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REVIEW

3,4′,5-*trans*-Trimethoxystilbene; a natural analogue of resveratrol with enhanced anticancer potency

Fahad S. Aldawsari · Carlos A. Velázquez-Martínez

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Summary Resveratrol is a phytoalexin produced by many plant species as a defence mechanism. Over the last decade, this polyphenol has been reported to be active against multiple targets associated with chronic disorders. However, its poor pharmacokinetic profile, as well as multiple discrepancies related to its *in vitro* and *in vivo* profile, has resulted not only on the study of suitable delivery systems, but the use of resveratrol derivatives. In this regard, the 3,4′,5-*trans*-trimethoxystilbene (TMS), a natural analogue of resveratrol, has emerged as a strong candidate. TMS has an enhanced anticancer profile compared to resveratrol, exhibiting higher potency than resveratrol, as shown by multiple reports describing an improved cancer cell proliferation inhibition, induction of cell cycle arrest, decreased metastasis, reduced angiogenesis, and increased apoptosis. In this review, we provide a concise summary of results reported in the literature, related to the similarities and differences between resveratrol and TMS, and we submit to the scientific community that TMS is a promising and (still) understudied natural agent candidate, with potential applications in cancer research. Nevertheless, based on the available evidence, we also submit to the scientific community that TMS may also find a niche in any other research area in which resveratrol has been used.

Keywords Resveratrol analogues · Anticancer · *In vivo* · Prostate cancer · Chemoprevention · Antioxidant

F. S. Aldawsari (✉) · C. A. Velázquez-Martínez
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2E1, Canada
e-mail: aldawsar@ualberta.ca

Abbreviations

AKT	Protein kinase B
AP-1	Activator protein 1
Bcl-2	B-cell lymphoma 2
Bcl-X_L	B-cell lymphoma-extra large
CAT	Catalase
CDKs	cyclin dependent kinases
COX	Cyclooxygenase
CYP450	Cytochrome P450
DMBA	7,12-dimethylbenz [a] anthracene
EGFR	Epidermal growth factor receptor
EMT	Epithelial mesenchymal transition
GSK	Glycogen synthase kinase
H_2O_2	Hydrogen peroxide
HO-1	Heme oxygenase-1
ICAM-1	Intercellular adhesion molecule
iNOS	Inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase
LDL	Low density lipoproteins
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MMP	Metalloproteinase
MTA1	Metastasis-associated protein 1
NF-κB	Nuclear transcription factor-kappa B
PI3K	Phosphoinositide 3-kinase
PPARγ	Peroxisome proliferator activated receptor gamma
SOD	Superoxide dismutase
STAT	Signal transducer and activator of transcription
TMS	3,4′,5-*trans*-trimethoxystilbene
TNF	Tumor necrosis factor
TPA	12-O-tetradecanoylphorbol-13-acetate
VCAM-1	Vascular cell adhesion protein 1
VEGF	Vascular endothelial growth factor.

Introduction

Resveratrol (3,4′,5-*trans*-trihydroxystilbene, Fig. 1) is a natural polyphenol which has shown a plethora of biological activities. These activities are attributed to its interference with multiple signalling pathways which include (but are not limited to) inflammatory mediators (e.g. COX-1/2, iNOS, TNF), transcription factors (e.g. NF-κB, β-catenin, STAT3, PPAR-γ), cell cycle regulatory genes (e.g. cyclins, CDKs, p53), angiogenic genes (e.g. VEGF, MMPs, ICAM-1), apoptotic genes (e.g. survivin, Bcl-2, Bcl-X_L), antioxidant enzymes (e.g. SOD, CAT, HO-1), protein kinases (e.g. AKT, PI3K, JNK) and many others [1]. Most of these targets are associated with carcinogenesis, and therefore, resveratrol has been shown to inhibit cancer initiation and cancer development.

In 1997, Jang et al. documented the first cancer preventive properties of resveratrol [2]. Since then, a considerable amount of work to elucidate the mechanism of action of resveratrol has been conducted, and there are several reviews describing the biological effects exerted by resveratrol both *in vivo* and *in vitro* [3–6]. Nevertheless, after nearly 18 years of continuous research into the chemopreventive effects of resveratrol, many questions and concerns have been raised about the potency, efficacy, and safety of this molecule [7–9]. Furthermore, despite the relatively high commercial success of several "alternative" products containing resveratrol (mainly in gelatin capsules), its low chemical stability [10], low bioavailability [10], high metabolic rate [10], and the lack of properly controlled clinical studies, make the use of this polyphenol controversial, to say the least, as an effective chemopreventive, adjuvant, or chemotherapeutic agent [7,11]. Moreover, it has been questioned whether the dose of resveratrol that has proven to be somewhat promising in animal models, can be reliably extrapolated to humans [7,8]. Consequently, all these issues have prompted the search for improved resveratrol analogues, as well as more efficient delivery systems [12,13].

