochemical, has been shown to reactivate NRF2 through the downregulation of DNMTs and HDACs in TPA-exposed JB6 P+ epidermal cells [41]. Both sulforaphane and tea polyphenols were found to suppress the expression of Bmi-1 and Ezh2, the highly expressed polycomb group proteins (PcG) and regulators of chromatin remodeling in skin cancer [59–62].

We reported the chemopreventive epigenetic effects of moringa isothiocyanate (MIC-1) in TPA-challenged JB6 P+ cells. We identified differentially methylated regions and differentially expressed genes, including the cancer-related genes Tmpt, Tubb3, and Muc2, the GTPases Gchfr and Igtp, and the cell cycle-related gene Cdc7 [63]. The Muc2 gene is reported to be induced by inflammatory factors (IL-1β, TNFα) via the NF-κB pathway[64]. The correlative analysis between transcriptome gene expression and the DNA methylome showed that MIC-1 treatment led to hypermethylation and downregulation of the Muc2 gene[63].

Terpenoids

We found that the synthetic triterpenoid CDDO (2-cyano 2,3-dioxoolean-1,9-dien-28-oic acid) blocked TPA-induced skin cell transformation dose-dependently at methylome and transcriptome levels in JB6 P+ cells. Five-day treatment (CDDO dose of 50 nM) revealed that LYL1 basic helix-loop-helix family members- Lyl1, Lad1, and Dennd2d genes-were the most significantly differentially expressed genes after CDDO treatment. The TPA-induced methylation status of Tmem253, Bco2, and Madd also was reversed by CDDO. Furthermore, CDDO significantly restored the NRF2-ARE pathway of Nqo1 that was inhibited by TPA by decreasing methylation of its CpG promoter[65]. We also determined that fucoxanthin (FX) reversed the TPA-induced transformation of JB6 P+ cells by decreasing methylation of the NRF2 promoter region and significantly reducing DNMT activity but not affecting HDAC activity [66].

An integrative study of the CpG methylome and RNA transcriptome after treatment with ursolic acid (UA) showed increased activity of antioxidant, anti-inflammatory, and anticancer pathways in UVB-induced nonmelanoma skin carcinogenesis. Yang et al. observed that central antioxidant genes, such as NRF2 and NQO1 were upregulated by UA treatment in the early phase of UVB-induced carcinogenesis, and significant hypomethylation of CpG sites of these genes was also revealed by the methylation analysis [67].

An epigenetic study with corosolic acid (CA) revealed novel molecular targets for the prevention of early stages of skin cancer. The results of methylation sequencing showed that biomarkers such as Smad-3, Tasp1, Uri1, Nsg2, Madd, Dusp22, and Rassf were hypermethylated by TPA challenge and were hypomethylated by CA treatment [68].

Lotus leaf ethanolic extract

Lotus leaf ethanolic extract is known to reduce the neoplastic transformation of JB6 P+ cells, potentially by activating the NRF2 pathway and regulating epigenetic DNA methylation and histone acetylation [69]. Several canonical signaling pathways were unveiled by Ingenuity Pathway Analysis (IPA) analysis indicating that the application of these phytochemicals was able to inhibit inflammatory response pathways (NF-κB signaling, IL-1 signaling) and activate NRF2-mediated antioxidative response in the skin cancer model[63, 68]. The studies of using phytochemicals to prevent skin cancer carcinogenesis are listed in Table 1.

Colorectal cancer prevention by dietary phytochemicals

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world and has a high incidence and mortality rate[70]. In the United States, according to the American Cancer Society (ACS), nearly double the number of young adults under 55 are being diagnosed with CRC today compared to a decade ago, and more are dying from the disease each year, hence there is an urgent need to identify causing factors and preventive strategy. BRAF mutations, microsatellite instability, KRAS mutations, and PIK3CA mutations all are implicated in CRC development. Dysregulation of the gene products such as growth factors, growth factor receptors, protein kinase, inflammatory cytokines, inflammatory enzymes, proapoptotic proteins, anti-apoptotic proteins, tumor suppressors, transcription factors, and their relevant signaling pathways are reported to be involved in carcinogenesis[71–73].

