Nanotechnology-mediated delivery of resveratrol as promising strategy to improve therapeutic efficacy in triple negative breast cancer (TNBC): progress and promises

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Nanotechnology-mediated delivery of resveratrol as promising strategy to improve therapeutic efficacy in triple negative breast cancer (TNBC): progress and promises

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ABSTRACT

Introduction: Triple-negative breast cancer (TNBC) presents unique challenges in diagnosis and treatment. Resveratrol exhibits potential as a therapeutic intervention against TNBC by regulating various pathways such as the PI3K/AKT, RAS/RAF/ERK, PKCδ, and AMPK, leading to apoptosis through ROS-mediated CHOP activationand the expression of DR4 and DR5. However, the clinical efficacy of resveratrol is limited due to its poor biopharmaceutical characteristics and low bioavailability at the tumor site. Nanotechnology offers a promising approach to improving the biopharmaceutical characteristics of resveratrol to achieve clinical efficacy in different cancers. The small dimension (<200 nm) of nanotechnology-mediated drug delivery system is helpful to improve the bioavailability, internalization into the TNBC cell, ligand-specific targeted delivery of loaded resveratrol to tumor site including reversal of MDR (multi-drug resistance) condition.
Areas covered: This manuscript provides a comprehensive discussion on the structure-activity relationship (SAR), underlying anticancer mechanism, evidence of anticancer activity in in-vitro/in-vivo investigations, and the significance of nanotechnology-mediated delivery of resveratrol in TNBC.
Expert opinion: Advanced nano-formulations of resveratrol such as oxidized mesoporous carbon nanoparticles, macrophage-derived vesicular system, functionalized gold nanoparticles, etc. have increased the accumulation of loaded therapeutics at the tumor-site, and avoid off-target drug release. In conclusion, nano-resveratrol as a strategy may provide improved tumor-specific image-guided treatment options for TNBC utilizing theranostic approach.

1. Introduction

Breast cancer poses a significant global challenge as a highly lethal disease affecting women, exacerbated by the adverse effects of chemotherapy, radiotherapy, and the critical issue of multi-drug resistance (MDR). It is the leading cause of death among women with an estimated 2.3 million new cases in 2020 which alone accounts for 30% of cancer in women [1,2]. The initial stage of breast cancer development is hyper-proliferation which may further lead to metastatic carcinoma. Considering the molecular basis of classification, it is categorized into hormone receptor-positive (HR+), human epidermal growth factor receptor-2 positive (HER2+), and triple-negative breast cancer (TNBC). TNBC is indicated by the negative expression of triple receptors (ER, PR, and HER2) [3]. Perou et al. characterized different molecular subtypes of breast cancer (Figure 1) in their research, considering overall survival and gene expressions as two major characteristics to form the basis of these subtypes [4]. Overexpression of luminal cells and basal cells tends to induce the longest and shortest survival, respectively. Both claudin and Her2 bring on shortage survival with the overexpression of the genes. Moreover, basal and

cloud subtypes exhibit heterogeneity and play a major role in turning into TNBC. Lehmann et al. have described six TNBC subtypes that retort different gene expressions against every chemotherapeutic action. Hence this creates a big obstacle in a way to select an effective and safe treatment for TNBC [5,6]. It is a highly aggressive invasive form that comprises nearly 15% of all breast cancer subtypes. It mainly includes basal/myoepithelial expression subtype that further indicates epithelial-mesenchymal transition (EMT) leads to genetic alteration [7]. TNBC is metastasized to visceral organs and is characterized by highly proliferative indices. It is prominently affecting the African women as well as premenopausal women having high body mass index (BMI). Approximately 50% of TNBC patients have a mutation in the BRCA1 gene, especially among those with a familial history of breast cancer [8–10]. These BRCA1 mutations are linked to impaired DNA repair mechanisms and heightened susceptibility to DNA Poly (ADP-ribose) polymerase inhibitors. Certain cancers that do not possess BRCA1 mutations often exhibit BRCA1-like characteristics due to the silencing of BRCA1 through methylation-induced processes. This silencing also results in the loss of

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other proteins involved in DNA repair [11]. This life-threatening form of breast cancer is generally associated with genetic mutations that retort different gene expressions against every chemotherapeutic action, ultimately creating a big obstacle in a way to select an effective and safe treatment for TNBC [12]. Resveratrol is a strong anti-oxidant compound with anticancer, anti-angiogenic, anti-inflammatory, and cardiovascular protective effects. It targets different cancer signaling pathways (PI3K/AKT, RAS/RAF/ERK, PKCδ, AMPK, and RhoA/Lats1/YAP, etc.) through stimulating reactive oxygen species (ROS), followed by diminished proliferation and invasion [13–16]. The anti-metastasis effects induced by resveratrol are further helpful in reducing the side effects of chemotherapy which is utilized in the treatment of TNBC [17]. However, the clinical efficacy of resveratrol is limited due to its poor biopharmaceutical characteristics (low aqueous solubility, instability of chemical moiety with rapid degradation followed by the *trans*-to-*cis* isomerization) and low bioavailability at the tumor site [18–20]. An innovative approach to overcome these limitations of resveratrol would be the advanced multifunctional formulation design utilizing nanotechnology for targeted delivery in TNBC [21–23]. The small nano dimension (<200 nm) of nanotechnology-mediated drug delivery system is helpful to improve the bioavailability, internalization into the TNBC cell, ligand-specific targeted delivery of loaded therapeutics to tumor site including reversal of MDR (multi-drug resistance). The different nanotechnology-mediated drug delivery systems (such as polymeric nanoparticles, lipid-based nanoparticles, and inorganic nanoparticles including hybrid nanoparticles) have been investigated for the treatment of TNBC [24,25].

This review focuses on providing a comprehensive discussion on the structure-activity relationship (SAR), underlying anticancer mechanism, and evidence of anti-TNBC activity of resveratrol in different *in-vitro/in-vivo* investigations. Furthermore, the manuscript highlights the significance of the utilization of the nanotechnology approach for the designing of resveratrol-loaded multifunctional nano-formulation for tumor-specific image-guided treatment options in TNBC.

2. Sources, chemistry, and structure-activity relationship (SAR) of resveratrol

Resveratrol, known as 3,4′,5-trihydroxystilbene, is a phytoalexin belonging to the stilbenol class of compounds naturally found in various plants. It was first isolated in 1940 from the roots of white hellebore (*Veratrum grandiflorum*). The most common source of resveratrol includes red wine ($0.1–14.3$ mg L^{-1}), white wine ($0.1–2.1$ mg L^{-1}), grapes ($0.16–3.54$ μg g^{-1}), blueberries (~32 ng g^{-1}), peanut ($0.02–1.92$ μg g^{-1}), pistachios ($0.09–1.67$ μg g^{-1}), *Polygonum cuspidatum* (0.524 mg g^{-1}), and *Rheum rhaponticum* (3.9 mg g^{-1}) [26,27]. Resveratrol (molecular weight: 228.24 g/mol) has a general structural formula of C_6-C_2-C_6, characteristic of phenylpropanoids, with phenolic rings connected through a styrene bond to form 3,5,4′-trihydroxystilbene. This compound serves as a natural phytoalexin released by plants in response to environmental stress [28,29]. Resveratrol has many synthetic analogs also including adducts conjugates and glucosidase. On heating isomeric *trans*-form converts to the *cis*-form. It is biosynthesized from *L*-phenyl alanine and *L*-tyrosine through the phenylpropanoid pathway. In the presence of stilbene synthase, coumaroyl-CoA, and 3-malonyl CoA serve as the two primary precursors for the biosynthesis of resveratrol [30,31]. It is present in plants in *trans*-form or *cis*-form, and occasionally in glucoside form. The *trans*-form of resveratrol is the predominant and more biologically active form compared to the *cis*-form [32–35]. The hydroxy group at 3, 5, and 4′ are supposed to be responsible for the anticancer and antioxidant activity of *trans*-resveratrol [36]. Stojanovic et al. investigated the influence of the spatial position of the hydroxyl group on the radical scavenging effect of *trans*-resveratrol and its analogues. In the case of *trans*-resveratrol and 4-hydroxy-*trans*-stilbene, the hydroxyl group present at *para*-
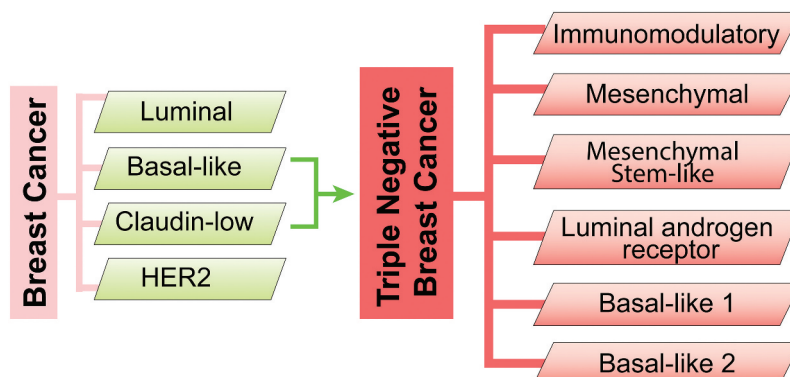