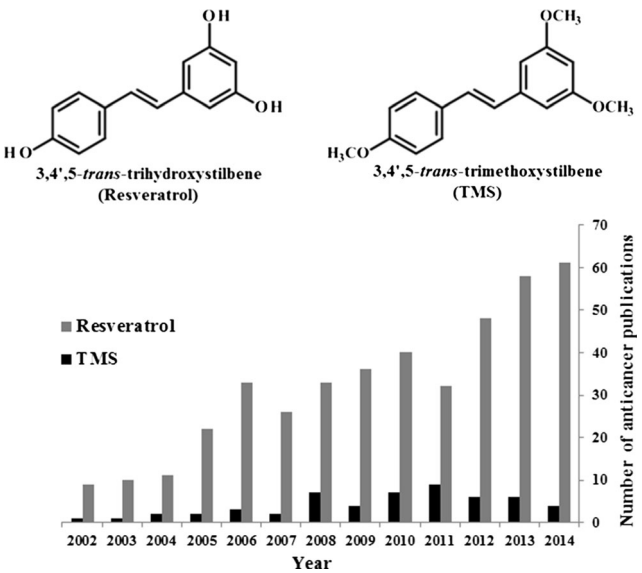

Fig. 1 Top—the chemical structures of resveratrol and trimethoxystilbene (TMS); Bottom—results of a literature search showing the number of publications describing the potential anticancer properties of both TMS (black) and resveratrol (grey), between the years 2002–2014

3,4′,5-*trans*-trimethoxystilbene (TMS) (Fig. 1), is a natural analogue of resveratrol which has been found to exhibit superior anticancer activities compared to resveratrol, on multiple targets involved in carcinogenesis. TMS has been described in the literature by different names, including "resveratrol trimethyl ether" (RTE) [14,15], MR-3 [16,17], M-5 [18], BTM-0521 [19], trimethoxy resveratrol [20], trimethylated resveratrol [21], and as described at the beginning of this paragraph TMS [22,23].

Comparatively speaking, TMS has been under the scientific community's radar for many years. In this literature review, we report the findings of a comprehensive literature search between the years 2002 and 2014 (Fig. 1), in which we compiled publications describing the potential anticancer properties of TMS which were a lot lower than those of its hydroxylated analogue resveratrol. Consequently, we considered essential to carry out a comprehensive literature search to gather available (and applicable) information to address the question of, whether or not this methoxylated stilbene derivative could constitute a suitable alternative to resveratrol. In the current review, we discuss available literature in which TMS has been studied (screened) as an anticancer or chemopreventive agent, regardless if this compound was compared to resveratrol or not. At the end of this review we submit two key findings. First, the more lipophilic and cell membrane-permeable TMS is not sufficiently understood, considering that its chemical structure only differs from that of resveratrol for having three extra methyl groups (small, lipophilic, and naturally occurring). Second, the potential anticancer profile of TMS is promising enough (despite the low number of publications including it) to merit additional studies, opening the door for future research projects in which this compound is used and compared to resveratrol.

Methods

A literature search was conducted in PubMed and Web of Science databases by searching key words "trimethoxy resveratrol", "TMS" and "trimethoxy stilbene". Then, the results were checked individually to make sure it is specific for the compound 3,4′,5-*trans*-trimethoxystilbene, and not for other related stilbenes. Chemical structural search was also performed using SciFinder database. Only articles in English language were retrieved. The first study described the

anticancer effects of TMS was published in 2002. For comparative purposes, we searched a key word of "resveratrol anticancer" in PubMed between 2002 and 2014 and this search revealed 394 papers. The total number of TMS anticancer publications in this review was 54 articles. The detailed number of publications per year can be found in Fig. 1.

TMS sources

The first documented natural source of TMS was reported in 1969 by Blair, G.E. and coworkers [24]. Petroleum ether extract of the plant *Virola cuspidate* (species from this plant genus have been used by South American Indians to prepare narcotic snuffs and as an arrow poison [24,25]) was used to isolate TMS [24]. Later, TMS was subsequently isolated from different plant genera [26–32]. Recent analytical studies of nutritional sources such as grape berries [33], grapevine [34], almonds [35] and peanuts [36,37] have revealed that resveratrol, but not TMS is contained in these edible sources. The majority, if not all of the TMS used in literature studies was chemically synthesized in laboratories. The frequent synthetic procedures utilized to obtain TMS involved chemical reactions, such as Wittig reaction [38], Heck coupling [39], Horner-Wadsworth-Emmons (HWE) reaction [40] and Perkin reaction [41], which produced TMS in moderate to good yields.

