Review Article

Chemoprevention by resveratrol and pterostilbene: Targeting on epigenetic regulation

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Abstract

Epigenetic mechanisms are essential in regulating normal cellular functions and play an important role during the disease developmental stages. However, aberrant epigenetic mechanisms may lead to pathological consequences such as cancer, neurological disorders, bone and skeletal diseases, cardiovascular dysfunction, and metabolic syndrome. The molecular mechanisms of epigenetic modification include DNA methylation, histone modification (acetylation, methylation and phosphorylation), and microRNAs (miRNAs). Unlike genetic modifications, epigenetic states of genes are reversible and can be altered by certain intrinsic and extrinsic factors. In the past few decades, accumulated evidence shows that dietary phytochemicals with chemopreventive effects are also potent epigenetic regulators. Resveratrol and pterostilbene are stilbenoids, which have been reported to have anti-cancer, anti-inflammatory, anti-lipid, and anti-diabetic properties. Stilbenoids are also reported to improve cardiovascular disease. By altering DNA methylation and histone modification or by modulating miRNA expression, resveratrol, and pterostilbene become potent epigenetic modifiers. In this review, we summarize these studies and underlying mechanisms of resveratrol and pterostilbene and their influence on epigenetic mechanisms. © 2017 BioFactors, 44(1):26–35, 2018

Keywords: *epigenetic; chemoprevention; resveratrol; pterostilbene*

Abbreviations: *3′UTR, 3′ untranslated region; Ago2, argonaute2; AhR, aromatic hydrocarbon receptor; AMPK, AMP activated protein kinase; AP-1, activator protein-1; ARH-I, aplasia Ras homolog member I; AURKA, aurora kinase; BCL-2, B-cell lymphoma 2; BMFs, buccal mucosal fibroblasts; BRCA-1, breast cancer type 1; CAD, coronary artery disease; CCNB1, cyclin B1; CDKs, cyclin-dependent kinase; CLU, clusterin; CRP, C-reactive protein; CSCs, cancer stem cells; DMNTs, DNA methyltransferases; eNOS, endothelial NOS; ERα, estrogen receptor-alpha; EZH2, enhancer of zeste homolog 2; GBM, glioblastoma multiforme; GSCs, glioma stem cells; H3K9, acetyl-H3lysine9; HAT, histone acetyl transferase; HDACs, type III histone deacetylases; HK2, hexokinase 2; HSL, hormone sensitive lipase; MCP-1, monocyte hemoattractant protein-1; miRNAs, MicroRNAs; MNNG, N-methyl-N′-nitro-N-nitrosoguanidine; MTA1, metastasis-associated protein 1; NAD^+, nicotinamide adenine dinucleotide$^+$; NAFLD, nonalcoholic fatty liver disease; NGFR, nerve growth factor receptor; NO, nitric oxide; NuRD, nucleosome remodeling deacetylation; OSF, oral submucous fibrosis; PDCD4, programmed cell death protein 4; PGR, progesterone receptor gene; PPARγ, peroxisome proliferator-activated receptor gamma; PTEN, phosphatase and tensin homolog; RANKL, receptor activator of NF-κB ligand; RASSF1A, Ras association domain-containing protein 1; RNAi, RNA interference; SAM, S-adenosyl-l-methionine; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca(2+)ATPase 2a; sirtuins, silent information regulator 2-related proteins; SMADs, SMA and Mad related proteins; SOD1, superoxide dismutase 1; STAT-3, signal transducer and activator of transcription 3; TAC, transverse aortic constriction; TAM, tumor associated macrophage; WAT, white adipose tissue; ZEB1, zinc finger E-box binding homeobox 1*

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1. Introduction

Stilbenoids are a group of polyphenols widely found in various plants, aromatic oils, and edible plants. Scholars have found that stilbenoids have a wide range of biological activities, such as anticancer, hypolipidemic, and antidiabetic properties as well as cancer chemopreventive activity [1], and so for phytoalexin [2]. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) was first isolated from the roots of white hellebore (*Veratrum grandiflorum O. Loes*) in 1940, and later, in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine. It is a natural polyphenol found in several plants including blueberries, mulberries, cranberries, peanuts, grapes, and wine [3]. It has been reported to have anti-cancer, anti-inflammatory, anti-cardiovascular disease and blood-sugar lowering properties [4,5].

