International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

Resveratrol: A Boon for Cancertherapy

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Date Of Submission: 20-03-2021 Date Of Acceptance: 05-04-2021

ABSTRACT: Cancer is a malignant growth or tumor resulting from an uncontrolled division of cells where normal cells acquires mutations in their genetic makeup, which cause the cells to consistently grow, colonize, and metastasize to other organs. Nowadays, natural source of anticancer treatment plays a leading role as an alternative to modern therapy. Resveratrol (RSV), trans-3,5,4-trihydroxystilbene, a natural stilbene, a phytoalexin and a non-flavonoid polyphenol was first isolated in 1940 as a constituent of the roots of white hellebore (Veratrum grandiflorum O. Loes), since found in various plants including grapes, berries and peanuts. It possesses anti-oxidant, anti-inflammatory, cardioprotective, and anticancer properties. Anticancer properties of resveratrol are recommended by its ability to subdue proliferation of a wide variety of cancer cells, including cancers of the breast, prostate, liver, colorectam, gastric, esophagus, head and neck, skin, lungs, pancreas, blood and brain tumors.Resveratrol influence all three stages of carcinogenesis like initiation, promotion, and progression by harmonizing signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis. The conclusion of this article is to introduce a potential candidate for the effective treatment of cancer in future by suppressing the proliferation of wide variety of human cancer cells.
KEYWORDS: Resveratrol, Anticancer

I. INTRODUCTION

Cancer is one of the most commonly identified diseases, and its related morbidity and mortality account for a very significant health problem worldwide. Although great endeavour have been made to discoveracure,cancerremainsavery eminentcauseofmortalityinhumans,andeffective treatment remains a forbiddingchallenge. Several customized care medicines, such as targeted therapies have emerged, providing ameliorated clinical outcomes for cancer patients. Cancer represents one of the most important health issues globally, with around 14 million new cases and 8.2 million cancer related deaths every year [1]. Cancer is a malignant growth or tumor resulting from an uncontrolled division of cells where normal cells acquires mutations in their genetic makeup, which cause the cells to consistently grow, colonize, and metastasize to other organs. Nowadays, natural source of anticancer treatment plays a leading role as an alternative to modern therapy. Naturally existing bioactive food components such as dietary polyphenols are acquiring great interest due totheirpotentialhealthbenefitasagentsthat prevent or inhibit the initiation and the progression of the disease.[2]

Resveratrol, trans-3,5,4-trihydroxystilbene, a natural stilbene, a phytoalexin and a non-flavonoid polyphenol was first isolated in 1940 as a constituent of the roots of white hellebore (Veratrum grandiflorum O. Loes), since found in various plants including grapes, berries and peanuts. It possesses anti-oxidant, anti-inflammatory, cardioprotective, and anticancer properties. Anticancer properties of resveratrol are recommended by its ability to subdue proliferation of a wide variety of cancer cells, including cancers of the breast, prostate, stomach, colon, pancreas, thyroid and ovarian carcinoma [3]. Substantial study over the past decade has shown both the chemopreventive and chemotherapeutic potential of resveratrol. It subdue the proliferation of a wide variety of human tumor cells in vitro. The antitumor activities of resveratrol are arbitrated through several cell signaling pathways and include cell cycle arrest, repression of tumor cell proliferation, installation of apoptosis and differentiation, depletion of inflammation and angiogenesis, and hindrance of adhesion, invasion, and metastasis [4].Thus resveratrol influence all three stages of carcinogenesis like initiation, promotion, and progression.In spite of the fact thatanti-carcinogenic action of resveratrol has been linked with a splendid amount of data primarily from human cell culture systems, emerging results of cancer prevention and therapy studies in

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

laboratory animal models provide persuasive proof that resveratrol can inhibit carcinogenesis in several organ sites. This evidence is encapsulated in this review, which also culminate basic mechanisms that provide a rationale for testing resveratrol clinically in human populations [5].

II. CHEMISTRY OF RESVERATROL

Resveratrol is a stilbenoid polyphenol, having two phenol rings linked to each other by an ethylene bridge. The chemical structure of resveratrol (trans-3,5,40-trihydroxystilbene) is recognized in two isomeric forms, cis- and trans-resveratrol. Trans form is dominant in terms of its frequenceanddifferentbiologicalactivitiesareattributed,namelyinpersuadingcellularresponsessuch as cell cycle arrest, differentiation, apoptosis, and to amplify cancer cells anti-proliferation [6].

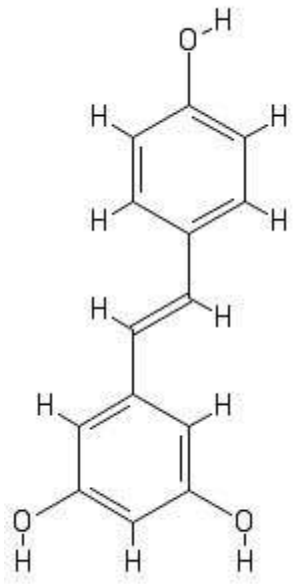

Figure 1: Chemical structure of resveratrol

Formal chemical name (IUPAC name) of resveratrol is (E)-5-(4-Hydroxystyryl)Benzene-1,3-Diol; 3,5,4'-Trihydroxystilbene (figure 1). Numerous aspects on chemistry of resveratrol are already being studied. It exists as two geometric isomeric forms: cis or Z and trans or E. When trans form is exposed to UV irradiation, they can undertake cis form. Trans-resveratrol powder was established to be stable under accelerated stability conditions of 72-75% humidity and 40^0C in the presence of air. The low resveratrol bioavailability was impeded its therapeutic application. So moderation of resveratrol structure has received marked attention from investigators and many resveratrol derivatives have been manufactured. Such as derivatives containing methoxyl, hydroxyl and halogen groups and all of them exhibit praising therapeutic potential [7]. Resveratrolisexistindietaryproductsasglycosylatedforms,investigated as piceid. Though plants and pathogens and even digestive tract of human consist of enzymes that are able to trigger polyphenols oxidation (as well as inactivation), the glycosylation stops enzymatic oxidation of resveratrol, hence conserving its biological effects and increasing its overall stability and bioavailability. Moreover, seeing that intestinal cells can absorb only resveratrol aglycone form, absorption process need glycosidases. Consequently, the presence of aglycone as well as glycosylated resveratrol content in nutriments and drinks may regulate its absorption rate [8]. Cis and trans forms of resveratrol are depicted in figure 2.

