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Resveratrol: Properties, Sources, Production and Their Medical Applications A Review

Anaheed H. Hameed[1], Shemaa A. Soud *[2], Maysaa A. Ali[3]

1Biotechnology Division, Applied Science Department ,University of Technology, Anaheed.H.Hameed@uotechnology.edu.iq, Baghdad,Iraq
*2Biotechnology Division,Applied Science Department ,University of Technology, Shemaa.A.Soud@uotechnology.edu.iq, Baghdad,Iraq
3 Biotechnology Division,Applied Science Department ,University of Technology, maysaali229@gmail.com

*Corresponding author email: Shemaa.A.Soud@uotechnology.edu.iq

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Abstract

Background:

Resveratrol(RVS) was described at first by Takaoka in 1939 as a bioactive part in the Veratrum grandiflorum plant roots.

Materials and Methods:

RVS a (3,5,4′-trihydroxy-trans-stilbene) a natural phenols which were founded in over than seventy plants, especially in grapes' skins and seeds, red wines and other human nourishments. The double bond of RSV has been synthesized by a Wittig condensation. While, bioproduction is launched from phenylpropanoid acid having cinnamic and 4-coumaric acids which were derived from amino acids. RSV over and over deferred the rate of infections, for example, atherosclerosis, cardiovascular sickness, diabetes type 2, malignancy and neurodegenerative illnesses.

Results:

Most of the studies dealt with RSV as an antioxidant and treatment for oxidative damage that causes damage in vivo, such as diabetes, neurodegeneration, heart disease, cancer and aging. RSV is several known for its powerful scavenging efficiency.

Conclusion:

In this research, sources,production and features of RSV are included as well as the previous data that was reviewed that dealt with the use of RSV as a therapeutic substance for managing aging skin, cancer treatment, diabetes, blood pressure and brain support

Key words:

Resveratol, Polyphenol, Therapeutic substance, Phytoalexin, Antioxidant.

Citation:

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الريسفيراترول خصائصه، مصادره ،طرق انتاجه وتطبيقاته الطبية: مراجعة

أناهيد حمدي حميد[1]، شيماء عبد الستار سعود[2] *،ميساء عادل علي[3]

1 فرع التقنيات الاحيائية ،قسم العلوم التطبيقية، الجامعة التكنولوجية، 100231@uotechnology.edu.iq ، بغداد ، العراق
2 فرع التقنيات الاحيائية ،قسم العلوم التطبيقية، الجامعة التكنولوجية، 100234@uotechnology.edu.iq ، بغداد ، العراق
3 فرع التقنيات الاحيائية ،قسم العلوم التطبيقية، الجامعة التكنولوجية، maysaali229@gmail.com، بغداد ، العراق

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الخلاصة

مقدمة:

وصف الريسفيراترول (RVS) لأول مرة من قبل Takaoka سنة 1939 في جذور Veratrum grandiflorum

طرق العمل:

هو من الفينولات الطبيعية (3,5,4′–trihydroxy–trans–stilben) الموجودة في أكثر من سبعين نباتًا ، خاصة في قشور وبذور العنب والنبيذ الأحمر والأغذية البشرية الأخرى. تم تخليق الرابطة المزدوجة لـ RSV بواسطة تكثيف Wittig. بينما يتم الإنتاج الحيوي من حمض فينيل بروبانويد الذي يحتوي على أحماض سينامك و 4–كوماريك مشتقة من الأحماض الأمينية . يعمل RSV مرارًا وتكرارًا على تأجيل معدل العدوى ، على سبيل المثال ، تصلب الشرايين ومرض القلب والأوعية الدموية ومرض السكري من النوع 2 والأورام الخبيثة والأمراض التنكسية العصبية.

الاستنتاجات:

تعاملت معظم الدراسات مع RSV كمضاد للأكسدة وعلاج للأضرار التأكسدية التي تسبب الضرر في الجسم الحي ، مثل مرض السكري والتنكس العصبي وأمراض القلب والسرطان والشيخوخة. تشتهر RSV بكفاءتها القوية كمضاد للأكسدة. في هذا البحث ، تم ايضاح مصادر RSV ، كما تم تضمين كيفية إنتاج و خصائص RSV .بالإضافة إلى البيانات السابقة التي تمت مراجعتها والتي تناولت استخدام RSV كمادة علاجية لإدارة شيخوخة الجلد وعلاج السرطان والسكري وضغط الدم وكداعم للدماغ.

