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Review Article

The Therapeutic Potential of Resveratrol in Gliomas

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ABSTRACT

Resveratrol (RSV) is found in most human foods especially fruits such as grapes, peanuts, strawberry, blueberry, cranberry, mulberry, lingberry, sparkleberry, bilberry and in flowers as well as leaves like butterfly orchid tree, eucalyptus, spruce, lily, gnetum and so many others. Functionally, RSV has the propensity to safeguard DNA as well as the induction of DNA repair. RSV is precipitously metabolized in the liver via phase-II detoxification enzymes leading to its principal urine excretion. RSV steered growth inhibition, induction of apoptosis and G0/G1-phase cell cycle arrest in an experiment involving glioma cells. RVS can block the triggering of signal transducer and activator of transcription (STAT3) signaling of glioma cells. RSV subdues STAT3 signaling via the inhibition of SRC or Janus kinase (JAK2) induction, thereby inducing growth inhibitory and apoptotic properties. RSV explicitly blocks both COX-1 and COX-2 in-vitro. In the cancer inflammatory milieu, the blockade effects of RSV on NF-κB could also lead to the blockade of TNF-α resulting in inhibition of cancer advancement as well as metastasis. Individually, RSV has proven to very potent in glioma cells. It is able to down-regulate glioma angiogenesis as well as metastasis. In combination with other agents, RVS augment its potency in glioma. RVS is able to cross the blood brain barrier (BBB) via gap junctions making it very efficient central nervous system medication. RVS after oral administration peaks in the blood stream after one hour meaning it acts very fast. This review focuses on the neuropharmacological role of RVS in glioma.

INTRODUCTION

Resveratrol (RSV) was original used in Japanese and Chinese traditional medicine in the treatment of many sickness (32,89). The primary functional component of RSV is derived from dried roots of *polygonum cuspidatum* (86,89). Studies have shown that RSV is found in most human foods especially fruits such as grapes, peanuts, strawberry, blueberry, cranberry, mulberry, lingberry, sparkleberry, bilberry and in flowers as well as leaves like butterfly orchid tree, eucalyptus, spruce, lily, gnetum etc. (32,36,67). Nevertheless, RSV is also found in wine, particularly red wine. Interestingly, the skin of red grapes and red wine are cogitated as main origins of resveratrol in foodstuffs or assorted drinks. The French people has considerably lesser occurrence of heart ailments although they eat high-fat diet (89,142). This "French Paradox" could be as a result of the presence of high quantity of RSV in the wine they consume (142). Furthermore, the Mediterranean's diet in the form of peanuts, grapes and wine also contain high quantities of RSV which makes them less prone to cardiovascular diseases. Several studies have proven that RSV is an antioxidant, anti-inflammatory, analgesic, antiviral, cardioprotective, neuroprotective as well as antiaging action (7,32,42). Nevertheless, RSV has proven to have chemo-preventive effects on numerous human ailments like osteoporosis and gastric ulcers besides the cardioprotective effect mentioned above (27,32).

STRUCTURE AND FUNCTIONS OF RESVERATROL

RSV is a white powder with a feeble yellow cast. It is a stilbene with a natural polyphenol configuration analogous to diethylstilbestrol and estradiol (32,86). Its molecular formula is $C_{14}H_{12}O_3$ and it is commonly referred to as 3,5,4'thihydroxystilbene. Other unconventional terms use to describe this compound are: 3,4',5-stilbenetriol, (E)-5- (7-hydroxystyryl) resorcinol, (E)-5- (4-hydroxystyryl) benzene-1,3-diol. RSV occurs innately as both *cis*- and *trans*- isomers. The *trans*- isomer is often used in classic laboratory studies because its more physical available have has higher biological activity than the *cis*-isomer. On the other hand, the *cis*-isomer is unstably and not commercial accessible (32,144).

Functionally, RSV has the propensity to safeguard DNA as well as the induction of DNA repair (17,89). Studies have proven that, at high dose, RSV does not only suppress cancer advancement but also inhibits the synthesis of RNA, DNA and

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proteins. Furthermore, RVS triggers structural chromosome aberrations, chromatin breaks, exchanging of weak aneuploidy, higher S-phase arrest as well as blocking of cell proliferation. It also reduces wound healing, endothelial and vascular cell growth factor as well as angiogenesis in healthy tissue cells thereby championing cell death (23,32,89). Further studies have proven that RSV at doses of 160 μM or higher reduces cell survival in human glioma U87 cells, while doses of 80 μM had no lethal outcomes (70,89). Nevertheless, lower doses of RSV recuperate cell survival as in cardio-protection as well as neuroprotection, while high doses accelerates cell death as in cancer therapeutics (15,32).

Furthermore, studies have revealed that RSV wields growth inhibitory consequences on glioma U251 cells in a time-dependent as well as dose-dependent manner, and autophagy and apoptosis play important roles in RVS-triggered death of U251 cells (72,151). Additionally, it has been proven that RSV inhibit numerous essential enzymes intricated in carcinogenesis. Some of these enzymes includes ribonucleotide reductase, NADH: ubiquinone oxidoreductase, and human cytochrome P450 (21,57). Most recently, it has been proven that RSV can act as a cancer chemo-preventive agent. Furthermore, RSV has been shown to inhibit tumor initiation, promotion, and progression in a variety of cell culture systems and animal models (54,163). Several studies proven that RSV activates the secretion of p53, Fas-Fas ligand system, mitogen-activated protein kinase (MAPK) as well as antiestrogenic activity. Additionally, RSV inhibits p4501A1, ribonucleotide reductase, ornithine decarboxylase, protein kinase C (PKC), DNA polymerase, cyclo-oxygenase as well as cell cycle progression and induces cellular apoptosis (21,138,151)

RESVERATROL AND APOPTOSIS

Numerous studies have established that autophagy plays a fundamental part in the regulation of self-renewal, differentiation, tumorigenic potential, and radio-sensitization of GSCs (151,170). RSV has proven to induce apoptotic cell death in several cancer cell lines. The well-studied cell lines comprise of hormone sensitive LNCaP prostate cells, hormone-insensitive DU 145 prostate cells, mouse myeloid leukemia cells, human B cell chronic leukemia cells, as well as several other human cancer cell lines such as MCF7, SW480, HCE7, Seg-1, and HL60 (47,57,59,87). Studies has shown that modifications in the secretion of Bcl-2 family of proteins, loss of mitochondrial function, expression of cytochrome C, and activation of caspases may be intricated in RVS-induced death, as exhibited in Bcl-2 over-secretion in U937 cells pancreatic carcinoma cells, mouse myeloid leukemia cells, normal and leukemic hematopoietic cells, and human Caco-2 colonic adenocarcinoma cells (57,97). Also, RSV can stimulate p53-independent apoptosis in human HCT116 colon carcinoma cells (51,80).