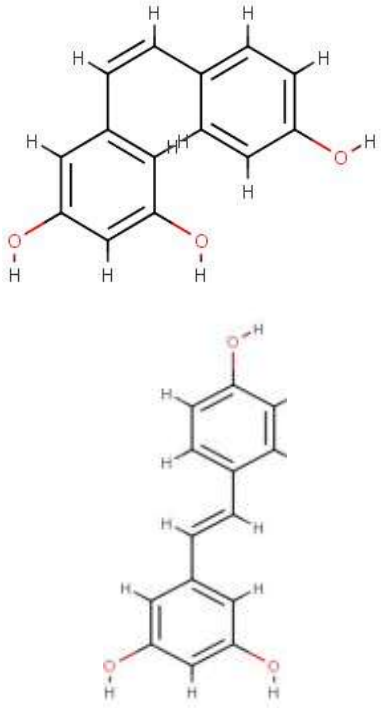

Figure 2: Chemical structure of cis- and trans-forms of resveratrol

CHEMICAL PROPERTIES	VALUES
Molecular Weight	228.24 g/mol
Hydrogen Bond Donor Count	3
Hydrogen Bond	3

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Acceptor Count	
Rotatable Bond Count	2
Exact Mass	228.078644 g/mol
Monoisotopic Mass	228.078644 g/mol
Topological Polar Surface Area	60.7 Å ²
Heavy Atom Count	17
Complexity	246
Defined Bond Stereocenter Count	1
Covalently-Bonded Unit Count	1

Table 1: Chemical properties of resveratrol

PHYSICAL PROPERTIES	CHARACTERISTICS
Physical description	Solid
Color/Form	Off white powder from methanol
Melting point	253-255^{0}C
Solubility	In water, 3 mg/100 mL
Vapour pressure	1.24X10-9 mm Hg at 25 °C (est)
Log P	log Kow = 3.10
Dissociation constants	pKa1 = 8.99 (phenol); pKa2 = 9.63 (phenol); pKa3 = 10.64 (phenol) (est)

Table 2: Physical properties of resveratrol

III. GENERAL MECHANISM OF ACTION OF RESVERATROL

Some molecular mechanism of resveratrol action consist of inhibition of prohypertrophic signaling molecules, development of myocardial Ca^{2+}handling, phosphorylation of Akt-1, GSK-3β and stress signaling (MKP-1) pathways and the depletion of oxidative stress and inflammation (iNOS, COX-2 activity, and ROS formation) [9]. Resveratrol notably reduced inflammation factors and malondialdehyde levels which is a marker of oxidative stress. These results showed that resveratrol treatment can improve cardiovascular function by decreasing myocardial ischemia-reperfusion injury, vasodilation and atherosclerosis. Reversibly, at physiological concentrations resveratrol persuades vasodilation and decreases hypertension and risk of cardiovascular diseases [10].

Antioxidantactivity of resveratroldependsuponthedisposition offunctionalgroupsonnuclearstructure. Hence substitution, configuration andtotalhydroxylgroups numberconsiderablyinfluence severalmechanismsofantioxidantactivity, examples include metalionchelation and radical scavengingpotentials. Antioxidantproperties of resveratrolhavebeenfavourably hiredtoprotectcellsagainst hydrogen peroxide-induced oxidative stress, in which the pre-treatment with resveratrol encouraged cell survivalandsheldingagainstUV irradiation-inducedcelldeath [11,12].

The immunomodulatory role of resveratrol was suggested 18 years ago with an inquiry that revealed, in which manner it inhibits the spread of spleen cells induced by interleukin-2 (IL-2), alloantigens or concanavalin A (ConA), and more effectively prevents the production of interferon-gamma (IFNγ) and IL-2 by lymphocytes and the production of IL-12 by macrophages or tumor necrosis factor alpha (TNF-α)[13]. By interrelating with number of molecular targets, resveratrol controls adaptive and innate immunity.It has been announced that resveratrol regulate immune action in a dose dependent manner, at low doses resveratrol invigorate the immune system, while on the contrary at high doses it induces immunosuppression [14].

The anticancer properties of resveratrol have been established by many in vitro and in vivo studies, whichever show that resveratrol is allowed to inhibit all carcinogenesis stages like initiation, promotion and progression. Many studies also provided proof that resveratrol not only acts a chemopreventive agent but also exhibit chemotherapeutic properties associated to its antioxidant, anti-inflammatory, pro-apoptosis and anti-proliferative activities [15]. Resveratrol is assumed to target intracellular signaling pathway components like regulators of apoptosis and cell survival, tumor angiogenic, and pro-inflammatory mediators and metastatic switches by regulating a distinct set of upstream kinases, transcription factors and their regulators [16]. Resveratrol have indicatedanti-proliferative and apoptotic effects on human cervical carcinoma by stimulating cell shrinkage in HeLa cells and apoptosis between the activation of caspase-3 and -9, downregulation of the expression of the anti-apoptotic proteins Bcl-2 and Bcl-extra-large in HeLa cells, upregulation of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

the expression of the pro-apoptotic B-cell lymphoma (Bcl)-2-associated X protein andenlarged expression of the p53, aproteinthatiscrucialforcellsurvivalandcellcyclepro gression. Resveratrol exert its anticancer action in pancreatic cancer cells by subduing the expression of NAF-1throughstimulation ofcellular reactiveoxygenspeciesaccumulation and Nrf2 signaling that lead to activation of apoptosis and prevent proliferation of pancreatic cancer cells [17]. Resveratrolalsoreducesthephosphorylation, acetylationandnuclear translocation of NF-κB and impede IGF-1R/Akt/Wnt pathways,iNOS expression in colon cancer cells and activates p53 to hampered cell and tumor development. Resveratrol has also shown assurance as part of combination therapy, especially in breast cancer. Around the world, many animal-based and in vitro studies have showed preventive anticancer activity in colon, cervical breast, lungs and prostate [18].