Pterostilbene (3,5-dimethoxy-4′-hydroxy-*trans*-stilbene) a natural methoxylated analogue of resveratrol, was first isolated from red sandalwood (*Pterocarpus santalinus*) and is one of the active constituents of *Pterocarpus marsupium*, which is used in traditional medicine for the treatment of diabetes [6]. Mainly found in blueberries, grapes, and several plant woods [7], pterostilbene has a similar structure to resveratrol in that the A ring 3 and 5 position was replaced by a methoxyl group. This, however, leads to its pro-lipophilicity being much greater than resveratrol and increases its advantages over bioavailability [8,9]. These advantages result in its stronger bioactivities including anticancer, antilipid, antidiabetic, and improved cardiovascular disease than those of resveratrol [1,10,11]. Various literature and reviews highlight the multiple biological activities of stilbenoids, yet only a few studies discussed the epigenetic mechanisms of resveratrol and pterostilbene. Therefore, in this review we focus on the potential epigenetic regulation of resveratrol and pterostilbene.

2. Targeting epigenetic mechanisms: Potential of resveratrol and pterostilbene in chemoprevention

Epigenetics is defined as the study of heritable changes in gene expression without any alteration of the DNA sequence itself [12]. The molecular mechanisms of epigenetic modification include DNA methylation, alteration of chromatin structure by post-translational modification of histone or non-histone proteins, and microRNAs (miRNAs). [13]. Epigenetic mechanisms have been shown to be essential in regulating normal cellular functions and play an important role during the developmental stages of diseases [14], such as cancer, metabolic syndrome, Alzheimer's disease, and other neurological disorders [15–17]. Epigenetic modifications are potentially reversible and can be modified by environment, diet, and lifestyle. Epigenetic mechanisms have been implicated in physiological responses to intrinsic and extrinsic environmental stimuli such as nutrition, radiation, exposure to chemicals, toxins, and hormones [18]. To control epigenetic modifiers through the consumption of dietary phytochemicals, is quite interesting. In this review, we focused on the role of resveratrol and pterostilbene as epigenetic modifiers. We discussed in detail the different mechanisms of epigenetic modifications in mammals and present a comprehensive overview of the knowledge about resveratrol and pterostilbene.

3. DNA methylation

The hypermethylation of DNA is a key epigenetic mechanism for the silencing of many genes, including those for cell cycle regulation, inflammatory, and stress response, DNA repair, and apoptosis [19]. DNA methylation is catalyzed by specific DNA methyltransferases (DMNTs), which use S-adenosyl-L-methionine (SAM) as the methyl group donor [20]. The reactivation of hypermethylated genes by the inhibition of DNMTs has become a promising area in cancer therapy and chemoprevention [21]. DNA methylation inhibitors such as decitabine have side effects and toxicity that are serious concerns. There is a great need for the development of effective and non-toxic inhibitors of DNMTs not only for therapy but also for chemoprevention. Resveratrol in combination with Vitamin D_3 was highly effective in reducing the methylation of *PTEN* (Phosphatase and tensin homolog) promoter and inducing expression of *PTEN* (Table 1), downregulating DNMT, and regulating p21 in ER-positive MCF-7 breast cancer cells, but had no notable effects on triple-negative MDA-MB-231 breast cancer cells [22]. In another study, the chemopreventive effects of resveratrol were demonstrated *in vivo* by pre-exposing aromatic hydrocarbon receptor (AhR) agonist-treated pregnant Sprague-Dawley rats with resveratrol, an AhR-antagonist, which led to lesser CpG methylation of the *BRCA-1* gene [23]. A genome-wide survey of DNA methylation signatures was performed in triple negative breast cancer cells exposed to resveratrol. The data showed that resveratrol treatment for 24 and 48 h decreased gene promoter hypermethylation and increased DNA hypomethylation [24]. Zhu et al. reported that DNA methylation of the tumor suppressor gene *RASSF1A* (Ras association domain-containing protein 1) can be reduced by resveratrol intake (twice daily for 12 weeks) in the breasts of women with a high breast cancer risk [25]. Diabetes mellitus is a clinical syndrome consisting mainly of glucose and lipid metabolism disorders. Resveratrol can change the cytokine genes in diabetic rat aortas through DNA methylation. The results showed that resveratrol inhibits the expression of proinflammatory cytokines and thus may have a protective effect on the aorta in hyperglycemia [26]. The combination of resveratrol and pterostilbene also leads to the reactivation of ERα expression in ERα-negative breast cancer cells in a time-dependent manner. It significantly reactivates the *ERα* status via its effects on DNA methylation and histone acetylation in ERα-negative breast cancer cells [27].

