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Dietary stilbenes as modulators of specific miRNAs in prostate cancer

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Accumulated experimental data have suggested that natural plant products may be effective miRNA-modulating chemopreventive and therapeutic agents. Dietary polyphenols such as flavonoids, stilbenes, and lignans, among others, have been intensively studied for their miRNA-mediated cardioprotective, antioxidant, anti-inflammatory and anticancer properties. The aim of this review is to outline known stilbene-regulated miRNAs in cancer, with a special focus on the interplay between various miRNAs and MTA1 signaling in prostate cancer. MTA1 is an epigenetic reader and an oncogenic transcription factor that is overexpressed in advanced prostate cancer and metastasis. Not surprisingly, miRNAs that are linked to MTA1 affect cancer progression and the metastatic potential of cells. Studies led to the identification of MTA1-associated pro-oncogenic miRNAs, which are regulated by stilbenes such as resveratrol and pterostilbene. Specifically, it has been shown that inhibition of the activity of the MTA1 regulated oncogenic miR-17 family of miRNAs, miR-22, and miR-34a by stilbenes leads to inhibition of prostatic hyperplasia and tumor progression in mice and reduction of proliferation, survival and invasion of prostate cancer cells *in vitro*. Taken together, these findings implicate the use of resveratrol and its analogs as an attractive miRNA-mediated chemopreventive and therapeutic strategy in prostate cancer and the use of circulating miRNAs as potential predictive biomarkers for clinical development.

KEYWORDS

stilbenes, miRNAs, MTA1, chemoprevention, interception, biomarkers, active surveillance, prostate cancer

Introduction

Countless efforts are aimed towards the development of cancer chemopreventive and therapeutic strategies with the use of natural bioactive polyphenols such as a large group of flavonoids, stilbenes, lignans, phenolic acids, and others (Asensi et al., 2011; Kang N.J et al., 2011; Miyata et al., 2019; Forni et al., 2021; Rudrapal et al., 2022). Polyphenols act on multiple targets in signaling pathways related to inflammation, oxidative stress and DNA damage, carcinogenesis, tumor cell proliferation, angiogenesis, and metastasis (Asensi et al., 2011; Zhao et al., 2020; Khan et al., 2021; Rudrapal et al., 2022). Studies over the past two decades have led to the development of the concept of “epigenetic prevention and therapy” for cancer, which includes regulation of genes by non-coding RNAs (ncRNAs)

(Shukla et al., 2019; Levenson, 2021). Non-coding RNAs regulate chromatin architecture (Taft et al., 2009) and control gene expression by negatively regulating gene expression through a number of mechanisms (Filipowicz et al., 2008). Among ncRNA, microRNAs (miRNAs, miRs) are small, single-stranded, sequence-specific RNAs that induce degradation or inhibit translation of their target mRNAs (Ventura and Jacks, 2009). MiRNAs modulations have been shown to be involved in many pathologies including inflammation and cancer. In cancer, miRNAs are designated as oncogenic (oncomiRs), which downregulate tumor suppressor (TS) or other genes involved in cell differentiation thereby contributing to tumor formation, or oncosuppressor miRs, which downregulate proteins with oncogenic activity (Shenouda and Alahari, 2009). MiRNAs expressed in a tissue-specific manner have a multi-target mode of action (Link et al., 2010). MiRNAs are gaining increasing attention as potential noninvasive diagnostic, prognostic, and predictive biomarkers in cancer because they are stable, highly sensitive, and easily detectable in extracellular fluids (Quirico and Orso, 2020; Wang J et al., 2020).

Numerous studies have investigated miRNA profiles and their regulation by dietary phytochemicals, and the accumulated data implicate natural polyphenols as attractive miRNA-mediated chemopreventive and therapeutic strategy options in solid tumors and hematological cancers (Dhar et al., 2011; Vanden Berghe, 2012; Kumar et al., 2016; Levenson and Kumar, 2020; Levenson, 2021). Prostate cancer is ideal disease for nutritional chemoprevention in the general population of elderly men due to its slow progression in and dependence on diet (Peisch et al., 2017; Matsushita et al., 2020). Unfortunately, the incidence of low-risk prostate cancer has increased in the last two decades. Active surveillance is accepted as a management option for favorable-risk prostate cancer. However, due to the heterogeneity of this population, the lack of personalized risk assessments and the absence of treatment, the long-term outcome of active surveillance is not satisfying for approximately 30% of patients (Dhawan et al., 2016; Moschini et al., 2017; Overland et al., 2019; Pastor-Navarro et al., 2021). Since active surveillance patients are diagnosed with either prostatic intraepithelial neoplasia (PIN) or early-stage cancer (Gleason <6), it is apparent that various carcinogenic signaling pathways are already activated and can lead to pathological or clinical progression. Thus, the active surveillance subpopulation of patients with varying cancer risks may benefit from more active, clinical-based nutritional chemopreventive, i.e., interceptive strategies. Natural bioactive compounds known for their anti-inflammatory, antioxidant and anticancer effects may represent risk-reducing agents recommended for cancer interception (Blackburn, 2011). Nutritional interception in intermediate- and high-risk active surveillance patients should target specific molecular pathways. Particularly, our group has shown that natural dietary stilbenes exhibit targeted chemoprotective, interceptive and therapeutic

effects against prostate cancer *in vitro* and *in vivo* (Kai et al., 2010; Li et al., 2013; Dhar et al., 2016; Butt et al., 2017; Kumar et al., 2019; Gadkari et al., 2020; Levenson, 2020; Hemani et al., 2022). This review will focus on the potential of natural stilbenes to protect against prostate cancer through the modulation of specific miRNAs that can conceivably be detected in bloodstream and urine and serve as prognostic and predictive biomarkers for certain populations of prostate cancer patients in the future.