Studies have shown that RSV steered growth inhibition, induction of apoptosis and G0/G1-phase cell cycle arrest in an experiment involving U251 glioma cells (57,72). It has been postulated that, in apoptosis, there is condensation and fragmentation of DNA. Nevertheless, conservation of organelles also persists throughout the process. Research has proven that RSV-stimulated apoptosis necessitates the triggering of caspase-3 and augmented expressions of cytochrome C. Conversely, p53 is essential for RVS-stimulated apoptosis in mouse JB6 epidermal or Hep G2 cells (51,57,69). Furthermore, RVS can trigger apoptosis via c-Jun-NH2-kinase in mouse JB6 epidermal cells, LNCaP, Hep G2, or DU 145 a mutant p53 prostate cancer cell line (69,75). Also, extracellular signal-regulated kinase and p38 mitogen-activated protein kinase have been implicated in the intervention of RSV-stimulation of p53 and apoptosis via the phosphorylation of p53 at serine 15 (69,75,123). I advocate further studies involving the stimulation of p53 in the induction of apoptosis in various glioma cell lines.

On the other hand, studies have also proven that ectopic secretion of dominant-negative mutant Cdk2 led to moderate mollification of apoptosis in human endothelial cells following growth factor dispossession (57,71). Studies have further shown that inhibitors of PKC signaling pathway subdues the proliferation and triggering of apoptosis in glioma cells (55,57,138). It has also been postulated that RSV may stimulate apoptosis in both wild-type and mutant p53 cell lines. Jiang et al demonstrated that RVS triggers apoptosis in both human glioma U251 and U87 cells. In these cell lines, RSV exercises its apoptotic properties via down-regulation of Bcl-2, Bcl-xL, and XIAP antiapoptotic proteins along with substantial up-regulation of Bax proapoptotic protein (57,134).

CELL CYCLE REGULATION AND DEREGULATION

Studies have shown that deregulation of the cell cycle has been meticulously linked to the advancement of several malignancies and anticancer medications like RVS has demonstrated to have modulatory effect on cell cycle related proteins like cyclins, cyclin-dependent kinase (CDK) as well as CDK inhibitors (57,160). These CDK inhibitors have proven to have down-regulatory effects on caspase-3 stimulation. Furthermore, hammering of these inhibitors has been associated with eccentric up-regulation of CDKs that is closely linked to apoptotic cell death (57,58). Advance studies have detailed that Olomoucine, a selective blocker of the cell cycle regulators, p34/cdc2 and CDK2, inhibits camptothecin-stimulated neuronal apoptosis in PC12 cells, sympathetic and cortical neurons, or tetrahydrobiopterin-stimulated apoptosis in PC12 cells after trophic factor depravation (4,57,96,138). RSV as well as its analogs has demonstrated to interfere in the signal transduction pathways, leading to the modulation of cell cycle modifiable proteins. It has also proven to responsible for stipulation of apoptosis in numerous malignant cell lines via diverse means, especially the via the p53-dependent pathway (44,140). It is now clear that the actions of Cmpd1 led to the forfeiture of cell sustainability, growth as well as survival of human glioma, breast, or pancreatic cancer cell. Cmpd1 also resulted in triggered cell cycle inhibition at the G2/M phase as well as apoptosis in human glioma cells cultures (140).

In brain tumors as well as several human malignancies, mutations in p53 championing its inactivation is now estab-

lished. However, the role of RVS in modulating it activation is still a matter of debate. Furthermore, RSV-activated protein kinase C as well as extracellular-signal-regulated protein kinases (ERK1/2) triggered COX-2 secretion and nuclear COX-2 buildup, with consequential p53 phosphorylation and apoptosis in cultured human glioma cells (44,76). Nevertheless, RSV blocked cell proliferation as well as initiation of G0/G1 growth arrest via the blockade of cyclin D1 expression leading to an apoptotic cell death process (44,57). Moreover, RVS triggered in-vivo neuroblastoma in mice leading to tumor cell death via the activation of mitochondrial intrinsic apoptotic pathway (136,141). Current studies indicate that RSV stimulates a deferment in cell cycle succession in human glioblastoma U87 cells either alone or in amalgamation with X-rays specifically due to deferment in the S phase (70,130). Studies have also demonstrated the participation of gap junction intercellular communication in cell cycle modulation. The gap junctions and gap junction intercellular communication are essential for typical cell cycling as well as cell growth control. Connexin 43 (Cx43), the most copious gap junction connexin in astrocytes and glioma cells, reduces as the grade of glioma/astrocytoma deteriorates, and an antithetical association between Cx43 secretion and cancer grade have now been found signifying that Cx has a significate role as a cancer suppressor (70,130). Interestingly, RSV stimulates a downregulation of phosphorylated Cx43 therefore upkeeps the open status of the gap junction channel and the safeguarding of the gap junction intercellular communication (70,130).

RESVERATROL AND AUTOPHAGY

Autophagy is a degradative course encompassing sequestration of cytoplasm and organelles into double-membrane vesicles that transfer the contents to lysosomes where recycling occurs (72). Furthermore, autophagy is a catabolic course comprising of the degradation of cytoplasmic proteins and organelles via lysosomal mechanisms. Studies has demonstrated that autophagy is often triggered in cancer cells during anticancer remedies like chemotherapeutic drugs or irradiation. Autophagy can both contribute to cell death as well as epitomize a machinery of defiance to these therapeutic modalities (30,151). Studies have proven that by stimulating autophagy, cancer cells recycle molecules for biosynthetic or metabolic reactions and consequently modifying themselves to adverse states after anticancer treatment. Also, assiduous triggering of autophagy can champion predetermined cell death (30,72,166). This kind of autophagy is permanent and is called type II programmed cell death or autophagic cell death unlike apoptosis which is called type I programmed cell death (72,166).

The machineries via which autophagy differentially affects cancer cell survival is still a matter of debate. I therefore propose further research in this direction. Current studies have shown that LC3 is the first mammalian protein that is unambiguously conscripted to autophagosome membranes (62,72). In programmed cell death (type II) or autophagy, there is usually an initial degradation of organelles followed by conservation of nucleus at the late stages (26,72). Therefore, autophagy act as a fundamental means via which cell survives. Furthermore, autophagy safeguards cells by preventing them from undergoing apoptosis (26,72). Li et al demonstrated that inhibition of autophagy with 3-MA considerably augmented the sub-G1 fraction and consequently stimulated U251 cells into cell death (72).

BIOAVAILABILITY OF RESVERATROL

Studies have shown that, in human models, oral ingestion of RSV is precipitously metabolized in the liver via phase-II detoxification enzymes leading to its principal urine excretion (44,147). Experimentally, the blood levels of RSV peaked at 2 mmol/l after an oral administration of ^{14}C-labelled RSV by human subjects (147). Furthermore, the plasma half-life was oscillating between 6.5 to 14.9 has observed in urinary excretion data. Nevertheless, the absorption of RSV appeared to be at least 70%. Therefore, RVS has a high absorption via the oral rout but a very low bioavailability in humans (44,147). As indicated early, RVS is abundant in many diets and wine. Studies have shown that 25mg dietary RSV is precipitously adsorbed and principally retained in the plasma as glucoronide and sulphate conjugates. Moreover, its metabolism is appreciably inhibited by other polyphenols due to competitive reactions with metabolizing phase-II enzymes, leading to an augmented concentration of the free form. Notwithstanding this, free aglycone is approximately unnoticeable in human plasma (44,147,157).

