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MINIREVIEW

The epigenetic potentials of dietary polyphenols in prostate cancer management[1]

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Abstract: Prostate cancer is a disease that is greatly affected by lifestyle, particularly diet, and is more prevalent in US and European countries compared with South and East Asia. Among several known causes and risk factors, nutrition plays an important role in prostate cancer pathogenesis. Various dietary components including polyphenols have been shown to possess anticancer properties. Dietary polyphenols have been the subject of extensive studies for the last decade because of their anticancer and chemopreventive potentials. Besides possessing various antitumor properties, dietary polyphenols also contribute to epigenetic changes associated with the fate of cancer cells and have emerged as potential drugs for therapeutic intervention. Various polyphenols have been shown to affect DNA methylation, histone posttranslational modifications, and microRNA expression patterns in prostate cancer. In this review, we discuss the contribution of dietary polyphenols to various epigenetic modifications in prostate cancer. Since prostate cancer and diet are intimately associated, polyphenol-rich diets that epigenetically modify tumor biology have great significance in the prevention and management of prostate cancer.

Key words: prostate cancer, dietary polyphenols, chemoprevention, epigenetics, DNA methylation, histone modification, microRNA, apoptosis, growth arrest.

Résumé : Le cancer de la prostate est une maladie grandement affectée par le style de vie, particulièrement la diète, et il est plus fréquent aux États-Unis et dans les pays européens comparativement à l'Asie de sud et de l'est. Parmi les nombreuses causes et facteurs de risques connus, la nutrition joue un rôle important dans la pathogenèse du cancer de la prostate. Plusieurs composants de la diète dont les polyphénols se sont révélés posséder des propriétés anticancéreuses. Les polyphénols alimentaires ont été l'objet d'études approfondies au cours de la dernière décennie à cause de leur potentiel anticancéreux et chimio-préventif. En plus de posséder différentes propriétés anti-tumorales, les polyphénols alimentaires contribuent aussi aux changements épigénétiques associés à la destinée des cellules cancéreuses, et ils sont apparus comme médicaments potentiels en vue d'une intervention thérapeutique. On a montré que les polyphénols affectaient la méthylation de l'ADN, les modifications post-traductionnelles des histones et les patrons d'expression des micro-ARN dans le cancer de la prostate. Dans cet article de synthèse, nous discutons de la contribution des polyphénols alimentaires aux différentes modifications épigénétiques dans le cancer de la prostate. Puisque le cancer de la prostate et la diète sont intimement liés, des diètes riches en polyphénols qui modifient de manière épigénétique la biologie tumorale sont d'une grande importance dans la prévention et la gestion du cancer de la prostate. [Traduit par la Rédaction]

Mots-clés : cancer de la prostate, polyphénols alimentaires, chimio-prévention, épigénétique, méthylation de l'ADN, modification des histones, micro-ARN, apoptose, arrêt de la croissance.

Introduction

Phenolic compounds are found in a large variety of foods such as berries, fruits, legumes, nuts, and vegetables, as well as beverages such as teas, coffees, beers, and wines. They are secondary metabolites, characterized by at least 1 aromatic ring bearing 1 or more hydroxyl groups, and can be classified into 2 major groups: flavonoids and nonflavonoids (see several important dietary polyphenols in Fig. 1). Dietary polyphenols have great value for their antioxidant properties and other biological activities, such as those that impact the cell cycle and modulate signal transduction pathways (Han et al. 2007). They are also known to have anticancer properties.

In recent years, epidemiological studies have clearly shown that polyphenol-rich diets seemingly lower the incidence of various cancers in certain populations (Chao et al. 2010; Kontou et al. 2011; Iwasaki and Tsugane 2011; Pauwels 2011). The molecular mechanisms that contribute to the chemopreventive nature of dietary polyphenols have been widely studied, and multiple molecular signaling pathways and gene targets have been identified (Fresco et al. 2006; Narayanan 2006; Ramos 2008). Dietary polyphenols have been shown to possess the ability to act on intracellular signaling networks, to arrest or reverse the process of carcinogenesis, and to trigger apoptosis in cancer cells (Ramos 2007; Fresco et al. 2010; Weng and Yen 2012). Recent studies have shown that