Stilbenes, miRNAs and cancer

Dietary stilbenes

Stilbenes are a class of polyphenols naturally found in a wide variety of a small and heterogeneous group of plants, including *Vitis vinifera*, *Vaccinium*, *Cissus adnata*, *Fallopia japonica*, *Polygonum cuspidatum*, and *Picea sitchensis* and *abies*, to mention some (Rimando et al., 2004; Riviere et al., 2012). More than 400 natural stilbenoids have been identified in plants (Shen et al., 2009) where they are produced in response to biotic and abiotic environmental stresses (Bavaresco, 2003). Family members of the stilbenoids have a C6-C2-C6 basic skeleton and consist of two or more phenolic rings linked by an ethane double bond. Natural stilbenes are composed of resveratrol derivatives and concentrated in dietary sources such as grapes, red wine, grape juice, peanuts, berries, passion fruit and some medicinal plants. There are several well-known dietary stilbenes such as resveratrol, piceid, resveratrol dimers pallidol, viniferins, and Gnetin C, pterostilbene, piceatannol, and astringin (Figure 1). Resveratrol (C₁₄H₁₂O₃) is the most widely studied stilbene compound, found mostly in grapes and red wine but also in cranberries, pistachios, and chocolate, has multiple and diverse pharmacological properties including antioxidant, anti-inflammatory and anticancer properties (Rauf et al., 2018; Galiniak et al., 2019; Kataria and Khatkar, 2019; Rudrapal, 2022). Pterostilbene (C₁₆H₁₆O₃) is a naturally occurring methoxylated analog of resveratrol, found in blueberries and grapes, with improved pharmacokinetic efficacy and more potent biological efficacy over resveratrol (Rimando et al., 2002; Rimando et al., 2004; Rimando et al., 2005; Kapetanovic et al., 2011; Hagiwara et al., 2012; Dhar et al., 2015b). Piceatannol (C₁₄H₁₂O₄) is another naturally occurring resveratrol metabolite, found in red wine, grapes, white tea or passion fruit, is recognized as a strong tyrosine kinase inhibitor in different types of cancer (Su and David, 2000; Vo et al., 2010; Kang C.H et al., 2011). Piceid, a major resveratrol glucoside in grape juices, demonstrated antiproliferative effects in epithelial and cancer cells (Su et al., 2013; Storniolo et al., 2014; Zhang T. et al., 2019). Piceatannol's glucoside, astringin (C₂₀H₂₂O₉), especially