RESVERATROL AND THE BLOOD-BRAIN BARRIER

Studies have shown that the BBB is a multifaceted structure performing fundamental functions such as a selective barrier for maintaining the cerebral microenvironment as well as main constituents conscientious to the barrier characteristics at the tight junctions (18,53,159). It is proven that interference of this tight junctions by drugs or disease leads to devastating modification that results in compromising the integrity of the BBB, therefore decreasing brain functions (18,50,53). It is evidence that VCAM-1 intermediates the binding of pathogenic $CD4^+$ T cells to the BBB endothelium, while ICAM-1 captures T cells on the BBB as well as aided in T cell diapedesis across the BBB (148). Studies have proven that RSV crosses the blood brain barrier (BBB) but the specific intracranial levels have not been proven. After crossing the BBB RSV displays pleiotropic molecular consequences resulting in the modifications of several diverse signaling pathways like NF-κB, Rb-E2F, p53, phosphatidylinositol 3-kinase (PI3K)/Akt, and MAPK pathways that are imperative for GBM proliferation (Figure 1) (1,22).

Nevertheless, RSV's ability to cross the BBB and integrate into brain tissue means that it could be a potent chemo-preventive as well as therapeutic agent in brain tumors (154). This was first evidence in an in-vivo study conducted in gerbils. Kuhnle et al established oral RSV is well absorbed via the small intestines into t the blood circulation system (154). Bertelli et al with a follow-up experiment demonstrated that RSV is maximum at the blood circulation

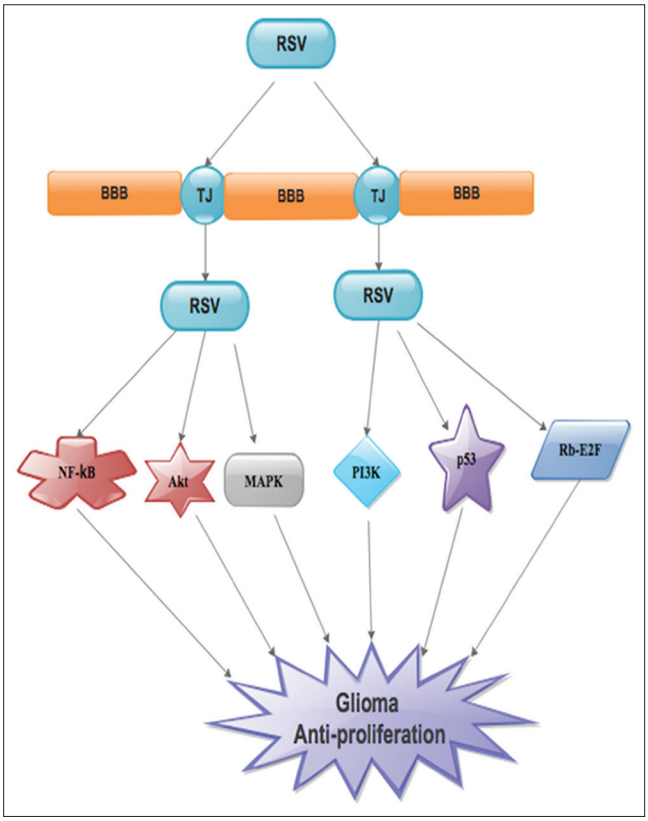

Figure 1. The mechanisms via which RSV is able to cross the blood brain barrier to carry out its anti-proliferative action

1 h after intravenous injection (8). In the blood circulation, RSV concentrations drop precipitously with a specious half-life of 4 h (154). Wang et al demonstrated that, in the blood stream, RSV was largely available in the glucuronide form, signifying that the compound was enraptured and reformed by the hepatic system (154). Their study further indicated that the concentrations of RSV in the brain are several-fold lower than those in the liver. They argue that this low levels of RSV in the brain tissue is questionable because of contamination during the analysis (154). It is further evidence that RSV can decrease high-fat diet-boosted LDL concentrations (18,84). It is also known that LDL is easily oxidized into oxLDL at the moieties of apolipoprotein B and lipids (18,84). Therefore, RSV is capable of reducing high-fat diet-triggered apoptotic injuries to cerebral vascular endothelial cells resulting in safeguarding the BBB destruction (18).

RESVERATROL AND MATRIX METALLOPROTEINASE

Matrix metalloproteinases (MMPs) are a group of zinc related neutral endopeptidases efficient in mortifying numerous constituents of the extracellular matrix (ECM) as well as basement membranes (40,103,134). It well known that mortification of ECM is fundamental for malignant cancer development, advancement, invasion, angiogenesis as well as metastasis (134). MMPs can be categorized into four distinct groups based on substrate predilections. These four categories are collagenases, gelatinases, stromelysins as well as membrane-linked MMPs. Studies have shown that, in human beings, gelatinase-A (MMP-2) and gelatinase-B (MMP-9) are the fundamental enzymes responsible the mortification type IV collagen, which is the principal constituent of the basement membrane (161,171). Sato and Seiki revealed that, human being, MMP-9 facilitator comprises cis-acting regulatory elements as well as transcription factors like AP-1 (-533 bp, -79 bp), NF-kB (-600 bp) and Sp1 (-588 bp), which contribute significantly to modification of the MMP-9 gene (115,116).

Studies have demonstrated that Higher concentrations of specific MMPs can be perceived in cancer tissue or serum of advanced cancer patients. Nevertheless, their functions as prognostic markers in cancer has been extensively scrutinized (134,143). Sato and Seiki further indicated that MMP-2 and MMP-9 are the precise MMPs implicated in cancer metastasis in human beings (115-117). It is now known that RSV inhibits the gelatinolytic actions of MMP-2 and MMP-9 in a concentration determined modus. Woo et al also confirmed that RSV inhibits MMP-9 gene transcription. It is evidence that RSV blocks phorbol myristate acetate (PMA)-mediated stimulation of c-Jun N-terminal kinase (JNK) as well as protein kinase C (PKC)-δ stimulation (161). Their revealed that NF-κB and AP-1 activity are appreciably decreased in an experiment to determine the molecular machinery via which RSV blocks PMA-mediated secretion of MMP-9 utilizing AP-1 and NF-kB. They further suggested that the aptitude of RSV to decrease MMP-9 secretion is attained through a decreased PKC-δ activity and reduced JNK stimulation. Therefore, RSV did not only influence AP-1 and NF-kB transcription factors but is also influenced signal molecules like JNK and PKC-δ (161).