One widely used rodent model is azoxymethane (AOM) and dextran sulfate sodium (DSS) driven colitis- associated CRC. AOM functions as a carcinogen inducing aberrant crypt foci, and DSS is an inflammatory agent damaging the colonic epithelium[74, 75]. Therefore, the AOM/DSS-driven mouse model is often used to induce inflammation and tumor initiation in CRC. Intractable epigenetic alteration has been linked to CRC development. In particular, aberrant methylation of the regulators is observed in an AOM/DSS-induced CRC or a DSS-induced inflammation mouse model[76]. Lipopolysaccharide (LPS) is a unique component of the outer cell membrane of the gram-negative bacteria and it induces inflammation via activating the Toll-like receptor 4 (TLR4)-mediated signaling pathways in intestinal epithelia cells[77]. Moreover, CRC patients are observed having higher LPS concentration in blood and CRC tissues than the healthy people. Consequently, LPS-challenged cellular model are often used *in vitro*[78, 79].

Polyphenols

Guo et al. demonstrated that curcumin (CUR) reduced methylation of the promoter region of the tumor suppressor gene - DLEC1 in human colon cancer HT29 cells through its demethylating effects. In addition, curcumin decreased protein expression of DNA methyltransferases and histone deacetylases[80]. Guo et al. subsequently confirmed the effect of curcumin on the epigenome on the inflammatory response in the AOM-DSS mouse model of colorectal cancer. Through a series of experiments including SureSelect methyl-seq and RNA-seq, they found that curcumin restored AOM-DSS-induced hypomethylation of Tnf. The hypomethylated state of inflammation-relevant genes such as Duoxa2, Gja1, Icam1, Igfbp4, Itgb2, Lgals9, and Pf4 were also reversed by curcumin, inhibiting the abnormally high expression of these genes induced by AOM/DSS[81].

In a study of the flavonoid dietary phytochemical luteolin (LUT), the epigenetic regulation of the NRF2-ARE pathway by LUT in HCT116 cells was studied. LUT was able to reduce the methylation of the NRF2 promoter region, leading to significant changes in the mRNA and protein expression levels of genes in NRF2 and its related genes (Ho-1 and Nqo1). Additionally, LUT treatment reduced protein level and enzymatic activities of DNMTs and HDACs which were associated with regulation of NRF2. All these results pointed to the potential anticancer activity of LUT[82].

Resveratrol, found in peanuts, red grapes, blue barriers, and rasberries, has been shown to prevent inflammation-driven colorectal cancer by altering the expression of miRNA-101b and miRNA-455 and down-regulating inflammatory stress markers such as p53[83, 84]. Altamemi et al. reported that resveratrol treatment reduced protein levels of IL-6 and TNF-α and raised the expression of two anti-inflammatory miRNAs, miRNA-101b and miRNA-455 in a DSS-induced colitis mouse model [84].

Isothiocyanates

In human colon cancer HCT116 and SW8409 cell lines, sulforaphane (SFN) or its analogs affect HAT/HDAC activity and decrease the expression of HDAC3, P300/CBP-associated factors, as well as KAT2A/GCN5 and DNMT1, while enhancing acetylation and degradation of repair proteins such as CtIP[85]. Additionally, SFN treatment in Caco-2 cells demethylated the NRF2 promoter region and thus activated the NRF2 signaling pathway. It was observed that DNMT expression was reduced by SFN treatment[86].

In Liu and Dey's study, a 0.12% phenethyl Isothiocyanate (PEITC)-enriched diet fed to mice lowered inflammation of the colonic mucosa and submucosa during AOM/DSS-induced colitis. Further *in vitro* experiments suggested the underlying mechanism was related to the inhibition of NFκB1 protein by PEITC treatment. Epigenetically, the mRNA expression of NFκB1 displayed an inverse correlation with tri-methylation of lysine 27 on histone 3 near the NFκB1 promoter region in a time-dependent manner. PEITC increased the level of H3K27me3 with a rise in the expression on the NFκB1 gene. PEITC mitigated colon carcinogenesis via modulating NFκB1 signaling[87].