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Abbreviations: ARHI, aplasia Ras homolog member I; BTG3, B-cell translocation gene 3; CREBBP, CREB binding protein; CYLD, cylindromatosis; DNMT, DNA methyltransferase; EGCG, epigallocatechin gallate; EPHB2, ephrin type-B receptor 2; FOXO3, forkhead box O3; GSTP1, gluthathione S-transferase P1; HAT, histone acetyltransferase; HDAC, histone deacetylase; KLK3/PSA, kallikrein-related peptidase 3/prostate-specific antigen; MBD2, methyl-CpG binding domain protein 2; MCM2, minichromosome maintenance complex component 2; MeCP2, methyl CpG binding protein 2; MTA1, metastasis associated 1; Neurog1, neurogenin 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2 PCAF, P300/CBP-associated factor; PEITC, phenethyl isothiocyanate; PTEN, phosphatase and tensin homolog; RARβ, retinoic acid receptor β; SFN, sulforaphane; SIRT1, sirtuin 1; TMPRSS2, transmembrane protease, serine 2; TRAMP, transgenic adenocarcinoma of the mouse prostate.

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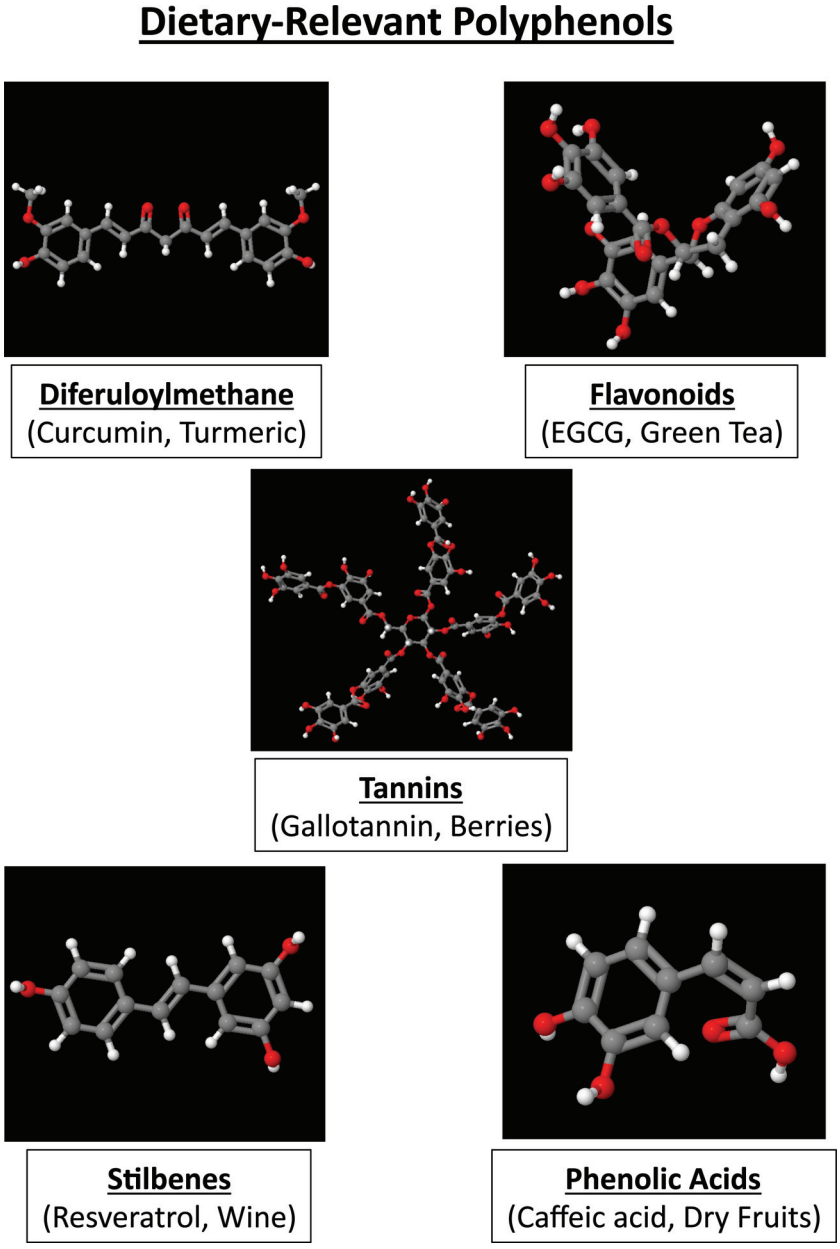
Fig. 1. Polyphenol families and structure of typical members known to have anticancer properties. Diferuloylmethane: curcumin, an antiinflammatory agent found in turmeric (a major component of curry); flavonoids: epigallocatechin gallate (EGCG), an antioxidant catechin found in green tea; tannins: plant secondary metabolites with antioxidant properties responsible for contributing to wine's astringency. Gallotannin is a gallic acid polymer found in berries. Stilbenes: diphenylethylene compounds. Resveratrol (trans-3,5, 4′trihydroxystilbene) is an antioxidant found in the skin of red grapes. Phenolic acids: formed by the combination of a phenolic ring with a carboxylic acid. Caffeic acid or 3-(3,4-dihydroxyphenyl)-2-propenoic acid is an antioxidant found in dry fruits. It is an intermediate in the synthesis of lignin.