الكلمات المفتاحية:

ريسفيراترول، بوليفينول ، مادة علاجية، فيتواليكسين، مضاد للأكسدة.

Citation:

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INTRODUCTION

An ethylene bridge connects two phenol rings to create the Resveratrol (3,5,4'-trihydroxy-trans-stilbene; RSV), RSV has classified as a polyphenols' stilbenoids group see Fig. 1). Natural phenols which were found in over than seventy plants, especially in grapes' skins and seeds, red wines and other human nourishments. It is a phytoalexin that demonstrates against microbes, including microorganisms and growths. As a characteristic of food fixing, various investigations have shown that RSV has a high cancer prevention agent potential [1]. RSV likewise displays antitumor movement, and is viewed as an expected contender for anticipation and therapy of a few kinds of malignancy [2]. To be sure, RSV anti-cancer characteristics were affirmed by numerous individuals in vitro and in vivo contemplates, which shows that RSV can repress all carcinogenesis stages (e.g., commencement, advancement and movement) [3]. Much more, other bioactive impacts, specifically as calming, anticarcinogenic, cardioprotective, vasorelaxant, phytoestrogenic and neuroprotective have likewise been accounted for. In any case, resveratrol application is as yet being a significant test for the drug industry, because it is poorly soluble and less bioavailability, just as unfriendly impacts [4].

Among the stilbenes, RSV is the primary bioactive molecule in red wine, and the advantageous impacts of the standard utilization of this refreshment have been ascribed to this molecule [5]. Notwithstanding, alongside the notable cell reinforcement and RSV cardioprotective exercises, as well as neuroprotective, phytoestrogens, and anticancer exercises. Curiously, it was exhibited that RSV can instigate apoptosis and cell capture in disease cells, proposing its job in influencing the cell cycle. Likewise, the adequacy of RSV as an antimicrobial and antiviral specialist has been clarified [6]. Much investigates exhibited the impact of RSV against various infections [7], including the varicella-zoster viruses, flu viruses, respiratory syncytial viruses, African swine fever viruses, human metapneumonia viruses, Epstein–Barr viruses, enterovirus, duck enteritis viruses, hepatitis C viruses, and HIV [8], acting through various instruments of activity.

Also, there was a clear demonstration by Berardi and his colleagues exhibited that in-vitro RSV applied portion subordinate anti-viral movement vs polyoma-virus, influencing the viral offspring DNA union [9]. Besides, it was as of late exhibited that RSV at a low µM portion viably obstructed HIV-1 disease in CD4 T cells using a decrease in the degrees of deoxynucleoside triphosphate, that were important for the opposite record of viral RNA; this impact is chiefly because of the hindrance of ribonucleotide reductase movement by RSV [10].

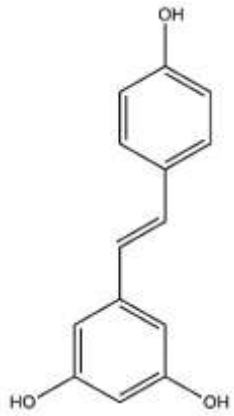


Figure 1. RSV chemical structure [1].

In this article, we pleasure accordingly represent some of the major points of RSV, their **properties**, sources, production and some of clinical hints for managing aging skin, cancer treatment, diabetes, blood pressure and brain support.

- Properties of RSV

RSV (3,5,4'-trihydroxy-trans-stilbene) is a stilbene a kind of natural phenols and a phytoalexin provided through some plants in response to damage or if the plant is below attack by pathogens, like microbes [11]. RSV sources in food involve blueberry, grape skin, raspberry, peanut, mulberry [12]. Although generally utilized as dietary additions and studied in human diseases laboratory models, there is no significant-quality confirmation that RSV enhances survival or has an impact on any individual disease [13]. Any of the major natural agricultural origins include berry, peanut, and grape [14].