In vitro anti-proliferative effects

Although the chemical structures of resveratrol and TMS are very similar, TMS has shown a higher cell proliferation inhibition than resveratrol against numerous cancer cell lines using *in vitro* cytotoxic assays (Table 1). As shown in Table 1, the potency of TMS to inhibit cancer cell proliferation varies according to the literature source, ranging from nearly equipotent profile compared to resveratrol [20], to up to 7-fold higher than resveratrol [18]. Perhaps the only exceptions are the SW480 [49] and PC-3 cells [42], in which resveratrol was more potent than TMS. The enhanced *in vitro* anticancer effect of TMS seems to be partially attributed to two main features. First, the three methoxy groups in the TMS structure enhance the lipophilic character of this molecule (calculated LogP values: TMS=3.85, resveratrol=3.06) [42], increasing cell membrane permeability, and ultimately its intracellular concentration of TMS [14,20,57]. Second, TMS has been reported to destabilize microtubule formation in cancer cells

Table 1 *In vitro* cytotoxic potencies of TMS versus resveratrol against several tumor cells; [a] Reported as GI_{50} (μM). [b] The IC_{50} was reported as (g/ml). [c] Reported as GI_{50} (μg/mL)

Cell line	Origin	Species	Resveratrol IC_{50} (μM)	TMS IC_{50} (μM)	Reference
DU-145	Prostate	Human	42.3	9.7	[20]
LNCaP	Prostate	Human	12.7	2.5	[20]
PC-3 M	Prostate	Human	31.5	23.3	[20]
PC-3	Prostate	Human	0.6±0.01	3.6±0.9	[42]
22Rv1	Prostate	Human	149.92	9.45	[43]
M-14	Skin	Human	31.0±3.1[a]	12.1±1.7 [a]	[44]
WI38VA	Skin fibroblast	Human	50	25–50	[45]
KB	Nasopharyngeal	Human	>80	10.2±0.5	[46]
A549	Lung	Human	6.9 [b]	0.8 [b]	[47]
CH27	Lung	Human	Not reported	92	[16]
HT-29	Colon	Human	45.3±4.4	16.1±5	[48]
Caco-2	Colon	Human	24.35±0.2	11.95±2.9	[48]
SW480	Colon	Human	20±3	54±8	[49]
MCF-7 (RF.M [erbB2])	Breast	Human	47.7	6.6	[18]
MDA-MB-231	Breast	Human	20.5±2.6	1.2±0.2	[50]
Hepa1c1c7	Liver	Mouse	>25	5.2	[51]
HepG2	Liver	Human	38.9±6	11.99±1.9	[52,53]
Vero	Kidney	Monkey	73.6	26.7	[32]
HeLa	Cervical	Human	No activity at 100 μM	13.3	[32]
SK-OV-3	Ovarian	Human	113	55.5	[32]
BXPC-3	Pancreas	Human	3.3 [c]	0.35 [c]	[54]
HL-60	Blood	Human	5±2	2.5±0.6	[55,56]

when administered at concentrations as low as 1.0 μM, whereas resveratrol does not exert this effect to a significant extent [58].

In regards to the conformational structure of TMS, it is a fact that the corresponding *cis* isomer of TMS has shown higher cancer cell proliferation inhibition than the *trans*-isomer. This is particularly true for human colon cancer HT-29 and Caco-2 cells [48] and mouse melanoma B16 F10 cells [59]. Nevertheless, considering that the *trans*-resveratrol has been, by far, the preferred isomer published in anticancer studies, the *trans*-TMS isomer has followed a similar pattern (most studies reported in the literature about this molecule were carried out with the *trans*-isomer).

An interesting observation related to the effect produced by resveratrol on cancer cell lines *in vitro*, is represented by a concentration-dependent biphasic effect. This phenomenon has been reported for several tumor cell lines including breast, colon, lung, prostate, leukemia [60], and liver [61]. This biphasic ("hormetic") action exerted by resveratrol is characterized by inhibition of cancer cell proliferation at high concentrations, whereas at lower concentrations resveratrol seems to *enhance* cancer cell proliferation [60]. To the best of our knowledge, this hermetic effect has not been reported for TMS, and it constitutes a highly promising research area, considering that it could be one essential area in which TMS could potentially have an advantage over resveratrol.

In vivo anti-proliferative effects (xenograft models)

The *in vivo* anticancer effects exerted by resveratrol have been studied in xenograft models using a wide variety of cancer cells; a comprehensive summary is shown in Table 2.

Out of twenty *in vivo* xenograft studies, eight used injections (i.v. or i.p) as the main route of administration, as this method assures complete absorption of the administered compound; these studies reported a significant anticancer profile as determined by a decrease in tumor size and weight [62,65,66,71–73,77,78]. However, when the compound is administered orally, it seems that the preferred method of study is to pretreat the animals with resveratrol (chemopreventive approach), before the subcutaneous injection of cancer cells [20,68,70]. In this regard, one report used as high as 150 mg/kg of resveratrol (oral dose) [79] to achieve the desired antiproliferative effect, which makes clear that bioavailability of this polyphenol represents an issue in these models.