dietary polyphenols have the potential to modulate epigenetic alterations by acting on DNA methylation status, affecting histone posttranslational modifications, and modulating microRNA (miRNA) expression (Link et al. 2010; Huang et al. 2011) and are very promising as chemopreventive and therapeutic agents against various cancers (Syed et al. 2007; Khan et al. 2008). Since epigenetic changes are reversible, modulation of epigenetic events are clinically relevant and are excellent potential targets for cancer prevention and therapy.

Epigenetic changes are a major driving force for the genesis and development of various cancers, including prostate cancer. Since prostate cancer is a relatively slow growing cancer and manifests itself in older age, chemoprevention by using diet or dietary components seems to be a more effective approach than postdiagnostic chemotherapy treatments. In this review, we discuss the epigenetic modifications by various dietary polyphenols and their significance in prostate cancer management.

Epigenetic potentials of dietary polyphenols

There are 3 major epigenetic mechanisms that control gene expression patterns as follows: DNA methylation, changes in chromatin composition and conformation, and miRNA. Aberrant DNA methylations, unusual patterns of histone modifications,

and altered miRNA expression have been reported to play an important role in prostate cancer (Abbas and Gupta 2008; Hoque 2009; Fendler et al. 2011; Jerónimo et al. 2011). Various dietary polyphenols have great potential to selectively reactivate tumor suppressor genes and repress oncogenes via epigenetic modifications.

Change in DNA methylation by dietary polyphenols

Methylation at CpG islands plays an important role in gene silencing. Changes in DNA methylation patterns have been associated with prostate cancer (Nelson et al. 2007; Hoque 2009). Hypermethylation of various tumor suppressor genes has been shown to lead to their silencing in prostate cancer. There is ample evidence that dietary polyphenols can alter the DNA methylation patterns in cancer and reactivate various genes (Yu and Wang 2008; Li and Tollefsbol 2010). In prostate cancer, epigallocatechin gallate (EGCG) (Fang et al. 2003) and genistein (Fang et al. 2005) reactivate the methylation-silenced retinoic acid receptor β (RARβ) gene in the prostate cancer cell lines PC3 and LNCaP. B-cell translocation gene 3 (BTG3) is a member of the antiproliferative BTG/Tob gene family and its promoter region is highly methylated in prostate cancer (Majid et al. 2010*a*). Majid et al. (2010*a*) showed that genistein treatment leads to reexpression of the BTG3 gene by demethylating its promoter region, decreasing DNA methyltransferase (DNMT) enzymatic activity and methyl-CpG binding domain protein 2 (MBD2) binding activity, and reducing expression of Dnmt1, Dnmt3A, and Dnmt3B in both LNCaP and PC3 cells. Genistein and daidzein both demethylate gluthathione S-transferase P1 (GSTP1) and ephrin type-B receptor 2 (EPHB2) promoter regions and enhance their expression in prostate cancer cell lines (Vardi et al. 2010).