TABLE 1 ***Resveratrol and pterostilbene altering DNA methylation***

Diseases	*Epigenetic mechanism(s)*	*Dose/Concentration*	*Reference*
Resveratrol			
Breast cancer	Decreases methylation at *PTEN* gene promoter	10–50 μM	[22]
Breast cancer	Decreases methylation at *BRCA-1* gene promoter	7 ppm (mix in diet)	[23]
Breast cancer	Increases methylation at *AURKA, CCNB1*, and *HK2* oncogene	100 μM	[24]
Breast cancer	Decreases methylation of the tumor suppressor gene *RASSF1A*	5 or 50 mg twice daily for 12 week	[25]
Diabetes	Increases methylation on IL-1β, IL-6, TNF-α, and IFN-γ	10 mg/kg/bw	[26]
	Decreases methylation on IL-10		
Resveratrol + Pterostilbene			
Breast cancer	Decreases methylation at *ERα* gene promoter	Res:15 μM + Pter:5 μM	[27]

AURKA: aurora kinase A (cell cycle regulators); CCNB1: Cyclin B1 (cell cycle regulators); HK2: Hexokinase 2 (Warburg effect mediator); RASSF1A: Ras association domain-containing protein 1; ERα: Estrogen receptor-alpha.

4. Histone modification

Histone deacetylation is often associated with transcriptional repression and gene silencing, since it promotes the chromatin of higher order structures and the recruitment of silencers. Among this superfamily is an HDACs class III which includes NAD^+-dependent deacetylases known as sirtuins (silent information regulator 2-related proteins) [28]. Resveratrol activates the SIRT1 catalytic core independent of its terminal domains, indicating the existence of a resveratrol binding site within the catalytic core of the enzyme. Inducing expression of BRCA1 led to increased SIRT1 expression by binding BRCA1 to the promoter of SIRT1 (Table 2), an increased SIRT1 expression in turn inhibited survivin by modulating histone H3K9 levels [29]. The *in vivo* study using SIRT1 mutant mice demonstrated that disruption of SIRT1 function p53 null background causes tumor formation and resveratrol mediated activation of SIRT1 reduced tumorigenesis. Topical application of resveratrol to the skin profoundly reduced tumorigenesis, yet the effect was reduced in SIRT1-null mice, suggesting resveratrol requires SIRT1-encoded protein for its protection In addition, resveratrol was shown to have a negative effect on *survivin* gene expression through histone deacetylation at the gene promoter and displayed a more profound inhibitory effect on BRCA-1 mutant cells both *in vitro* and *in vivo* [30]. Resveratrol also prevented epigenetic silencing of tumor suppressor gene *BRCA-1* by the AhR in human breast cancer MCF-7 cells by modulating acetylation of H3K9, and H4, the association of mono-methylated-H3K9 and, DNMT1, and methyl binding domain protein-2 with the promoter of the *BRCA-1* gene [31]. The other studies found that on various prostate cancer cell lines MTA1 (Metastasis-associated protein 1) identified as a progression-related protein. There is a significant elevation in acetylation of p53 and induction of apoptosis in LNCaP and DU145 cells deficient in MTA1, suggesting antiapoptotic functions for MTA1. Using prostate cancer cells, Kai et al. demonstrated that resveratrol was able to cause downregulation of MTA1, destabilize the NuRD (Nucleosome remodeling deacetylation) complex, and thus allow p53 acetylation. Furthermore, the activation of p53 was shown to induce pro-apoptotic pathways causing apoptosis in prostate cancer cells [32]. Pterostilbene exhibited a sevenfold greater potency in downregulating MTA1 and increasing p53 acetylation than resveratrol in DU145 prostate cancer cells. In the same study, the MTA1-dependent increase in p53 acetylation upon pterostilbene treatment *in vivo* was superior to that induced by resveratrol [33]. The result showed that resveratrol treatment of human bladder cancer EJ cells was found to lead to a remarkable S-phase arrest and apoptotic cell death accompanied by loss of phosphorylation of STAT-3, leading to downregulation of the STAT-3 pathway as well as decreased nuclear translocation of SIRT1 and p53 [34]. Resveratrol in the role of HDAC inhibitor has also been demonstrated in glioma cells and human-derived hepatoblastoma cells [35]. In another article, resveratrol promoted the synthesis and accumulation of ARH-I (Aplasia Ras homolog member ICAD), an imprinted tumor suppressor that positively regulates autophagy and effectively inhibits cell migration in ovarian cancer cells [36]. Resveratrol exerts neuroprotective effects by inhibiting dopaminergic neurotoxin 1-methyl-4-phenylpyridinium [MPP(+)]-induced dopaminergic