Figure 1. Breast cancer and its subtypes along with TNBC and its six subtypes.
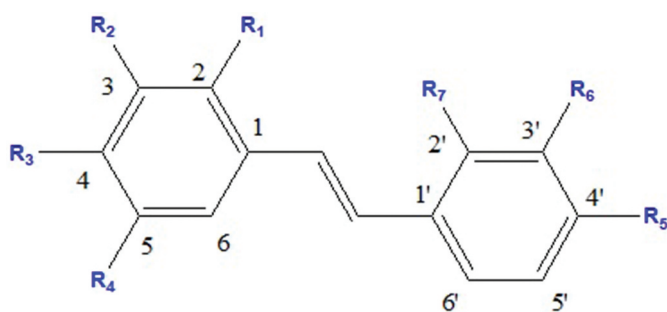
Figure 2. Chemical structure representation of resveratrol moiety for SAR.

position was found more effective compared to the analogue (3,5,-dihydroxy-*trans*-stilbene) which contains a hydroxyl group at *meta*-position [37]. In another study, Stivala et al. the authors investigated the effect of the spatial position of the phenolic hydroxyl group and stilbenic double bond on the antioxidant and anti-proliferative activity of *trans*-resveratrol and its analogues. The study finding showed that the 4'-hydroxy group in trans-confirmation is required for the antioxidant and anti-proliferative activity of *trans*-resveratrol and its analogues. The enhanced antioxidant and anti-proliferative activities in the case of *para*-hydroxy containing *trans*-resveratrol and its analogues are due to high intermolecular hydrogen bonding interaction which provides stability to the molecule [38]. The resveratrol analogs that lack hydroxy group at these positions (OH groups at R_2 and R_4) such as compounds 4, 6, 7, and 8 have no anticancer activity [39]. The methoxy and ethoxy derivatives of resveratrol were found to be more effective against TNBC. Lion et al. investigated the anticancer potential of 2-methoxy-3'-hydroxystilbene (9), 2-methoxy-4'-hydroxystilbene (10), monoethoxystilbene (11), and dimethoxystilbene (12) against MDA-MB-468 cell lines and observed more effectiveness of methoxy and ethoxy derivatives compared to pure resveratrol [40]. Figure 2 represents the chemical structure of resveratrol moiety for SAR.
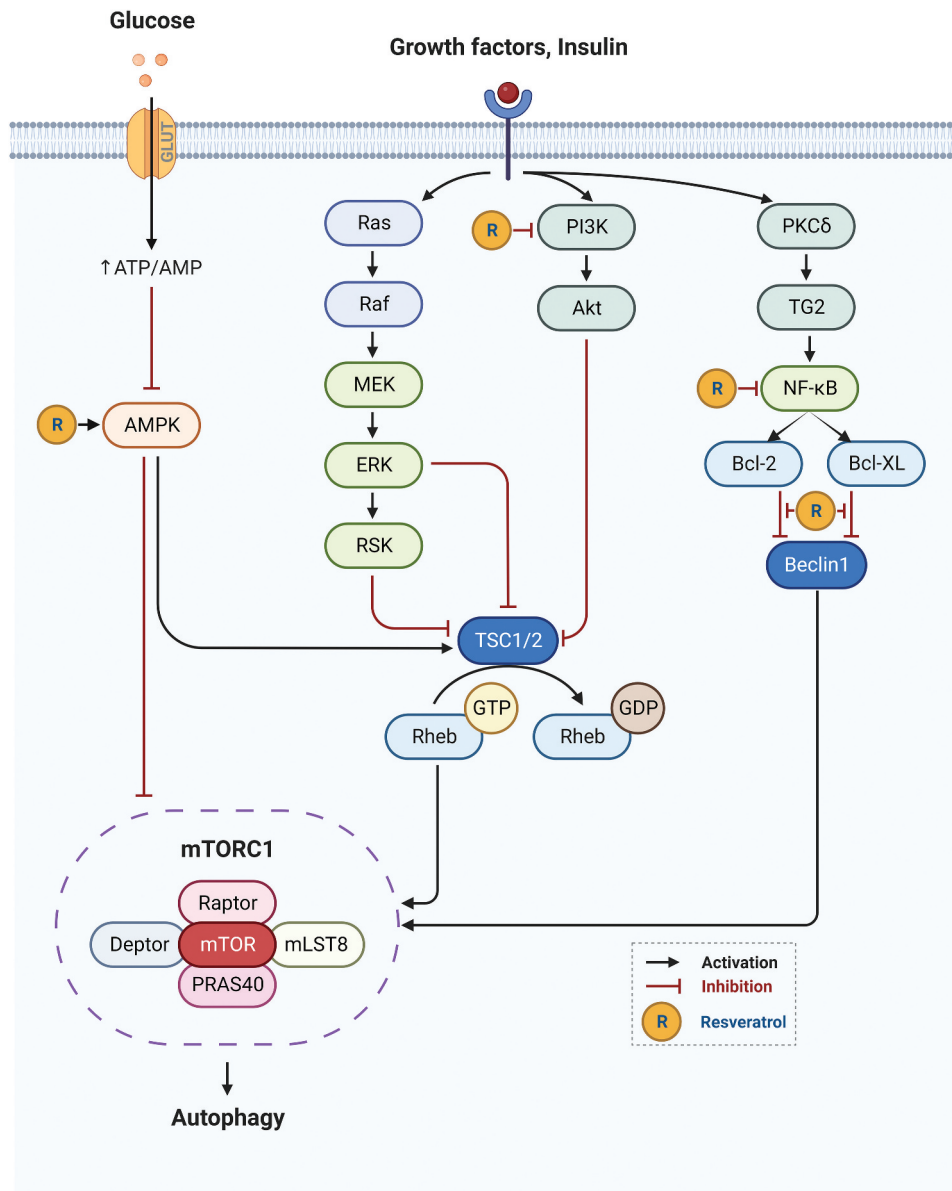
The structural characteristics and anticancer activity of resveratrol moiety and its analogs are summarized in Table 1.

3. Underlying mechanism of action of resveratrol in TNBC

Resveratrol acts by affecting the diverse signal-transduction pathways. Resveratrol mediates its anti-cancer activity through various mechanisms such as autophagy, arresting tumor cell proliferation, inhibiting tumor cell migration, suppressing tumor progression, and inducing apoptosis, etc [41–44]. Estrogen receptor-α (ERα)-negative breast cancer represents a subtype of TNBC that is known to be clinically more aggressive. Kala and Tollefsbol, have done an experimental study that shows resveratrol inhibits DNA methyltransferase (DNMT) and histone deacetylase (HDAC) to regulate the expression of ERα [45]. In combination with pterostilbene stimulates ERα-dependentresponseto17β-estradiol (E2)-mediated cellular proliferation and impedes the action of antagonist 4-hydroxytamoxifen (4-OHT)-mediated inhibition of cellular proliferation in ER-α-negative breast cancer cells. A programmed cell suicidal death is a phenomenon called apoptosis that occurs in the absence of some essential survival factors. However, two types of caspase are involved in this process known as initiator caspase (caspase 8 and 9) and effector caspases (caspase 3 and 7). Some specific death-inducing ligands also potentiate cell death. Two signaling pathways are responsible for the activation of this caspase [46]. The intrinsic pathway regulates the release of specific caspase-activating factors from mitochondria while the extrinsic pathway transmits signals from extracellular death ligands across the plasma membrane. Resveratrol shows caspase 3-mediated apoptosis and downregulates the expression of anti-apoptotic proteins (BCL-2, BCL-XL). Resveratrol induces ATG (Autophagy-related genes) dependent autophagy in TNBC. It stimulates the up-regulation of AMPK (Adenosine monophosphate kinase) that inhibits mTOR (Mammalian target of rapamycin 1) by the activation of TSC1/2. Resveratrol is involved in the inhibition of cytochrome P450 isoenzyme CYP1A1 as well as responsible for the modulation in NF-κB (nuclear factor-kappa B). Moreover, resveratrol also downregulates the expression of various cell proliferation genes like PI3K, PCNA, and cyclin D1. Various apoptosis regulatory pathways, including tyrosine kinases, caspase and other signaling pathways (phosphoinositide 3-kinase (PI3K)/AKT and modulating

Table 1. SAR of resveratrol and its analogs.