Pandey et al. (2010) reported that green tea polyphenol reactivates GSTP1 by demethylating its promoter and regions distal to the transcription factor binding sites in LNCaP cells. They showed that green tea polyphenol inhibits DNMT enzymatic activity by blocking the catalytic binding site, preventing cytosine binding, and downregulating DNMT1 expression at both mRNA and protein levels in a dose- and time- dependent manner in LNCaP cells. Green tea polyphenol also alters the expression patterns of MBD1, MBD4, and methyl CpG binding protein 2 (MeCP2) in the LNCaP prostate cancer cell line and decreases the occupancy of MBD2 on the GSTP1 promoter region (Pandey et al. 2010). EGCG is a major component of green tea polyphenol. EGCG inhibits DNMT enzymatic activity and triggers reexpression of GSTP1 in LNCaP cells (Pandey et al. 2010). Henning et al. (2012) reported recently that brewed green tea significantly inhibits DNMT1 mRNA and protein expression levels in androgen-dependent human LAPC4 prostate cancer cell xenografts.

Curcumin is a phenolic compound present in the popular Indian spice turmeric (*Curcuma longa*). Curcumin induces neurogenin 1 (Neurog1) gene expression by partial demethylation of various CpG islands at the promoter region in LNCaP cells (Shu et al. 2011). In their recent study, Khor et al. (2011) showed that curcumin demethylates CpG islands at the promoter region of nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) gene, reexpressing NFE2L2 (also known as Nrf2) in TRAMP-C1 cells. The TRAMP-C1 cell line was derived from a heterogeneous 32-week primary tumor in the prostate of TRAMP (transgenic adenocarcinoma of the mouse prostate) mouse. TRAMP-C1 is tumorigenic when grafted into syngeneic C57BL/6 hosts (Foster et al. 1997). Curcumin was also shown to inhibit the activity of recombinant CpG methyltransferase M.SssI in a cell-free condition, suggesting that the demethylation of these CpG islands was due to inhibition of DNMT activity as opposed to inhibition of DNMT expression (Khor et al. 2011). The recombinant CpG methyltransferase M.SssI enzyme has significant structural similarities with the DNMT1 catalytic domain and can methylate all cytosine residues within the double-stranded dinucleotide (5′-CG-3′) recognition sequence. Significant inhibition of CpG methyltransferase M.SssI activity by curcumin in a cell-free medium indicates a direct physical interaction with the enzyme; however, further studies are needed to understand the molecular interactions between curcumin and different DNMTs.

A recent study by Hsu et al. (2011) indicated that sulforaphane (SFN) reactivates cyclin D2 by demethylating a section of the promoter region rich in Sp1 and c-Myc binding sites (CG-rich) in LNCaP cells. They also showed that SFN causes global hypomethylation and downregulation of DNMT1 and DNMT3b.

The ability to reactivate tumor suppressor genes by counteracting the aberrant hypermethylation of their promoters, a phenomenon commonly associated with prostate cancer, makes dietary polyphenols excellent candidates for clinical studies. This, combined with their ability to inhibit the expression and activity of DNMTs, give them enormous potential as chemopreventive agents. The low toxicity of polyphenols and other dietary supplements, like isothiocyanates, make them attractive candidates for combination therapies. More studies that focus on combining polyphenols with other dietary chemopreventive agents are needed to unlock the full potential of these easily found, relatively safe compounds.

Changes in chromatin composition and structure by dietary polyphenols

Histone posttranslational modifications are involved in the recruitment of various chromatin remodeling proteins, resulting in enhanced or reduced accessibility of *cis*-acting sites to the transcriptional machinery. These epigenetic events associated with chromatin relaxation and compaction are very important in the regulation of gene expression. Since aberrant patterns of histone posttranslational modifications are an integral part of cancer pathophysiology, therapeutic and (or) chemopreventive agents having the potential to influence or alter regulation of these modifications can have a broad spectrum of antitumor effects. In recent years, it has been shown that dietary polyphenols can affect the dynamic changes in histone posttranslational modifications in prostate cancer and, in doing so, can exhibit anticancer properties.

Apigenin, a plant flavone present in various fruits and vegetables, has shown promising chemopreventive effects in prostate cancer (Shukla and Gupta 2010). Pandey et al. (2011) reported for the first time that apigenin treatment can potentially affect chromatin structure by inhibiting class I HDACs (HDAC1, HDAC2, HDAC3, and HDAC8) in both in vitro and in vivo prostate cancer models. They also found that apigenin downregulates HDAC1 and HDAC3 at both the transcriptional and translational level and increases global H3 and H4 acetylation in highly metastatic PC3 and androgen receptor positive 22Rv1 prostate cancer cells. Furthermore, apigenin increases histone acetylation of histone H3 over the promoter of p21/waf1, a cell cycle regulatory protein, and increases its expression. In an in vivo study with PC3 xenograft in athymic nude mice, apigenin intake caused a decrease in HDAC enzymatic activity and HDAC1 and HDAC3 expression levels (Pandey et al. 2011).