Resveratrol has several neuroprotective roles in various neurodegenerative declension, such as Huntington's Parkinson's and Alzheimer'sdiseases,alcohol-induced neurodegenerativedisorders andamyotrophiclateralsclerosis[19]. Resveratrolreducescholinergicneurotransmission,ox idative stress, and brain-derived neurotrophic factor expression, promotes anti-amyloidogenic cleavage of APP,β-amyloid peptides clearance and decreases neuronal apoptosis. A meta-analysis revealed thatresveratrolnotablydecreasedPOMS (ProfileofMoodStates) includingfatigue and vigorbuthad noremarkableeffecton cognitive and memoryperformance [20].

Resveratrol conveyed antibacterial activity against Gram-positive bacteria and time-kill assays revealed that its outcome were due to its bacteriostatic action. Nevertheless, the mechanism fundamental to its antibacterial activity is not clearly recognized. Alongside these activities, it also reveals androgen-lowering and antiproliferative effects on theca-interstitial cells of ovary. Besides it employs a cytostatic but not cytotoxic action in granulosa cells, while hindering vascular endothelial growth factor (VEGF) expression and aromatization [21]. These effects may be of clinical significance in conditions related withandrogen excess,theca-interstitial cell hyperplasia and abnormal angiogenesis like polycystic ovary syndrome. Additionally, resveratrol may increase ovarian follicular reserve and lengthen ovarian life span, platter as a prospective anti-aging agent.Resveratrol-glycoside was more effectual than resveratrol against hepatitis B virus. Piceatannol,containing onemorehydroxylgroup,was investigatedashavingstrongerimmunomodulatory, anti-inflammatory, anti-leukemic, anti-leishmanial, and protein-tyrosine kinase inhibitoryeffects. Supplementation of resveratrol has benefits in type 2 diabetes patients, counting lowering ofglycated haemoglobin (HbA_{1c}),blood glucose, insulin levels, insulin resistance and the advance of HDL levels and fasting blood glucose [22].The general mechanism of action of resveratrol against different human diseases are depicted in figure (1).

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Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

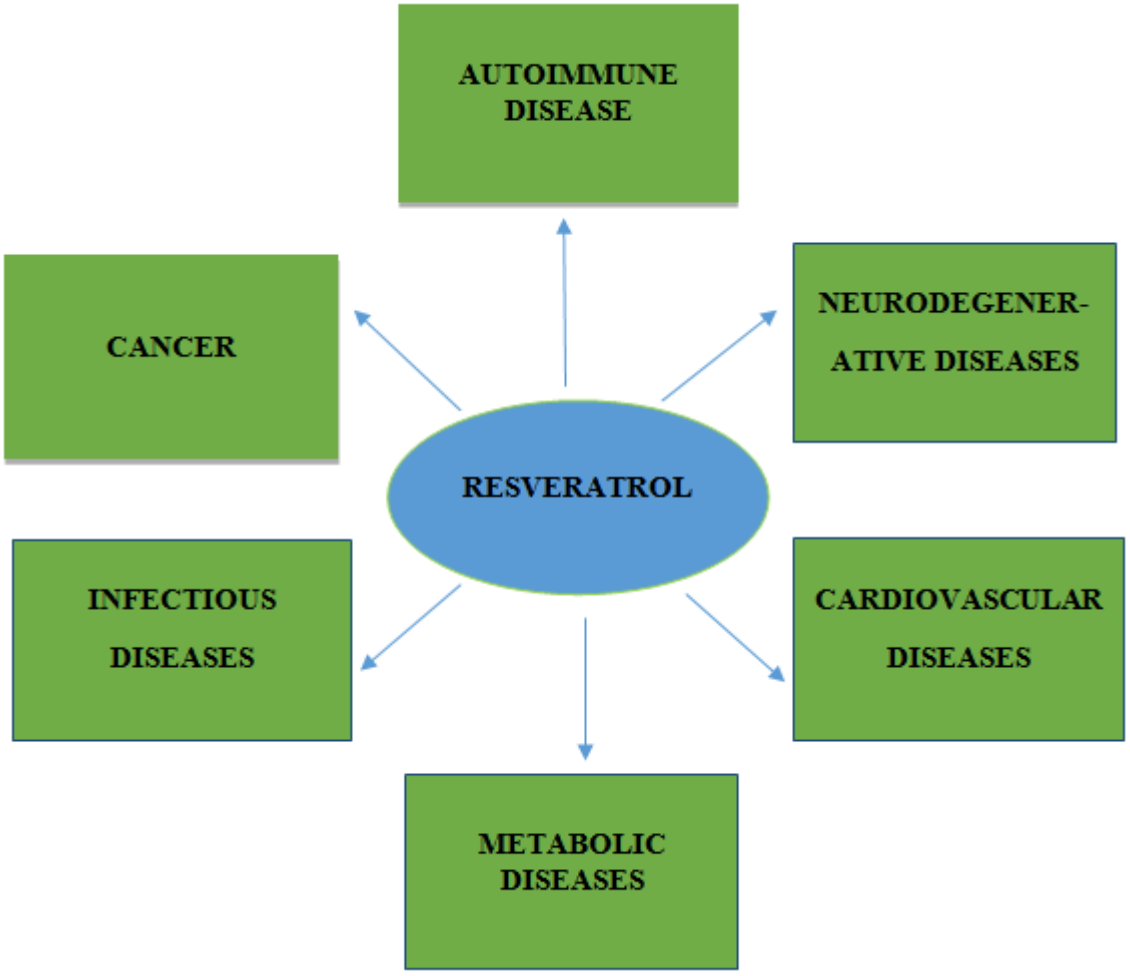

Figure (1): General mechanism of action of resveratrol against different human diseases.

IV. PHARMACOLOGICAL ACTIONS OF RESVERATROL ON CANCER

i. Head and neck cancer

Head and neck cancer is the sixth topmost commoncancer and is the eighth main cause of death in the world. An in vitro study on head and neck cancer cells of human disclosed that RSV exhibit downregulation of various STAT-3-related gene expressions and impeded invasion, proliferationand cell cycle arrest, counting apoptosis, between induction of SOCS-1 mRNA and protein [23]. Another investigation revealed that combination of RSV and curcumin reserved in vitro and in vivo cancer growth by inducing PARP cleavage and increasing BAX/BCL-2 ratio and by hindering ERK1 and ERK2 phosphorylation. Besides, RSV treatment was shown to impede cell viability, regulate Bax/BCL2 apoptotic signaling through activation of AMPK activity and induce apoptosis of C666-1 cells by cleavage of caspase-3. An in vitro study on nasopharyngeal cancer in human revealed that RSV treatment, downregulated the expressions of hypoxia-inducible factor-1alpha (HIF-1 alpha) protein and BCL-2, upregulated caspase-3 protein and lessen the phosphorylation ofp-4EBP1,Akt1, p70S6K and cell cycle regulatory proteins to impede cancer progression [24]. In a study on nasopharyngeal carcinoma cells Hep3B and HT1376, RSV was investigated to impede cell survival and had anti-apoptotic mechanisms by suppressing NP63 expression; these proposed that NP63 and not P53 was a molecular target of RSV. RSV reduced cell growth and enhanced chemo- and radio- sensitivity counting cancer invasion of head and neck squamous cell carcinoma (HNSCC) cells which embellished the anticancer property of RSV is intervened via regenerating gene (REG) III expression pathway [25].