Studies have shown that MMPs are over-secreted in human gliomas. Furthermore, glioma invasiveness is piquantly interconnected to the proteolytic exploits of MMPs (44,90,100). It is now clear that MMP-2 and MMP-9 secretion are associated with the development, advancement spread as well as the level of malignancy of gliomas in human beings (41,44,121). Nevertheless, the secretion of MMP-1, MMP-11 and MMP-19 has also been implicated in the WHO categorization of malignant gliomas in human beings (44,131,153). Moreover, augmented secretion MMPs have also been implicated in glioblastoma multiformes as compared to low-grade astrocytomas or normal brain. The modification of low-grade astrocytomas to glioblastoma multiformes has been depicted with an alteration of pro-MMP-11 resulting in secretion of an effective enzyme (44,131).

RESVERATROL ON GLUTAMATE UPTAKE AND GLUTAMINE SYNTHETASE

Studies have shown that brain tissue is specifically susceptible to oxidative injury. This could perhaps because of its extreme utilization of oxygen resulting in consequential production of excessive amounts of reactive oxygen species (ROS)1 during oxidative phosphorylation (16,33,111). Also, secretion of enzymes like monoamine oxidase and tyrosine hydroxylase in brain results in hydrogen peroxide (H_2O_2) production. This H_2O_2 is usually a natural by-product during the normal brain energy utilization process (33). Studies have

shown that brain tissue is rich in iron. This iron facilitates the generation of harmful oxygen-free radical species. Moreover, the brain is comparatively poorly furnished with defensive antioxidant enzymes or antioxidant complexes (16,33). Studies have evidence that ROS generation results in destruction to cerebral tissue in numerous nervous disorders. Most cardinal among them are ischemia-reperfusion injury and neurodegeneratives dieases. Furthermore, astrocytes have been implicated in oxidative-stress intermediated neuronal fatality (82,101,135). This implicative role of astrocytes is beneficial because they safeguard neurons from cell death triggered by H_2O_2 and nitric oxide (31). Additionally, astrocytes deliver glutathione derivatives to adjacent neurons (34,35).

Numerous factors in vitro have been implicated in the modulation of glial morphology and proliferation. These factors comprise of intracellular calcium, redox milieu, acidification as well as substrate protein milieu (3,33). It is evidence that the modulation of glutamate concentrations in the synaptic cleft by glutamate transporters sited predominantly in astroglia is fundamental in circumventing excitotoxic injury. Studies have proven that RSV is capable of inhibiting interleukin-6 formation in astrocyte cultures deficient in oxygen and glucose (33,152). Nevertheless, in vivo, RSV mitigated neuronal cell death as well as astrocyte to global ischemia in gerbils' models (154).Studies have established that RSV is capable regulating glutamate uptake in C6 glioma cells. It is further evidence that RSV could influence the redox milieu of glutamate transporters in C6 glioma cells as well as support their actions within minimum range of 0.1–100 μM (154). Besides, RSV could inhibit glutamate uptake autonomously resulting in its antioxidant actions (94). Protein kinases like PKC, PKD and phorbol ester-responsive kinases have also been implicated in the modulation of glutamate and RSV has proven to inhibitory influence these kinases (33,49).

RESVERATROL AND HMGB1 IN GLIOMA

High mobility group box 1 (HMGB1) is a non-histone, DNA-binding protein that primarily dwells in the nucleus and is associated with the alteration of transcription, DNA repair and chromatin steadiness (108,109,132). Studies have shown that the translocation of HMGB1 out of the nucleus is initiated by it acetylation resulting in its relocation. Advance studies have proven that HMGB1 after translocation in the cytoplasm binds to receptors like toll-like receptor 2 (TLR2), TLR4 or receptor for advanced glycation end products (RAGE), resulting the stimulation of numerous complexes of inflammatory responses (104,107,168). Studies have demonstrated RSV blocks HMGB1 translocation out of the nucleus, via the stimulation of sirtuin 1 (Sirt1), a NAD^+-dependent class III protein deacetylase (78,162,168). Nevertheless, deacetylation of HMGB1, which results in it detention in the nucleus, is averted when Sirt1 protein interacts with numerous lysine residues at NLS location of HMGB126. Also, RSV is capable of increasing Sirt1 generation in the nucleus resulting in the deacetylation HMGB1, which in turn results in its built-up in the nucleus (162). Furthermore, nicotinamide and SIRT1 siRNA knockdown experiments confirmed that RSV augments the SIRT1-mediated suppression of HMGB1 nucleocytoplasmic translocation in vivo and in vitro. RSV has proven to an effective SIRT1 stimulator with anti-inflammatory activities that can upregulate SIRT1 and decrease severe liver damage after sepsis (162). To the best of my knowledge, no research has been done on the pathogenic or the therapeutic roles of HMGB1 on RSV in gliomas. I therefore propose studies geared towards this direction.

THERAPEUTIC SIGNING PATHWAYS OF RESVERATROL IN GLIOMAS

Yu et al. proposed that RVS can block the triggering of signal transducer and trigger of transcription (STAT3) signaling of medulloblastoma cells. They further indicated that RVS may further stimulate medulloblastoma cells into growth arrest and apoptosis (167). It was also anticipated that amalgamation of low-dose calorie limitation and RVS can trigger autophagy by blocking the mTOR pathway and/or by stimulating the AMPK pathways to safeguard 26-month-old rat hearts from doxorubicin-triggered toxicity (37,151). In adapting a strategy of augmenting radio-sensitivity of GSCs, they are of the view point that the blockade of the antiapoptotic responsibilities of the Bcl-2 family members and blockade of the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathway controlling autophagy could be novel hence ought to be reconnoitered (60,151).

It is evidence that STAT3 binds to the miR-21 facilitator using ChIP analysis. It is also indicated that STAT3 inhibitor ominously decreased miR-21 secretion Therefore, STAT3 stimulation inhibited by RSV also participated in the decreasing the secretion of miR-21 (149). Several studies have indicated that STAT3 over-stimulation is connected to a wide range of cancers and more specifically gliomas. It is recognized as a principal modulator of biological routes championing cancer growth (11,149). Additionally, the STATs groups display an imperative function in typical cytokines signaling as well as advancement of which STAT3 is predominantly fundamental in critical cell functions such as maintenance of cell cycle, apoptosis, cell transformation, migration and invasion (13,150). Furthermore, STAT3 signaling facilitates cell cycle via upregulation of Cyclin D1 and cMyc resulting in cells survive during apoptosis as well as participates in carcinogenesis (28). Nevertheless, STAT3 is prerequisite for cells motility. Therefore, STAT3 blockade decreases cell migration which aids its influence on microtubule dynamics (91). Also, STAT3 is intricated in modification of matrix metalloproteinases (MMPs) which are fundamental enzymes for carcinomatous cells invasion as well as distortion of extracellular matrix (2,120). Thus, STAT3 is currently considered as a substantial hypothetical curative agent for a wide range of cancers and very specifically glioma. More to the point, it's imperative to understand mechanisms via which STAT3 modulates its targets as well as be controlled (11,150).