Structural characteristics									
R_1	R_2	R_3	R_4	R_5	R_6	R_7	Resveratrol and its analogues	Anticancer activity	Ref.
H	OH	H	OH	OH	H	H	*trans*-Resveratrol (1)	OH group at R_2 and R_4 responsible for anticancer activity (catechol moiety)	[36]
H	OH	H	OH	OH	H	H	Z-resveratrol (2)		
H	OH	H	OH	OH	H	H	cis-Stilbenoid (3)		
H	OH	H	OH	H	H	H	Pinosylvin (4)	Resveratrol analogues 6, 7, and 8 lack catechol (OH groups at R_2 and R_4); and have no anticancer activity	[37]
H	OH	OH	H	H	H	H	O-Dihydroxystilbene (5)	O-Dihydroxystilbene was found more potent antioxidant and effective against Jurkat cells and HL-60 leukemia cells compared to resveratrol	[35]
H	OH	H	OH	H	H	H	3,5-Dihydroxistilbene (6)	Resveratrol analogues 6, 7, and 8 lack catechol (OH groups at R_2 and R_4); and have no anticancer activity	[37]
H	H	OH	H	OH	H	H	4,4'-Dihydroxistilbene (7)		
H	H	OH	H	H	H	H	4-Hydroxistilbene (8)		
OCH$_3$	H	H	H	H	OH	H	2-Methoxy-3'-hydroxystilbene (9)	Methoxy and ethoxy analogues of resveratrol were found more effective against MDA-MB-468 cell lines compared to resveratrol	[40]
OCH$_3$	H	H	H	H	H	OH	2-Methoxy-4'-hydroxystilbene (10)		
H	H	OC$_2$H$_5$	H	H	H	H	Monoethoxystilbene (11)		
H	H	OCH$_3$	H	H	OCH$_3$	H	Dimethoxystilbene (12)		

Figure 3. Resveratrol modulates the autophagy process by regulating various signaling pathways such as the PI3K/AKT, RAS/RAF/ERK, PKCδ, and AMPK signaling pathways. "Image created with BioRender.com."

the mitogen-activated protein kinase pathway (MAPK) pathways should be targeted to improve the prognosis in TNBC [47,48] (Figure 3).

Resveratrol was reported to suppress 7, 12-dimethylbenz -[a]anthracene (DMBA)-induced breast carcinogenesis by inducing signaling pathways that accentuated apoptosis in cancer cells [49]. In mammary tissues, the treatment with resveratrol tends to produce decreased expression and activity of 5-LOX and TGFb1 and also indicates less DNA damage [50].

3.1. Immune cells and cytokines

Resveratrol has been reported to enhance the immune response against TNBC. It can promote the activation and cytotoxicity of CD8+ T cells [51]. Resveratrol can modulate the tumor microenvironment, making it more favorable for antitumor immune

responses. It reduces the immunosuppressive activity of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [52]. Resveratrol enhances the proliferation and activation of CD4+ and CD8+ T cells, promoting their antitumor functions. It can also increase the production of cytokines such as interferon-gamma (IFN-γ) by T cells, further contributing to antitumor immune responses [51]. It increases the secretion of pro-inflammatory cytokines such as interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α), which are essential for immune activation and cytotoxicity [41] Figure 4(a).

3.2. Protein activation and upregulation

Resveratrol promotes apoptosis in TNBC cells by activating caspases, a family of cysteine proteases that play a central role in programmed cell death. Specifically, resveratrol
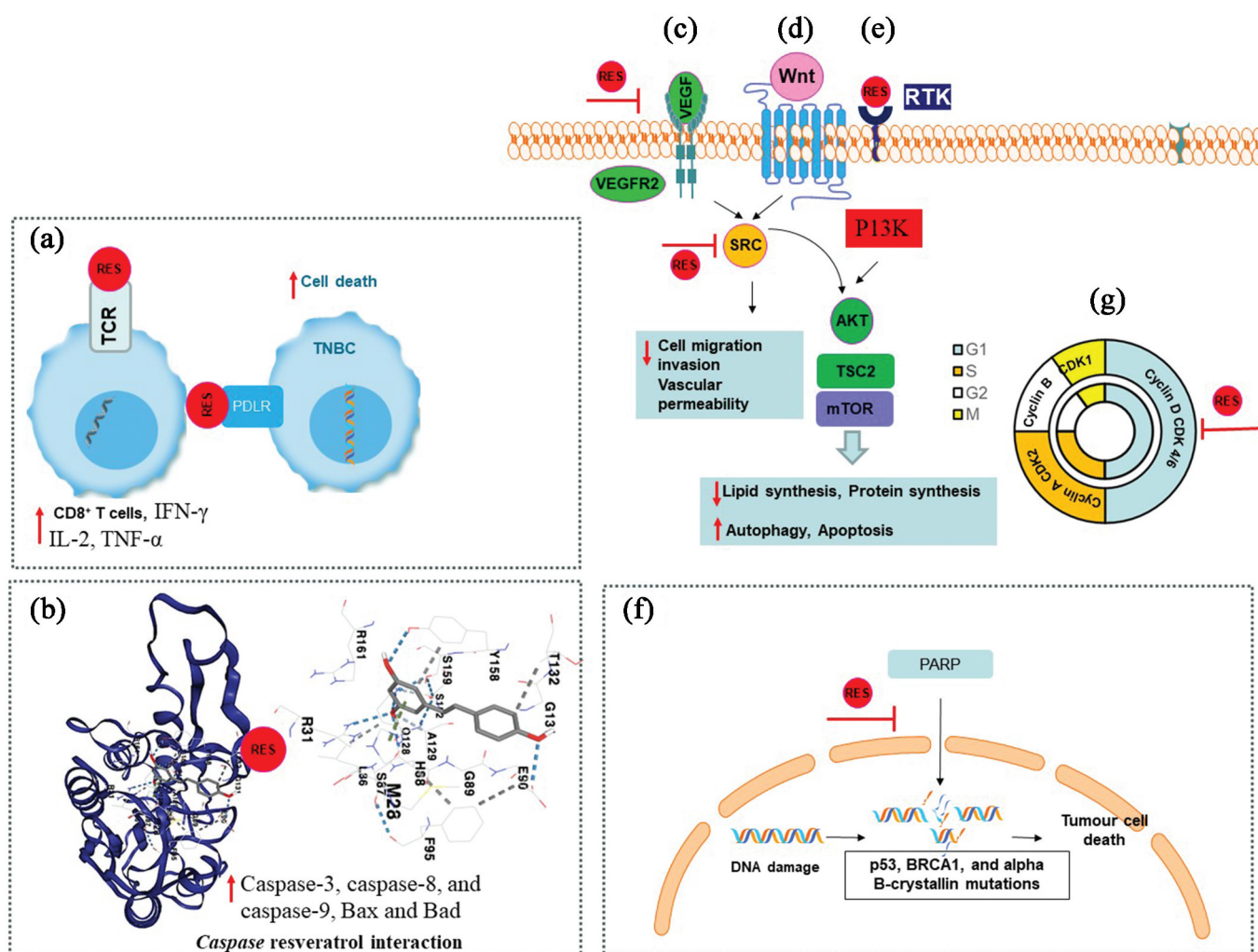
Figure 4. Schematic depiction of the molecular mechanisms of resveratrol in TNBC (Triple Negative Breast Cancer) treatment. (a) Resveratrol (RES) acts as a ligand on T-cell receptor (TCR) activates T-cell proliferation and thus causes increased production of CD4/CD8 cells resulting in induction of efficient immune responses against tumors. It also acts on Programmed Cell Death Ligand 1 (PDL1) receptor (PDLR) suppresses tumorigenesis by inhibiting cancer-cell survival and inducing cell death. (b) Caspase induced apoptosis and resveratrol interaction with caspase. Activation of caspases triggers cell death upregulates Bax and Bad and downregulates anti-apoptotic proteins Bcl-2. (c) Resveratrol inhibits VEGF production and VEGFR expression in TNBC resulting in inhibition of signaling molecule Rous sarcoma (SRC) thus cell invasion, migration, and vascular permeability. (d) Inhibitory action of resveratrol on Wnt signaling pathway. (e) The PI3K/AKT/mTOR pathway activation causes chemoresistance and survival of TNBC. Resveratrol produces inhibitory action through the inhibition of tyrosine kinase receptor (RTK) and Gprotein-coupled receptors and induced autophagy and apoptosis. (f) PARP (Poly ADP-ribose polymerase) inhibiting the DNA excision and repair. (g) Cyclin-dependent kinase (CDK) pathway downregulated by resveratrol resulting in inhibition of CDK4 and CDK6 which are overexpressed and hyperactivated in TNBC halts the cell cycle progression, leading to cell cycle arrest G1 Phase.

activates caspase-3, caspase-8, and caspase-9 in TNBC cell lines (MDA-MB-231, MDA-MB-436 and MDA-MB-468) [53]. Activation of these caspases triggers a cascade of events that ultimately leads to cell death in TNBC. It upregulates pro-apoptotic proteins such as Bax and Bad while down-regulating anti-apoptotic proteins like Bcl-2 in TNBC [53]. Bax and Bad are known to promote apoptosis by disrupting the mitochondrial membrane integrity and releasing cyto-chrome c, which further activates caspase-9. Conversely, Bcl-2 inhibits apoptosis by preventing the release of cytochrome c. Resveratrol's modulation of these proteins shifts the bal-ance in favor of apoptosis in TNBC cells. It also activates tumor suppression proteins such as p53 and p21 in TNBC [53]. p53 is a crucial transcription factor that regulates cell cycle arrest and apoptosis in response to DNA damage Figure 4(b).