Pterostilbene, a dimethylated resveratrol to esophageal squamous cancer (EC109) cells in

International Journal of Pharmaceutical Research and Applications
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humans and found its anticancer effects like decrease in adhesion, cell viability, migration and caspase-3 action and enhance ERS (endoplasmic reticulum stress) related molecules like GRP78, p-eI2F-alpha,ATF6, p-PERK and CHOP and gathered that the anticancer activity is due to the stimulation of ERS signaling pathway. In an oral cancer (SCC9) cells, RSV treatment impeded expression of MMP-9 protein, additionally to inhibition of the JNK1/2 and ERK1/2 signaling pathway. RSV investigated to be cytotoxic by increasing cell cycle arrest and decreasing cell migration ability and revealed synergistic action merged with irradiation in oral squamous cell carcinoma (PE/CA-PJ15) cells and also, an in vitro study revealed that RSV inhibited migration and invasion as well as adhesion of OSCC cells [26]. In a research experimented in a C57BL/6 mice in which tongue tumorigenesis is persuaded by 4-nitroquinoline-1-oxide (4NQO) found that mice fed with grape seed extract/RSV had reduced tumor incidence collated to that of control through regulating AMPK activation thereby persuading autophagy and apoptosis. RSV is also revealed to impede cell growth and enhance cell differentiation in anaplastic thyroid carcinoma (ATC) cells by switching on Notch1 signaling. It was found that RSV subduing anchorage or invasiveness independent growth of head and neck cancer cells controlled by several EMT markers in vitro and also decreased tumor growth in vivo in mice head and neck cancer model [27]. RSV was found to inhibit growth of cell and induces DNA damage as well as apoptosis in HNSCC cells independent of Smad4 expression in both in vitroand in vivo studies. A study of medullary thyroid (MTC) cancer revealed that when RSV is treated to MTC cells, it suppressed cell growth through caspase-3 dependent apoptosis and reduced chromogranin and ASCL1 whereas persuaded Notch2 expression. A study of thyroid cancer revealed that RSV treatment enhance p53 dependent apoptosis and p53 expression through Ras-MAPK signaling pathway [28].

ii. Colorectal cancer

Nutrition, lifestyle, and food habits greatly influence the development of colorectal cancer. A study revealed that RSV impeded proliferation of colorectal cancer cells and decreased drug resistance byinhibiting epithelial-mesenchymal transition (EMT)-associated molecules and downregulating the NF-κB pathway, such as the transcription factor Slug and mesenchymal marker vimentin, which in turn upregulate the epithelial marker E-cadherin [29]. RSV enhances the phosphorylation and caused the proteasomal humiliation of T-cell factor 4, resulting in the TCF-mediated and beta-catenin-mediated transcriptional activity; these events enhanced apoptosis in human colorectal cancer cells. It was found that RSV revealed chemotherapeutic effect against colon cancer cells by cell cycle arrest via downregulation of the cyclinD1/CDK4 complex. Another study found that Sirt1 signaling pathway was one of the main mechanisms by which RSV employs its actions on colorectal cancer cells. Western blot and qRT-PCR analysis of LNA-anti0miR-200c transfected cells showed increased expression level of ZEB-1 and vimentin along with decreased expression level of E-cadherin which result in increased migration of HCT-116 cells but treatment of RSV altered EMT to MET phenotype by upregulating mir-200c in colorectal cancer cells [30]. Sonic hedgehog (Shh) protein increased the migration and proliferation rate of HCT-116 cells and increased expression level of Gli-1, Ptch and Smo protein, but following treatment of RSV the migration rate and cell viability decreased through suppression of Gli-1, Ptch and Smo protein level. It was also showed that RSV effectively inhibited cell proliferation of colon cancer cells like HCA-17, SW480, HT29 by inhibiting expression of cyclooxygenase-2 and prostaglandin receptor and persuading apoptosis [31].

The study concerning RSV dose-response relationship on a mice model of colorectal cancer revealed that low RSV dose oppressed the cancer development increased efficiently than 200 times higher dose by upregulating the expression of the p21 protein and activating AMPK. The colorectal cancer stem cells (CCSC) prompted from HCT116 cells when treated with RSV resulted in reduced CCSC proliferation in a dose and time dependent manner, thereby apoptosis and cell cycle arrest at G0/G1 phase including the upregulation of MICA/B expression enhance cell immunogenicity [32]. It was found that RSV impeded cell growth progression of HCT-116 by switching on p53, persuading apoptosis and DNA damage through type-II topoisomerase poisoning. Clinical studies of colorectal cancer revealed that RSV decreased cancer cell growth by increasing apoptosis in cancer tissues and managing the expression of WNT pathway target genes. Another study confirmed that RSV inhibited the invasion and migration of LoVo cells in a dose dependent manner by suppressing the expression of Vimentin