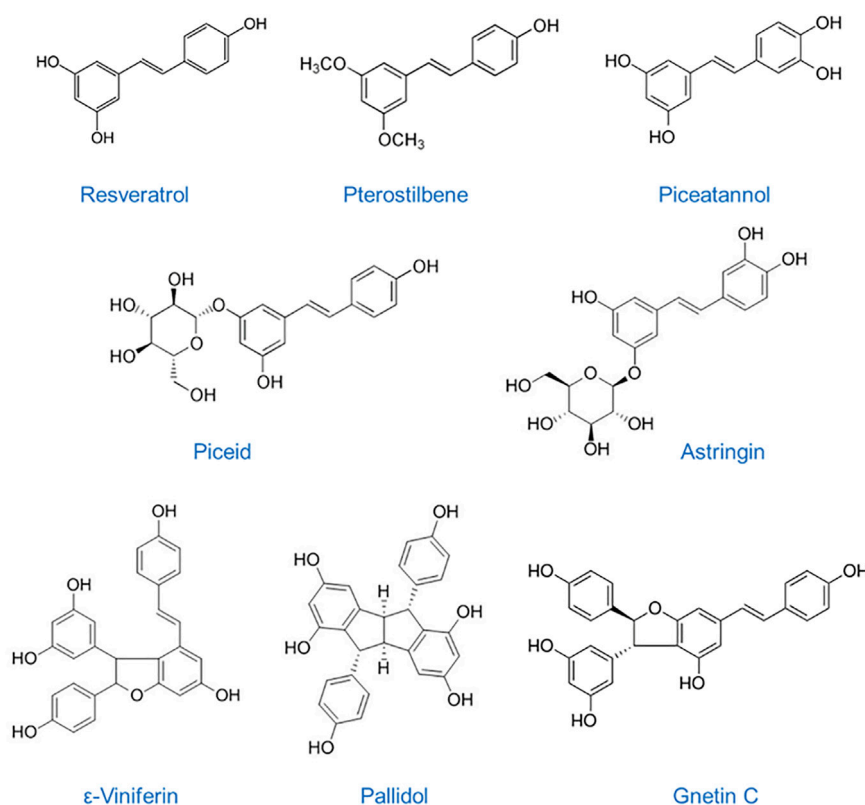


FIGURE 1

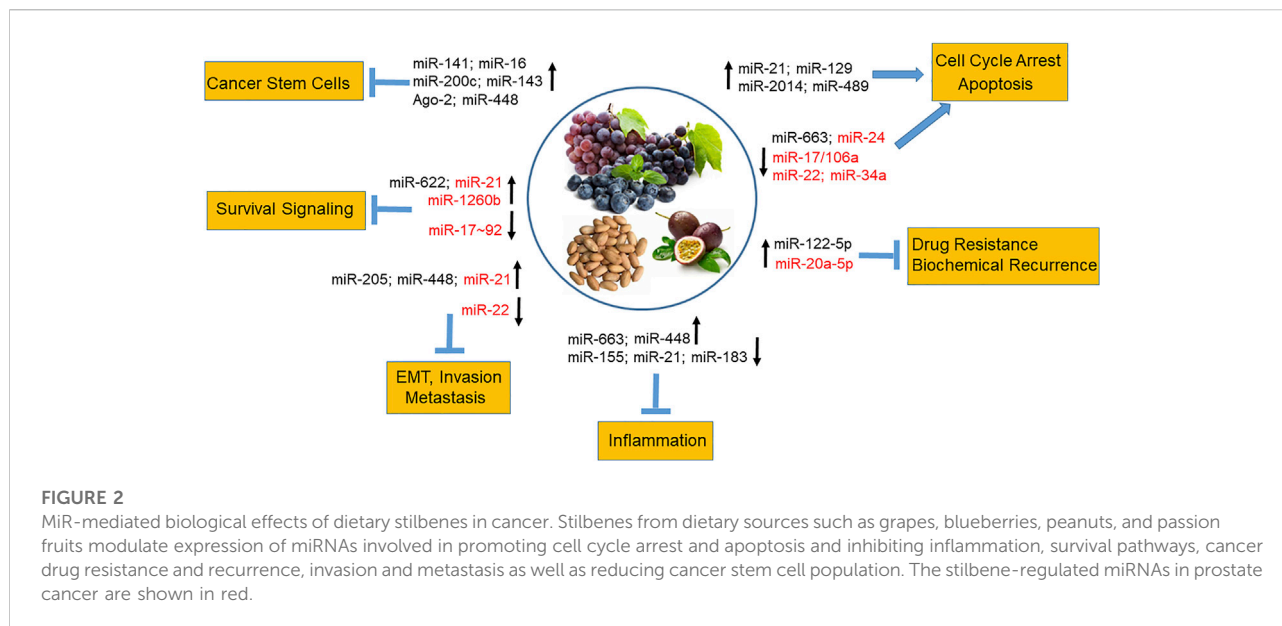
Chemical structures of dietary stilbenes: Resveratrol, *trans*-3, 4', 5-trihydroxystilbene, MW: 228.24 g/mol; Pterostilbene, *trans*-3,5-dimethoxy-4'-hydroxystilbene, MW: 256.30 g/mol; Piceatannol, *trans*-3,5,3',4'-tetrahydroxystilbene, MW: 244.24 g/mol; Piceid, *trans*-resveratrol-3-O-glucoside, MW: 390.39 g/mol; Astringin, *trans*-piceatannol-3-β-D-glucuronide, MW: 406.38 g/mol; ε-Viniferin, *trans*-epsilon-resveratrol dimer, MW: 454.50 g/mol; Pallidol, tetracyclic homodimer resveratrol, MW: 454.48 g/mol; Gnetin C, dimer resveratrol, MW: 454.48 g/mol.

found in red wine, has been shown to function as potential cancer-chemopreventive agent by a mechanism different from that of resveratrol (Waffo-Teguo et al., 2001). Moreover, a recent report demonstrated potent anti-angiogenic effect of astringin as well as of resveratrol dimers ε-viniferin, ω-viniferin, and pallidol (C₂₈H₂₂O₆), also concentrated in grapes and red wine (Fernandez-Cruz et al., 2019). Gnetin C (C₂₈H₂₂O₆), a resveratrol dimer found in melinjo (*Gnetum gnemon*) seed extracts that are commonly used in Indonesian cuisine, possesses a broad spectrum of the same pharmacological activities as other stilbenes with the advantage of superior bioavailability and biological efficacy (Narayanan et al., 2015; Kumar et al., 2019; Gadkari et al., 2020). Chemopreventive effects of dietary stilbenes are mainly due to their anti-inflammatory and antioxidant activity but also direct targeting of multiple signaling pathways involved in carcinogenesis, cancer progression and metastasis. Importantly, accumulated data suggest that the beneficial effects of dietary stilbenes may be in part attributed to their epigenetic properties, including regulation of DNA methylation, histone modifications, and, notably,

modulation of the expression of miRNAs/miRs (Kumar et al., 2015; Kumar et al., 2016; Kumar and Levenson, 2018; Levenson, 2021).

Stilbene-regulated miRNAs in cancer

In a high-throughput analysis of miRNA expression in response to stilbenes, modulated miRs were identified as essential for controlling cancer growth, survival, metabolism, motility, apoptosis, angiogenesis, and metastasis (Tili and Michaille, 2011). In general, studies have shown that stilbenes inhibit oncomiRs and upregulate oncosuppressor miRs. For example, resveratrol has been shown to upregulate miR-21, miR-129, miR-2014, and miR-489 in rodent mammary tumors tissues (Qin et al., 2014) and a number of other oncosuppressor miRs, causing cell cycle arrest and cell death in breast cancer cells (Venkatadri et al., 2016). In chemoresistant breast cancer cells, resveratrol restored cell chemosensitivity by upregulating miR-122-5p (Zhang W. et al., 2019). Resveratrol and pterostilbene reduced the cancer stem-like cells population