TABLE 2 ***Resveratrol and pterostilbene altering histone modification***

Diseases	*Epigenetic mechanism(s)*	*Dose/ Concentration*	*Ref.*
Resveratrol			
Breast cancer	Activation of SIRT1 and inhibition of Survivin and increase *BRCA-1* promoter	50 μM	[30,31]
Prostate cancer	Down regulation MTA1, leading to destabilization of MTA1/NuRD thus allowing acetylation/activation of p53	1–100 μM	[32,33]
Bladder cancer	Attenuated phosphorylation STAT3, down regulation STAT3 downstream genes (survivin, cyclinD1, c-Myc, and VEGF)	100–200 μM	[34]
Liver cancer	Inhibition of HDACs and histone hyperacetylation	5–100 μM	[35]
Ovarian Cancer	Up regulation ARH-I and down regulation STAT3	100 μM	[36]
Neurodegeneration	Suppresses SIRT1-mediated p53 acetylation	10–100 μM	[37]
Memory impairment	SIRT1 activator	200 mg/kg/bw	[38]
Oral submucous fibrosis	HMTs enhancer (up regulation EZH2, H3K27me3) and inhibits ZEB1	25–100 μM	[39]
Cardiovascular dysfunction	Up regulation of SIRT1 and deacetylation of *eNOS*	10 μM	[40]
Diabetic cardiomyopathy	Activation of SIRT1 and increase SERCA2a promoter activity	100 mg/kg/bw	[41]
Renal injury	Suppression of p53 acetylation	100 μM	[42]
		10 mg/kg/bw	
Osteoclastogenesis	Activation of SIRT1 and decrease NF-κB acetylation	5 μM	[43]
Fatty liver disease	Up regulation of SIRT3 and SIRT4	4 g/kg(mix in diet)	[44]
Obesity and insulin resistance	Increase SIRT1 activity	200 nM	[45]
		12.5 and 225 mg/kg	
Pterostilbene			
Prostate cancer	Increase in MTA1-mediated p53 acetylation	5–100 μM	[33]
Resveratrol + Pterostilbene			
Breast cancer	Activation of SIRT1 and inhibition of both telomerase activity and γ-H2AX expression	Res:15 μM + Pter:5 μM	[46]
Breast cancer	Increase acetyl-H3, acetyl-H3lysine9 (H3K9), and acetyl-H4 activity	Res:15 μM + Pter:5 μM	[27]

MTA1: metastasis-associated protein 1; NuRD: Nucleosome remodeling deacetylation; HDAC: type III histone deacetylase; HAT: histone acetyl transferase; ZEB1: zinc finger E-box binding homeobox 1; PGR: progesterone receptor gene; SERCA2a: sarcoplasmic/endoplasmic reticulum Ca(2+)ATPase 2a.

neuron loss in cultures of organotypic midbrain slices. Additionally, both resveratrol and the sirtuin activator NAD reduce the effects of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG). This DNA alkylating agent induces dopaminergic neurotoxicity by the deacetylation of p53 [37]. The research presented the evidence of epigenetic dysregulation (*i.e.*, altered DNA methylation and hydroxymethylation) of memory-related genes, including *SIRT1* within the hippocampus of obese mice. Experiments strongly implicate reduced hippocampal *SIRT1* as being a principal pathogenic mediator of obesity-induced memory impairment, and resveratrol plays as a *SIRT1* activator in this article [38]. Oral submucous fibrosis (OSF) is a precancerous condition of the oral mucosa without specific therapeutic drugs. The zinc finger E-box binding homeobox 1 (ZEB1) plays a pathogenic role in the induction of the myofibroblast activity of buccal mucosal fibroblasts (BMFs) and contributes to the pathogenesis of OSF. Resveratrol epigenetically inhibits ZEB1 expression to suppress the myofibroblast activity of fibrotic BMFs and may serve as a dietary supplement for OSF patients [39]. Cigarette smoke-mediated oxidative stress is implicated in endothelial dysfunction, and it contributes to the downregulation of *SIRT1*, thus leading to acetylation of *eNOS*, which results in reduced nitric oxide (NO)-mediated signaling in HUVECs. However, resveratrol protects against cigarette smoke and H_2O_2-induced SIRT1 levels and increased acetylation of *eNOS*, thereby reducing endothelial dysfunction [40]. Type 1 and type 2 diabetes are independent risk factors for cardiovascular diseases. In mice, treatment with streptozotocin produces a progressive decline in cardiac function and in Sarcoplasmic/endoplasmic reticulum Ca(2+)ATPase 2a (SERCA2a) and SIRT1 protein levels. Reduced SERCA2a expression has been shown to play a significant role in cardiac dysfunction in diabetic cardiomyopathy. Resveratrol improves streptozotocin-decreased cardiac function and upregulates SERCA2a levels [41]. Resveratrol also protects against cisplatin-induced cytotoxicity in mouse proximal tubular cells, an effect that contributes to ameliorating cisplatin-induced acetylation of p53. SIRT1 activation by resveratrol decreases cisplatin-induced apoptosis while improving the glomerular filtration rate, suggesting a protective role for resveratrol in cisplatin-induced kidney injury [42]. Receptor activator of NF-κB ligand (RANKL), a member of the tumor necrosis family, is known to be involved in osteoclast differentiation and bone loss. Pretreatment with resveratrol blocks RANKL-induced NF-κB activation by inhibiting p300 HAT. Upregulation of SIRT1 by resveratrol induces SIRT-1-p300 association in bone-derived and preosteoblastic cells. This upregulation also blocks NF-κB transcriptional activation as well as the final step in osteoclastogenesis [43]. Oral administration of resveratrol reduces obesity and fatty liver formation induced in C57Bl/6J mice by a high-fat diet. Resveratrol prevents hepatic steatosis and hepatocyte ballooning by the induction of skeletal muscle SIRT3 and SIRT4 expression, suggesting beneficial effects of resveratrol against nonalcoholic fatty liver disease (NAFLD) [44]. In addition, resveratrol enhances leucine-mediated AMP activated protein kinase, SIRT1, and SIRT3 activity in 3T3-L1 adipocytes and in muscle cells. Mice fed leucine combined with resveratrol and a high fat diet had increased adipose SIRT1 activity, muscle glucose, and palmitate uptake. Resveratrol also improves insulin sensitivity and reduces inflammatory markers (*PTEN*, IL-6, MCP-1, adiponectin) as well as adiposity, which suggests the beneficial effect of resveratrol on obesity, insulin resistance, and diabetes induced by a high fat diet [45].