It has been difficult to reconcile the different results reported in the literature on the efficacy and potency of resveratrol in prostate cancer, since there is conflicting evidence showing that resveratrol in some cases is an effective inhibitor of cancer cell proliferation [20,67,68], whereas in other studies it shows negligible activity compared to the control group [81,82]. These discrepancies may be attributed to differences in cell type, dose, route of administration, and different treatment

Table 2 Xenograft models used to confirm the *in vivo* anticancer properties of resveratrol. In these studies, resveratrol significantly reduced tumor cell growth compared to control

Resveratrol (dose, mg/kg)	Route of administration	Cell line	Tissue origin	Reference
100	i.v.	SUM159	Breast	[62]
40	Oral gavage	MCF-10A-Tr	Breast	[63]
50	Oral gavage	MDA-MB-231	Breast	[64]
50, 100, 200	i.p.	SKOV3	Ovary	[65]
50, 100	i.p.	PA-1	Ovary	[66]
30	Oral gavage	PC-3	Prostate	[67]
20	Oral gavage	PC-3 M-MM2	Prostate	[68]
50	Oral gavage	LNCaP-Luc	Prostate	[20]
40	Oral gavage	MIA-PaCa2	Pancreas	[69]
10, 50	Oral gavage	MIA-PaCa2	Pancreas	[70]
15, 30, 60	i.v.	A549	Lung	[71]
20	i.p.	A549/VC	Lung	[72]
20	i.p.	CNE-2Z	Nasopharynx	[73]
10, 50	Oral gavage	FaDu	Pharynx	[74]
40	Oral gavage	BGC-823	Stomach	[75]
20, 40	Oral gavage	HNC-TIC	Head-neck	[76]
20	i.p.	Mz-ChA-1	Bile duct	[77]
20	i.p.	T24	Bladder	[78]
150	Oral gavage	HCT-116	Colon	[79]
10, 20, 30	Not specified	A431	Skin	[80]

protocols (chemopreventive vs chemotherapeutic). In addition to these discrepancies, resveratrol has also been associated with a decrease ("worsening") in the survival rate of SCID mice in which the prostate cancer cells LAPC-4 were used [83].

In agreement with the experiments reported for prostate cancer cells, similar findings have been described for other cancer cells such as melanoma cells [DM738 ([82], and DM443 [84]]. In these reports, authors showed a weak anticancer activity of resveratrol compared to the control group. Furthermore, resveratrol even *enhanced* tumor cell proliferation in xenograft models using melanoma MDA-MB-435 cells, relative to the effect observed in the control [85]. Finally, this lack of significant activity was also reported in xenograft models using acute lymphoblastic leukemia (SEM cells), in which a detailed analysis showed no significant difference between control- and resveratrol-fed mice [86]. Possible explanations for these variations among the *in vivo* anticancer effects of resveratrol are resveratrol dose (considering the "hormetic" characteristic mentioned earlier in this review), the integrity of resveratrol-mixed diet or the sex of experimental animals (taking in consideration that resveratrol is a phytoestrogen).

TMS has been much less studied in xenograft experiments, and therefore, an objective comparison between TMS and resveratrol is difficult at this point. Nevertheless, one of the few reports describing the *in vivo* anticancer profile of TMS involved nude mice and prostate cancer LNCaP-Luc cells [20]. In this study, authors report the oral administration of TMS (50 mg/kg); this agent exerted significant decrease in tumor formation and tumor progression compared to the control group [20]. In another study, TMS (50 mg/kg, i.p.) produced a similar anticancer effect on colon cancer cells (COLO 205) when injected three times per week for 23 days to nude mice [87]. TMS showed a significant reduction of tumor growth accompanied by a significant inhibition of tumor/body weight ratio [87]. Finally, in a complementary study, TMS (10 mg/kg i.p.) exerted a significant reduction of both tumor weight (21 % decrease), and tumor volume (45 % decrease) of colon cancer cells (HT-29) in mice [48].

According to these results, it is reasonable to assume that the anticancer profile of TMS seems to be higher than that exerted by resveratrol. However, it is also evident that to date, the data is limited and merits further studies.

TMS and apoptosis

The effects exerted by resveratrol and TMS on apoptosis seem to be similar for both agents, at least according to the evidence presented by a recent study by Weng et al. , in which they evaluated the apoptotic effects produced by both TMS and resveratrol. Authors reported that human lung carcinoma cells (A549 and CH27) experienced a significant degree of apoptosis when incubated in the presence of these stilbenes at concentrations ranging from 10 to 100 μM [16]. Using flow cytometry and staining (Annexin V-FITC and PI), TMS and resveratrol increased the number of cells undergoing apoptosis in a dose-dependent manner. However, the increasing inhibition of cell proliferation exerted by TMS on CH27 cells was not correlated with the extent of apoptosis [16], and therefore, authors suggested that additional mechanisms, other than apoptosis, could be involved in the anticancer effects exerted by TMS on these cells [16]. This is another distinguishing feature of TMS compared to resveratrol.