Several studies have demonstrated that RSV subdues STAT3 signaling via the blockade of SRC or JAK2

stimulation, resulting in the stimulation of growth restriction and apoptotic consequences in cultured human breast, prostate, and pancreatic tumor cells and the v-SRC–transformed mice fibroblasts and natural killer (NKs) cells with malignant properties (19,137). The STAT group of cytoplasmic transcription factors is typically stimulated ephemerally through TYR phosphorylation via JAKs, SRC as well as growth factor receptor TYR kinases. Studies have shown that phosphorylation usually results in STAT or STAT dimerization, nuclear translocation as well as gene transcription that promote cell growth, differentiation, proliferation, inflammation and many physiologic responses to growth factors and cytokines (14,19). Further studies have evidenced that functional STAT3 is predominant in numerous human cancers such as pancreatic, breast cancers and more importantly glioblastoma. STAT3 typically epitomizes a precarious intermediary of malignant transformation and cancer progression (19,85). Additionally, functional STAT3 facilitates carcinogenesis partially through dysregulation of gene secretion resulting in uninhibited growth and partially via survival of cells, enriched cancer angiogenesis, metastasis as well as the oppression of cancer immune reconnaissance (85,165).

Currently, there is enough substantiation that the blockade of STAT3 signaling characterizes one of the machineries via which anticancer cell interact with RSV (19,68,137). Nevertheless, the blockade of STAT3 action may happen circuitously via the blockade of SRC and JAKs stimulation (68,137). Numerous RVS referents have been investigated in terms of better-quality in human anticancer cells that harbor atypically functional STAT3, resulting in the isolation of one hypothetically extra functional agent. This (E)-4- (3,5-dimethoxystyryl) phenyl acetate (Cmpd1) analog more effectively blocked constitutive STAT3 tyrosine705 phosphorylation while augmenting STAT3 serine727 phosphorylation in cancer cells. These occurrences above was directly related to the stimulation of mitogen-activated protein/extracellular signal-regulated kinase (MEK)–Erk1/2MAPK or pErk1/2MAPK (19). It is further evidence that the blockade of (MEK)–Erk1/2MAPK stimulation inhibited Cmpd1-triggered pSerine727 STAT3 which in turn annulled the inhibitory consequences of Cmpd1 on pTyrosine705 STAT3, signifying that Erk1/2MAPK stimulation is prerequisite for Cmpd1-dependent alteration of both STAT3 serine727 and tyrosine705 phosphorylation actions (19). Nevertheless, Cmpd1 additionally triggered pMammalian target of rapamycin (mTOR), pSRC, pAkt, pHsp27 as well as p-p38 inhibited pSTAT1 and thus had no substantial consequences on pEpidermal growth factor receptor (pEGFR) as well as pJAK2 (19). It is further proven that RSV analog Cmpd1 facilitates prompt blockade of atypically functional STAT3 in cancer cells. This action resulted growth inhibitory consequences in U251MG, MDA-MB-231 as well as Panc-1 cells (68,85).

ANTI-INFLAMMATION ACTIONS OF RESVERATROL IN GLIOMA

Inflammatory cytokines performance imperative functions in the development and advancement of several kinds of cancers (25,113). Throughout carcinogenesis, transformations in the microenvironment usually stimulate cytokine secretion that involves a positive feedback comprising of the triggering of leukocytes which in turn triggers more cytokine secretion. Several studies have indicated that RSV explicitly blocks both COX-1 and COX-2 in-vitro but the inhibitory roles COX-2 by RSV and gene secretion is still a matter of debate between researches (44,54). Thus, RSV-stimulated anti-inflammatory roles could be due to blockade of COX-1 and COX-2 (Figure 2). It is evidence that NF-κB triggers the over-secretion of the COX enzymes which in turn augmented angiogenesis (Figure 2) (127). Furthermore, alteration of NF-κB movement was linked to the blockade of COX-2 secretion. This was demonstrated in experiment involving in the neuroprotective exploits of RSV on β-amyloid-triggered toxicity in cultured rat astroglioma C6 cells (Figure 2) (44,65).

RSV can thus be a hypothetical chemo-preventive agent that restricts cancer advancement. Nevertheless, it's inhibitory consequence on COX function is one of the promising molecular machineries conscientious to its anticancer functions (65). It is clear that RSV blocks glioma cell growth via miRNAs secretions such as miR-21, miR-30a-5p as well as miR-19 (Figure 2) and thus reduces COX-2 release (29,149). Dao et al demonstrated that RSV both effectively rescinded LPS- and miR-146a mimic triggered COX-2 release in Raw264.7 (29). They indicated that the functions of miR-146a-5p in RSV inhibited LPS-triggered COX-2 in macrophages. Studies have shown that higher NF-κB-linked gene secretion in vigorously drifting glioma cells in-vitro as well

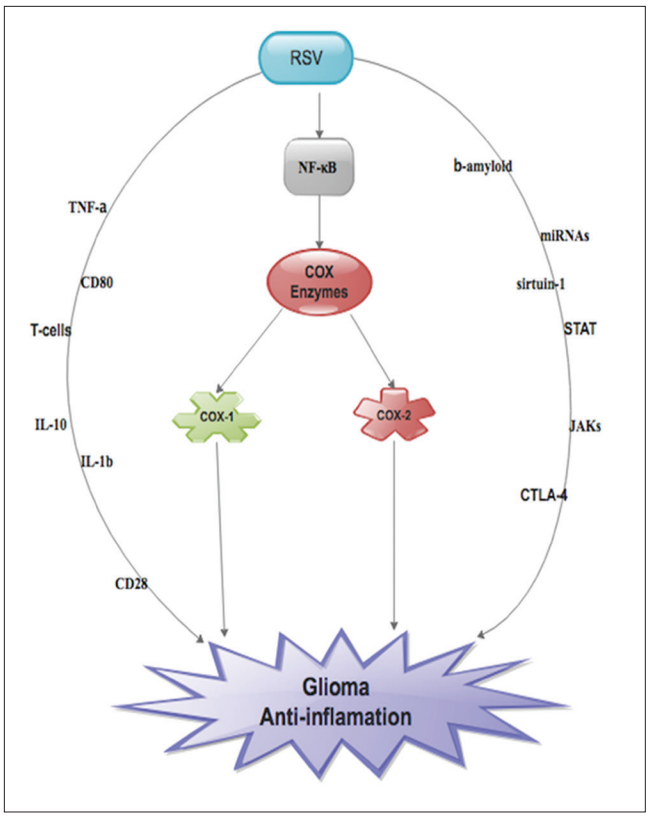

Figure 2. The mechanism via RSV is able to elicit it anti-inflammation effects in the glioma microenvironment

as infiltrating cells in-vivo. This indicates that the function of NF-κB in migration and invasion actively contributes to improvements in invasive glioma cell as well as survival (44). Studies have also demonstrated that RSV blocks both NF-κB and activator protein-1 stimulation triggered by diverse spurs that comprises of diverse intracellular signaling pathways in-vitro (81,98). The axiological triggering of NF-κB has been detected in malignant glioblastoma. This has proven to be meticulously linked to the resistance of tumor necrosis factor-α (TNF-α) immunotherapy (113).