Betalain

The betaine pigment indicaxanthin (IND) from cactus fruit exhibited anti-inflammatory and cytotoxic activity in a variety of colorectal cancer cell lines. Ragusa et al. concluded that IND affected autophagic activity by promoting the demethylation of CpG islands in promoters of ATG7 and ATG3 in Caco-2 cells. In addition, the up-regulation of the expression of LC3-II and Beclin1 by IND can further promote the formation and fusion of autophagosomes in Caco-2 cells[88].

Water extract of *Ilex rotunda* (WIR)

A standardized water extract of *Ilex rotunda* (WIR) was analyzed to evaluate the potential role of a microRNA (miRNA)-dependent mechanism for the prevention of colon cancer. WIR, with its rich content of triterpenoids, restored the up-regulated levels of miR-31–5p that were triggered by AOM/DSS administration in C57BL/6 mice and inhibited ectopic expression of LATS2 and YAP genes that were regulated by miR-31–5p[89].

Through epigenetic modulation, phytochemicals regulate the NRF2-ARE signaling pathway to exert antioxidant effects and mediate the NFκB signaling pathway against inflammation. Table 2 lists the phytochemicals that have been shown to have potential for preventing colorectal cancer.

Prostate cancer prevention by dietary phytochemicals

Prostate cancer (PCa) is a leading cause of male death associated with cancer in the United States[90]. The development from prostatic intraepithelial neoplasia to androgen-independent invasive carcinoma is a long-term process, which may take years to decades[91]. During tumor progression, genetic and epigenetic alterations are involved[92]. Two murine models have been developed to study PCa. (1) Transgenic adenocarcinoma of mouse prostate (TRAMP) mouse model is commonly used. TRAMP mice, incorporating SV40 early-region tumor antigens, mimic human prostate carcinogenesis and exhibit tumor transformation via interactions with tumor suppressor gene products[93, 94]. The NRF2-ARE signaling pathway is reported to be gradually downregulated during tumorigenesis in TRAMP mice[95]. (2) Phosphatase and tensin homolog located on chromosome 10 (*PTEN*) mouse model is another commonly used PCa model. *PTEN* is a tumor suppressor gene and one of the most frequently mutated/deleted genes in PCa[96]. *PTEN* deletion has been strongly linked to inflammation. In prostate-specific *PTEN* null mice, the expression of CXCL8/IL-8, a pro-inflammatory chemokine promoting tumorigenesis is increased [97]. More importantly, *PTEN* deletion impacts the epigenome and transcriptome of prostate cells. This hypothesis was examined in a prostate-specific *PTEN*-KO mouse prostatic adenocarcinoma model through DNA methyl-Seq and RNA-Seq analyses. Loss of *PTEN* drove global changes in DNA CpG methylation and transcriptomic gene expression and was strongly associated with activation of several inflammatory and immune molecular pathways during PCa development[98]. These findings yield biomarkers of the critical molecular pathways that can be targeted by phytochemicals via epigenetic regulation for the prevention and treatment of PCa in human trials.

Polyphenols

Li et al. investigated the epigenetic effects of the synthetic curcumin analog FN1 in TRAMP C1 cells. FN1 was synthesized by coupling pyridyl aldehyde with tetrahydrothiopyran-4-one.[99]. FN1 treatment in TRAMP C1 cells demethylated the NRF2 promoter region, restored NRF2 expression, and increased the level of downstream genes, such as NQO-1, HO-1, and UGT1A1. FN1 also significantly reduced levels of DNMT1, DNMT3a, DNMT3b, and HDAC 4[93]. The investigation of the effects of other synthetic curcumin derivatives, E10 and F10 was conducted. E10 and F10 were synthesized by coupling the substituted benzaldehyde with tetrahydropyran-4-ones and tetrahydrothiopyran-4-one, respectively[99]. The results showed that both compounds were more potent in increasing NRF2 expression than curcumin and SFN. F10 mitigated the summation of H3k27me3 and induced hypomethylation on the NRF2 promoter. F10 also downregulated DNMTs (DNMT1, DNMT3a, DNMT3b) and HDACs (HDAC1, HDAC4, and HDAC7). F10 can restore the NRF2 signaling pathway via demethylation, reduction of DNMTs and HDACs, and suppression of H3k27me3 accumulation [100].