in mammary tumor formation *in vivo* by upregulating the expression of oncosuppressor miR-141, miR-16, miR-200c, miR-143 and Ago-2, a key regulator of miRNA homeostasis and biogenesis (Hagiwara et al., 2012). Seventy-one miRNAs were regulated in human lung cancer cells by resveratrol (Bae et al., 2011) including TS miR-622, which targets K-ras (Han et al., 2012). The miRNA-mediated link between inflammation and cancer under resveratrol treatment was demonstrated by revealing upregulation of anti-inflammatory and oncosuppressor miRNAs, such as miR-663, and downregulation of pro-inflammatory and oncogenic miRs, such as miR-155 and miR-21 (Tili et al., 2010a; Tili et al., 2011; Latruffe et al., 2015). Importantly, studies have reported subsequent mechanistic experiments, in which the identification of mRNA target transcripts whose levels were modified by stilbenoids, were validated on mRNA and/or protein levels. For example, resveratrol anti-inflammatory activity occurred *via* targeting the miR-663-mediated AP-1 signaling pathway (Tili et al., 2010a) and through modulating miRs involved in TGF β signaling in human colorectal cancer cells (Tili et al., 2010b). Pterostilbene inhibited tumor growth and metastasis in breast cancer xenografts *via* induction of miR-205 expression, which targeted the Src/Fak signaling (Su et al., 2015) and suppressed glioblastoma through the miR-205/GRP78 axis (Huynh et al., 2015). A different study found that pterostilbene-induced modulation of miR-448/NF- κ B axis resulted in suppression of the generation of breast cancer stem cells and metastatic potential (Mak et al., 2013). Further, pterostilbene downregulation of oncogenic miR-663, whose expression is correlated with poor prognosis in endometrial cancer patients, led to induction of pro-apoptotic BCL2L14 in endometrial cancer cells *in vitro* (Wang et al., 2017). Another natural analog of resveratrol, piceatannol,

exhibited inhibition of colorectal cancer cell growth and induction of apoptosis by inducing miR-129-mediated downregulation of BCL-2 (Zhang et al., 2014). Furthermore, piceatannol inhibited Sp-1-mediated ADAM17 expression and the TNF α /NF- κ B pathway in human leukemia cells by downregulating Akt/Foxo3-mediated miR-183 expression (Liu and Chang, 2012). Figure 2 summarizes reported miR-mediated biological effects of stilbenes in various cancers including prostate cancer (see below).

Stilbene-regulated miRNAs in prostate cancer

In prostate cancer, oncomiRs expression correlates with high Gleason score and clinical recurrence (Ambs et al., 2008; Brase et al., 2011) and can be easily detected in serum, plasma and urine (Ambs et al., 2008; Selth et al., 2012; Sapre and Selth, 2013; Jeon et al., 2020; Hasanoglu et al., 2021), which signifies future utilization of miR-regulated pathways as potential targets as well as prognostic and predictive biomarkers.

Differential miRNA expression profiling in LNCaP prostate cancer cells treated with resveratrol revealed considerable modulation of a set of 51 miRNAs, from which 23 miRNAs (putative oncomiRs) were significantly downregulated and 28 miRNAs (putative oncosuppressor miRs) were significantly upregulated (Dhar et al., 2011).

The downregulated by resveratrol miRs included miR-7, miR-24, miR-1260 and miR-17~92 (miR-17, miR-20a, miR-20b, miR-92b) and miR-106ab clusters. Subsequently, a growing body of evidence has revealed that many of these miRNAs act as oncogenes in prostate cancer. For instance,

miR-7 has been found to be upregulated in castrate-resistant prostate cancer (CRPC) clinical samples (Xie and Jiang, 2015). Downregulation of miR-24 induced apoptosis in DU145 prostate cancer cells by upregulating its target pro-apoptotic FAF1 protein (Qin et al., 2010). Multiple miRNAs-TGF β checkpoints that control TGF β /SMAD signaling in progression of prostate cancer were identified (Javed et al., 2020). For instance, overexpression of oncomiR-1260b resulted in reduced levels of tumor suppressor SMAD4 leading to prostate cancer progression. Interestingly, miR-1260b was also significantly downregulated by another natural polyphenol known for its anticancer properties, i.e. genistein that promoted SMAD4-mediated apoptosis in prostate cancer cells (Hirata et al., 2014). Overexpression of miR-20a has been detected in tumor tissue samples of prostate cancer patients with a Gleason score of 7–10 (Pesta et al., 2010). Moreover, a high miR-20a-5p expression in prostate tumor tissues was identified as one of the five miRNAs that may, as a panel, be used as a potential diagnostic biomarker (Damodaran et al., 2021) and as an independent predictor for biochemical recurrence (Stoen et al., 2021). The oncogenic role of miR-20a/CX43 (Li et al., 2012) and miR-20a/miR-17/ATG7 (Guo et al., 2016) in prostate cancer was also reported. The miR-17~92 and paralog miR-106a~363 and miR-106b~25 are commonly described as oncogenic in many cancers (Kolenda et al., 2020) including prostate cancer, in which they have been validated clinically as significantly upregulated compared to normal samples (Taylor et al., 2010). Importantly, miR-17~92 and miR-106ab have been directly linked to the tumor suppressor PTEN (Olive et al., 2010; Poliseno et al., 2010), one of the frequently defective genes in primary and metastatic prostate cancer (Li et al., 1997). In consequent studies, using functional luciferase reporter assays, it was demonstrated that ectopically expressed miR-17, miR-20a and miR-106b directly target *Pten* 3'UTR to reduce its expression in DU145 and 22Rv1 prostate cancer cells. Notably, these effects were rescued upon treatment with resveratrol and pterostilbene (Dhar et al., 2015b). Moreover, pterostilbene treatment diminished the miR-17/106a-promoted tumor growth in DU145-Luc prostate cancer xenografts through miR-mediated upregulation of PTEN mRNA and protein levels in tumor tissues, causing apoptosis (Dhar et al., 2015b). A different report demonstrated resveratrol-induced reduction of prostate cancer growth and metastasis through Akt/miR-21/PDCD4 pathway (Sheth et al., 2012).