It is clear that TNF-α, a pro-inflammatory cytokine partakes in carcinogenesis via signaling pathways that are interrelated with both pro-apoptotic and antiapoptotic reactions (113,146). Several studies have shown that TNF-α triggers apoptosis in some cancers and glioma cells are one of the exception in this phenomenon because these cells are resistant to TNF-α-triggered apoptosis (139,146). As indicated earlier, motility and invasion of glioma cells are stimulated via the triggering of NF-κB resulting in the axiological release of TNF-α (5,113). Studies have proven that both triggered and axiologically released NF-κB partakes in cancer advancement as well as metastasis (61,113). Therefore, blockade effects of RSV on NF-κB could also lead to the blockade of TNF-α resulting in inhibition of cancer advancement as well as metastasis (113). I therefore propose further studies in this direction.

On the other hand, studies have demonstrated that a wide range of immune cells like T cells and macrophages are prospective targets via which RSV may exhibit its anti-inflammatory potentials (78,148). Nevertheless, isolation of the precise target cells via which RSV exhibit its anti-inflammatory potentials may be challenging because many immune cells generate TNF-α, IL-1β, as well as IL-10 (Figure 2). In conclusion, the feasible machineries via which RSV elicit it anti-inflammatory consequence encompasses the triggering of sirtuin 1 and the triggering of apoptosis via T cells as well as modifying NF-κB and JAKs/STAT signaling pathways (Figure 2) (14,126,154). Furthermore, RSV also exhibits its anti-inflammatory properties by blocking lymphocyte proliferation resulting in decreased secretion of CD28/CTLA-4 and CD80 co-stimulatory molecules as well as by triggering both caspase-dependent and caspase-independent apoptosis in stimulated T-cells (Figure 2). These effects where demonstrated in tentative rat models of allergic-encephalomyelitis (44,128).

RESVERATROL AND GLIOMA ANGIOGENESIS

Angiogenesis is the sprouting of new vessels out of old vessels during tumor advancements and metastasis. Studies have evidence that RSV could subdue angiogenesis as well as cancer development in RT-2 glioma rat modules (55,138). Numerous studies have shown that angiogenesis stimulates cancer growth as well as proliferations in the number of routes via which cancer cell metastases. Clinically, it is now clear that the number blood vessels in malignant tumor interrelates with the outcomes of patients with cancer (138,155). Also, studies have evidence that angiogenesis partakes in the development, advancement as well as metastasis in malignant gliomas (99,105,138). Pathologically, the sprouting of new blood vessels is triggered by cytokines as well as growth factors. The release of these cytokines and growth factors have proven to be interconnected with neovascularization (43,106,138). It has been proven that these angiogenic factors above partakes in tumor vascular cell proliferation, invasion as well as differentiation of the neovasculature (43). Studies has demonstrated that these angiogenic factors binds to precise receptors on the endothelial cells resulting in the triggering of gene secretion as well as proliferation of endothelial cells. They further excite endothelial cells to generate proteolytic enzymes that causes distraction of the matrix as well as migration and invasion of adjacent structures (112,138).

Nevertheless, the sprouting of new blood vessel has also been associated with extent VEGF expression in gliomas (43,112). Naturally, the consequences of VEGF are intermediated by tyrosine kinase receptors such as KDR (kinase domain region) as well as fms-like tyrosine kinase 1 (flt-1), which preferentially bind to VEGF (Figure 3) (138,145). Moreover, the KDR/flk-1 receptor also intermediate in the mitogenic spur in retort to VEGF. However, the proliferative consequences of VEGF after binding to KDR/flk-1 on endothelial cells results in the triggering of the MAPK signaling pathway (Figure 3) (83,138). Studies have shown that MAPK comprises of four subtypes such as ERK, p38 MAPK, ERK5/big MAPK 1 (BMK1), and JNK (93,138). Therefore, triggering this MAPK pathway in turn result in augmentation VEGF which in turn results in tumor development, invasion, as well as generation of angiogenic factors

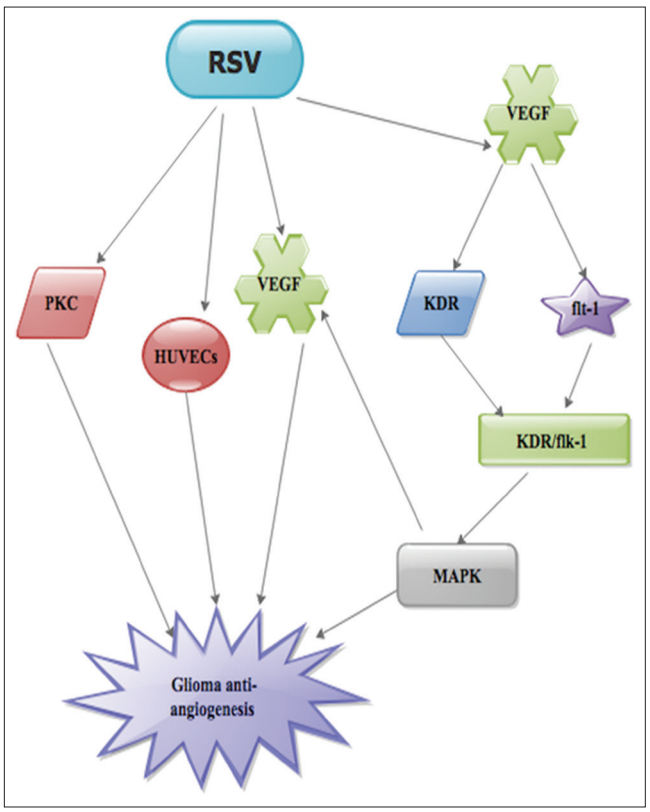

Figure 3. The mechanisms through which RSV is able to elicit it anti-angiogenic effects in glioma

(Figure 3). Nevertheless, VEGF and its receptor alone can also display autocrine or paracrine consequences on cancer cells (138,145).

RVS has also proven to safeguard blood vessels from arteriosclerosis, restrain platelet aggregation as well as decrease the production of eicosanoid (129,138). The inhibitory role of RSV on angiogenesis, capillary-like tube sprouting has been confirmed in human umbilical vein endothelial cells (HUVECs) as in mouse lung cancer modules (66,138). Several studies have evidenced that RSV has an anti-angiogenesis influence because it is a PKC blocker (66,133). It is further evidence that PKC is very essential in the modulation of glioma cells growth since glioma cells secrets higher concentrations of PKC. Furthermore, augmented exploits of PKC are interconnected with glioma cells proliferation (24). It is further shown angiogenesis contributed significantly to glioma malignancy. This was evidence in experiment in which the number of sprouting vessels in glioma was interconnected to the level of malignancy (12,138).