RSV is the main component of red wine since it is already in the red grape skin and concentrated as a ferment of wine, in the environment, RSV is a phytoalexin, which works to preserve plants from pressure, invisible radiation, and some fungal diseases [15]. Pharmaceutical class in this compound sparked when it was proposed that RSV might be effective for the low percentage of heart attacks noticed in the French culture whose nutrition is huge in saturated lipids. This event, issued by S. Renaud and. M.de Lorgerial as the French Paradox was assigned to a decreased red wine absorption [16]. Considering that time, RSV was the topic of dynamic continuing investigation to prove its anti-aging benefits and strength [17].

Research has demonstrated that RSV ties to various cell-signaling molecules providing it to change beneficial health impacts in various ways [18]. RSV was anti-inflammatory (Inhibition of expression of genes in proinflammatory substances, as

well as a pro (by improved plasma absorption and insulin responsiveness) (leading to suppression of tumor cell proliferation, adhesion, invasion, and metastasis, reduced signs of inflammation, angiogenesis, and induction of apoptosis and differentiation) activities [19]. It also represents a vasodilator, platelet inhibitor and has significant cardio-protective impacts [20]. Current investigations have proposed that RSV might likewise be efficient when used topically to treat skin aging [21].

In mammals, it was seen that a low-calorie diet comparable to the ordinary utilization of RSV over and over deferred the rate of infections, for example, atherosclerosis, cardiovascular sickness, diabetes type 2, malignancy and neurodegenerative illnesses [22]. In the two cases, a few proteins, which are significant in support of homeostasis, are enacted. As depicted over, the essential instrument of RSV's activity in the cell is an enactment of sirtuin 1 [23]. In spite of numerous investigations, this instrument is as yet disputable. Some have scrutinized the capacity of resveratrol to direct activation of SIRT1. Based on this investigation it was exhibited unequivocally that resveratrol by implication actuates SIRT1.

Park and his colleagues showed the direct activity of RSV inhibition of cyclic nucleotides phosphodiesterase (PDE), which proposes an increase in 3',5'- cyclic adenosine monophosphate (cAMP), actuation of the trade "guanine nucleotide Epac1" and growth of intracellular calcium CaMKKβ regulating kinase action [24]. CaMKKβ kinase by phosphorylating AMPK enacts it, finally, it takes the control of the cholesterol association pathway of unsaturated fat, insulin and an expansion in the degree of NAD^+ that indicates preliminaries of SIRT1 (Fig. 2) [23]. Different system though is the phosphorylation and preliminaries of SIRT1 through protein kinase PKA, whose actuation is improved by an expansion level of cAMP [25].

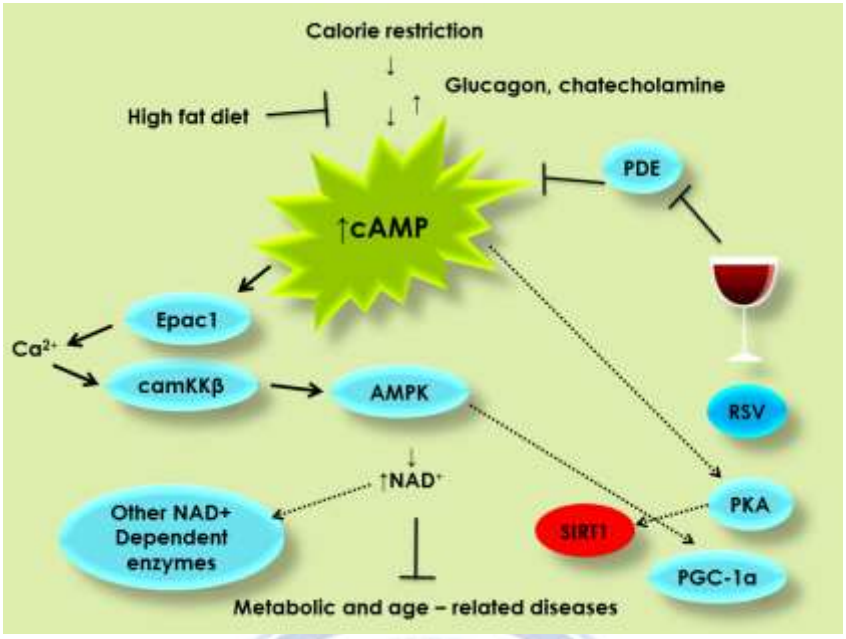


Figure 2. SIRT1 activation mechanism by RSV [23].