SFN inhibits HDAC enzymatic activity in PC3 xenografts and increases global acetylation of histones H3 and H4 (Myzak et al. 2007). Clarke et al. (2011) showed that SFN exhibits a similar effect in mouse prostate tissue. SFN inhibits HDAC enzymatic activity and also significantly reduces various class-I and class-II (HDAC4 and HDAC6, respectively) HDAC expression levels in prostate cancer benign prostatic hyperplasia (BPH1; a benign hyperplastic prostatic epithelial cell line), LNCaP, and PC3 cells. They further reported that SFN treatment leads to increased acetylation of histone H3 lysines 9 and 14 over the p21 promoter, as well as the nonhistone α-tubulin protein specifically in prostate cancer cell lines. In contrast, SFN had no significant effect on normal prostate

PrEC cells, indicating that SFN's specificity makes it a good candidate for prostate cancer prevention and treatment.

Pandey et al. (2010) showed that green tea polyphenols inhibit HDAC enzymatic activity, as well as alter the expression pattern of HDAC1, HDAC2, and HDAC3 at both mRNA and protein levels in LNCaP cells. They further showed that green tea polyphenol increases the global H4 and H3K9/18 acetylation in a time-dependent manner. This study provides a rationale for the chemopreventive role of green tea polyphenol because of its epigenetic modifying potential at the level of both DNA methylation and chromatin remodeling.

Genistein upregulates the tumor suppressor p21 and p16 genes by affecting chromatin composition and structure in prostate cancer cells (Majid et al. 2008). The upregulation of both p21 and p16 is linked with an increase in histones H3 and H4 acetylation as well as H3K4 dimethylation (H3K4me2) in LNCaP, DuPro (androgen insensitive), and RWPE-1 cell lines. Furthermore, genistein significantly increases the expression level of CREB binding protein (CREBBP), E1A binding protein p300 (EP300), P300/CBP-associated factor (PCAF), and histone acetyltransferase 1 (HAT1) genes at the transcriptional level in both LNCaP and DuPro cells (Majid et al. 2008). Kikuno et al. (2008) showed that genistein can also upregulate the tumor suppressor p53, forkhead box O3 (FOXO3a), and cylindromatosis (CYLD) genes by altering chromatin. Genistein downregulates the expression of the protein deacetylase sirtuin 1 (SIRT1) in both LNCaP and PC3 cells and induces its nuclear-to-cytoplasmic translocation). In LNCaP cells, genistein reduces promoter occupancy of SIRT1 on the p53 and FOXO3a promoter resulting in decreased H3K9 deacetylation. However, in PC3 cells, reduced occupancy of SIRT1 on the FOXO3a promoter with increased H3K9 acetylation and decreased H3K9 methylation were observed (Kikuno et al. 2008). Interestingly, phosphatase and tensin homolog (PTEN) and CYLD (a deubiquitylating enzyme associated with the turban tumor syndrome) promoters also showed a genistein-induced increase in H3K9 acetylation and decreased H3K9 methylation in both LNCaP and PC3 cell lines, indicating its ability to selectively induce the expression of various tumor suppression genes in prostate cancer. Genistein modifies the chromatin composition by increasing H3 and H4 acetylation and H3K4 di- and trimethylation at the promoter region of BTG3, also known as abundant in neuroepithelium area (ANA), a protein that can interact with the chromatin remodeling protein chromatin assembly factor 1 (CAF1) (Majid et al. 2010*a*). They also showed that genistein increases the HAT enzymatic activity in both LNCaP and PC3 cells (Majid et al. 2010*a*). Genistein also inhibits HDAC6 expression in LNCaP cells (Basak et al. 2008).