The upregulated by resveratrol miRNAs in prostate cancer included miR-1469, miR-612, miR-149, miR-638, miR-654-5p, miR-1908, miR-1915, miR-1231, miR-939, miR-671-5p (Dhar et al., 2011), many of which are currently documented as oncosuppressor miRNAs in several types of cancer (Jin et al., 2020; Li et al., 2021; Liu et al., 2020a, b; Tan et al., 2016). For

example, a recent study demonstrated that miR-149 could inhibit AR expression and reduce the activity of PI3K/Akt1 signaling in castrate-resistant cells (Zhao et al., 2021) and also regulate RGS17-mediated oncogenic effects (Ma et al., 2021) revealing its tumor suppressor nature in prostate cancer. The tumor suppressive role of miR-1231 targeting EGFR in prostate cancer and reducing cell proliferation, migration, and invasion was recently demonstrated (Wang Y et al., 2020). The authors propose diminished miR-1231 levels as a prognostic biomarker for advanced prostate cancer. MiR-654-5p was among fifteen AR downregulating miRNAs that decreased androgen-induced proliferation of prostate cancer cells (Ostling et al., 2011). Another miR, upregulated by resveratrol (Dhar et al., 2011), namely miR-939-3p, was decreased in prostate cancer tissues and cell lines compared to normal adjacent tissues and normal epithelial cell line. MiR-939-3p acted as an oncosuppressor miR through the long non-coding RNA (lncRNA) brain cytoplasmic RNA1 BCYRN1/HDAC11 oncogenic axis in prostate cancer (Huo et al., 2020). Interesting results were reported on the overexpression of spermidine synthase (SRM) in prostate cancer tissues and miR-1908-mediated regulation of SRM, which controls the secretion of extracellular vesicles (EV) in prostate cancer (Urabe et al., 2020). Finally, upregulation of EV-associated miR-1915-3p was concomitant with improved survival time along with two other miRNAs, but only miR-1915-3p was associated with longer recurrence-free survival as an independent prognostic marker in prostate cancer patients with low and high Gleason scores and of various races (Ali et al., 2021). It is important to notice that detailed experimental mechanistic studies to prove biological consequences of stilbene modulated oncosuppressive miRNAs in prostate cancer are lacking. Of note, miR-1469 have been reported to be induced by genistein resulting in promotion of apoptosis *via* inhibition of the Mcl-1 pathway in laryngeal cancer cells (Ma et al., 2018).

The role of some miRNAs in cancer is complex and ambiguous: these miRNAs have been reported as both oncogenic and oncosuppressors. However, while this controversy can be attributed to the cell specificity, organ tissue microenvironment and various targets for a given miR, a disagreement about the behavior of a given miR in the same type of cancer is less understandable. For example, although recognized as a tumor suppressor in some tumors (Li et al., 2019; Xin et al., 2019; Wang et al., 2021) the unexpected oncogenic role of miR-671-5p associated with targeting tumor suppressor SOX6 in prostate cancer has been recently reported (Yu et al., 2018). Moreover, oncosuppressor miR-149 was found to be overexpressed in CRPC samples (Zhu et al., 2015) and has been seen as an oncogenic miR associated with syndecan-1 and inhibiting SOX2, NANOG, and Oct4 tumor suppressors (Fujii et al.,

TABLE 1 Confirmed Oncogenic miRNAs in Prostate Cancer^a.

Stilbene	miRNA	Identified Target	Associated information or Event	References
No treatment	miR-7		Upregulated in CRPC clinical samples	Xie and Jiang, (2015)
	miR-24	FAF1	Apoptosis in DU145 cells	Qin et al. (2010)
“Genistein”	miR-1260b	SMAD4	Apoptosis in PC3 cells	Hirata et al. (2014)
No treatment	miR-20		Overexpressed in aggressive prostate cancer	Pesta et al. (2010)
			Potential diagnostic marker	Damodaran et al. (2021)
			Predictor for biochemical recurrence	Stoen et al. (2021)
No treatment	miR- 20	CX43	PCa-2b cell proliferation, tumor growth	Li. et al. (2012)
No treatment	AR/miR-20a/miR-17	ATG7	Autophagy	Guo et al. (2016)
No treatment	miR-17~92		Upregulated in clinical samples	Taylor et al. (2010)
Resveratrol	miR-17~92	PTEN	Reduced cell proliferation and xenograft tumor growth	Dhar et al. (2015b)
Pterostilbene				
Resveratrol	miR-106a~363	PTEN	Reduced cell proliferation and xenograft tumor growth	Dhar et al. (2015b)
Pterostilbene				
Resveratrol	miR-106b~25	PTEN	Reduced cell proliferation and xenograft tumor growth	Dhar et al. (2015b)
Pterostilbene				
Resveratrol	Akt/miR-21	PDCD4	Cancer growth and metastasis	Sheth et al. (2012)
Grape extract-Diet	MTA1/c-miR-34a	p53	Reduced PIN in <i>Pten</i> ^{+/f} ; <i>Cre</i> ⁺ mice	Joshi et al. (2020)
	MTA1/c-miR-22	p21		
Pterostilbene-Diet	MTA1/c-miR-34a		Reduced hgPIN in <i>R26</i> ^{MTA1} ; <i>Pten</i> ^{+/f} ; <i>Cre</i> ⁺ mice	Hemani et al. (2022)
	MTA1/c-miR-22			
No treatment	MTA1/miR-22	E-cadherin	Invasion in RWPE1 & LNCaP cells	Dhar et al. (2017)