3.3. Inhibition of VEGF/VEGFR2 expression

Resveratrol has been shown to downregulate the expression of VEGF/VEGFR2, reducing the production of this growth factor. VEGF is a key driver of angiogenesis, and by inhibiting its expres-sion, resveratrol may interfere with the formation of new blood vessels that support tumor growth. It can modulate the activity of proteins such as NF-κB, HIF-1α, and mTOR, which are linked to VEGF expression, tumor progression, and angiogenesis Figure 4(c).

3.4. Effect on wnt-signaling pathway

Resveratrol has been investigated for its potential to modulate the Wnt signaling pathway in TNBC, including studies in (BT-20, HCC1937, HCC1395, MDA-MB-231, and MDA-MB-468) cell lines. It has been reported to inhibit the nuclear translocation

of beta-catenin, this inhibition reduces beta-catenin's activity as a transcriptional coactivator, resulting in the downregulation of Wnt target genes involved in cell proliferation and survival [54]. In TNBC cell line studies, resveratrol has downregulated the expression of Wnt ligands, such as Wnt3a and Wnt1. By reducing the availability of Wnt ligands, resveratrol interferes with the initiation of the Wnt signaling cascade survival [55]. Whereas it upregulates the expression of Wnt pathway inhibitors, including Dickkopf-1 (DKK-1), in TNBC cell lines. DKK-1 antagonizes the Wnt pathway by binding to LRP5/6 co-receptors. Increased levels of Wnt inhibitors counteract the effects of Wnt ligand survival [56] Figure 4(d).

3.5. PI3K/AKT/mTOR pathway-induced autophagy and apoptosis

Animal studies have provided compelling evidence of resveratrol's inhibitory effects on the PI3K/AKT/mTOR pathway in TNBC. Resveratrol has demonstrated its ability to effectively inhibit PI3K in animal models survival [57]. PI3K plays a central role in the uncontrolled growth and survival of TNBC cells by phosphorylating phosphatidylinositol lipids, thereby initiating downstream signaling events. Furthermore, resveratrol's inhibitory impact extends to AKT, a serine/threonine kinase, which holds a central position in the PI3K/AKT/mTOR pathway, promoting cell survival and proliferation by phosphorylating various target proteins [58,59]. Intriguingly, TNBC animal models have demonstrated resveratrol's ability to induce autophagy, a cellular process responsible for the degradation and recycling of damaged cellular components [60]. Inhibition of the PI3K/AKT/mTOR pathway and its induction of autophagy collectively contribute to the promotion of apoptosis, a crucial programmed cell death process specifically targeted in TNBC [61]. Additionally, TNBC animal research has elucidated resveratrol's role in generating reactive oxygen species (ROS) within TNBC cells [62]. Elevated ROS levels induce cellular stress, and resveratrol's activation of the CHOP (C/EBP homologous protein) pathway has been confirmed as a key mediator of endoplasmic reticulum stress-induced apoptosis in TNBC animal studies [57]. CHOP activation subsequently leads to the upregulation of death receptor 4 (DR4) and death receptor 5 (DR5), further amplifying the apoptotic response in TNBC cells [58–62] Figure 4(e).

3.6. Effect on PARP (poly ADP-ribose polymerase) pathway

Resveratrol has been reported to inhibit PARP enzymes, impairing the repair of DNA breaks [63–65]. PARP is involved in the base excision repair (BER) pathway, repairing damaged DNA bases [66]. Resveratrol's PARP inhibition disrupts BER, preventing DNA damage repair and potentially causing genomic instability and cell death [64]. It can lead to the accumulation of unrepaired DNA damage within cancer cells, triggering cell cycle arrest and apoptosis, effectively inhibiting cancer cell growth [65]. By impairing DNA repair mechanisms through PARP inhibition, resveratrol enhances cancer cells' sensitivity to DNA-damaging agents, improving the efficacy of conventional cancer treatments [63]. Additionally, resveratrol's

inhibition of PARP may help maintain NAD+ levels in cancer cells, supporting their survival [64,65] Figure 4(f).

3.7. Effect on cyclin-dependent kinase (CDK) pathway

In TNBC animal models, such as xenograft mice or patient-derived xenograft (PDX) models, resveratrol has been observed to exert inhibitory effects on the CDK pathway [67]. CDKs are a group of enzymes that regulate the cell cycle by phosphorylating target proteins, allowing cell cycle progression. Resveratrol's activity in these models has resulted in the downregulation of key CDKs, including CDK4 and CDK6, which are often overexpressed and hyperactivated in TNBC [68]. Inhibition of CDK4 and CDK6 halts the cell cycle progression, leading to cell cycle arrest. In vitro studies using TNBC cell lines, such as MDA-MB-231 and HCC1937, have also demonstrated resveratrol's ability to inhibit the CDK pathway [69]. Resveratrol treatment in these cell lines has been associated with reduced expression and phosphorylation of CDKs and their regulatory partners, such as cyclins [69]. This inhibition prevents the activation of CDK complexes, specifically CDK4/6-cyclin D1, which are critical for G1 phase progression. By blocking these CDK complexes, resveratrol induces cell cycle arrest at the G1 phase in TNBC cell lines (Figure 4G).

4. Significance and efficacy of resveratrol in treatment of TNBC: contemporary research

The TNBC is associated with genetic mutations such as p53, BRCA1, and αB-crystallin. TNBC due to gene mutation may lead to some histopathological changes such as inflammation, proliferation, and fibrosis, contributing to the aggressive nature of TNBC [5].

Patients with TNBC face a higher risk as it metastasizes rather than normal molecular breast cancer. However, the lungs and the brain are the two primary sites for the reoccurrence of TNBC. Dillon et al. have also illustrated that TNBC is delineated by a broad range of genetic mutations including alteration of Aurora kinase A (AURKA), tumor protein p53 (TP53), kinase insert domain receptor (KDR), and myelocytomatosis oncogene (MYC) amplification [70].

Conventional anticancer drugs that are used to treat the molecular type of cancer and HER2-breast cancer include taxanes, cyclophosphamide anthracycline, epidermal growth factor receptor (EGFR) inhibitors, antiandrogens and poly ADP ribose polymerase inhibitors (PARP inhibitors). Additionally, Platinum-based chemotherapy has demonstrated efficacy for combating TNBC [71]. Numerous experimental studies have highlighted the ability of resveratrol to inhibit the tumor growth and induce apoptosis in TNBC. Resveratrol has been implicated in wide range of cellular targets and effects, including its application in different cancers particularly TNBC and type 2 diabetes. The tumor cells have an increased dependency on the glycolytic pathway and often overexpression of the glucose transporter 1 (GLUT1). Targeting glucose metabolism as an approach in TNBC treatment involved the inhibition of glucose transporters in TNBC cells that resulted an energy deprivation state and facilitate autophagy in TNBC [72] (Figure 3).

4.1. *In-vitro* investigations highlight significance of resveratrol and its combination in TNBC

Hung et al. investigated the role of pterostilbene, a natural analog of resveratrol in enhancing tumor necrosis factor-related apoptosis-induced ligand (TRAIL) in TNBC cell lines BT-20 and MDA-MB-468 [73]. The result shows that pterostilbene induced apoptosis in a dose-dependant manner. Their findings revealed that pterostilbene significantly induced apoptosis, associated with increased expression of death receptors DR4 and DR5 and reduced expression of decoy receptors DcR-1 and DcR-2. Additionally, pterostilbene decreased the levels of antiapoptotic proteins, including c-FLIPS/L, Bcl-2, surviving, and XIAP. The study's findings suggest that pterostilbene enhances TRAIL-induced apoptosis, which is the process of programmed cell death triggered by TRAIL. This effect is achieved through the activation of the ROS-mediated CHOP pathway. As a result of this pathway activation, the expression of death receptors DR4 and DR5 is up-regulated and further promotes apoptosis. This investigation provides evidence that pterostilbene exhibits potentiation of TRAIL-induced apoptosis by activating the ROS-mediated CHOP pathway, leading to increased expression of death receptors DR4 and DR5 [73].