Curcumin is a well-known HAT inhibitor that selectively degrades CBP/p300 proteins and effectively blocks hyperacetylation of histones in PC3M cells (Marcu et al. 2006). A recent study by Shah et al. (2012) revealed that curcumin significantly reduces histone H4 acetylation at the kallikrein-related peptidase 3/prostate-specific antigen (KLK3/PSA) and Ttansmembrane protease, serine 2 (TMPRSS2) enhancer regions in LNCaP, 22Rv1, and androgen-insensitive C4-2 cell lines. CBP and p300 recruitment was also decreased by curcumin treatment at the KLK3/PSA enhancer in LNCaP and C4-2 cells. Shu et al. (2011) showed that curcumin alters the chromatin composition at the Neurog1 gene by decreasing trimethyl H3K27 (H3K27me3) and diminishing MeCP2 binding. Furthermore, curcumin decreases global H3K27me3 levels, alters the expression levels of various HDACs, increasing HDACs 1, 4, 5, and 8 while decreasing HDAC3 in LNCaP cells. Curiously, despite an overall increase in HDAC expression, overall HDAC activity was shown to be decreased by curcumin treatment. Global histone H3 and H4 acetylation are increased by curcumin in a dose-dependent manner in LNCaP cells (Shankar and Srivastava 2007).

Phenethyl isothiocyanate significantly increases global H3 acetylation and H3K4 mono/di/trimethylation and decreases H3K9 trimethylation in LNCaP cells. It also induces p21 expression by acetylating its promoter region (Wang et al. 2008). Quercitin increases HDAC enzymatic activity, leading to a significantly reduced H3 and slightly decreased H4 acetylation, leading to inhibition of survivin (a member of inhibitor of apoptosis family) gene expression that results in TRAIL-induced apoptosis in both DU-145 and PC3 cells (Kim et al. 2008). Narayanan et al. (2003) showed that resveratrol, a phenolic compound found in red wine, induces p300/CBP expression in LNCaP cells.

The chromatin remodeling potential of dietary polyphenols is yet another reason for their consideration as chemopreventive agents. Polyphenols upregulate HAT activity, while simultaneously downregulating HDAC activity. They also downregulate DNMT activity, leading to a global hypomethylation. The reestablishment of these hallmarks of epigenetic activation leads to the renewed expression of tumor suppressor genes commonly silenced in prostate cancers. Curcumin's ability to downregulate histone acetylation, and thus activation of certain oncogenes, as well as prevent global DNA hypermethylation, demonstrates the versatility and specificity of these dietary agents.

Change in miRNAs expression profile by dietary polyphenols

miRNA silences the expression of various genes at the posttranscriptional level. Each miRNA has hundreds of targets and plays an important role in cellular physiology. Alterations in miRNA expression patterns are reported in various cancers including prostate cancer (Catto et al. 2011; Kasinski and Slack 2011; Lujambio and Lowe 2012). Cancer cells upregulate various miRNAs that target tumor suppressor genes and downregulate miRNAs that suppress oncogenes. Recent studies have indicated that dietary polyphenols alter the pattern of miRNA expression in prostate cancer. These effects of polyphenols have great therapeutic and chemopreventive value in prostate cancer management.

In a recent study, Siddiqui et al. (2011) showed that EGCG downregulates miR-21 and upregulates miR-330 in a xenograft model implanted with androgen-sensitive human prostate cancer CWR22Rnu1 cells. The miR-21 is oncogenic and promotes prostate cancer growth (Ribas et al. 2009); however, miR-330 acts as a tumor suppressor and induces apoptosis in prostate cancer (Lee et al. 2009).

Dhar et al. (2011) reported that resveratrol significantly downregulates 23 miRNAs (including several oncogenic miRNAs) and up-regulates 28 miRNAs (including several tumor-suppressor miRNAs) in LNCaP cells. This study indicates that resveratrol has the potential to modulate thousands of genes via deregulation of several miRNAs in prostate cancer. Although a lot of miRNA targets are not yet validated in prostate cancer, future studies based on in vitro and in vivo prostate cancer models will be helpful to understand the wide range of antitumor effects of these polyphenols.