RSV from Chemistry to Biology

RSV has described at first by Takaoka in 1939 as a bioactive part in the Veratrum grandiflorum roots [26], throughout a long time RSV has acquired an incredible interest by logical exploration, which has broadly considered its natural movement [27]. Artificially, RSV (3,5,40 - trihydroxystilbene) is a 14-carbon skeleton stilbene with a molecular weight of 228.25 g/mol. The chemical structure comprises of two aromatic rings with 3, 5, and 40 located hydroxyl groups, joined by a twin of styrene bond that is liable for the presence of the cis-and the high stability trans-RSV isomers [28]. It is as a couple of geometric isomers: trans and Cis (as in Fig. 3). The trans-resveratrol and cis-resveratrol could be free or connected to glucose molecules. The trans-isomer may undergo the process of formalization to the cis-form when exposed to invisible light. A method declared photo-isomerization [29]. Trans-isomer with powder-form have been found to be stables following conditions of 75% moisture with 40 °C in an air [30]. The trans-form is also stabilized through the transport protein addition. RSV was quite stable in this grapes skins in addition to pomace taken beyond fermentations and storied for a time.

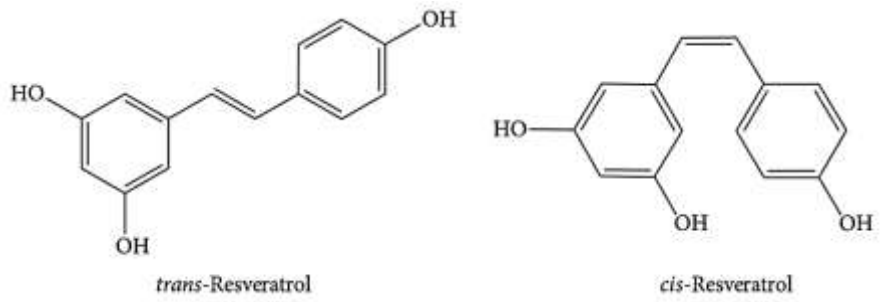


Figure 3. RSV isomers chemical structures [28].

Annunziata and his colleagues recently conducted a comprehensive study on the effect of using biologically active compounds derived from plants, specifically polyphenols, including RSV, which have a distinctive and effective effect against HSV infection [31] (see Fig. 4 for illustration).