Another study evaluated the efficacy of resveratrol and its twenty-eight analogs in ER-positive (ZR-75-1) and TNBC cell lines (MDA-MB-231, MDA-MB-157, and BT-549) [74]. The results showed that both resveratrol and its analogs exhibited significant dose-dependent cytotoxic effects on the cancer cell lines. The study also shows that resveratrol causes apoptosis *via* the caspase pathway [74]. In another investigation, an effective concentration (16.37 ± 4.72 μM) of resveratrol significantly inhibits the motility of metastatic TNBC cells [75]. It blocks the phosphorylation of extracellular signal-related kinase (ERK1/2), thereby inhibiting tumor cell migration. Yar Saglam et al. investigated the anticancer effects of resveratrol in combination with FL118 (camptothecin synthetic derivative) in MDA-MB-436 and MDA-MB-468 cell lines [76]. The administration of resveratrol enhances the sensitivity of TNBC cells to FL118-induced cell death and supress the processes of epithelial-to-mesenchymal transition, along with invasion, and migration. The sequential administration of resveratrol and FL118 inhibited cell viability and caused significant apoptosis of both TNBC cell lines. Similarly, Huber et al. conducted a study to evaluate the impact of resveratrol and pterostilbene on TNBC cells (BT-20, HCC1395, MDA-MB-231, and MDA-MB-468) [77]. The findings revealed that both resveratrol and pterostilbene effectively supress the Wnt-signaling pathway in TNBC cells, demonstrating a dose-dependent response.

In a study conducted by Lucas et al. to investigate the effect of combined resveratrol and piceatannol on the expression of programmed cell death ligand 1 (PD-L1) in Cal51 TNBC cell lines [78]. The results showed synergistic upregulation of PD-L1 when resveratrol and piceatannol were combined. This induction of PD-L1 expression was mediated *via* the HDAC3/p300-mediated NF-κB signaling pathway. Kala et al. studied the positive impact of combining resveratrol and pterostilbene in HCC1806 and MDA-MB-157 cell lines [79]. The combination of resveratrol and pterostilbene produced synergistic inhibition of both cell lines attributed to the inhibition of SIRT1 and DNMT enzymes, along with alterations in DNA damage. Notably, this combination significantly inhibited cell growth, leading to apoptosis and cell cycle arrest. In another study, Schlachterman et al. evaluated the combined effect of resveratrol, quercetin, and catechin in the MDA-MB-231 cell line. The combined treatment significantly reduced cell proliferation, and blocked cell cycle progression in *in-vitro* analysis [80].

4.2. *In-vivo* investigations highlight significance of resveratrol and its combination in TNBC

In vivo studies have further corroborated the promising anticancer effects of resveratrol and its combinations in TNBC. Han et al. conducted a study that demonstrates the ability of resveratrol to attenuate the metastasis of TNBC to the lungs in the 4T1 tumor model in mice [81]. Resveratrol effectively inhibit lung metastasis by enhancing local anti-tumor immunity. This effect involves several mechanisms, including increased cytotoxic activity of CD8+T cells. Resveratrol treatment elevated the levels of type 1 cytokines, such as IFN-γ and IL-2, in the lungs, further contributing to the anti-tumor immune response. One of the key factors involved in the enhanced cytotoxic activity is the down-regulation of PD-1 expression on pulmonary CD8+T and CD4+T cells. PD-1 is an immune checkpoint molecule that can suppress the function of T-cells and impede their anti-tumor activity. By reducing PD-1 expression, resveratrol allows CD8+T and CD4+T cells to exert their cytotoxic effects more effectively, thus enhancing the local anti-tumor immune response. Overall, study findings confirm that resveratrol plays a crucial role in suppressing TNBC lung metastasis by elevating local anti-tumor immunity and boosting the cytotoxic activity of CD8+T cells, potentially through the down-regulation of PD-1 expression on pulmonary T cells [81].

In another investigation, Garvin et al. investigated the role of resveratrol in *in-vivo* models using nude mice (ERα, ERβ+, and MDA-MB-231) [82]. The resveratrol treatment significantly reduced tumor growth and angiogenesis in these models. Similarly, Liang et al. studied the antitumor effects of resveratrol in animal models using BALB/c nude female mice [83]. Resveratrol treatment increased TNBC cell toxicity primarily through influencing genes associated with apoptosis and the p53 signaling pathway. Additionally, the resveratrol-induced apoptosis was predominantly mediated through DNA polymerase δ catalytic subunit gene 1 (POLD1). It plays a pivotal role as the main replicase in eukaryotic DNA replication, specifically involved in synthesizing the lagging strand and demonstrating significant 3′-5′ exonuclease activity. Beyond its central role in replication, Pol δ actively participates in the repair of damaged DNA. The occurrence of mutations in Pol δ has been linked to the advancement of cancer, emphasizing its critical function in preserving genomic integrity [83]. Yang et al. studied the efficacy of resveratrol and cisplatin combination in TNBC [84]. Resveratrol synergistically enhanced cisplatin's effect on cell migration and invasion and tumor growth. The combination significantly reduced the expression of fibronectin, vimentin genes. These genes are responsible for maintaining cell shape, preserving cytoplasmic integrity, stabilizing cytoskeletal interactions, regulating cell signaling, influencing migration, and facilitating cell adhesion It also decreased

the expression of phosphorylated protein kinase B (PKB/AKT), phosphatidylinositol 3-kinase (PI3K), Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), Sma2, and Smad3, which were induced by TGF-1. Additionally, this combination treatment increased E-cadherin expression. Resveratrol enhanced the inhibition of tumor growth while mitigating body weight loss and kidney function impairment caused by cisplatin in MDA231 ×enograft models. These findings suggest that the combination of resveratrol and cisplatin holds promise as a potential therapeutic strategy for inhibiting tumor growth and minimizing the cisplatin's adverse effects [84]. Schlachterman et al. demonstrated the combined effect of resveratrol, quercetin, and catechin (dose level of 5 and 25 mg/kg b.w., thrice a week by oral gavage for 117 days) in MDA-MB-231 breast tumor xenograft in a nude mouse model. The combined treatment significantly inhibits tumor growth [80].

The multitarget therapy has huge opportunities to overcome many concurrent obstacles in cancer therapy particularly in treatment approach for TNBC. Recently, inhibition of Topoisomerase II enzyme and p53-MDM2 (p53 cavity in MDM2) protein complex by the same resveratrol molecules for multitarget therapy was investigated through ligand-based screening involving docking, simulation, and validated in TNBC cell lines (MDA-MB-231). The results of this investigation support the antitumor activity of resveratrol at IC50 (105 µM) and suitable for multitargeting therapy against TNBC [85]. Indeed, the safety, efficacy, and bioavailability of resveratrol is already reported in > 250 clinical trials, with an additional various ongoing clinical trials. It is well documented to improve the therapeutic effect in patients suffering from various diseases including colorectal cancer, breast cancer, and multiple myeloma [86]. Recent investigation further validate the significance of resveratrol in treatment of TNBC through metabolomics analysis which exert their chemosensitizing and reversal of MDR effects [87]. Table 2 Summarizes contemporary research carried out employing resveratrol alone and its combination as anticancer therapeutics in the management of TNBC.

5. Biopharmaceutical challenges in delivery of resveratrol in TNBC

Resveratrol exhibits limited solubility in water (0.03 mg/mL) with logP 3.10. However, it is readily soluble in organic solvents such as ethanol, dimethyl sulfoxide, and phosphate buffer at pH 7.2, where its solubility reaches approximately 100 µg/mL. Resveratrol has demonstrated promising anticancer potential in various in vitro studies. However, these findings have not been consistently supported by in vivo studies [33,51,88–93]. The oral absorption of resveratrol in humans is about 75%, but due to extensive metabolism in the intestine and liver, its oral bioavailability is significantly less than 1% [88,94]. The poor water solubility of resveratrol and extensive metabolism contribute to its low bioavailability. In a study examining the absorption and bioavailability of a single oral dose of 25 mg of resveratrol, researchers observed a peak concentration of resveratrol below 10 ng/mL at 0.5–2 hours after administration. The plasma concentrations of resveratrol's total metabolites were in the range of 400–500 ng/mL [95,96]. Another study investigated the absorption and bioavailability of resveratrol using a dose escalation method dose ranging from 25–5,000 mg. With increasing doses, there was a linear increase in plasma concentration, indicating no saturation or potential efflux. Even at the highest dose (5,000 mg), the peak plasma levels of resveratrol only reached ~500 ng/mL. The authors concluded that the low bioavailability of resveratrol may be due to limited water solubility and its extensive metabolism [97,98].

Table 2. Summarizes contemporary research carried out utilizing resveratrol alone and its combination as anticancer therapeutics in the management of TNBC.