Genistein downregulates miR-221 and miR-222 in prostate cancer PC3 cells, resulting in upregulation of the tumor suppressor ARHI gene (Chen et al. 2011). Genistein also upregulates miR-1296 leading to downregulation of its target minichromosome maintenance complex component 2 (MCM2) (Majid et al. 2010*b*). The MCM gene family is upregulated in various cancers and is involved in DNA replication by forming MCM2–MCM7 helicase complex. Rabiau et al. (2011) recently showed that genistein and daidzein differentially deregulate miRNAs expression profiles in LNCaP, PC3, and DU145 cell lines. They found that genistein and daidzein both alter the expression of various miRNAs, including downregulation of oncogenic miR-125b, miR-155, miR-211, miR-367a, and miR-320, and upregulation of tumor-suppressor miR-15a. In a recent study, Shi et al. (2011) demonstrated that miR-125b directly targets proapoptotic p53, Bak1, and Puma genes and promotes growth of prostatic xenograft tumors. Interestingly, miR-15a acts as a tumor suppressor gene in prostate cancer and controls cell proliferation, cell survival, and invasion (Bonci et al. 2008). An alteration in miRNA profile by dietary polyphenols shows their

Table 1. Epigenetic potentials of dietary polyphenols in prostate cancer.

S. No.	Dietary polyphenols (experimental doses)	Epigenetic modifications	Targets and mechanisms	Fate of cancerous cells	References
1.	Apigenin (20–50 μmol/L)	Histone modification	Decreases HDAC enzymatic activity with downregulation of HDAC1 and HDAC3 and increase in global H3 and H4 acetylation. Upregulation of p21 with increased promoter H3 acetylation.	Cell cycle arrest, apoptosis, and tumor growth inhibition	Pandey et al. 2011
2.	Curcumin (2.5–30 μmol/L)	Histone acetylation and DNA methylation	Reduces occupancy of CBP and p300 at KLK3/PS enhancer. Decreases H4 acetylation at KLK3/PS and TMPRSS2 enhancer regions. Decreases HDAC enzymatic activity and global H3K27me3 level. Decreases MeCP2 binding at Neurog1 promoter and H3K27me3 level. Decreases HAT activity and degradation of CBP/p300. Alteration of various HDACs, DNMTs, and MBD2 expression pattern. Demethylation and reactivation of Neurog1 and Nrf2 genes.	Growth inhibition and apoptosis	Shah et al. 2012; Marcu et al. 2006; Shu et al. 2011; Shankar and Srivastava 2007; Khor et al. 2011
3.	Daidzein (110 μmol/L)	MicroRNA and DNA methylation	Alteration in miRNAs expression. Demethylation and reexpression of GSTP1 and EPHB2 genes.		Rabiau et al. 2011; Vardi et al. 2010
4.	Epigallocatechin-3-gallate (5–60 μmol/L)	DNA methylation and microRNA deregulation	Inhibition of DNMT enzymatic activity and reactivation of GSTP1. Downregulation of miR-21 and upregulation of miR-330 in tumor xenograft model. DNA demethylation and reactivation of RARβ.	Growth inhibition and apoptosis	Pandey et al. 2010; Siddiqui et al. 2011; Fang et al. 2003
5.	Genistein (1–50 μmol/L)	DNA methylation, histone posttranslational modifications, and microRNA deregulation	Upregulation of BTG3 gene by promoter demethylation, increase in global H3 and H4 acetylation and H3K4 di- and trimethylation. Decreases enzymatic activity of DNMT and MBD2 and increases HAT enzymatic activity. Demethylation and reexpression of GSTP1 and EPHB2 genes. Demethylation and acetylation of H3K9 at PTEN and CYLD promoters and H3K9 acetylation at p53 and FOXO3a promoters. Increases acetyl-H3 and -H4 and H3-dimethyl-K3 at p21 and p16 promoter regions. Downregulation of SIRT1 and HDAC6 expression, and nuclear to cytosolic localization of SIRT. Alteration in various miRNAs expression patterns. Restores tumor suppressor ARHI gene by downregulating miR-221 and miR-222 levels. Upregulation of miR-1296 leads to downregulation of MCM2 gene.	Inhibition of proliferation, colony formation, and invasion; Apoptosis and cell cycle arrest	Majid et al. 2010*a*; Kikuno et al. 2008; Chen et al. 2011; Majid et al. 2008, 2010*b*; Basak et al. 2008; Rabiau et al. 2011; Vardi et al. 2010
6.	Green tea polyphenol (5–25 μmol/L)	DNA methylation and chromatin remodeling	Inhibition of DNMT enzymatic activity and expression, demethylation of GSTP1 promoter, and alteration in MBD1, MBD4 and MeCP2 expression. Inhibition of HDAC activity and downregulation of HDAC1, 2, and 3 levels, increase in global H3 and H4 acetylation including K9/18 H3 acetylation. Class-I HDAC proteosomal degradation.	Cell cycle arrest and apoptosis	Pandey et al. 2010; Thakur et al. 2012
7.	Phenethyl isothiocyanate (0.5–10 μmol/L)	Histone modification	Increases global acetyl-H3 and methyl-H3K4, and decreases in methyl-H3K9. Increases H3 acetylation at p21 promoter.	Cell cycle arrest	Wang et al. 2008
8.	Quercetin (10–200 μmol/L)	Histone acetylation	Increases HDAC enzymatic activity that causes decreasesd H3 acetylation and survivin gene repression.	Synergetic apoptosis with TRAIL	Kim et al. 2008