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

and increasing the expression of E-cadherin along with the inhibition of TGF-beta1/smads signaling pathway. In an in-vivo study, 150 - 300 ppm RSV was given to mice revealed 60% inhibition of tumor production and the remaining 40% of mice developed tumors which had lost Kras expression in which a therapeutic assay where mice had developed tumor revealed97% decrease in tumor size and complete disappearance of tumors in 33% of remaining mice[33]. Additionally, RSV inhibited the Kras expression which averted the formation and growth of colorectal tumors. A study on colon cancer in HCT116 cells showed that RSV impeded cell proliferation in vitro including in a xenograft tumor via upregulating the expression of PTEN, whereas decrease AKT phosphorylation, and the expression of protein mRNA and protein of beta-catenin are reduced by RSV in a dose dependent manner proposing the collaborationof WNT/beta-catenin pathway. A systematic study of actions of RSV on colorectal cancer cells like Caco-2 and HCT116 cells demonstrated an outstanding anti-cancer property of RSV via expression of leptin and c-Myc, downregulation of glycolytic enzymes and content of vascular endothelial growth factor in which the apoptotic markers were upregulated in the colorectal cancer cells which were calorie impoverished proposing that calorie restriction pathway may be the basis of the cell death [34]. It was found that RSV increased ROS (intracellular reactive oxygen species) resulting increase in autophagy that persuaded caspase dependent apoptosis in HT-29 and COLO 201 cells, proposing that autophagy also linked the apoptosis in human colon cancer cells. When tannic acid and RSV are treated to Caco-2 cells, Bak protein percentage ratio, FADD protein % ratio and apoptotic index values increased in a dose and time dependent manner increases apoptosis in mitochondrial and death receptor pathways. A study of effect of RSV on HT-29 cells showed that RSV induced apoptosisthrough mitochondria apoptosis pathway stimulated by production of ROS. Another in vitro study found that RSV result in apoptosis in human colon cancer cells (HT-29 and WiDr) in a dose-contingent manner comprising downregulation of telomerase activity (TLMA) in colon cancer cells. A study revealed that RSV activated caspase-2 upstream of mitochondria which is not related upon anti-oxidant property of NF-kappaB inhibition but persuaded conformational changes in Bax/Bak with following release ofapoptosis-inducing factorcytochrome-C, and endonuclease-G [35].

iii. Liver cancer

The major principle of hepatocellular cancer is infection with hepatitis C and hepatitis B virus. Lifestyle and diet were also considered as feasible risk factors of liver cancer [36]. A study reported that RSV impeded the growth of HepG2 cells by lowering the levels of cyclin D1, by inhibiting the levels of AKT pathway and p38 MAP kinases. Analysis of cell cycle in liver cancer murine models showed that treatment with RSV at 10 and 15 mg/kg body weight notably inhibited liver cancer by 36.3% and 49.3%, by reducing expression of p34cdc2 and cyclinB1 proteins. An alike study on a murine model of liver cancer showed that RSV, moreover to 5-FU treatment, persuade an S-phase arrest of H22 cell growth and thereby enhanced the antitumor effects of chemotherapy [37]. It was found that RSV notably reduced the proliferation of HepG2 cells and showed its antitumor effect by repressing the expression of the VEGF (vascular endothelial growth factor) gene. In an in vitro study of HepG2 hepatocellular carcinoma cells, a RSV analog known as phoyumbene B was set up to be more effectual than RSV in impeding cell proliferation by inducing apoptosis and G2/M cell cycle arrest by upregulating Bax and downregulating Bcl-2, additionally inhibition of invasion ability of the cells was also reported [113].

In a study the hepatocellular cancer (HCC) cells were found to have higher expression of MLCK (Myosin light chain kinase) where RSV treatment downregulated MLCK expression which stimulated apoptosis and subdued tumorigenesis suggesting MLCK might be associated with occurrence of HCC. An investigation using male wistar rats revealed that administration of RSV at early or late stage of the liver cancer remarkably decreased carcinogenesis via inducing apoptotic pathway. It was investigated that the effect of RSV and its analog on HCC discovered the anti-invasive property of RSV which reduced protein expression of MMP-2 and MMP-9 thereby enhanced the expression of TIMP-2 and TIMP-1 and also investigated that treatment of RSV can impede hepatocarcinogenesis persuaded by DENA (diethylnitrosamine) in Sprague-Dawley rats by apoptotic pathway mediated via upregulation of Bax expression and downregulation of BCL-2, similar study showed that RSV caused chemoprevention of hepatocarginogenesis by reducing expression levels of HSP70 (heat shock protein), NF-kappaB and COX-2. In HepG2 cells line, RSV impeded growth of human and rat

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Volume 6, Issue 2 Mar-Apr 2021, pp: 223-237 www.ijprajournal.com ISSN: 2249-7781

hepatoblastoma cells by limiting the cell cycle progression. Another study of hepatoma showed the anti-oxidative as well as anti-invasive activity of RSV but no indication of inhibition of cell growth of hepatoma AH109A cells ex vivo and in vitro environment [39]. In an investigation RSV is reported to inhibit cell growth and decrease ROS production via apoptosis and cell cycle arrest but it also increase eNOS, iNOS and thus enhances NOS activity. Study on HCC has investigated that RSV reduced hepatocyte growth factor prompted invasion of HepG2 cell invasion by an unrevealed mechanism. RSV subdued proliferation of HCC cells in dose-dependent manner by impeding c-Met signaling pathway in vitro additionally to remarkable inhibition of tumor growth in vivo in a xenograft model [40].

iv. Esophageal cancer

Therapy of esophageal cancer cells- EC109 with Pterostilbene (a RSV analog), decreased tumor cell migration, adhesion, and intracellular glutathione and enhanced thecaspase-3 activityapoptotic index, and ROS levels [41]. In an F344 rat model of esophageal tumorigenesis persuaded by N-nitroso methyl benzylamine, intraperitoneal and oral RSV treatment at 1–2 mg/kg and 2 mg/kg, decreased the number of tumors by inhibiting prostaglandin E2 and COXs. A study showed that RSV inhibited the growth of EC-9706 in a dose- and time-dependent manner via apoptosis by upregulating the expression of Baxgene and downregulating the expression of Bcl-2 gene. Another study showed that RSV subdued esophageal adenocarcinoma cell proliferation by p27kip1 upregulation, which is controlled by S-phase kinase-associated protein 2 and 26s proteasome downregulation.Another study showed the chemopreventive property of RSV in rats that are uncovered to chemical carcinogens [42].