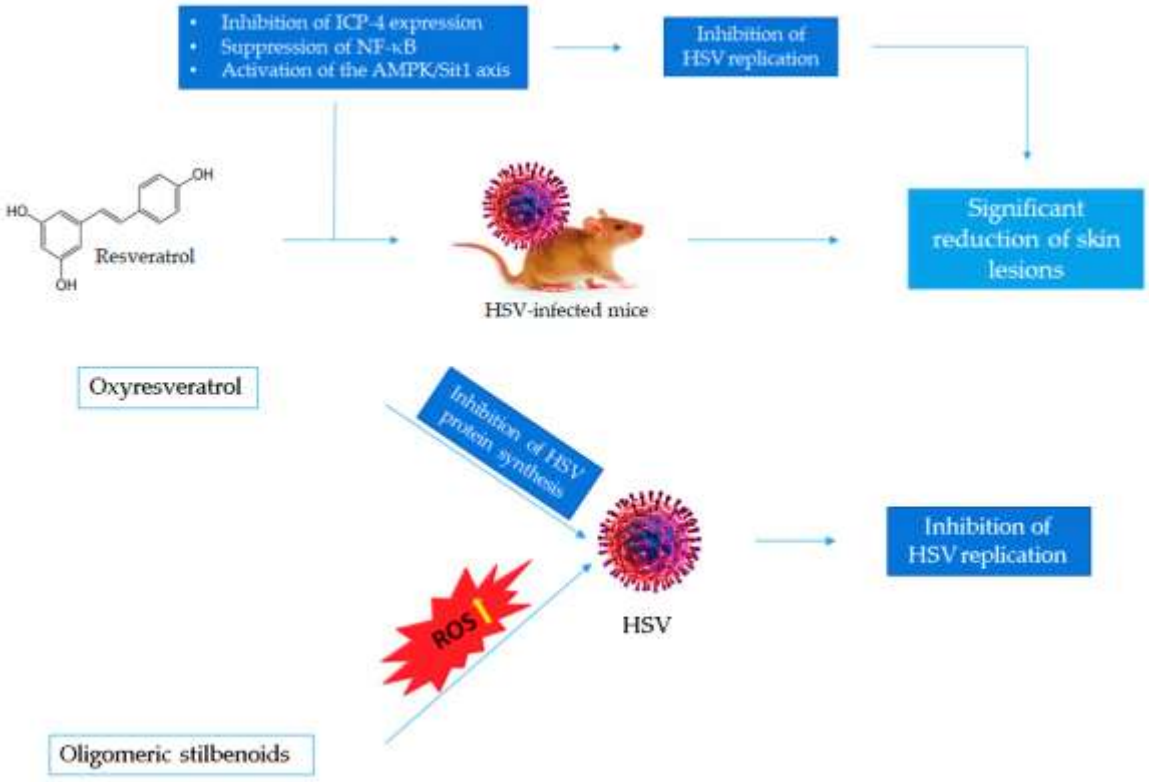


Figure 4. The main mechanisms of RSV and its derivatives against HSV infection [31].

- **Sources of RSV**

RSV transpires in wine meanwhile red wine is produced, the "must" is utilized-skin, seed, and stem [32]. The must is transmitted in the mixture for a continued time as the wine ferment and the oligomeric proanthocyanidin (OPC) like RSV emerge, yielding red wine its original flavor and colour [33] as in Fig. 5. With white wine, the must is

carried out fresh so it does not darken nor absorbed as usual OPC. The grapes extract has OPC but seems not to give the same health advantages as red wine the injury to the grape skin, created through the process of making wine, improves RSV levels [34]. RSV is found in grapevines. It happens in the wine, root, seed, and stalk, yet its most significant concentration is in the skin of the grape wine also includes RSV [35]. The RSV concentration in red wine is considerably more chief white wine. The principal variation between red wine and white wine generation, in addition to the grape utilized, is that for the red one in the skin and seed and involved in the method, while white one is essentially cooked from the juice, basically avoiding the usage of grape skin and seed [36].

Romero-Pèrez and his colleagues estimated the RSV levels in 36 grape squeezes and found that RSV is about ten times higher in red juices than that in the white juices. The extra fluctuation was additionally noticed: the complete RSV content went from 0.69 to 14.47 mg/l in the red juice and 0 to 1.44 mg/l in white one [37].

As found by Li and his group of researchers in 2006 in grape berries, the new squeezes from the wine-production grape assortments had more absolute RSV content than the business juices. Along these lines, grape juice, specifically red grape juice, might be an elective dietary source to wine to accomplish the advantageous impacts [38].

While the winemaking method, RSV, in addition to other phenols, such as quercetin, catechin, gallocatechin, procyanidin, and prodelphinidin, are extricated from the grape skin through a method named maceration. Moreover grape and wine, dietary origins of RSV have peanut and mulberry [22]. RSV is also found in important values in the root and stem of the plant Polygonium cuspidatum Sieb. Et Zucc [39].

It is also common that the human diet contains polyphenols, which are usually one of the most abundant plant metabolism groups. RSV is produced as an active defense agent against fungi and has beneficial factors for human health. RSV researches were significantly expanded in PubMed information base since 1997 where the first research about the anticancer impact of such molecules was reported [40].