Isothiocyanates

In the study by Zhang et al., Sulforaphane (SFN) treatment demethylated the first five CpGs of the NRF2 promoter in TRAMP C1 cells and activated mRNA and protein levels of NRF2 and NQO-1. SFN treatment attenuated DNMT1, DNMT3a, and HDACs 1, 4, 5, and 7 at the

protein level while enhancing acetyl-histone 3 levels which bound to the NRF2 promoter[101]. SFN exerted its preventive effects via epigenetically modulating the NRF2 promoter region and re-activating the NRF2-ARE signaling pathway in TRAMP C1 cells.

The study using TRAMP mice by Wu et al. observed that the phenethyl Isothiocyanate (PEITC) diet reversed or attenuated the induction of cell cycle/Cdc42 signaling, inflammation, and cancer-related signaling in the prostate tissues of TRAMP mice. Pathway analysis revealed differences in signaling between wild-type and TRAMP mice, including pancreatic adenocarcinoma signaling activation in TRAMP mice. Analyzing DNA methyl sequencing data led to the observation of PEITC-activated reduction of global methylation alteration in PCa development. Integration of DNA methylation and RNA expression profiles of TRAMP and TRAMP+PEITC identified PEITC reversed the inverse correlation between RNA expression and DNA methylation in 28 genes. Among these genes, Arhgap40, Ebf4, kcnq4, and Papln were validated by qPCR [91].

In addition to decreasing global methylation, PEITC can prevent PCa cell invasion via upregulation of miRNA-194. Zhang et al. stated that PEITC treatment in LNCaP cells upregulated the expression of miRNA-194, which targeted bone morphogenetic protein 1 (BMP1) and further inhibited the expression of central oncogenic matrix metalloproteinases, MMP2 and MMP9. The axis of miRNA-194/ BMP1/ MMP2/9 unveiled the regulation of PCa cell metastasis by PEITC[102].

Terpenoids

Combinatorial treatment with natural compounds including ursolic acid (UA), curcumin (CUR), and resveratrol (RES) was studied in HMVP2 cells and male FVB/N mice subcutaneously injected with HMVP2 cells. The results showed that the treatment with UA+CUR and UA+RES could inhibit prostate tumorigenesis and account for critical regulation of cancer metabolism [103]. In a recent study, Wang et al. observed that UA exerted its protection against tumor development initiated by *PTEN* deletion at different stages of PCa. UA treatment decreased *PTEN* KO-triggered differentially methylated regions (DMRs) and reversed *PTEN* KO-induced overexpression of PCa-relevant oncogenes, Has3, Cfh, and Msx1. Correlation analysis of differentially expressed genes (DEGs) and DMRs revealed that the mRNA expression of the tumor suppressor gene (BDH2) and oncogenes (Ephas, Isg15, Nos2) were correlated with the CpG methylation status of the promoter region in the UA-treated group at the early phase. The pathway analysis indicated that UA treatment reversed *PTEN* KO-activated inflammatory pathways, such as NF-κB signaling, IL-6 signaling, and IL-8 signaling[104]. Cellular and animal studies on the prevention of PCa indicate that phytochemicals provide the restoration of the NRF2-ARE signaling pathway through demethylation of the NRF2 promoter region and diminishment of DNMTs and HDACs expression.

Benzoquinone

Su et al. examined the anticancer properties of Z-Ligustilide (Lig) and supercritical CO2 extract of *Radix Angelica Sinensis* (RAS) in TRAMP C1 cells. RAS is a dried root of

Angelica sinensis and has been served as medicinal plant and supplementary food for centuries. Lig is one of bioactive compounds from a lipophilic extract of RAS[105]. The finding suggested that NRF2 expression was restored via epigenetic changes. This led to increased mRNA and protein levels of NRF2 and its target genes such as HO-1, NQO1, and UGT1A1. The treatment of Lig and RAS extract demethylated the first five CpGs and significantly reduced the relative amount of methylated DNA in the NRF2 promoter region. Additionally, Lig and RAS extract treatment inhibited DNA methyltransferase activity in TRAMP C1 cells[105]. Table 3 summarizes the phytochemicals that affect epigenetic pathways and are used to inhibit PCa growth and contribute to cancer prevention.