^aThese miRNAs, are putative stilbene-regulated onco-miRs previously identified by Dhar et al. (2011); c-miR, circulating miR detected in serum.

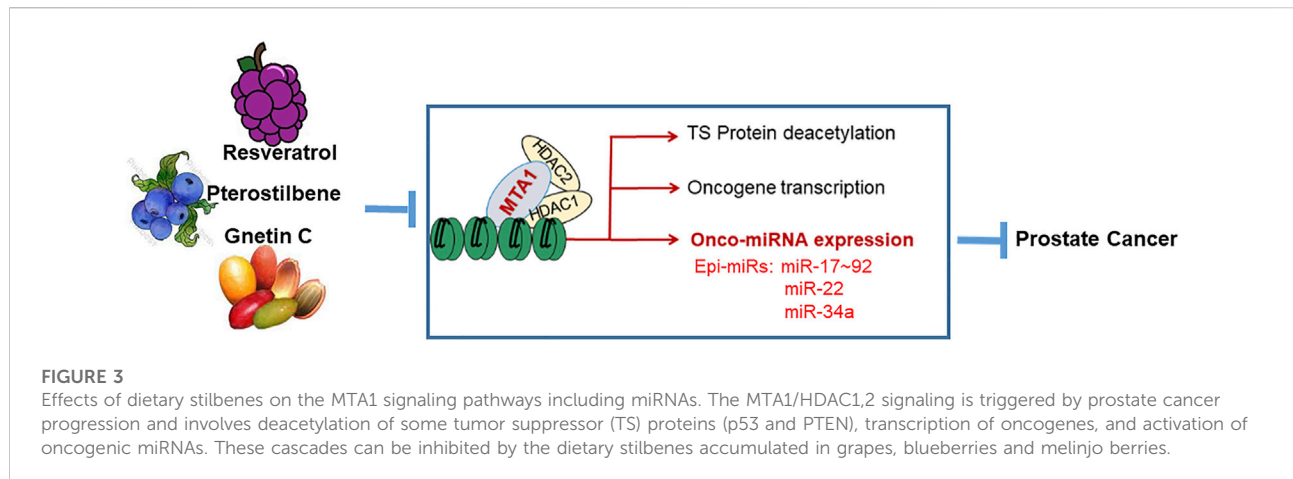
TABLE 2 Confirmed Oncosuppressor miRNAs in Prostate Cancer^a.

Stilbene	miRNA	Identified Target	Associated information or Events	References
No treatment	miR-654-5p	AR	PSA, LNCaP cell proliferation	Ostling et al. (2011)
No treatment	miR-149	AR	CRCP 22-Rv1 cells	Zhao et al. (2021)
		P13K/Akt1		
No treatment	miR-149-5p	RGS17	Viability, proliferation, migration of 22Rv1 and C4-2 cells , high in prostate cancer tissues	Ma et al. (2021)
No treatment	miR-1231	EGFR	Cell proliferation, migration, invasion in DU145, 22Rv1, PC3, and VCaP, high in prostate cancer tissues	Wang Y et al. (2020)
No treatment	miR-939-3p	BCYRN1/HDAC11	Cell proliferation,	Huo et al. (2020)
			Decreased in prostate cancer tissues vs. normal	
No treatment	miR-1908	SRM	22Rv1 cells, high in prostate cancer tissues	Urabe et al. (2020)
No treatment	miR-1915-3p		Upregulation was linked to recurrence-free survival	Ali et al. (2021)
			Independent prognostic marker	

^aThese miRNAs are putative stilbene-regulated oncosuppressor miRs previously identified by Dhar et al., 2011.

2015). Tables 1, 2 summarize confirmed oncogenic (Table 1) and oncosuppressor miRs (Table 2) in prostate cancer earlier identified as resveratrol-regulated (Dhar et al., 2011). The

data regarding the functions and exact roles of identified stilbene-regulated miRNAs in prostate cancer are incomplete and require further studies.



Stilbenes as inhibitors of MTA1 signaling and associated miRNAs in prostate cancer

Understanding the specific molecular mechanisms of premalignancy and cancer progression opens opportunities for developing targeted interceptive measures. It is largely acknowledged that natural polyphenols, particularly stilbenes have pleiotropic anti-inflammatory and anticancer effects acting through various signal transduction pathways such as NF- κ B, AP-1, and MAPK signaling among others.