In a similar study, both TMS and resveratrol induced apoptosis on a clone of the MCF-7 breast cancer cell line, in which it had been inserted a mutant p53 gene. According to this report, the "I_pC_{50}" values (expressed as the concentration of compound needed to inhibit cell proliferation by 50 %), for TMS and resveratrol were 6.9 μM and 27 μM respectively [18]. This indicates a 4-fold increased activity of TMS compared to resveratrol. However, in wild type MCF-7 cells TMS and resveratrol showed more or less the same potency with I_pC_{50} values=7.5 and 9.2 μM respectively. Authors suggested that the improved antiproliferative effect exerted by TMS might be p53 independent [18]. Finally, in the same report authors provided additional evidence to suggest a significant difference in the mechanism of antiproliferative activity between TMS and resveratrol; they used other two variants of the clone MCF-7 cell line possessing the mutant p53 protein, which were modified to be resistant to 2′-deoxy-5-fluorouridine and arabinosylcytosine. In this model, TMS showed a 2.5-fold higher potency compared to resveratrol [18].

The hypothesis that TMS could terminate cancer cell proliferation through a p53-independent mechanism is supported by the works of Hsieh et al. In the first paper, authors described that both TMS and resveratrol did not change p53 mRNA levels in LNCaP cells [88], but in the second report in which they used MCF-7 cells, TMS decreased the expression of a downstream target of p53, namely the transcription factor p53R2, whereas resveratrol showed the opposite effect [89]. Of note, resveratrol's upregulation of p53 has been reported in mouse skin exposed to the carcinogen DMBA [90] as well as in the MTA1 silenced human prostate cancer DU145 and LNCaP cells [91]. These different regulations of p53 by resveratrol and TMS further confirm the different mechanisms by which these natural agents alter tumor cell proliferation.

Additional evidence supporting a significant difference between TMS and resveratrol, is the report published by Daniele et al. , in which they tested the *in vitro* apoptotic effects of several stilbenes on myeloblastic acute leukemia cells (HL-60), using the Annexin *V* test and morphological examination. They found that the apoptotic effect (expressed as AC_{50}) induced by TMS was 10–12 times

higher than that of resveratrol (4.0±2.1 μM and 50±6 μM respectively) [55].

The human androgen-responsive prostate cancer cell (LNCaP) has also been used to evaluate the effects of several resveratrol analogues on cell cycle and apoptosis [92]. Using flow cytometry, Wang et al. reported that resveratrol induced cell cycle arrest (at G1/S) after 72 h post-treatment, whereas TMS produced a significant effect at the G2/M phase much sooner than resveratrol (as early as 24 h post-treatment) [92]. In the same study, cell cycle arrest was also determined by measuring the expression of the cyclin inhibitors CDKN1A and CDKN1B (mRNA level). In this regard, resveratrol showed a significant upregulation of both cyclin inhibitors at 25 μM. In contrast, TMS upregulated both CDKN1A and CDKN1B at much lower concentrations (1 and 5 μM respectively) [92]. Additionally, it was observed that resveratrol exhibited a weak apoptotic effect, while TMS showed a significant dose-dependent action at concentrations as low as 5 μM [92]. Importantly, the apoptosis-associated caspase 3/7 activation demonstrated that TMS (but not resveratrol), led to about six-fold induction in caspase activity compared to control [92]. Authors suggested that despite the similarity in chemical structures between resveratrol and TMS, each stilbene exerts different effects on LNCaP cells [92]. Finally, TMS did not induce ceramide accumulation (a pro-apoptotic marker) in MDA-MB-231 cells, despite having a high antiproliferative effect [50], whereas resveratrol showed a significant ceramide accumulation [50].

TMS and angiogenesis

Alex D. et al. [93], studied the anti-angiogenic properties of TMS and resveratrol in two models: an *in vitro* model using HUVEC cells, and an *in vivo* model of blood vessel formation in transgenic Zebrafish embryos [93]. The results of the *in vivo* experiment showed that resveratrol had a negligible effect on blood vessel formation at the highest test compound concentration (100 μM) [93]. In contrast, TMS exerted significant inhibition of angiogenesis at 10 and 30 μM, compared to the control (untreated) group [93]. Authors suggested that TMS might target the EGFR, which could explain the reduction in neovascularization [93]. They also found that TMS (at 100 μM) caused about 4-fold downregulation of VEGFR-2 mRNA compared to control [93]. In a similar study, Belleri M et al. [58] studied the anti-angiogenic properties of TMS and resveratrol using endothelial cells of murine, bovine, and human origin [58]. They observed that TMS was at least 30 times more potent than resveratrol in all assays (type-I collagen gel invasion, morphogenesis on Matrigel, sprouting within fibrin gel, and endothelial cell proliferation) [58].