Summary

Skin, colorectal, and prostate cancers are increasing in new cancer cases in the US. Cancer development is a long process. It encompasses an imbalance of oxidative stress and excessive inflammation that cause the dysfunction of multiple signaling pathways leading to cancer initiation and progression. Many phytochemicals in our everyday diet possess powerful antioxidant and anti-inflammatory properties that are hallmarks of cancer prevention. Recent evidence suggests that epigenetic modulation of these critical signaling pathways by phytochemicals is related to their antioxidant and anti-inflammatory effects. For example, modulation of the NRF2-ARE signaling pathway and the NF-κB signaling pathway has been shown to contribute to the overall efficacy of cancer prevention by phytochemicals.

Despite a wide range of promising dietary phytochemicals that have been reported to have preventive activity in preclinical research, the translation of dietary phytochemicals to clinical use has been limited. Only a few of these agents are applied to the clinical studies. There is an urgent need to expedite the testing of these agents in clinical trials involving appropriate high-risk individuals with the proper dosing, formulation, biomarker endpoints (surrogate and tissue targeted), and integration of pharmacokinetic (PK)-pharmacodynamic (PD) inputs. Taken together, this article summarizes the latest preclinical research and hypotheses on cancer prevention by dietary phytochemicals via epigenetic modulation in cancers of the skin, colorectum, and prostate. In the general population, cancer prevention with a healthy lifestyle composed of exercise and consuming vegetables, fruits, herbs, and spices is a convenient and logical way to ingest a wide range of phytochemicals that can protect against cancer development. For higher-risk individuals, pharmacological doses of a combination of bioactive phytochemicals and/or phytochemical combinations with pharmacological agents of low toxicity would be logical to test for preventing cancer development [44, 45].

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Abbreviations

AOM	Azoxymethane
B[a]P	Benzo[a]pyrene
BMP1	Bone morphogenetic protein 1
CA	Corosolic acid
CDDO	2-cyano 2,3-dioxoolean-1,9-dien-28-oic acid
CpG	5’-C-phosphate-G-3’
CRC	Colorectal cancer
CUR	Curcumin
DEG	Differentially expressed gene
DMR	Differentially methylated region
DNMT	DNA methyltransferases
DSS	Dextran sulfate sodium
FX	Fucoxanthin
HAT	Histone acetyltransferase
HDAC	Histone deacetylases
IND	Indicaxanthin
Lig	Z-Ligustilide
LUT	Luteolin
MIC-1	Moringa isothiocyanate
miRNA	MicroRNA
MMP	Matrix metalloproteinases
NMSC	Non-melanoma skin cancer
PCa	Prostate cancer
PcG	Polycomb group proteins
PD	Pharmacodynamics
PEITC	Phenethyl Isothiocyanate
PK	Pharmacokinetics
PTEN	Phosphatase and tensin homolog located on chromosome 10

RAS	Radix Angelica Sinensis
SFN	Sulforaphane
TPA	12-O-tetradecanoylphorbol-13-acetate
TRAMP	Transgenic adenocarcinoma of mouse prostate
UA	Ursolic acid
UV	Ultraviolet
WIR	Water extract of *I. rotunda*

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Table 1.

Dietary phytochemicals with activity for skin cancer prevention via epigenetic mechanisms.

Phytochemicals	Cellular/ Animal Model	Epigenetic Mechanism	Reference
Tea catechins	A431 cells	Restore silenced tumor suppressor genes, p16INK4a and Cip1/p21 via decreasing global DNA methylation and increasing histone acetylation	52
Apigenin	JB6 P+ cells	Demethylation coupled with reduction of DNMT and HDAC activity.	55
Pelargonidin	TPA-induced JB6 P+ cells	Reduce protein levels of genes encoding DNMTs and HDACs and decrease DNA methylation in the Nrf2 promoter region.	56
Sulforaphane	TPA-induced JB6 P+ cells	Reactive Nrf2 via downregulation of DNMTs and HDACs	41
Moringa isothiocyanate	TPA-induced JB6 P+ cells	MIC-1 treatment led to hypermethylated and downregualted on the Muc2 gene.	63
CDDO	TPA-induced JB6 P+ cells	Restore Nrf2-ARE pathway by reducing methylation of Nqo1 promoter region.	65
Fucoxanthin	TPA-induced JB6 P+ cells	Decreasse methylation of the Nrf2 promoter region and significantly reduce DNMT activity.	66
Ursolic acid	UVB-exposed female SKH-1 hairless mice	CpG sites of key antioxidant genes (Nrf2, Nqo1) were significantly reversed and hypomethylated by UA treatment in early UVB-induced carcinogenesis.	67
Corosolic acid	TPA-induced JB6 P+ cells	Potential biomarker genes for early skin carcinogenesis such as Smad-3, Tasp1, Uri1, Nsg2, and more were hypermehtylated and hypomethylated by CA treatment.	68
Lotus leaf ethanolic extract	JB6 P+ cells	Activate the NRF2 pathway and regulate epigenetic DNA methylation and histone acetylation.	69