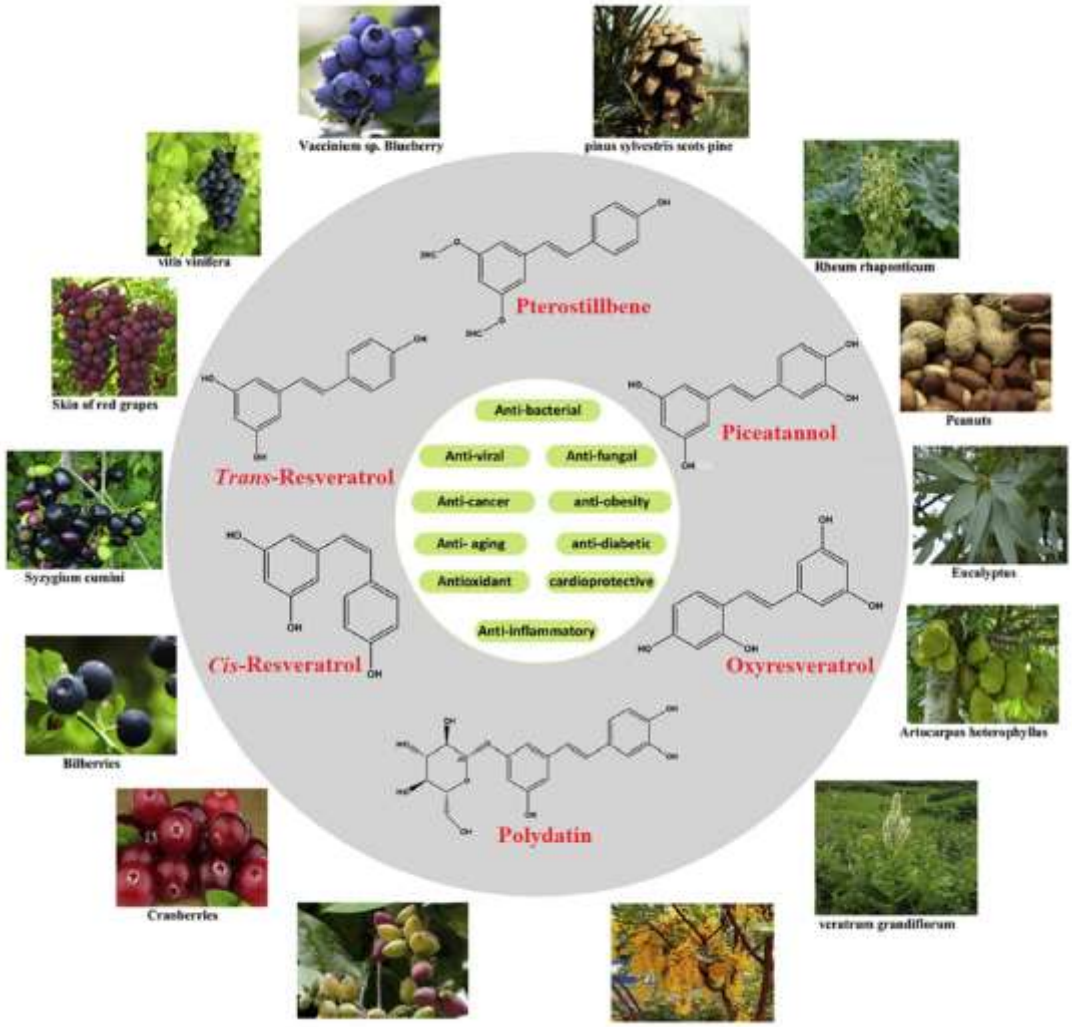


Figure 5. RSV Sources, their derivatives and therapeutic influence[34].