The combination of resveratrol and pterostilbene induced SIRT1 downregulation through the inhibition of both telomerase activity and γ-H2AX expression in HCC1806 breast cancer cells, and affected DNA damage and repair [46]. Another research showed that combinatorial resveratrol and pterostilbene revealed an increase in enrichment of acetyl-H3, acetyl-H3lysine9 (H3K9), and acetyl-H4 active chromatin markers in the ERα promoter region. This treatment also resulted in a significant change in HDAC and histone acetyl transferase (HAT) enzyme activity [27].

Resveratrol is a well-known activator of SIRT1, a member of the mammalian sirtuins that are highly conserved protein deacetylases. There is an increasing amount of evidence that resveratrol can improve the outcome of diseases such as metabolic disorder, coronary artery disease, inflammatory and chronic diseases as well as aging by upregulating SIRT1 [47].

5. MicroRNAS

miRNAs are small noncoding regulatory RNA's that bind to sequences in the 3′UTR (3′ untranslated region) of target genes and decrease the stability of nascent mRNA and/or protein translation, which results in decreased production of the target protein [48]. Importantly, miRNAs have some desirable characteristics for clinical application: disease specificity, exceptional stability in various types of clinical samples, and the ability to respond to therapy [49]. Resveratrol-mediated miRNA modulation regulates key antiapoptotic and cell cycle proteins including Bcl-2, X-linked inhibitor of apoptosis protein and CDKs (Table 3). Modulating miRNAs with mimics or inhibitors further validated a key role for miR-542-3p in MCF-7 and miR-122-5p in MDA-MB-231 breast cancer cell death in response to resveratrol [50]. Another study showed that resveratrol promotes expression and activity of Argonaute2 (Ago2), a central RNA interference (RNAi) component, that inhibits breast cancer stem-like cell characteristics by increasing the expression of a number of tumor suppressive miRNAs including miR-16, miR-141, miR-143, and miR-200c. Importantly, resveratrol-induced Ago2 resulted in a long-term gene silencing response [51]. Specific miRNAs have been reported to be aberrantly expressed in prostate cancer; they are implicated as oncogenes or as tumor suppressors and found to be upregulated or downregulated [52]. Using miRNA microarrays, it was determined that 23 miRNAs were significantly downregulated and 28 miRNAs were significantly upregulated after resveratrol treatment. The downregulated miRNAs included miR-17–92 and miR-106ab clusters with well recognized