In prostate cancer, metastasis associated protein 1 (MTA1) signaling is aberrantly activated due to overexpression of MTA1 and activation of associated pathways. Increased expression of MTA1 is associated with high Gleason score, recurrence, and metastasis in prostate cancer (Hofer et al., 2004; Dias et al., 2013). MTA1 plays a critical role in different stages of prostate cancer, including chronic inflammation, tumor growth, epithelial-to-mesenchymal transition (EMT), invasion, migration, angiogenesis and metastasis (Levenson et al., 2014). Studies have demonstrated the MTA1-mediated chemopreventive and therapeutic effects of natural stilbenes in prostate cancer (Levenson, 2020). Both resveratrol and pterostilbene inhibited survival pathways and induced apoptosis in prostate cancer through downregulation of the MTA1/HDAC1, 2 units of the NuRD complex, which resulted in the promotion of acetylation and reactivation of tumor suppressors p53 and PTEN (Kai et al., 2010; Dhar et al., 2015b). The inhibitory effects of resveratrol and pterostilbene on MTA1-mediated angiogenesis involving HIF-1 α , VEGF, and IL-1 β were also consistently reported (Kai et al., 2011; Li et al., 2013; Dhar et al., 2016; Butt et al., 2017; Hemani et al., 2022). We have also shown the MTA1-mediated and MTA1 independent chemopreventive and therapeutic value of Gnetin C in prostate cancer *in vitro* and *in vivo* (Kumar et al., 2019; Gadkari et al., 2020). Importantly, stilbenes can inhibit MTA1-associated oncogenic miRNAs (Figure 3).

MTA1, an epigenetic reader and “master co-regulator” and transcription factor, plays a role in direct or indirect transcriptional activation/suppression of specific genes including miRNAs (Manavathi and Kumar, 2007). MiRNAs that are regulated by epigenetic factors are called Epi-miRs (Valeri et al., 2009; Dhar et al., 2017; Levenson, 2020). MTA1-associated stilbene-regulated Epi-miRNAs have been identified by a systematic analysis and review of the results from the following three high-throughput analyses in prostate cancer: the identification of resveratrol responsive miRNAs using miRNA microarrays in LNCaP cells (Dhar et al., 2011), the identification of MTA1-associated miRNAs by differential miRNA microarrays profiling in LNCaP MTA1 knockdown cells (Dhar et al., 2017), and the identification of prostate tissues transcriptional targets of MTA1 by ChIP-Seq from prostate-specific *Pten*-deficient mice fed with pterostilbene-diet (Dhar et al., 2016).

Our special interest in oncomiR/PTEN axis came from previous studies, in which we and others showed upregulation of PTEN protein levels by resveratrol in prostate cancer cells (Wang et al., 2010; Dhar et al., 2011), one mechanism of which was the inhibition of MTA1-mediated deacetylation and inactivation of PTEN (Dhar et al., 2015a). In parallel, resveratrol downregulated miR-17-92, miR-106a~363, and miR-106b~25 clusters in prostate cancer cells (Dhar et al., 2011). Further, miR-17, miR-20a, and miR-106b directly targeted the 3'UTR of *Pten*, an event that was reversed by resveratrol and pterostilbene in prostate cancer cells (Dhar et al., 2015b). Moreover, the reduced levels of circulating miR-17 and miR-106a in the sera from mice treated with pterostilbene - led to reduced tumor growth and revealed the potential of stilbene-responsive miRs as chemopreventive and predictive biomarkers in prostate cancer (Dhar et al., 2015b). In addition, miRNA profiling of MTA1-knockdown cells revealed direct regulation of miR-92b by MTA1, among others (Dhar et al., 2017).

Other candidate MTA1-associated stilbene-regulated miRs are miR-22 and miR-34a (Dhar et al., 2017). According to publicly available prediction algorithms, oncomiRs miR-22 and miR-34a target tumor suppressors p21 and p53, respectively. An inverse relationship between MTA1/miR-22 and p21 and MTA1/miR-34a and p53 was demonstrated in MTA1 knockdown prostate cancer cells (Joshi et al., 2020). Notably, MTA1-associated miR-22 and miR-34a were regulated by low-fat and high-fat diets supplemented with grape powder fed to mice prone to developing PIN (*Pten*^{+/f}, *Pb-Cre*⁺). These two PIN-derived circulating oncomiRs further were detected in murine serum, in which they showed statistically significant reduced levels in mice fed with diets supplemented with grape powder containing not only stilbenes but other polyphenols (Joshi et al., 2020). In a different set of experiments using a high-risk premalignant prostate cancer mouse model (*R26*^{MTA1}; *Pten*^{+/f}, *Pb-Cre*⁺) fed a diet supplemented with pterostilbene (100 mg/kg diet), we registered MTA1-targeted chemoprevention along with reduced circulating miR-22 and miR-34a levels in response to pterostilbene treatment (Hemani et al., 2022). As the same miR can target multiple mRNAs, studies have reported miR-22 direct targeting of PTEN in prostate cancer (Poliseno et al., 2010) and downregulation of PTEN protein levels in RWPE1 prostate cancer cells ectopically expressing miR-22 (Dhar et al., 2017). Another valuable MTA1-associated miRNA/target axis was identified from miRNA profiling studies and was functionally validated in prostate cancer: the miR-22/E-cadherin axis (Dhar et al., 2017). E-cadherin is a valid adhesion factor that plays an essential role against EMT leading to invasion and metastasis (Frixen et al., 1991; Perl et al., 1998; Onder et al., 2008). In addition to correlative observation of aggressive DU145 and PC3M prostate cancer cells with high MTA1/miR-22 and low E-cadherin expression compared to “good” RWPE1 and LNCaP cells, meta-analysis of patient tumor samples indicated a positive correlation between MTA1 and miR-22 and a negative correlation between MTA1 and E-cadherin, supporting their inhibitory effect on E-cadherin expression. MTA1-induced drastic downregulation of E-cadherin was further shown in the prostate tissues of prostate-specific transgenic mice overexpressing MTA1 (*R26*^{MTA1}; *Pb-Cre*⁺). Mechanistically, MTA1-induced overexpression of miR-22 reduced expression of E-cadherin resulting in increased cell invasiveness and migration of prostate cancer cells and the link between miR-22 and its putative target E-cadherin mRNA was demonstrated using reporter constructs of the 3′-UTR of E-cadherin. MTA1-promoted miR-22-regulation of this adhesion factor makes the MTA1/miR-22/E-cadherin axis critical for promoting tumor invasiveness in prostate cancer cells (Dhar et al., 2017). Bearing in mind that miR-22 is a confirmed regulator of EMT (Song et al., 2013), its role as a prognostic and predictive biomarker in advanced prostate cancer and a potential therapeutic target becomes essential.