Table 1 (*concluded*).

S. No.	Dietary polyphenols (experimental doses)	Epigenetic modifications	Targets and mechanisms	Fate of cancerous cells	References
9.	Resveratrol (1–100 μmol/L)	Chromatin remodeling and microRNA deregulation	Destabilization of the MTA1/HDAC1/p53 complexes. Upregulation of 28 tumor suppressor miRNAs and downregulation of 23 oncogenic miRNAs.	Apoptosis	Kai et al. 2010; Dhar et al. 2011
10.	Sulforaphane (5–30 μmol/L)	DNA methylation and histone acetylation	Reactivation of cyclin D2 by promoter demethylation and downregulation of DNMTs. Inhibition of HDAC enzymatic activity and downregulation of various class-I and class-II HDAC genes. Increases p21 promoter H3 acetylation and overexpression of p21 protein. Inhibition of HDAC enzymatic activity and increases global H3 and H4 acetylation in vivo.	Growth inhibition, cell cycle arrest, and apoptosis	Hsu et al. 2011; Clarke et al. 2011; Myzak et al. 2007

wide-spectrum epigenetic remodeling potentials. Because miRNAs have several hundred targets, much more study is needed to really understand the true potential of this facet of epigenetic regulation and how it can be manipulated with dietary agents.

Conclusions and future perspective

Epigenetic mechanisms are involved in the silencing of various tumor suppressor genes and activation of several oncogenes in prostate cancer. Highly complex but well-coordinated epigenetic events, along with activation/deactivation of various signaling pathways, are involved in the development of prostate cancer and finally metastasis into different organs. Since prostate cancer is slow growing and manifests in a later stage of life, chemoprevention using suitable dietary polyphenols or in combination with other dietary agents seem to be more helpful in prostate cancer management. Recent studies have indicated that dietary polyphenols are very good epigenetic modulators and act on different epigenetic levels including DNA methylation, chromatin structure, and miRNA. Another property that makes them very unique is that they have very little or no toxicity for the normal cells. Based on the available data, dietary polyphenols with their epigenetic remodeling properties seem to be emerging as future epigenetic drugs for prostate cancer chemoprevention and therapy. However, additional clinical trials are required to further explore the potential usefulness of these dietary polyphenols. Various dietary agents, which are discussed in this review, such as green tea polyphenols, SFN, genistein, and quercetin, are in various stages of prostate cancer clinical trials. The results of these studies will provide more insights in their therapeutic and chemopreventive potentials. However, to optimize therapeutic efficiency, various parameters, such as optimal dose, route of administration, optimal period, bioavailability, toxicity, as well as a single or combinatorial approach will have to be determined. It is important to point out that the vast majority of these compounds have been tested as purified substances at concentrations that would be achievable through daily use of their product of origin (e.g., a 15 μmol/L SFN dose is obtained by consumption of about 100 g of broccoli sprouts).

Epigenetic drug development is a new field of research with very high potential (Perry et al. 2010). With the advancements in the field of cancer diagnosis and biomarker research, early detection of tumors and risk assessments are much easier than ever before. In the light of these developments, use of dietary agents and dietary polyphenols in particular has great promise in prostate cancer therapeutics and chemoprevention. A lot of research is still needed to understand the molecular basis of the epigenetic changes caused by these polyphenols. To date, we have a very limited understanding and most of the data are just indicative rather than mechanistic and descriptive in this new field. Future mechanistic studies as well as combinatorial studies using different combinations of various polyphenols will be more helpful in the development of a new line of epigenetic drugs. In the future, these chemopreventive and therapeutic epigenetic drugs might be able to replace current chemo and radiotherapies that have much more adverse and painful effects for the patients. Table 1

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