TABLE 3 ***Resveratrol and pterostilbene modulate miRNAs levels***

Diseases	*miRNA*	*Dose/Concentration*	*Ref.*
Resveratrol			
Breast cancer	miR-122-5p and miR-542-3p↑	50–100 μM	[50,51]
	miR-16, miR-141, miR-143, and miR-200c↑		
Prostate cancer	miR-17–92, miR-106a and miR106b↓	5–100 μM	[53,54]
	miR-21↓		
Colorectal cancer	miR-663↑; miR-34c↑	50–100 μM	[29,55]
		100 mg/kg/bw/day	
Pancreatic cancer	miR-21↓	10–100 μM	[56]
Non-small cell lung cancer	miR-299-5p, miR-194, miR-338-3p, miR-582-3p, and miR-92a-2↑	60 or 120 μM	[57]
Neuroblastoma	miR-137↑	50 μM	[58]
Leukemia	miR-16-1 and miR-15a↑	15–100 μM	[59]
Cardiac hypertrophy	miR-155↓	150 mg/kg/bw, 1 day	[60]
Lipogenesis	miR-539-5p↑	30 mg/kg/bw/day	[61]
Pterostilbene			
Breast cancer	miR-16, miR-141, miR-143, and miR-200c↑	25–50 μM	[51,62,63]
	miR-448↑	2.5–10 μM	
	miR-205↑	5 mg/kg/bw, 5 times/week	
		10 mg/kg/bw, 3 times/week	
GBM	miR-205↑	1–5 μM	[64]
		2 mg/kg/bw, 3 times/week	
Metabolic syndrome	miR-377↓	10–40 mg/kg/bw/day	[65]
Resveratrol + Pterostilbene			
Prostate cancer	miR-17-5p and miR-106a-5p↓	Res: 50–100 μM	[66]
		Pter: 50 μM	

oncogenic properties while the upregulated miRs included several tumor suppressors [53]. Another study showed that resveratrol reduced the expression of various prostate-tumor associated miRNAs, including miR-21, in androgen receptor negative and highly aggressive human prostate cancer cells PC-3M-MM2 [54]. In human SW480 colon cancer cells, resveratrol treatment results in the downregulation of several oncogenic miRNAs that target Dicer1 and tumor suppressor factors such as the programmed cell death protein 4 (PDCD4) and PTEN. An increase of miRNA-663 was reported to target Activator Protein-1 through the Jun signaling pathway. A tumor suppressor miRNA targeting transcripts of transforming growth factor TGF-β1 was also found in resveratrol treated cells. In human SW480 colon cancer cells, decreased levels of several oncogenic miRNAs known to target Dicer1, PDCD4, PTEN, and the key effectors of the TGF-β signaling pathway were found after resveratrol treatment. Using luciferase assays, it was found that resveratrol targets the 3′-UTR of TGF-β1 transcripts by upregulating miR-663, and this is related to decreases in the transcriptional activity of SMA and Mad related proteins [29]. The anticolorectal cancer effect of resveratrol was partially but specifically through upregulating