Therapeutics	In vitro/In vivo model	Research Outcome	Ref.
Resveratrol analogue & pterostilbene	BT-20 and MDA-MB-468 cell lines	Induces apoptosis through the activation of the ROS-mediated CHOP pathway, ultimately resulting in the upregulation of death receptors DR4 and DR5.	[73]
Resveratrol	ZR-75-1; and MDA-MB-231, MDA-MB-157, and BT-549 cell lines	Resveratrol causes apoptosis via the caspase pathway	[74]
Resveratrol & FL118	MDA-MB-436 and MDA-MB-468 cell lines	Resveratrol sensitizes TNBC cells to FL118-induced cell death, epithelial to mesenchymal transition, invasion, and migration	[76]
Resveratrol & pterostilbene	BT-20, HCC1395, MDA-MB-231, and MDA-MB-468 cell lines	Inhibits the Wnt-signaling pathway in TNBC	[77]
Resveratrol & piceatannol	Cal51 cell lines	The combined effect of resveratrol and piceatannol caused the induction of PD-L1 via HDAC3/p300-mediated NF-κB signaling pathway.	[78]
Resveratrol & pterostilbene	HCC1806 and MDA-MB-157 breast cancer cell lines	The combination of resveratrol and pterostilbene exhibits synergistic inhibition of both cell lines, resulting in a potent anticancer effect. This effect is attributed to the inhibition of SIRT1 and DNMT enzymes, leading to apoptosis and cell cycle arrest.	[79]
Resveratrol	4T1 tumor model in mouse	Resveratrol enhanced cytotoxic activity by down-regulated PD-1 expression on pulmonary CD8+T and CD4+T cells	[81]
Resveratrol	MDA-MB-231 breast tumor xenograft in a nude mouse	Significantly lowers tumor growth and decreases angiogenesis in nude mice.	[82]
Resveratrol	MDA-MB-231 cell lines	Resveratrol mediates apoptosis by reducing POLD1 expression	[83]
Resveratrol & cisplatin	MDA-MB-231 cell lines and MDA231 ×enograft	The combination of resveratrol and cisplatin significantly reduced the expression of fibronectin, vimentin, p-AKT, p-PI3K, p-JNK, p-ERK, Sma2, and Smad3 induced by TGF-1; and increased the expression of E-cadherin	[84]
Resveratrol, quercetin, and catechin	MDA-MB-231 breast tumor xenograft in a nude mouse	Combined treatment significantly inhibits tumor growth	[80]

6. Utilization of nanotechnology to improve anticancer activity of resveratrol in TNBC

The majority of biological investigations have primarily focused on *in vitro* settings, utilizing cell or tissue models, as well as subcellular fractions. Nevertheless, when translating these studies to *in vivo* animal models of disease, it has proven challenging to reproduce the observed effects. Similarly, demonstrating the efficacy of resveratrol in humans *in vivo* has been an elusive task, with no compelling studies available thus far [99,100]. One of the primary factors contributing to the inconsistencies between *in vitro* and *in vivo* results could be attributed to the poor biopharmaceutical characteristics and limited bioavailability of resveratrol *in vivo*, particularly following oral administration. Consequently, concentrations of resveratrol at potential sites of action within tissues or cells have not yet reached adequate levels to establish its effectiveness in humans [101–103].

Utilization of nanotechnology particularly for the fabrication of nanoparticulate systems of polymeric/lipidic/inorganic origin has emerged as a promising therapeutic platform with vast application in the treatment of various diseases including different cancers. These nanoparticulate systems, when well-designed, possess the capability for site-specific delivery of loaded therapeutics and significantly enhance the effectiveness of encapsulated therapeutics [24,104,105]. They achieve this by improving solubility, enabling prolonged circulation or controlled drug release, facilitating targeted delivery to specific disease sites, and minimizing the untoward effects [106]. Moreover, nanoparticulate systems can be formulated for different routes of administration, including parenteral, topical, oral, and inhalation routes [107,108]. It can be optimized to overcome the delivery barriers associated with emerging therapeutics such as oligonucleotides, mRNA, and DNA which offer immense potential as safer alternatives to viral vectors in various therapeutic applications [109]. Resveratrol is an active phenolic compound that shows its

antineoplastic effects in respect of its anti-proliferative, anti-tumorigenic, and anti-metastatic properties. It acts as a selective estrogen receptor modulator (SERM) drug. The co-administration of resveratrol with estrogen elicits both agonistic (estrogen mimetic) and antagonistic effects indicating a tissue-specific response [110]. It is not very effective when taken orally because of its poor bioavailability. On an oral administration, resveratrol undergoes conjugation reactions followed by glucuronidation, methylation, and sulfation. Hence the *trans*-resveratrol gets converted into glucuronic acid and sulfates that accumulate in the urinary tract. Promising results are not optimal even at higher doses. In human beings, the plasma half-life is reported to be 4–8 hours only [111]. The pharmacokinetic profile of resveratrol is associated with its short half-life, rapid elimination, and undesirable biotransformation that leads to low bioavailability at the site of action. To counteract the poor bioavailability associated with resveratrol and improve its therapeutic efficacy in TNBC, nanotechnology as an approach has come to the frontline [102].

6.1. Advanced multifunctional formulation of resveratrol against TNBC

Advanced multifunctional formulation design (Illustrated in Figure 5) utilizing nanotechnology for targeted delivery of resveratrol in TNBC were investigated in recent years. Oxidized modified mesoporous carbon nanoparticles (oMCNs) were explored to the improve biopharmaceutical characteristics of resveratrol against TNBC. Mesoporous carbon nanoparticles have good absorption properties and higher drug loading efficiency (compared to silica nanoparticles) specifically for aromatic therapeutics. It easily encapsulates the crystalline nature of drugs into nanopores with transformation into an amorphous state and is greatly helpful in improving
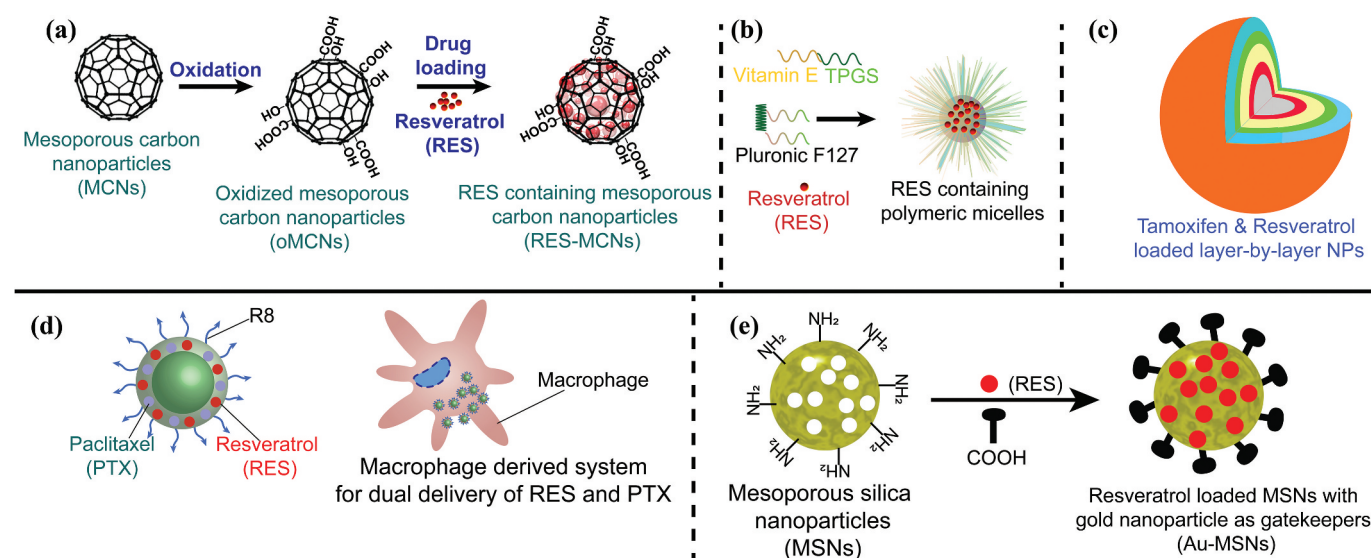
Figure 5. Advanced multifunctional formulation of resveratrol against TNBC. (a) Oxidized modified mesoporous carbon nanoparticles (oMCNs) containing resveratrol. (b) Resveratrol loaded polymeric micelles of pluronic F127 block copolymer and vitamin E-TPGS as an emulsifier. (c) Layer-by-layer nanoparticles (LbL) based on lipid-based drug delivery systems and liquid crystalline nanoparticles (LCNPs) developed for dual delivery of resveratrol and tamoxifen. (d) Macrophage-derived carrier encapsulating R8 (cell penetrating peptide - octaarginine) conjugated liposome for dual delivery of resveratrol and paclitaxel. (e) Gold nanoparticles to design multifunction nanoparticulate system conjugating mesoporous silica nanoparticles (MSNs) for the delivery of resveratrol against TNBC.
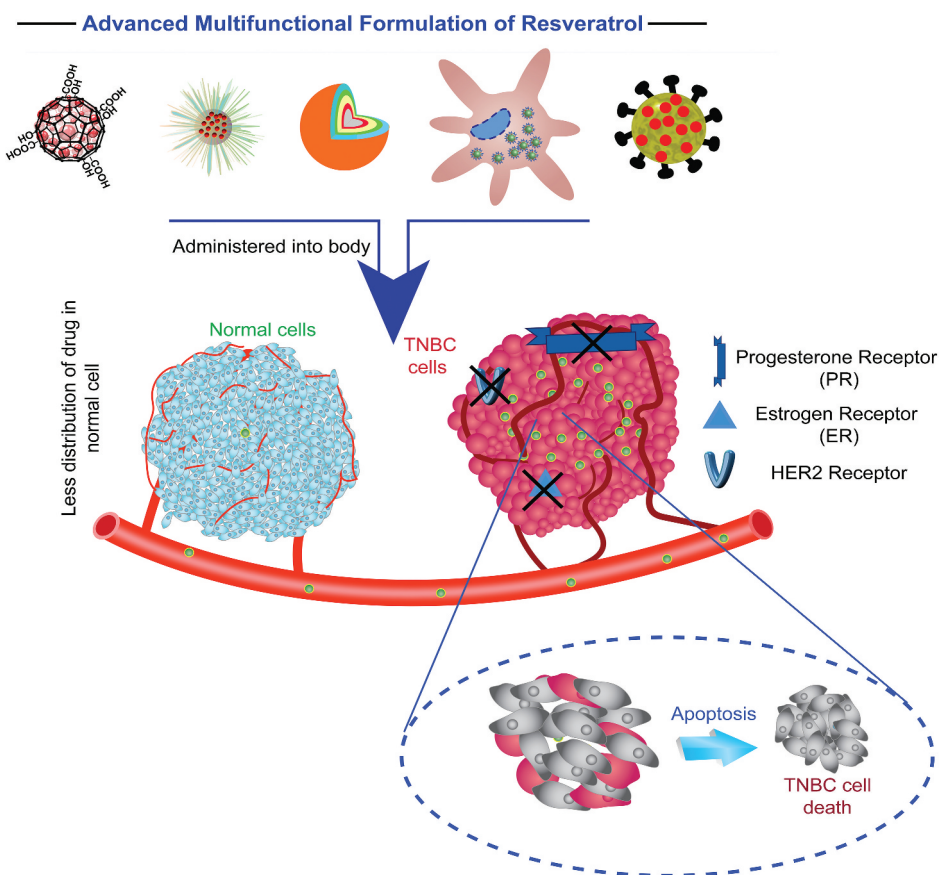
Figure 6. Schematic illustration highlights the impact of advanced multifunctional formulation of resveratrol on TNBC cell.