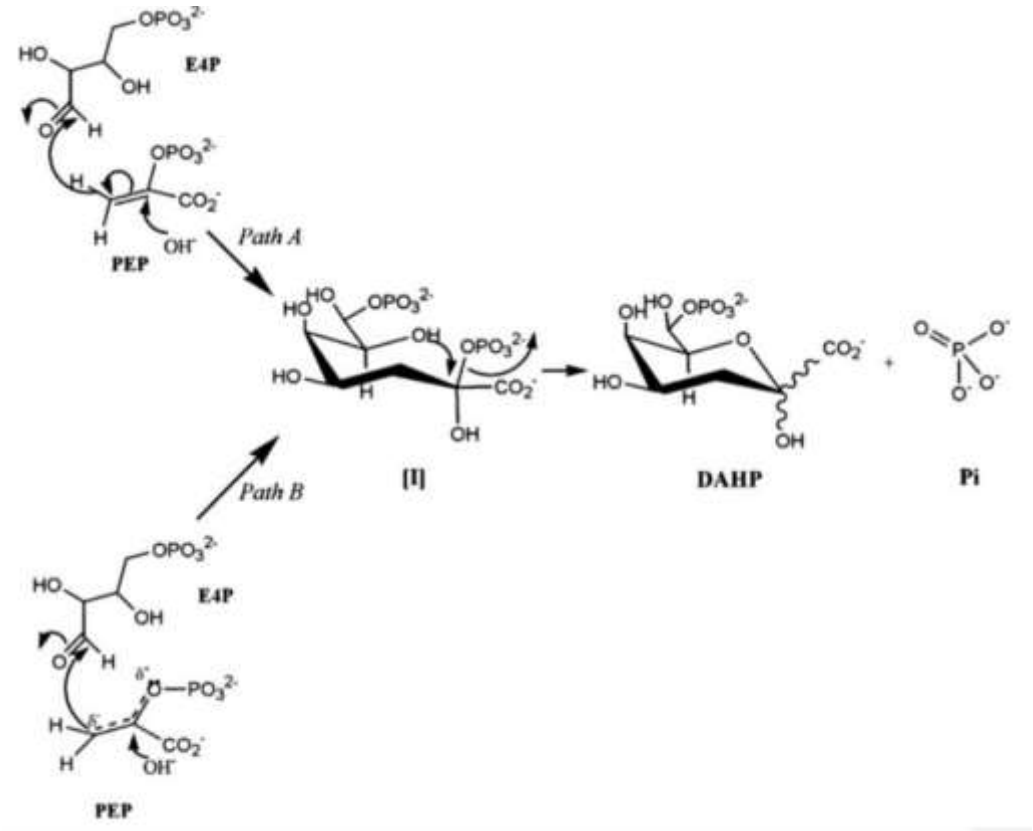
Production of RSV

The double bond of RSV has been formed by a Wittig condensation between a phosphorus ylide and a silylated hydroxybenzaldehyde [40]. The method described by Moreno-Manas and Pleixats was used to synthesize the compound.

This was prepared by reaction of (3,5dihydroxyphenyl) methyl tri-phenyl-phosphonium bromide with 4-tri-methyl-silyloxybenzaldehyde in the presence of phenyl-lithium over the intermediate salt, was obtained whose hydrolysis led to RSV. The crude product was recrystallized from ethanol-water, affording pure RSV in 20% to 30% yield [41].

RSV bioproduction is launched from phenylpropanoid acid having cinnamic and 4-coumaric acids which were derived from amino acids (aromatic). The biosynthesis of

amino acids begins by the 3-deoxy-d-arabinose-heptulosonate-7-phosphate (DAHP) synthase that catalyzes the water removal of phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P) to form DAHP in microorganisims, DAHP synthase happens as 3 isomers, anyone controlled by feedback-inhibition mechanism (Scheme 1) [42].



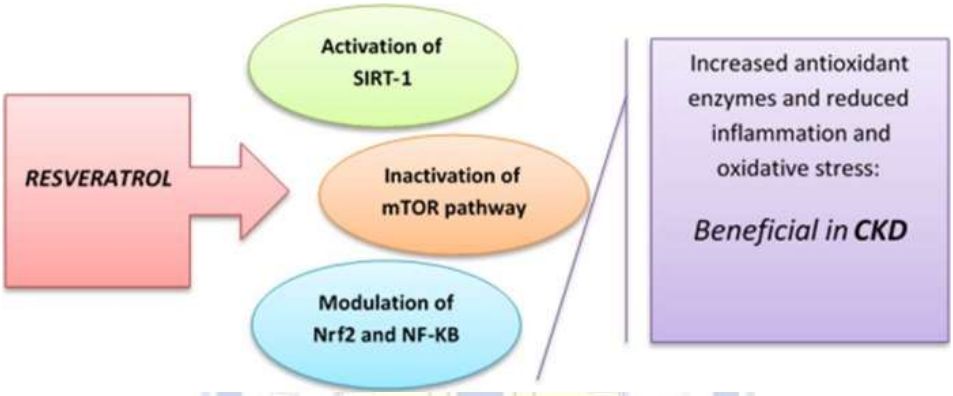
Scheme 1. Proposed reaction mechanisms for DAHP synthase.