Table 2.

Dietary phytochemicals with activity for colorectal cancer prevention via epigenetic mechanisms.

Phytochemicals	Cellular/ Animal Model	Epigenetic Mechanism	Reference
Curcumin	HT-29 cells	Demethylate the promoter region of DLEC1. CUR treatment lowers protein level of DNMTs and some HDACs.	80
Curcumin	Male C57BL/6 mice challenged by AOM/DSS	Restore AOM-DSS-induced hypomethylation of Tnf and reverse hypomethylation of several inflammation relevant genes.	81
Luteolin	HCT116 cells	Reduce methylation of Nrf2 promoter region and activate the Nrf2-ARE signaling pathway. LUT treatment declined DNMTs and HDACs.	82
Resveratrol	DSS-induced colitis in Male $Apc^{Min/+}$ C57BL/6 mice	Increase the level of two anti-inflmmatory miRNAs: miRNA-101b and miRNA- 455.	84
Sulforaphane or its analogs	HCT116 cells and SW8409 cell	Regulate HAT/ HDAC activities and the relevant DNA repair/ damage singaling pathways.	85
Sulforaphane	Caco-2 cells	Demethylate the Nrf2 promoter region and activate the Nrf2 signaling pathway. Reduce expression of DNMT.	86
Phenethyl Isothiocyanate	Male C57BL/6 mice challenged by AOM/ DSS; SW480 cells	Increase the methylation near the NFκB1 promoter region and thus decrese the mRNA expression of NFκB1.	87
Indicaxanthin	Caco-2 cells	Hypomethylate the promoter regions of ATG7 and ATG3 and further promote autophagic activity.	88
Water extract of *Ilex rotunda*	C57BL/6 mice challenged by AOM/DSS	Restore the level of miR-31–5p raised by AOM and DSS to further inhibit YAP accumulation in the nuclesu.	89

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Table 3.

Dietary phytochemicals with activity for prostate cancer prevention via epigenetic mechanisms.

Phytochemicals	Cellular/ Animal Model	Epigenetic Mechanism	Reference
Curcumin analog FN1	TRAMP C1 cells	Demethylate the Nrf2 promoter region and decrease the level of DNMT1, DNMT3a, DNMT3b, and HDAC 4.	93
Curcumin derivatives F10	TRAMP C1 cells	Demethylate the Nrf2 promoter region, inhibition of H3k27me3 accumulation, and downregulation of DNMTs and HDACs.	100
Sulforaphane	TRAMP C1 cells	Demethylate the Nrf2 promoter region, decrease the level of DNMT1, DNMT3a, and HDACs 1, 4, 5, 7, and raise the Ac-H3 level.	101
Phenethyl Isothiocyanate	Male TRAMP mice	Reduce the global methylation in PCa carcinogenesis and reverse the TRAMP-induced changes in transcriptome and methylome.	91
Phenethyl Isothiocyanate	LNCaP cells	Upregulate miRNA-194 and further inhibit expression of MMP2 and MMP9 to prevent metastasis.	102
Ursolic acid	*PTEN*-KO mice	Reduce differentially methylated regions and the overexpression of PCa-associated oncogenes (Has3, Cfh, and Msx1) induced by *PTEN* deletion. Regulate the methylation status of promoter of tumor suppressor genes and oncogenes in the early-stage development of PCa.	104
Z-Ligustilide (Lig) and Radix Angelica Sinensis (RAS) extract	TRAMP C1 cells	Hypomethylate the Nrf2 promoter region and reduce DNMT activity.	105