the aqueous solubility of hydrophobic therapeutics. Furthermore, oxidized modification of mesoporous carbon nanoparticles minimizes the hydrophobic characteristics of conventional mesoporous carbon nanoparticles. Fan et al. studied the cytotoxic effects of oxidized mesoporous carbon nanoparticles (illustrated in Figure (5a)) of resveratrol (oMCNs-NP) in TNBC utilizing MDA-MB-231 cell lines and compared them with pure resveratrol [112]. The study results show resveratrol-oMCNs-NPs have higher cytotoxic activity in MDA-MB-231 cell lines of TNBC compared to pure resveratrol. The authors also reported apoptotic effects of resveratrol-oMCNs-NPs (36.8%) significantly higher compared to pure resveratrol (21.2%) at a dose of 100 mM. A cancer therapeutic conjugate system was explored to improve the anticancer efficacy in different carcinomas. Recently Aljoubori AA et al. have investigated such a system against TNBC for dual drug delivery of resveratrol and tamoxifen [113]. Layer-by-layer nanoparticles (LbL) based on lipid-based drug delivery systems and liquid crystalline nanoparticles (LCNPs) were developed for dual delivery of resveratrol and tamoxifen (illustrated in Figure 5(c)). It involved the fabrication of LCNPs for resveratrol and tamoxifen utilizing glyceryl monooleate, ethanol, and poloxamer-407. After that, LbL-coated system was prepared by mixing this negatively charged LCNPs with cationic chitosan solution, and subsequently second negatively charged layer was added over LCNPs (loaded with resveratrol & tamoxifen) by titrating with anionic hyaluronic acid solution to

modified as targeted nanoparticulate system for overexpressed hyaluronan receptor in TNBC. The promising results observed in *in vitro and in vivo* investigation prove its worth as multifunctional nanoparticles for combinatorial therapy in TNBC. Polymeric micelles (illustrated in Figure 5(b)) were explored by Gregoriou Y et al. for the delivery of resveratrol in TNBC using pluronic F127 block copolymer and vitamin E-TPGS as an emulsifier [114]. The developed nanoparticulate system of particle size <200 nm has revealed higher cellular uptake and reduced the viability of TNBC cells (MDA-MB-231) significantly compared to control cells.

Recently, macrophages have been widely investigated as a promising cellular carrier for the delivery of anticancer therapeutics and drug-loaded nanoparticulate systems to the tumor microenvironment [115]. It is mainly because of their natural characteristics like biodegradability, biocompatibility, lack of immunogenicity, crossing biological barriers, long circulating half-life, and opportunity of migration and accumulation at a site of tumor due to inflammation. Different researcher has explored the potential of macrophage-derived carriers for the delivery of resveratrol against postoperative TNBC recurrence [116,117]. Qiu et al. have reported a dual delivery (resveratrol and paclitaxel) approach utilizing macrophage-derived carriers (illustrated in Figure 5(d)) against postoperative TNBC recurrence [116]. It was observed that the developed system exhibit efficient tumor-targetability, particularly in postoperative condition. The impact of advanced

Table 3. Multifunctional nanoparticulate system of resveratrol and its combination for the treatment of TNBC.

Type of nano-formulation	Formulation description	In-vitro and in-vivo model	Significance of study	Ref.
Carbon nanoparticles	Oxidized mesoporous carbon nanoparticles of resveratrol (oMCNs-NP)	MDA-MB-231 cells	Resveratrol nanoparticles showed apoptotic effects (36.8%) and it was significantly higher compared to pure resveratrol (21.2%) at 100 mM dose	[112]
Lipid nanoparticles	Layer-by-layer lipid nanoparticle of tamoxifen and resveratrol	CAL-51 cells	Combinatorial therapy of resveratrol induces apoptosis in TNBC cells with biocompatibility for human red blood cells	[113]
Polymeric micelles	Resveratrol containing pluronic F127 copolymer block with Vitamin-E TPGS micelles having particle size <200 nm	MDA-MB-231 cells	Developed for diagnosis and therapy as a theranostic system and higher uptake efficiency in TNBC cells.	[114]
Macrophage-derived carriers	Dual delivery of paclitaxel and resveratrol through macrophage-based carrier	4 T1 cells	Inhibit tumor recurrence in both ectopic and orthotopic 4T1 postoperative recurrence models.	[116]
Macrophage-derived carriers	Octaarginine (R8)-modified liposomes loaded with resveratrol and indocyanine green (ICG) then ingested to macrophage		Synergistic photothermal and anti-inflammatory effects for postoperative TNBC with drug release trigger through inflammation.	[117]
Hydrogel	Resveratrol loaded click-crosslinked hyaluronic acid system for in-situ gel formation in tumor for depot formation	MDA-MB-231 cells and female nude mice	Successful depot formation after intratumoral injection and maintained release of resveratrol for extended period.	[118]
Gold nanoparticles	Gold nanoparticles functionalized with selenol-modified uPA-peptides and silica mesoporous nanoparticle	MDA-MB-231 cells and TNBC tumor-bearing mice	Targeted delivery of resveratrol results generation of a high level of NAD(P)H indicating reductive stress instead of oxidative stress in TNBC	[119]
Polymeric nanocomplex	Resveratrol loaded chitosan nanoparticles with particle size <200 nm	MDA-MB 231 cells	Inhibited cell proliferation at lower IC_{50} value and stimulated intrinsic apoptotic pathway	[120]

multifunctional formulations of resveratrol on TNBC cells are illustrated in Figure 6. Ren K et al. in their investigations utilized macrophage-derived carriers as a multi-mode drug release system for a combination of photothermal and anti-inflammatory therapy against postoperative TNBC recurrence [117]. A macrophage-based drug delivery system was fabricated by encapsulating the resveratrol and indocyanine green (ICG) in octaarginine (R8)-modified liposomes and drug-loaded system subsequently ingested by macrophages. It was observed that the developed system exhibited effective tumor-targetability through inflammatory tropism of macrophages and significant near-infrared (NIR) photothermal activity against TNBC.