Tseng et al established that RSV inhibited VEGF secretion in glioma cells as well as blocked the proliferation of the HUVECs in a concentration and time-determined mode (Figure 3) (138). They suggested that the blockade of the proliferation of the endothelial cells directly or indirectly characterize the inhibition of the new blood vessel sprouting in cancer. They also therefore concluded that RSV has an anti-angiogenesis consequence on glioma. To substantiate that, RSV inhibited glioma-triggered angiogenesis in-vivo, they demonstrated that MVDs were markedly decreased in gliomas treated with 40 mg/kg of RSV per day as compared to controls and gliomas treated with 10 mg/kg of RSV per day (138).

GLIOMA METASTASIS AND RESVERATROL

Proficient cancer invasion necessitates mortification of the extracellular matrix (ECM) at the invasion in and around the cancer macroenvironment (44,113). The invasiveness of glioma also relies on proteolysis of the ECM, a multifaceted consequence developing around the adjacent tissue during cancer cell invasion. Studies have shown that urokinase plasminogen activator (uPA) and its precise receptor (uPAR) contributes immensely in the invasive progressions in glioblastoma (113). Several studies have shown that secretion of genes of the uPA/uPAR system in humans modulates extracellular mediators likes growth factors and cytokines. Intracellularly, the uPA/uPAR system also signals via β-catenin and transcription factor like NF-κB (Figure 4) (113). RVS may inhibit metastasis via this pathway. It is now known that during cancer invasion, ECM adjacent the malignant glioma experiences transformation resulting in release of a secreted protein and acidic rich cysteine (SPARC), a matricellular glycoprotein that intermediates cell-matrix communications (44,92). Studies have demonstrated that SPARC is aberrantly secreted in numerous solid tumors as well as malignant gliomas. It is evident that SPARC protein concentrations are associate with glioma invasion in vitro and in vivo (102,118,124).

Therefore, SPARC is a promising target in brain cancer therapy since it is release in lower concentrations in the normal adult brain, but highly concentrations in gliomas. It is confirmed that augmented SPARC secretion the microenvironment is associated to poor survival in glioma patient signifying that the decrease in SPARC is indeed of therapeutic advantage (Figure 4) (44,102,124). It is well established that RSV can trigger a dose-determined decrease in SPARC gene as well as secreted protein release in human glioblastoma cells in vitro (45,102). Nevertheless, SPARC has also proven to alter glioma cells survival under the innocuous circumstances that border the tumor leading to a decrease in apoptotic quotient (44,124). It is further indicated that a decreased in SPARC secretion in turn results in a reduced glioma cell survival as well as invasion (46,125). Additionally, SPARC modifies glioma development and advancement by augmenting glioma matrix as well as inhibiting glioma vascularity via decreasing VEGF secretion (Figure 4) (45,125). Thus, SPARC is a promising target via RSV intention therapeutic reminder can be focused on because this pathway inhibits glioma invasion. We therefore propose further research focus on this target (44,45).

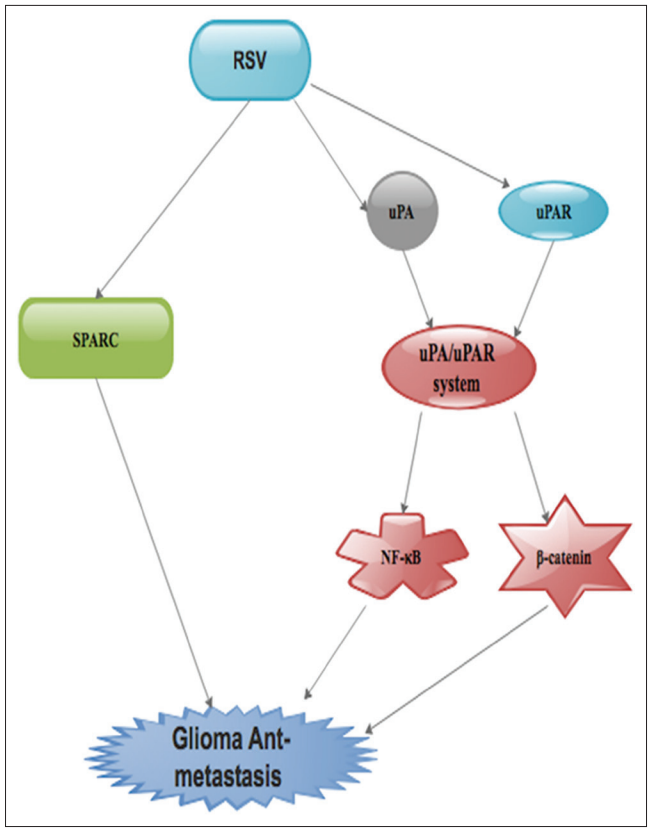

Figure 4. The mechanisms via which RSV is able to subdue or prevent metastasis in glioma

THERAPEUTIC EFFICIENCY OF RESVERATROL AND OTHER AGENTS

Besides the individual potent therapeutic roles of RSV descripted above, several studies have assessed the efficient function of RSV with other therapeutic modalities in gliomas. Below are so of the combination and their effects in glioma.

RADIOSENSITIZATION EFFECT ON RESEVERATROL IN GLIOMA

Studies have shown that glioma stem cells (GSCs) are resilient to radiotherapy (151). This resistant feature makes prognosis of GSCs very poor even with radiation therapy and other treatment modalities combined (77,151). It now clear that radioresistance is the foremost impediment in glioma radiotherapy. It is postulated that utilization of radiosensitizer are fundamental means of overpowering radioresistance as well as augmenting prognosis. Wang et al established that RSV has substantial augmented radiosensitization capabilities in both in vitro and in vivo nude mouse model of GSCs (151). They indicated that this combination has synergistic antitumor properties like blockade of proliferation, triggering of autophagy, facilitation of apoptosis as well as preclusion of DNA repair. They therefore concluded that a combination of RSV and radiation augmented radiosensitization of GSCs relatively via autophagy (151). Furthermore, DNA destruction a principal target of radiation in the cellular system. It is proven that the DNA repair pathway a crucial trigger of resistance to radiation. Nevertheless, Alterations in the quantities of DNA repair proteins has been implicated in resistance to anti-cancer treatment regimens (6,10).