TMS and cancer metastasis

In a relatively recent paper by Yang et al. , authors reported the anti-metastatic properties of TMS using a human lung cancer A549 cell line, by measuring the effects of this compound on MMP, MAPK, NF-κB, and AP-1 [17]. In this regard, TMS (5 μM) significantly decreased the migratory, adhesive and invasive properties of the A549 cancer cell line by 39, 34 and 22 % respectively. Additionally, they observed that TMS decreased both the activity and mRNA levels of the MMP-2 protein in a time-dependent manner [17]. A possible mechanism for the downregulation of MMP-2 by TMS, was studied by examining the phosphorylation pattern of JNK and p38 proteins; TMS reduced the phosphorylation levels in both JNK and p38 [17]. In the same paper, authors also reported the effects of TMS on the transcriptional factors NF-κB and AP-1, which are two of the main proteins associated with multiple pathophysiological disorders including inflammation, angiogenesis, cancer cell migration, invasion and metastases. Yang et al. observed that treatment of human lung cancer A549 cells with TMS led to a time-dependent reduction in the protein levels of NF-κB (p65 subunit), as well as AP-1 in the nucleus [17].

In agreement with the previous report, the ability of TMS to downregulate the AP-1 protein in cancer cells was further confirmed by Deck et al. in a report using human embryonic kidney cells (293 T/AP-1-luc) [94]. Incubation of these cancer cells with TMS (at 15 μM) resulted in a significant reduction in AP-1 activation (calculated IC_{50}=3.8 μM) [94]. In contrast, resveratrol (at 15 μM) and under the same experimental conditions, has shown more than one-fold induction of AP-1 compared to TPA-treated cells [94].

In another study, Weng et al. investigated the anti-invasive properties exerted by both TMS and resveratrol, on hepatocarcinoma HepG2 and Hep3B cells [95]. Authors found that TMS and resveratrol decreased the activities of MMP-9 and MMP-2 in Hep3B cells in a dose-dependent manner [95]. Also, incubation of HepG2 cells with TMS and resveratrol had a marked decrease in the invasion of these cells by about 60 and 80 % respectively [95], and similar results were obtained with Hep3B cells [95]. However, the reported anti-invasive potency determined for TMS in Hep3B cells (IC_{50}=1 μM) was significantly higher than that determined in HepG2 cells (IC_{50}=50 μM) [95].

The epithelial-mesenchymal transition (EMT) is an important mechanism by which primary cancers cells are able to invade (metastasize) other tissues and organs [96]. E-cadherin is a receptor which plays a major role in cell adhesion, and the decreased expression of this protein is a characteristic feature of a tumor cell undergoing EMT [96]. In this regard, it has been observed that EMT-associated transcriptional factors such as snail and slug, reduce the expression

of E-cadherin. Tsai et al. studied the alterations in EMT-related markers in MCF-7 cells upon incubation with resveratrol and TMS treatment [96]. Authors observed that both stilbenes were able to increase, significantly, the levels of E-cadherin in MCF-7 cells treated with these compounds. Of note, the concentrations used in this experiment were relatively not toxic to cells (20 μM) [96]. Furthermore, TMS and resveratrol decreased the levels of the EMT-related protein snail [96]. Interestingly, upon transfection of MCF-7 cells with an E-cadherin promoter gene, TMS, and not resveratrol, showed a significant effect reinstating the epithelial marker E-cadherin activity [96].

Another interesting example of how the naturally occurring stilbenes resveratrol and TMS are able to inhibit cancer metastasis is the study of the β-catenin protein. This molecule, along with E-cadherin, work to maintain proper cell to cell adhesion and epithelial integrity [96]. Elevation of free β-catenin in cytoplasm activates the Wnt/β-catenin signalling pathway, and ultimately, initiates EMT in some cancers [96]. Moreover, the Wnt/β-catenin signalling pathway modulates several other genes including c-myc and cyclin D1 [96]. In this regard, and as a regulatory mechanism, the protein GSK-3β is one of the main components that proteolytically degrades β-catenin and maintains its normal levels [96]. Tasi et al. observed that incubation of MCF-7 cells with TMS significantly decreased GSK-3β phosphorylation, resulting in a significant accumulation of free (active) GSK-3β [96]. Furthermore, authors also reported that TMS exerted three important changes on the β-catenin signalling pathway in MCF-7 cells. First, TMS decreased the level of β-catenin in a dose-dependent manner, along with a marked decrease in its nuclear translocation [96]. Second, TMS triggered β-catenin ubiquitination, and consequently, it produced significant β-catenin degradation [96]; and third, TMS exerted a substantial reduction in the mRNA levels of the β-catenin target genes c-myc and cyclin D1 [96]. Taken together, these results provide a strong case to suggest that TMS could have an enormous impact in restoring normal epithelial characteristics in cancer cells [96].