Conclusion

Identifying miRNAs linked to specific signaling pathways that are critical for prostate tumor progression and metastasis might provide novel targeted chemoprevention and therapeutic opportunities. Pharmacological modulation of miRNA activities, specifically by dietary stilbenes may have tremendous impact in interceptive approaches for different stages of prostate cancer. The results from our studies suggest that miR regulation is conserved among stilbene family members and that the identified MTA1-miRNA network regulated by stilbenes plays a significant role in prostate cancer progression. These miRNAs are particularly attractive because they can be detected in serum or urine as “liquid biopsy” biomarkers essential for diagnosis, prediction of interception/therapy response, and prognosis in prostate cancer. Studies have also reported beneficial miR-mediated effects of stilbenes in combination with other natural polyphenols in various cancers. Due to their unique chemical structure, different classes of polyphenols may produce specific miR-mediated gene regulation, which may culminate in synergistic beneficial effects. Further studies have the potential of improving the goals of personalized medicine, specifically concerning personalized interception using miRNA-modulating natural products with potential chemopreventive and therapeutic benefits in prostate cancer.

Author contributions

Manuscript is written and approved by ASL.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

ADAM17 disintegrin and metallopeptidase domain-containing protein 17

Akt v-akt murine thymoma viral oncogene (protein kinase B)

AP1 jun proto-oncogene

AR androgen Receptor

ATG7 autophagy related 7

Ago-2 argonaute 2

BCL-2 B-cell lymphoma 2

BCL2L14 B-cell lymphoma like 14

BCYRN1 brain cytoplasmic RNA 1

ChIP-Seq chromatin immunoprecipitation sequencing

CRPC castrate resistant prostate cancer

CX43 connexin 43 (Gap junction alpha 1 protein, GJA1)

DUI45 human prostate cancer cell line

EGFR epidermal growth factor receptor

EMT epithelial-to-mesenchymal transition

Epi-miRNA epigenetic miRNA (ribonucleic acid)

EV extracellular vehicle

FAF1 fas-associated factor 1

Fak focal adhesion kinase

Foxo3 forkhead box O3

GRP78 glucose-regulated protein 78

HDAC1/2 histone deacetylases 1 and 2

HDAC11 histone deacetylase 11

HIF-1 α hypoxia inducing factor 1

IL-1 β interleukin 1 Beta

K-ras kirsten rat sarcoma virus

LNCaP human prostate cancer cell line

lncRNA long non-coding ribonucleic acid

Luc luciferase

MAPK mitogen-activated protein kinase

Mcl-1 myeloid cell leukemia 1

miR microRNA (ribonucleic acid)

miRNA microRNA (ribonucleic acid)

mRNA messenger RNA (ribonucleic acid)

MTA1 metastasis-associated protein 1

mPIN mouse PIN

NANOG homeobox protein, a transcription factor in embryonic stem cells

ncRNA non-coding RNA

NF- κ B nuclear factor kappa-light-chain-enhancer of activated B cells

NuRD nucleosome remodeling and deacetylase complex

Oct4 homeobox protein, a transcription factor in embryonic stem cells

OncomiR oncogenic miRNA

PC3 human prostate cancer cell line

PDCD4 programmed cell death 4

PI3K phosphatidylinositol 3-kinase/serine/threonine kinase PKB

PIN prostatic intraepithelial neoplasia

PTEN phosphatase and tensin homolog deleted in chromosome 10

Ptenf/f Pten gene, floxed

Pten+/*f* Pten heterozygous mice (Pb-Cre4+, Pten+/*f*)

RGS17 regulator of G protein signaling

R26MTA1 rosa26 locus; R26MTA1: MTA1 overexpressing mice

22Rv1 human prostate cancer cell line

RWPE1 human prostate cancer cell line

SMAD4 mothers against decapentaplegic homolog 4

SOX2 SRY (sex determining region Y)-box 2

SOX6 SRY (sex determining region Y)-box 6

Sp-1 specificity protein 1

Src proto-oncogene tyrosine-protein kinase

SRM spermidine synthase

TGF β 1 transforming growth factor β 1

TNF α tumor necrosis factor alpha

TS tumor suppressor

3'UTR 3 prime untranslated region

VEGF vascular endothelial growth factor