EFFECTS OF RESVERATROL ON THE RADIOSENSITIVITY OF IODODEOXYURIDINE

Iododeoxyuridine (IUdR) is halogenated pyrimidines analogues. It is one the most effective non-hypoxic radiation sensitizers (64,119). It is a thymidine analogue so it able to insert itself into DNA during the cell cycling. Therefore, an augmented quotient of proliferation causes an up-regulation radio sensitization. The quantity of radio sensitization directly reflected the amount of thymidine substitution during DNA replication (158). Studies has shown that the absorption of IUdR declines in spheroid culture (64). It is proven that hypoxia, a conjoint phenomenon in gliomas leads to a decrease in the sensitivity of glioma cells to radiation as well as chemotherapy. This phenomenon is triggered via the hypoxia inducible factor-1 alpha (HIF1-α) pathway (122). Studies have shown that HIF1-α often translocate from cytoplasm to nucleus under hypoxia environments resulting in its binding to HIF1-β to forms the HIF1 complex (64,122). It stimulates about 60 diverse functional genes resulting in the augmentation of oxygen delivery. Therefore, blockade of HIF1-α results in sensitization of resistance in glioma cells to the cytotoxic consequence of Radiation as well as chemotherapy. Studies have proven that RSV blocks HIF1-α protein release during hypoxia circumstance (64,122). A conformational study indicated that RVS's blockade effect results in significantly build-up hypoxia-induced HIF1-α protein in cancer cells but did not alter HIF1-α mRNA concentrations (122,169). Furthermore, RSV extremely blocked HIF-1 a protein secretion by altering both protein translation as well as HIF1-α protein mortification (39). It is therefore confirmed that RSV to augmented the IUdR absorption in hypoxia cells (64).

THE EFFECT OF RESVERATROL ON NANOG IN GLIOMA STEM CELLS

Nanog is one of the key transcriptional factors in embryonic stem cells (ESCs) derivation (114). Studies have demonstrated that Nanog secretion is coordinated at the transcriptional phase. It is evidence that coordination positively via LIF-STAT3 as well as bone morphogenetic protein-Brachyury pathways, and negatively via transcription factor 3 and p53 (95,114). Functionally, Nanog is fundamental for initiating and conserving the pluripotent milieu of stem cells (95). Sato et al established that RVS restrains self-renewal aptitude of GSCs by decreasing sphere development, stem cell marker secretion, carcinogenicity as well as facilitates their differentiation (114). Nevertheless, evanescent inhibition of Nanog by siRNA terminated GSCs self-renewal aptitude, carcinogenic potentials as well as triggered their differentiation. Sato et al demonstrated further that RSV therapy augmented phosphorylation and stimulation of p53. They observed that Nanog mRNA was also decrease after RSV therapy which implies that RS-stimulated p53 directly inhibited Nanog mRNA secretion. They concluded that RS-stimulated p53 might directly inhibit Nanog secretion via an augment proteasome-determined mortification in GSCs (114).

THE EFFECT OF RESVERATROL AND TEMOZOLOMIDE IN GLIOMA

Temozolomide (TMZ) is alkylating derivative currently use for the treatment of glioma. In GBM patients with extreme intracellular levels O (6)-methylguanine DNA-methyltransferase (MGMT) TMZ does not seem to beneficial (48,52). Studies have demonstrated that Notch-1 activation-dependent p53 restoration actively participated in RSV-triggered apoptosis in GBM A172 and T98G cells. Furthermore, the stimulation of p53 intensely inhibited the secretion of MGMT, signifying that it could be combined with TMZ to easy the resistance hitch through alteration in NF-κB-MGMT signaling (52,73,74). It is known that RSV can efficiently block the subcellular, nuclear translocated NF-κB (subunit p65) which is the fundamental effector of NF-κB-MGMT signaling pathway. Therefore, RSV is capable of blocking NF-κB-MGMT pathway thereby averting TMZ-resistance (52). Further studies are needed in this direction. A current study revealed that a combination of RSV and TMZ significantly blocks the proliferation of GBM cells as well as triggered more apoptosis than TMZ alone (52).

THE EFFECT OF RESVERATROL ON POKEMON IN HUMAN GLIOMA CELLS

POK erythroid myeloid ontogenic factor (Pokemon) has many other names like LRF, OCZF, and FBI-1. Pokemon is trigger protein that binds precisely to short transcripts constituent of HIV-1 facilitator gene (88,164). It is now clear that Pokemon can also trigger Tat action on HIV, augment NF-κB-facilitated transcription as well as block human ADH5/FDH gene release (88,110,164). Research

has demonstrated that Over-secretion of the Pokemon gene dwindles the release ARF gene, which also trigger the mortification of p53 as well as oncogenic alteration. Nevertheless, knockdown of the Pokemon gene also led to blockade of oncogene-intermediated cellular alteration as well as cell imbecility trigger and apoptosis (79,164). Yang et al established that an amalgamation of RSV and TMZ appreciably augmented the suppressive consequence of RSV on the release of Pokemon (164). Furthermore, over-secretion of Pokemon lessened RSV-triggered cell apoptosis, imbecility as well as antiproliferative consequences. Also, over-secretion of Pokemon decreased the synergistic effects of RSV on TMZ. Yang et al further demonstrated that Pokemon facilitator shelters numerous putative Sp1 components. They revealed that Sp1 is associated with the modulation of Pokemon gene (164). They therefore established that Pokemon is associated with RSV-stimulated biological consequence. They further indicated that RSV reduces Pokemon secretion via the blockade of Sp1 DNA binding action as well as inducing HDAC1 and p300 conscription (164).

RESVERATROL AND SULFORAPHANE IN GLIOMA CELL LINES

Studies have proven that sulforaphane has anticancer potentials because it able restrain angiogenesis as well as augment endothelial response to cancer invasion (9,56). It is now known that sulforaphane has prophylactic as well as curative properties in diverse cancers both in vitro and in vivo (38). Studies have shown that sulforaphane blocks cancer growth by decreasing cancer promotors and metabolites resulting in the stimulation of detoxification (56,156). Further studies have proven that pro-apoptotic subgrouping like Bcl-2, Bax and Bak, are associated with sulforaphane-triggered apoptosis (20). In human GBM T98G and U87MG cells, Sulforaphane triggers apoptosis via the stimulation of calcium-dependent calpain as well as caspase-3 activity (63). Individually, RSV and sulforaphane has proven to regulate Akt signaling pathway in diverse cancer cells. Nevertheless, combination of RSV and sulforaphane at low concentrations (25 mmol/l) significantly regulated cell proliferation, migration as well as death in human U251 glioma cells. Moreover, apart from the effects above, RSV and sulforaphane combination triggered lactate dehydrogenase secretion, reduced pro-survival Akt phosphorylation as well as augmented caspase-3 stimulation (56,44).

CONCLUSIONS

RSV, a stilbenoid with a natural polyphenol configuration analogous to diethylstilbestrol and estradiol is a promising therapeutic agent in glioma. Individually, RSV has proven to very potent in glioma cells. It is able to down-regulate glioma angiogenesis as well as metastasis. In combination with other agents, RVS augment its potency in glioma. RVS is able to cross the BBB via gap junctions making it very efficient central nervous system medication. RVS after oral administration peaks in the blood stream after 1h meaning it acts very fast. I therefore propose further studies into the neuropharmacological roles of glioma most especially in glioma. Furthermore, to the best of our knowledge, no research has been done on the pathogenic or the therapeutic roles of HMGB1 on RSV in gliomas. I herefore propose studies geared towards this direction.

AUTHORS' CONTRIBUTIONS

S.A.R guarantor of integrity of the entire concepts, design and writing of the manuscript.

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