Metastasis-associated protein 1 (MTA1) is one member of the nucleosome remodeling and deacetylating co-repressor complex (NuRD) which is involved in protein deacetylation and transcriptional regulations [97]. Recently, MTA1 was found to be upregulated in numerous cancers such as breast, head and neck, ovarian, gastrointestinal and lung [98]. Furthermore, it has been observed that elevated MTA1 expression is associated with angiogenesis, poor prognosis and high tumor grade [98]. Resveratrol has showed a dose-dependent reduction in MTA1 protein level in both DU145 and LNCaP cells [91]. Perhaps the only report which investigated the effects of TMS on MTA1 is the study by Kun Li and coworkers [97]. In this paper, TMS significantly downregulated MTA1 protein level in PC-3 M cells (ED_{50}=55.1 μM) while TMS effects were less pronounced in LNCaP cells (ED_{50}>100 μM) [97]. Under the same experimental conditions, resveratrol was active in reducing MTA1 level in PC-3 M and LNCaP cells with ED_{50} of 74.5 and 35.1 μM respectively [97].

TMS and radical scavenging/antioxidant findings

The anticancer/chemopreventive actions of natural antioxidants are commonly attributed to their ability to scavenge reactive oxygen species (ROS) [99]. This scavenging mechanism is mediated through antioxidant proteins such as CAT, SOD, HO-1 and peroxidase enzymes. In this particular case, the evidence for a difference in the mechanisms of action exerted by resveratrol, and its methylated analogue, TMS, requires a detailed analysis. In this regard, there are literature reports describing the inability of TMS to induce these antioxidant enzymes. For example, Basini et al. reported that TMS, at concentrations of up to 100 μM, did not increase the activity of the free radical-scavenging enzymes peroxidase, catalase, or SOD in swine granulosa cells [100]. In a different study reported by Li et al. , authors described that TMS showed only a "weak" antioxidant activity by a limited scavenging effect on superoxide anion (O_2^-), and the hydroxyl radical (OH^-), as determined by an ethanol-induced gastric mucosal injury assay in rats [19].

In accordance with the reports described in the previous paragraph, Kim at al. reported a time- and concentration-dependent increase in the expression of the antioxidant enzyme HO-1, in murine neuronal HT22 cells, when incubated in the presence of resveratrol [23]. On the other hand, they also observed that TMS did not increase the expression (or the activity) of HO-1 [23]. Along with these results, Son et al. observed a similar effect in a different setting, in this case using RAW264.7 cells; they reported that resveratrol increased the expression and the activity of HO-1, but not TMS [101].

Another variable adding to the complexity about the role of antioxidant compounds on cancer treatment/prevention, is the observation that resveratrol has been reported to exert pro-oxidant effects, which could lead to DNA damage [99,102]. In this regard, Rossi et al. found that TMS exerted an improved protective profile compared to resveratrol, as evaluated by the ability of these compounds to prevent the H_2O_2-induced DNA damage in CHO cells (comet assay) [102]. In a different paper, Zheng et al. demonstrated that TMS did not induce oxidative DNA damage in calf DNA, when incubated in the presence of Cu (II), using an ethidium bromide binding assay, whereas resveratrol exerted a "minor" DNA damage [99].

In a different paper published in 2014, Liu and coworkers reported the effects of resveratrol and TMS on the reduction of H_2O_2 levels in a hypoxia-induced pulmonary artery hypertension (PAH) rat model [22]. In this study, resveratrol and TMS

showed a nearly equipotent effect, by causing a marked decrease in hydrogen peroxide levels as measured both in both plasma, and lung tissues. Authors suggested that the ability of TMS to decrease H_2O_2 levels confirms its antioxidant properties, despite not having the characteristic free phenol groups of resveratrol and other antioxidant phenolic compounds [22]. To discuss this last point in more detail, it has been described in the literature that the antioxidant scavenging ability of polyphenols is associated with the presence of free hydroxyl groups in the aromatic rings of stilbenes [102]. Moreover, it has been hypothesized that the hydroxyl groups present in resveratrol are an essential structural feature to (1) induce HO-1 [23,101], and (2) scavenge free radicals through a hydrogen transfer mechanism [103].

Therefore, why and how does TMS exert an antioxidant profile comparable to that of resveratrol? The answer to this question has been initially described in two different papers published by Zheng et al. , and Rossi et al. In these papers, authors proposed that TMS scavenges hydroxyl radicals via an electron transfer process [99,102]. However, at this point it is evident that the radical scavenging/antioxidant profile produced by TMS needs the support of complementary studies in which it is carried out a side-by-side comparison between this compound and its hydroxylated analogue resveratrol.