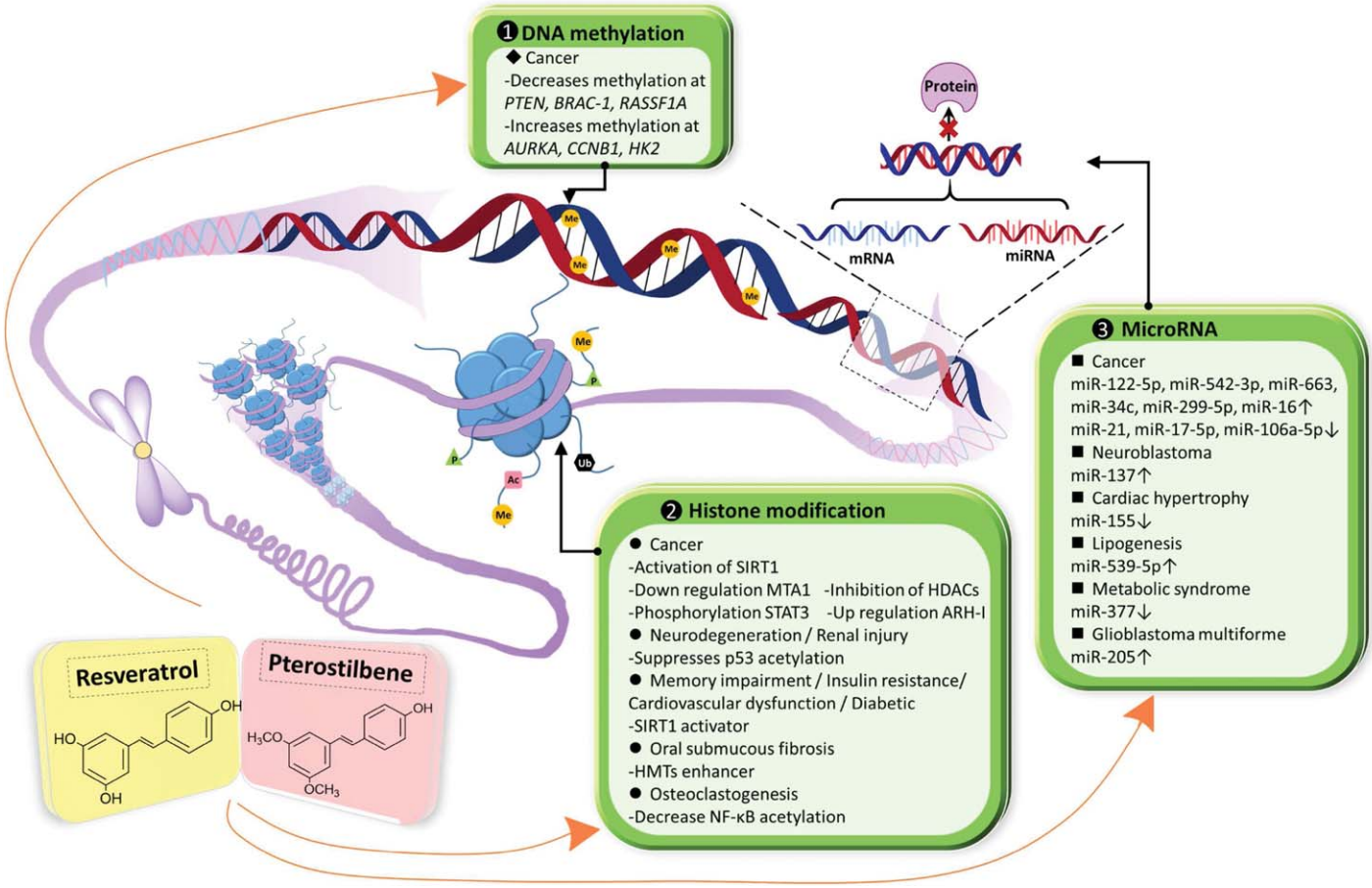

FIG 1

Schematic representation of epigenetic regulation by resveratrol and pterostilbene in disease chemoprevention. Resveratrol and pterostilbene either alone or in combination showed promising results against various diseases. The major types of epigenetic modification, such as DNA methylation, histone modification, and miRNA-mediated gene silencing in epigenetic targeting by resveratrol and pterostilbene in disease prevention. (1) DNA methylation is a covalent modification involving the addition of a methyl group to the carbon-5 position of a cytosine residue (2) Histone modifications refer to covalent post-translational modifications of N-terminal tails of four core histones, including methylation (Me), acetylation (Ac), phosphorylation (P) and ubiquitylation (Ub). (3) miRNAs are negative regulators of genes transcription by binding to mRNA sequences.

miR-34c, which further knocked down its target KITLG and the effect was enhanced in the presence of p53 probably through inactivating the PI3K/Akt pathway [55]. Resveratrol can also decrease the expression of miR-21. Down regulation of miR-21 expression can inhibit BCL-2 expression in PANC-1, CFPAC-1, and MIA Paca-2 pancreatic cancer cells [56]. Resveratrol also changes the miRNA pattern in A549 human non-small cell lung cancer cells. There are 71 miRNAs that are upregulated in resveratrol treated cells compared with untreated cells, and some of the miRNAs (*e.g.*, miR-299-5p, miR-194, miR-338-3p, miR-758, miR-582-3p, and mir-92a-2) exhibited greater than 20-fold changes in expression in resveratrol-treated cells compared with the control. By using an miRNA target-prediction program, the authors identify several target genes of these miRNAs related to apoptosis, cell cycle regulation, cell proliferation, and differentiation [57]. Ren et al. presented for the first time an epigenetic mechanism involving miR-137-mediated EZH2 (Enhancer of zeste homolog 2) repression in resveratrol-induced apoptosis and tumor suppression of neuroblastoma, which would provide a key potential therapeutic target in neuroblastoma treatment. EZH2 reduction further led to decreased H3K27me3 levels and reactivation of neuroblastoma tumor suppressor genes CLU (clusterin) and nerve growth factor receptor [58]. The results indicate that resveratrol induces apoptosis in a time and dose dependent manner in CCRF-CEM acute lymphoblastic leukemia cells. In addition, increased expression level of miR 16-1 and miR 15a by means of resveratrol in CCRF-CEM cells might have a role in apoptosis induction and predisposition. According to the results, resveratrol can be regarded as a dietary supplement to improve the efficacy of antileukemia therapies [59]. Fan et al. investigated the molecular effects of miR-155 on cardiac hypertrophy, focusing on the role of breast cancer type 1 susceptibility protein (BRCA1). The results showed that resveratrol alleviated the severity of hypertrophic myocardium in a mice model of cardiac hypertrophy by TAC (transverse

aortic constriction) treatment. Resveratrol relieved cardiac hypertrophy and restored cardiac function by the activation of BRCA1 in cardiomyoctyes. BRCA1 inactivation can increase expression of miR-155, contributing to cardiac hypertrophy [60]. The upregulation of miR-539-5p is involved in the inhibition of *de novo* lipogenesis induced by resveratrol in white adipose tissue (WAT). The microarray showed that 3 miRNAs were decreased and 13 were increased after resveratrol treatment. Among those miRNAs increased, miR-129, miR-328-5p, and miR-539-5p showed predicted target genes (pparγ: peroxisome proliferator-activated receptor gamma, hsl: hormone sensitive lipase and sp1: SP1 transcription factor) relevant for triacylglycerol metabolism in WAT in the miRWalk database [61].