v. Gastric cancer

Gastric cancer (GC) is the second most common source of cancer-associated impermanence since it is difficult to be investigate in the early phase. Because it is usually diagnosed in the advanced stages, prediction is poor despite the availability of therapies such as chemotherapy, surgery and radiotherapy [43]. RSV can prevent Helicobacter pyloriinfection by impeding its growth. It also reduces oxidative stress by inhibiting H. pyloriinduced ROS (Reactive Oxidant Species) production, which is a source of cancer.RSV reversed the doxorubicin resistant property of SGC7901/DOX cells back to doxorubicin sensitive cells which ensued to increased apoptosis in vitro decreased migration/invasionand prevented tumor growth in vivo, additionally RSV impeded AKT pathway to reverse the EMT (epithelial-mesenchymal transition). It was showed that RSV prevented gastric cancer cell growth by inhibiting cell cycle in MGC803 cells by subduing PI3K/AKT/PTEN signaling pathway. The in vitroexperiments performed were revealed that RSV decreased metastasis and invasion in gastric cancer cells by inducing EMT and Hedgehog signaling pathway [44]. When gastric cells were exposed to RSV in combination with DMS (dimethyl sphingosine) the cytotoxicity due to RSV pointed up that inhibition of sphingolipid metabolism increases RSV chemotherapy in human gastric cancer (HT-29 and SNU-1) cells. In a study of gastric cancer cells, RSV was found to imitate a role of dihydroceramide desaturase inhibitor which resulted in accretion of dihydroceramide in cells that concluded that RSV eventually induced autophagy through dihydroceramide in HGC-27 cells with no apoptosis. It was found that to subdue proliferation of human adenocarcinoma gastric cancer (AGS), trans-resveratrol impeded phosphorylation of ERK1/2 through MEK1/2 resulted in inhibition of c-Jun activation [45]. In an another investigation, it was found that apoptotic signaling pathway of different cells of gastric adenocarcinoma cells answered disparately to the treatment of RSV. For example in SNU-1 cells, RSV downregulated surviving resulted in activation of cytochrome C oxidase and caspase-3 activities was observed in KATO-III and AGS cells in return to RSV treatment. In addition,chemopreventive and inhibitory effect of RSV against gastric adenocarcinoma cells like SNU-1 may be due to the ability of RSV to produce NO from NOS showing its antioxidant action [46].

vi. Prostate cancer

Prostate cancer is the most common cancer in men and a major source of cancer deaths. A study showed that RSV impeded Akt, a crucial regulator of the miR-21 gene in PC-3M-MM2 cells, to decrease invasiveness and viabilityof a tumor in vitro as well as in vivo [47]. Another research found that RSV treatment inhibited the expression of Gli1 and decreased lipopolysaccharide-induced markers of EMT; these findings showed the inhibitory effect of RSV onLNCaP and PC-3 cell lines. It was concluded that RSV was a potential

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drug for prostate cancer because it impeded tumor growth, angiogenesis and metastasis by increasing the therapeutic efficacy of TRAIL via activation of the FOXO transcription factor. It was also found that both the apoptotic and antiproliferative effects of RSV on human prostate cancer cells were mediated by deactivation of NF-κB activity, which was linked with PI3K inhibition. RSV in combination with docetaxel when treated resulted to cell cycle arrest and apoptosis through cell cycle inhibitors (P21, WAF1, CIP1, P27KIP) and upregulation of P53 expression in prostate cancer cells. RSV was also found to reduce cell viability, disrupt mitochondrial membrane potential and modify cell morphology leading to abnormal expression of Bcl2 and Bax protein but had no action on caspase-3.RSV was also found to decrease DDX5 (known as P68) protein expression and result in cell death by impeding the mTORC1 pathway in prostate cancer cells [48]. It was revealed that RSV downregulated metastasis linked protein 1 (MTA1), a PTEN inhibitor which in turn causing inhibition of AKT pathway and thus managing prostate cancer progression. In LNCaP-FGC cells, when RSV treatment showed the inhibition of Interlukin-6/dihydrotestosterone (IL-6/DHT) induced androgen receptor (AR) transcriptional activity and to a certain extent mediated via suppression of STAT-3 reporter gene activity to inhibit prostate cancer [49].

RSV was found to have cytotoxic effect in a time as well as dose dependent manner in CWR22 (prostate carcinoma cell) in vitro but had no effect in the in vivo study. In addition, RSV when used in combination with radiation therapy resulted to increased anti-proliferative effect via downregulation of cyclinB, cyclinD and cdk2 and upregulation of p15, p21 and p53 [50]. RSV impeded proliferation of AR-positive hormone non-responsive (CWR22Rv1) cells along with decreased expression of NFkappaB p65 through signaling pathway in the presence of NQO2 protein. It was investigated that RSV could sensitize androgen independent prostate cancer cells to apoptosis via multiple mechanisms such asIAPs, Akt, Bax in DU145 cells and PC-3 cells. In a study of transgenic adenocarcinoma mouse prostate males, the dietary RSV fed to the mouse showed significant reduction in cell proliferation, increase inestrogen receptor-beta, androgen receptorand insulin-like growth factor (IGF)-1 and insulin-like growth factor-1 receptor suggesting the subdue of prostate cancer development. Another study proposed that RSV caused sensitization of DU145 (human prostate cancer) cells toaccumulation of ceramide and ionizing radiation which is a potential mediator of anti-cancer activity persuaded by RSV [51]. Another study on LNCaP cells showed that RSV inhibited the proliferation of the cells by stopping cell cycle at S phase and by inhibiting DNA synthesis [52].

vii. Pancreatic cancer

Pancreatic cancer is a lethal disease with a very poor expectation with low survival rate due to late stage detection of the cancer as most of the pancreatic cancer patients are symptomless until advanced stage of the disease [53]. A study showed that RSV subdued the development of ROS-induced pancreatic cancer by impeding hedgehog signaling proteins, which also subdued the levels of MMP2 and uPA proteins. RSV stimulated apoptosis in colo 317 and capan 2 cells by upregulated the protein expression of P21 and P53 and stimulating caspase 3 in pancreatic cancer cells. Another research showed that different pancreatic cancer cells (PANC-1,ASPC-1 and BXPC-3) had different responses to RSV-persuaded apoptotic cell deathby regulating the expression of Bcl-2, Bcl-xL, caspases, XIA and Bax. RSV treatment of human pancreatic cancer stem cells in Kras (G12D) mice impeded growth and evolution of pancreatic cancer,inhibition of migration, invasion, and EMT and caspase-dependent apoptosis.RSV subdued ROS persuaded pancreatic cancer progression by impeding the P38 MAPK and ERK signaling pathways. Furthermore, Pterostilbene (derivative of RSV) impeded in vitro cell proliferation bymitochondrial membrane depolarization,caspase activation and cell cycle arrest in pancreatic cancer [54]. A study found that RSV activated apoptosis by activation of AMPK, inhibited cell growth and increased sensitivity to gemcitabine by stopping YAP expression in pancreatic cancer cells. In another study, RSV in combination with apocynin impeded cell proliferation and stopped cell cycle progression at G1 phase with inactivation of Akt-GSk3beta and ERK1/2 and cyclin D1 downregulation in a human and rodent's pancreatic cancer cells. In an investigation, RSV inhibited cell growth through induction of apoptosis via downregulation of downstream target proteins of Hedgehog pathway such as (Gli1, Ptc1, CCND1, BCL-2) in pancreatic cancer PANC-1 cells. It was reported that when RSV is treated to pancreatic cells, it showed a notable reduction in cell proliferation via upregulation of MIC-1 (Macrophage inhibitory