Pharmacokinetics of TMS

It has been established that resveratrol undergoes extensive phase II metabolism after it is absorbed, yielding both sulfate and glucuronide conjugates as the two major metabolites [11]. In addition to these conjugates, resveratrol is metabolized by phase I (CYP450 enzymes) as well, producing piceatannol, which has an additional phenol group adjacent to the 4-hydroxyl group of the parent compound [104,105]. It is perhaps noteworthy that piceatannol is also produced by some plants. In a different study, Rivera et al. suggests that TMS could be a resveratrol prodrug, [21]. However, this assumption needs further testing and many more supporting studies.

There have been a few complementary pharmacokinetic studies, in which several research groups have tried to correlate the anticancer effect observed with stilbenes, and their plasma concentrations. Some of these studies were previously described in this review under the heading "*In vivo* antiproliferative effects". In one study, injection of resveratrol to nude mice using an osmotic mini pump (required to administer about 50 mg for 14 days), was followed by measurements of resveratrol serum concentration in 10 different tumor samples [82]. In this regard, authors found that only two out of 10 samples had a "detectable" level of free resveratrol, whereas the resveratrol sulfate and the resveratrol glucuronide metabolites were detected in all samples [82].

In another study, Dias et al. reported that the oral administration of resveratrol or TMS to nude mice (50 mg/kg dose, administered every-other-day, for 52 days), resulted in an average serum concentration of resveratrol and TMS around 0.02±0.01 μg/mL and 0.94±0.55 μg/mL respectively, which clearly shows a greater extent of metabolic degradation experienced by resveratrol, compared to TMS [20].

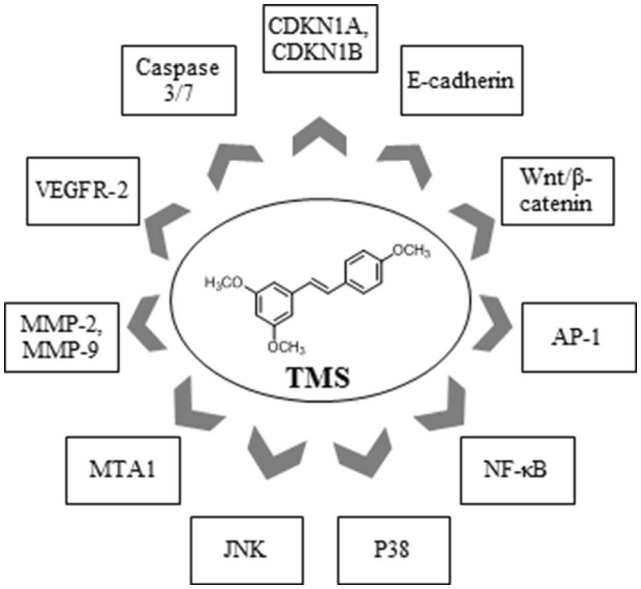

Fig. 2 Summary of targets involved in carcinogenesis which are altered by TMS

Finally, in a recent study Lin et al. assessed the pharmacokinetic profile of TMS in rats. In this report, authors calculated that after a single i.v. dose (5 mg/kg) of TMS, this compound displayed a half-life=8.5±2.2 h [14]. In agreement with the study by Dias (previous paragraph), the calculated clearance for resveratrol was 8- to 9-fold higher (faster elimination) than that calculated for TMS [14]. In this regard, authors also made a very interesting and useful observation; TMS had a negligible bioavailability (<1.5 %) when it was administered orally if suspended in a suitable vehicle, whereas its bioavailability is increased significantly (up to 46.5±4.8 %) when this compound was administered using a solution of methylated-β-cyclodextrin [14].

These observations suggests that, for any subsequent studies carried out with TMS, it will be essential to consider not only the intrinsic physicochemical and pharmacological properties of this molecule, but also the use of suitable excipients that modulate and increase the oral bioavailability of this promising, and so far, understudied stilbene.

Conclusion

3,4′,5-*trans*-Trimethoxystilbene (TMS), the naturally occurring methoxylated analogue of resveratrol, is a promising natural agent candidate displaying enhanced anticancer properties. It inhibits cancer cell proliferation in multiple *in vitro*

assays to a greater extent compared to resveratrol. Furthermore, TMS has shown a unique and different anticancer profile distinguishing it from the parent polyphenol; *in vitro* screening assays demonstrate that TMS is capable of inducing cycle arrest and apoptosis by different mechanisms of action than those observed for resveratrol, and in some cases, with an improved potency and efficacy. The overall targets through which TMS interfere with carcinogenesis are summarized in Fig. 2. However, due to the limited number of reports on the anticancer properties of TMS, the pharmacological potential of this compound is still somewhat limited. In this regard, we realize that this is not at all a disadvantage, but a window of opportunity in which there are many potential research projects that could address the ultimate question about whether or not TMS represents a better candidate than resveratrol. The evidence so far seems to suggest this premise.

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Conflict of interest The authors report no conflict of interest.

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