Another advanced pharmaceutical system was developed by Shin GR et al. for the delivery of resveratrol against TNBC [118]. It was a parenteral depot system that converted into in situ gel after intratumoral injection in TNBC. The fabrication of this click-crosslinked system of resveratrol involved the Diels – Alder click reaction between resveratrol-loaded tetrazine-modified hyaluronic acid and resveratrol-loaded trans-cyclooctene-modified hyaluronic acid through double syringe injection system for in-situ gel formation (Depot formation) at a physiological condition in the tumor microenvironment of TNBC. The developed system is helpful in inhibiting tumor growth due to sufficient resveratrol exposure and induction of apoptosis against TNBC cells. Liu et al. have explored the potential of gold nanoparticles to design multifunction nanoparticulate system conjugating mesoporous silica nanoparticles (MSNs) for the delivery of resveratrol against TNBC [119]. The developed system is basically a stimuli-responsive targeted-release system of mesoporous silica nanoparticles utilizing Au-Se-bonded gold nanoparticles as gatekeepers to deliver the loaded resveratrol for the treatment of TNBC (illustrated in Figure 5(e)). The urokinase-type plasminogen activator (uPA) is overexpressed in TNBC and selected as the

stimuli-responsive enzyme for this advanced formulation design. The mesoporous silica nanoparticles were synthesized as NH2-MSNs. The peptide substrate containing the uPA-specific peptide sequence (glutamic acid and selenocysteine terminals) was labeled with rhodamine-B and conjugated to functionalized gold nanoparticles by Au-Se bonds. The developed functionalized gold nanoparticles capped the pore entrances of the MSNs through amide bonds (NH2-MSNs). Rhodamine-B was utilized in this formulation development as a tracer to monitor the delivery of resveratrol and the progress of therapy against TNBC. When uPA at high concentrations in The developed theranostic system (simultaneous delivery of therapeutic and imaging agent) at the tumor site cleaved the specific peptide due to high concentration of uPA, released resveratrol from the pore of stimuli-responsive MSNS and simultaneously restored the fluorescence of Rhodamine-B for the functioning as a tracer against TNBC.

It was observed that the resveratrol-loaded nanoparticulate system was helpful in improving the water solubility and accumulation of resveratrol to the targeted tumor site and decreasing rapid metabolism. It provides a proof-of-concept that a nanoparticulate system of polymeric/lipidic/inorganic origin is helpful in overcoming the biopharmaceutical challenges associated with the anticancer delivery of resveratrol and ultimately enhances the therapeutic efficacy of resveratrol in TNBC. Borzorgi et al. synthesized resveratrol-loaded chitosan nanoparticles (Res-Cs-NPs) and investigated their efficacy in stimulating apoptosis in MDA-MB 231 cell lines. The Res-Cs-NPs size was about 200 nm with resveratrol entrapment efficiency of 52.34 ± 0.16%. The Res-Cs-NPs showed a significant antiproliferative effect compared with pure resveratrol. Res-Cs-NPs also showed enhanced cell toxicity (viable cells after 48 h about 37.84 ± 4.2%) compared to pure resveratrol [120]. Different multifunctional nanoparticulate systems of resveratrol and its combination for the treatment of TNBC are summarized in Table 3.

7. Conclusion and future directions

The multitarget nanotechnology-mediated therapy has huge opportunities to overcome many concurrent obstacles (such as MDR, poor biopharmaceutical attributes of therapeutics, exposure of anticancer drug release to healthy tissues, lack of targeted therapy to cancerous cells) in cancer therapy particularly in treatment approach for TNBC. Resveratrol appears as a promising anticancer drug candidate in various *in-vitro* studies but fails its effectiveness in *in-vivo* investigations due to its poor biopharmaceutical characteristics. Its chemical instability, rapid elimination, short half-life, undesirable degradation, and biotransformation pose a major challenge in its use as an anticancer therapeutics. To overcome these limitations, nanotechnology offers a promising way to encounter bioavailability and pharmacokinetic issues associated with resveratrol to cure breast cancer including TNBC efficiently and effectively.

Nano-formulations of resveratrol, including liposomes, nanotubes, micelles, and nanoparticles, have demonstrated the ability to improve biopharmaceutical properties including oral bioavailability. These formulations address key challenges such as improving water solubility, targeting tumor site accumulation, and reducing rapid metabolism through nano-encapsulation. Moreover, these nano-formulations can be designed to selectively accumulate at the tumor site, allowing for a higher concentration of resveratrol to reach the TNBC cells. Additionally, they can protect resveratrol from degradation and metabolism, leading to a prolonged circulation time in the body and increased therapeutic efficacy. Advanced pharmaceutical formulations utilizing nanotechnology-mediated drug delivery (such as oxidized mesoporous carbon nanoparticles, macrophage-derived vesicular system, functionalized gold nanoparticles, etc.) have increased the accumulation of loaded therapeutics at the tumor-site of TNBC, and avoid off-target drug release. The fabrication of nano-resveratrol as advanced pharmaceutical formulation may provide improved tumor-specific image-guided treatment options for TNBC utilizing theranostic approach (imagaing and progress of therapy simultaneously measure through same cargo/delivery system). Overall, the utilization of nanoformulations represents a promising strategy to optimize the delivery system of resveratrol for the treatment of breast cancer, particularly in the context of TNBC.

8. Expert opinion

TNBC is characterized by the absence of Estrogen receptors, progesterone receptors, and HER-2 receptors. It is a life-threatening breast cancer that metastasizes to visceral organs and is also associated with genetic mutation. However, no standard chemotherapy has been available to treat TNBC yet. Research studies revealed the dose-dependent cytotoxic effect of Resveratrol and its analogs on TNBC cell lines. It exhibited cytotoxic effects on TNBC via different mechanisms including the caspase pathway, Wnt signaling, and p53 signaling pathway, and could also block the phosphorylation of extracellular signal-related kinase (ERK1/2). Moreover, resveratrol showed the potential to increase the sensitivity of TNBC cells to other anticancer agents (such as camptothecin derivatives, piceatannol, and cisplatin) in different preclinical investigations.

A study indicated that resveratrol exhibits inhibition of lung metastasis in TNBC by down-regulation of PD-I expression on pulmonary CD8^{+}T and CD4^{+}T cells. Hence, in the future resveratrol could be explored as a potential adjuvant molecule to treat TNBC along with other anticancer agents in pre-clinical as well as in clinical settings. However, the clinical efficacy of resveratrol is limited due to its poor biopharmaceutical characteristics and low oral bioavailability. The nanoparticle system could offer a potential platform to deliver resveratrol and other anticancer agents in combination for the treatment of TNBC. The resveratrol loaded-nanoparticulate system could offer various benefits such as improvement in oral bioavailability due to their submicron size and enormous surface area, enhancement in the accumulation of resveratrol in TNBC cells via the enhanced permeability and retention (EPR) effect of nanoparticles, provided the surface for functionalization with active targeting ligands (like folate, hyaluronan) to target TNBC cells effectively. It can also be exploited to load or tag with diagnostic/imaging agents including quantum dots along with therapeutic agents as 'cancer theranostics' (or theragnostics) for the detection/imaging of therapy progression in TNBC. Limited research studies are available that indicate that resveratrol could potentiate the sensitivity of other anticancer agents in TNBC. Hence, in our opinion more research studies are required to establish resveratrol potential to treat TNBC along with different cancer chemotherapeutics. Additionally, various multifunctional nanoparticles of polymeric/lipidic/inorganic origin should also be explored further to improve the delivery and targetability of resveratrol in TNBC. Multifunctional nanoparticulate systems possess the capability of targeted delivery, noninvasive imaging, and tumor response which facilitate overcoming endothelial cell layers and bypassing multidrug-resistant P-glycoprotein barriers associated with TNBC. Potential cell surface targets including urokinase plasminogen-activated receptors (uPAR), EGFR, IGF-1 R, Wnt receptors, MUC-1, CD44, and folate receptors can be utilized for improved drug delivery to TNBC. Gold-based and carbon-based theranostic systems should also be explored in combination with resveratrol for the image-guided treatment of TNBC. Moreover, a macrophage-derived extracellular vesicular system should also be explored further to target TNBC cells via the LFA-1 protein expressed on the surface of TNBC due to inflammation. Furthermore, Quantum dots and carbon-based nanoparticles can be coupled to provide diagnostic and therapeutic capabilities to nanoparticles as a theranostic system for image-guided therapy. However, the lack of pharmacokinetic data for these developed advanced nanoformulations of resveratrol in humans limits the translation of these developed nanoformulations from pre-clinical to clinical settings. Therefore, to achieve successful use of resveratrol for the treatment of TNBC, the researchers must also focus on the pharmacokinetic evaluation of the developed targeted nanoparticulate system loaded with resveratrol and cancer chemotherapeutics for active targeting to TNBC exploiting overexpressed molecular targets on its cellular surface. Moreover, safety perspectives and the fate of developed multifunctional nanoparticulate systems should also be evaluated extensively in suitable in-vivo models to further establish any possibility of toxicity to healthy tissues/organs.

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Declaration of interest

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