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cytokine) gene showed its key role in RSV induced anti-cancer property [55].

viii. Brain tumors

Glioblastoma is the most macabre form of brain tumor in adults and has poor prognosis. It was showed that RSV induced apoptosis and inhibited cell growth in T98G and A172 glioblastoma cells by restoring wild-type P53 expression and stimulating Notch-1 in a time and dose dependent manner. Another study indicated RSV as a potential anti-tumor agent for glioblastoma multiforme (CD133+) cells in vitro and in vivo, by reducing the invasion ability, impeding the self-proliferating capacity of the brain tumor, and enhancing apoptosis by radiotherapy via suppression of the STAT3 pathway [56]. Glioblastoma-initiating cells play remarkable roles in the onset, recurrence as well as the growth of glioblastoma multiforme. Though glioblastoma is highly impervious to temozolomide, addition of RSV increased the sensitivity of these glioblastoma-initiating cells to temozolomide and persuaded apoptosis via double-stranded DNA breaks, counting an increase in differentiation of glioblastoma-initiating cells via STAT3 inactivation. A study on c-Myc expression in medulloblastoma cells found that c-Myc downregulation by RSV was an important source for the subdue of medulloblastoma activity via growth inhibition, apoptosis,and cell cycle arrest of medulloblastoma tissues and cell lines (UW 229-2 and UW 228-3). A recent study revealed that RSV was able to subdue cell proliferation,decrease cell motility, and increase cell death by regulating EMT activators and WNT signaling pathway in glioma stem cells (GSC). In a study on GSCs, RSV was found to reduce tumor-initiating ability and self-renewal of GSCs by impeding Nanog through activating P53/P21 pathway. In an in vitro and in vivo investigation, RSV was found to trigger senescence of glioma cells and resultin inhibition of cell growth by suppression of mono-ubiquitination of histone H2B at K120 [57]. Another study showed that RSV persuaded cell cycle arrest at S phase with rise in histone H2AX phosphorylation in human glioblastoma cells by impeding recombinant human TOPO II alpha to decatenate kDNA which function as TOPO II poison [58].

ix. Leukemia

Chronic myelogenous leukemia (CML) is a cancer of the white blood cells that occurs due to a reciprocal translocation between chromosomes 22 and 9 [59]. It was discovered that treatment with RSV (20–100 µM) persuaded phosphorylation and apoptosis of histone H2AX in CML K562 cells via regulation of P38 and JNK, which are linked with the MAPK pathway. When ALL (acute lymphoblastic leukemia) CCRF-CEM cells were treated with RSV, there was dose-dependent cell death along with upregulation of miR15a and miR16-1 expressions, as detected by real-time PCR (polymerase chain reaction). A study concluded that RSV impeded proliferation of T-cell ALL cells by persuading cell cycle arrest, autophagy and apoptosis viaactivation of the P38-MAPK signaling pathway and suppression of the Akt/mTOR/p70s6k/4E-BP1 pathway.In an another study, hydroxylated RSV analogs were investigated to induce cell death, go along by loss of mitochondrial potential, loss of superoxide dismutase activity, oxidative stress, and increased activity of caspase-9 and caspase-3. It was showed that RSV associated with histone deacetylase inhibitors induced cell death via generation of ROS,induction of DNA damage and stimulation of an extrinsic apoptotic pathway including upregulation of death receptor-5 [60].

x. Lung cancer

Lung cancer is the leading cause of cancer worldwide due to highest lethality rate. The risk factors for lung cancer include cigarette smoking, chemicals (such as polycyclic aromatic hydrocarbons), indoor air pollution, genetic factors (such as chromosome abnormalities, mutations, and structural hydrocarbons) and diseaseassociated factors (such as chronic obstructive pulmonary disease and chronic bronchitis) [61]. RSV has been reported to augment etoposidepersuaded cytotoxicity in human non-small cell lung cancer (NSCLC) cells by AKT-mediated expression of the X-ray Repair Cross-Complement Group-1 protein and downregulating ERK1/2. A similar study on NSCLC showed that RSV increased the anticancer effect of cisplatin by triggering mitochondrial dysfunction and cell apoptosis. RSV has been proven to impede transforming growth factor (TGF)-β1-persuaded EMT, which is known to enhance metastasis and invasion of carcinoma. A RSV analog (3,44′-trihydroxy-transstilbene) (10-80 µmol/L) inhibited cell viability ofA549 cells,NSCLCby persuading apoptosis, enhancing acidic compartments in cells, GFP-LC3 labelled autophagosomes and LC3-II accumulation in the cells, also result in the cell death accentuated, when

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autophagy was impeded by an autophagy inhibitors (like 3-methyladenine and wortmannin) [62].

xi. Breast Cancer

Breast cancer has a decreasing episode, it remembers the second leading source of cancer mortality in women in US. The treatment plan available for breast cancer are radiation, chemotherapy and surgical resection of tumors and hormonal treatment may also be given for post-menopausal women [63]. It was showed that RSV treatment persuaded breast cancer cell apoptosis by downregulating HER2 and FASN genes synergistically. RSV treatment reduced the cyclin-D1 andβ-catenin expression in vitro as well as in vivo. Another study showed that RSV notably decreased 60% of the tumor volume under in vivo conditions and increased doxorubicin-induced death of multidrug-resistant breast cancer cells in vitro. RSV or triacetyl-RSV induced apoptosis and cell cycle arrest and initiated P53 activation in MDAMB231 and MCF-7 breast cancer cells to sway the cancer cell proliferation. In an experimental rat model of mammary tumor, it was showed that 0.001% of RSV daily dietary supplement for 24 week decreased DNA damage, cell growth, enhanced apoptosis and levels ofTGF-β1,5-lipoxygenase and NF-κB [64].