Pterostilbene inhibited the migratory and invasive potential of triple-negative MDA-MB-231 and Hs578t cells, accompanied by the upregulation of E-cadherin and downregulation of snail, slug, vimentin, and ZEB1. In this study, mechanistic investigations revealed a significant upregulation of miR-205, which resulted in the reduction of Src expression in pterostilbene-treated breast cancer cells. In addition, pterostilbene suppressed tumor growth and metastasis in MDA-MB-231-bearing NOD/SCID mice by reducing Src/Fak signaling; this observation was consistent with negative correlations between miR-205 and Src expression in both normal and malignant breast tissues. These findings provide support for the usage of pterostilbene as an inhibitor of EMT process and potential candidate for adjuvant therapy [62]. Mak et al. showed that pterostilbene treatment can dose dependently overcome M2 TAM-induced enrichment of CSCs and the metastatic potential of breast cancer cells. Pterostilbene suppressed NF-κB, Twist1, vimentin, and increased E-cadherin expression. Using siRNA technique, the results demonstrated that pterostilbene-mediated NF-κB downregulation was correlated to an increased amount of miRNA 448. *In vivo* study proved that pterostilbene-mediated suppression in tumorigenesis and metastasis was validated by noninvasive bioluminescence in mice bearing M2 TAM cocultured MDA-MB-231 tumor [63]. Glioblastoma multiforme (GBM) is the most aggressive type characterized by relapse and resistance even with the combination of radiotherapy and chemotherapy. The presence of glioma stem cells (GSCs) has been shown to contribute to tumorigenesis. Pterostilbene-treated GSCs exhibited suppressed self-renewal and irradiation-resistant abilities. Pterostilbene-mediated effects were associated with an increase of miR-205. The results provided evidence that the GRP78/miR-205 axis played an important role in GSC maintenance and irradiation resistance. Pterostilbene treatment suppressed GSC development via negatively modulating GRP78 signaling [64]. miRNAs-377 acted as a biomarker of oxidative stress in the renal cortex of fructose-fed rats, which correlated with podocyte injury and albuminuriain metabolic syndrome. Antioxidant pterostilbene was found to ameliorate fructose-induced hyperuricemia, podocyte injury, and albuminuriain rats. More importantly, pterostilbene inhibited podocyte miR-377 overexpression to increase SOD1 and SOD2 levels and suppress the $O2^{-}$/p38 MAPK/TXNIP/NLRP3 inflammasome pathway activation *in vivo* and *in vitro*, consistent with the reduction of oxidative stress and inflammation. These findings suggest that miR-377 plays an important role in glomerular podocyte oxidative stress, inflammation, and injury driven by high fructose [65].

In prostate cancer, studies with stilbenes have demonstrated miRNA-mediated (miR-17-5p and miR-106a-5p) therapeutic strategy and proposed circulating miRNAs as predictive biomarkers for clinical development. The results having epigenetic targets in prostate cancer provide a rationale for studying pterostilbene's synthetic analogs as a candidate for epigenetic drugs with future applications in prostate cancer [66].

6. Conclusions

This review article provides a comprehensive summary on the dietary phytochemicals resveratrol and pterostilbene. Their potential beneficial effects may in part be attributable to their epigenetic properties including changes in DNA methylation, histone modifications, and in the expression of miRNAs. The most important difference between genetic and epigenetic alteration is that epigenetic changes are reversible, but genetic changes are usually not. Epigenetic changes thus become attractive targets for treating various diseases. Resveratrol and pterostilbene not only restore the hypomethylated and hypermethylated status of key tumor suppressor genes and oncogenes, but also improve the outcome of diseases by activating SIRT1 (Fig. 1). Many studies show that the patterns of miRNAs are tightly regulated and involved in crucial biological processes. Impairment of miRNA function has been implicated in tumorigenesis and other disease. Moreover, some research indicates that instead of the treatment using only resveratrol or pterostilbene, the combinatorial effect proved better. In summary, the data examined in this review provides new insights into the epigenetic effects of resveratrol and pterostilbene, and suggests that resveratrol and pterostilbene are promising candidates for chemopreventive and chemotherapeutic treatment strategies.

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Conflicts of Interest

The authors declare no conflict of interest.

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