xii. Skin cancer

RSV has been shown to initiate fatuity in human A431 squamous cell carcinoma cells by downregulation of Rictor protein expression and beleaguerment of its auto-lysosome form, resulting in subductionof skin cancer progression and adaptation of cytoskeleton [65]. A study on a mouse model of skin tumor reported that RSV regulated cell survival and apoptosis by downregulating BCL-2, upregulating Bax and P53, surviving expressions and regulating the PI3K/AKT pathway. An in vitro and in vivo study of skin cancer found that the synergistic effect of 5-FU and RSV caused cell cycle arrest of A431 and TE-1 cancer cells at S-phase as well as apoptosis with enhanced protein levels of cleaved caspase-3, cleaved PARP,p53, and Bax/Bcl-2 ratio [66]. It was investigated that oral administration of RSV notably suppressed ultraviolet-persuaded skin tumorigenesis in p53 (+/-)/SKH1 mice that were highly tumor sensitive via Akt-mediated downregulation of TGF-β2. RSV subdued the development of human skin squamous cell carcinoma A431 cells in nude mice via downregulation of protein expression of surviving and caspase-3-dependent apoptotic pathway. After numerous exposures of SKH-1 nude mice model to ultraviolet B, RSV was topically applied on the skin thereby immunohistochemical and immunoblot analysis revealed that the anti-proliferative property of RSV was linkedvia the regulation of cell cycle regulatory proteins, likely through inhibition of the MAPK pathway. RSV reduced the viability of immortalized human keratinocytes phosphorylation of ERK1/2 and dephosphorylation of Akt, which is linked to the generalization of p66Shc-Ser36 phosphorylation [67].

V. SIDE-EFFECTS OF RESVERATROL

There are many studies that indicated RSV as an anticancer therapeutic agent, but some studies have mentioned the negative impacts of RSV. RSV has been investigated to upregulate BCL-xL mRNA expression,downregulate PTEN-mRNA expression resulting in survival and proliferation of liver cancer HepG2 cells [68]. Another study stated that, in oral administration to the animal models, RSV stockpiled in various internal organs, especially in the liver, heart, stomach, and kidneys. Another drawback of RSV is its poor bioavailability, which precludes its notable healing functions. A trial study suggested that by controling circulatory function in the brain, RSV could improve cognition and mood and decrease the chances of dementia in post-menopausal women and in other populations at threat. RSV has been shown to have important effects in high-fat diet and obesity. Thus it increased the expression of fasting-induced adipogenic factor in the intestines of mice cater for a high-fat diet and increasedthe progression of obesity. It was found that RSV used in pregnancy caused an unknown variation in fetal pancreatic development. Thus this study notify about RSV administration to pregnant women [69]. In a study of eight healthy subjects who administered 2 g RSV twice per day for eight days, six enduredmild episodic diarrhea and one showed rash and headache. In an extended study of 24 months in rats and 18 months in mice, chronic exposure to RSV at a daily dose of <1g/kg showed no adverse effects but on the other hand, oral intake of >3 g/kg per day resulted in neuropathy, liver toxicity and renal toxicity in a group of rats [70].

VI. RESVERATROL NANOFORMULATION FOR CANCER THERAPY

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Nanoparticulate drug delivery systems are being widely used for the purpose of solving the problems faced by the drug delivery. It provide methods for targeting and releasing therapeutic compounds in much specific regions. They have the potential to eliminate or at least ameliorate many challenges associated with drug distribution. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size range from 10 nm to 1000 nm. Polymeric materials have been mostly used for the preparation of nanoparticles. The drug of interest is dissolved, entrapped, adsorbed, linked or encapsulated into the nanoparticle matrix [71].Nanoparticulate technology is currently being used in cancer in different ways, including for imaging, diagnosis, detection, and, most essentially in therapy.Targeting the development of a drug is one of the challenges in nanoformulation. The nanoparticles could be coupled with targeting moieties that will allow these nanoconjugates to reach directly to the targeted tumor sites and facilitate the release of their payload to decrease the unwanted toxicity thereby provide better efficacy [72].

By the preparation of resveratrol nanoformulation, the poor solubility and low oral bioavailability of resveratrol can be enhanced which inturn increases the in vitro overall stability of the final product. Facilitatetargeted drug delivery for the treatment of cancer by enhancing antioxidantandantitumoralactivitiesduetothehigher RSV concentration close to the therapeutic targets.The therapeutic potential of RSV-nanoparticles has been highlighted by many studies conducted on various tumors and cancer cell lines. At the core of nanoparticles, RSV conserve all of its health benefits, which are released closer to the tumor with the help of carrier. Additionally, the presence of targeting agentsinside the nanoparticle structureor on the nanoparticle wall absolutely increases antitumor activities of RSV-loaded nanoparticles.Thefirstnanoformulationofresveratrol wascarried out with chitosan nanoparticles. That study proposed that chitosan nanoformulations have a sustainedrelease in vitro.Thus nanotechnology approaches could help to control the pharmacokinetics issues of bioactive compounds by overcoming first-pass metabolism, enhancement in intracellular penetration and control delivery,increased bioavailability, trounce enterohepatic recirculation, protection against degradation, and reduced potential toxicity [73].

VII. CONCLUSION

Increasing number of studies on RSV provides perception into the molecular pathways and mechanisms of action of the RSV on cancer. In this review, I summarize the recent studies of RSV on the molecular pathways and mechanisms of actions across major cancers. Resveratrol showed all of the proapoptotic and antiproliferative properties to be an anticancer agent. However, these effects are mostly obtained in vitro or with small rodents at concentrations that are too high to be adaptable with its low availability in vivo. RSV impeded cell cycle regulation,angiogenesis, invasion, metastasis, and induced autophagy and apoptosis mediated via the regulated cell cycleassociated proteins. Therefore, more active experimental research on RSV can give us a deeper comprehension of its therapeutic effects on cancer.

VIII. FUTURE PERSPECTIVES

In this review, the recent novel nanotechnology approachesusedtodeliversustainedlevelsofresveratrol have been covered up and discussed. To date, no resveratrol-based nanosystems have been accepted for clinical use, and this would provide a hidden agenda for further development of research on inventive nanodevices able to integrate the chemopreventive prospect of resveratrol.

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