Six reactions which control be enzymes were converted DAHP to chorismate (CHO), the parent of l-phenylalanine (l-Phe) and l-tyrosine (Tyr) these odorous acids are the last results of greatest microorganism biosynthetic pathways. Although, in plants and some microorganisms, these acids are intermediate in the pathway for the secondary metabolite synthesis, like phenylpropanoids [43].

In the initial level of synthesis of phenyl-propanoids, l-Tyr with l-Phe perform transform to the phenylpropanoid, cinnamic and 4-coumaric acids, individually, through PAL and TAL enzymes, which is then turned to cinnamoyl-CoA and p-Coumaroyl-CoA by 4-coumarate-CoA ligase (4CL) were formed by the reaction of Cinnamic acid and cinnamate-4-hydroxylase (C4H). Malonyl-CoA is reacted with 4-coumaroyl-CoA through STS bowing RSV one molecule [44].

- **RSV as an antioxidant**

Most of the studies dealt with RSV (Scheme 2) as an antioxidant and a treatment for oxidative damage that causes damage in vivo, such as diabetes, neurodegeneration, heart disease, cancer and aging. RSV is known for their powerful scavenging efficiency. One of the usual distinctive characteristics of this phenol is that it presents dual scavenging activity. Moreover, direct scavenging's RSV enhances the intracellular appearance of other commonly happening enzymatic antioxidants [35].



Scheme 2, Beneficial effect of resveratrol in CKD by its antioxidant characteristics

RSV up-regulates the appearance of nuclear factor/E2/related factor/2 (Nrf2), a transcription factor, which manages several genes efficient for oxygen reactive detoxification differences. As an example, factor/E2/related factor/2 is understood to improve the generation of glutathione synthetase (GSH), the enzyme that is the rate-limiting action in the synthesis of the antioxidant glutathione [45]. Besides, RSV was given to raise naturally-occurring enzymatic scavengers having super-oxide dismutase, catalase, and heme oxygenase, therefore, improving intracellular scavenging activity. The direct radicals antioxidant characteristics of pure RSV are quite organized and seem to be very dependent on the hydroxyl group position. Investigations become approved RSV to be an efficient antioxidant of hydroxyl, superoxide, and metal produced free radicals [45].

Lastly, RSV inhibits peroxidation of lipid through Cu-chelating and through action synergistic with scavengers before-mentioned as E-vitamin. These connected influences give RSV a novel antioxidant able to both antioxidant on its own and progressing intrinsic scavenging activity [46].

- **The role of RSV and skin aging**

While the clinical brands of normal aging vary considerably related to external or photo-aging, the molecular and cellular mechanism is related [21]. Aging of the skin is considered to be made through an improved in-situ generation of reactive oxygen varieties (ROS), that event from a mitochondrial function disruption and severe pressure response to various environmental indignities such as ding solar radiation. There is more reliable confirmation that central, as well as outward skin aging, are compared with depletion of commonly occurring scavengers that serve as a protection mechanism toward damaging free radicals [47].

If moved un-checked, ROS may immediately break cell membrane, protein, and DNA. Also, ROS apply to the molecular mechanism and cellular mechanism which quicken skin aging including up-regulation of transcription factors, these factors are accountable for the generation of metalloproteinases (MMPs), the enzyme that breaks down collagen [48]. In-vitro investigations have proved that RSV effectively downregulates both AP-1 and NFkB and hence assists an important function in defending dermal collagen and diminishing skin pain [49].

Replacement therapies of estrogen mitigate collagen degeneration and improve the clinical indications of skin aging. In vitro studies have shown that RSV efficiently down controls both AP-1 and NFkβ, therefore, assist a key role in conserving dermal collagen and diminishing skin infection [50]. The appearance of these different characteristics, RSV gives a multi-mechanistic strategy that makes it a notably hopeful factor for the therapy of different skin aging. A comparable impact was found on treating matured and photodamaged skin with an uncommon mix of a few enemies of oxidants comprising of RSV, baicalin, and nutrient E. These cell reinforcements were incompletely adequate to revive matured skin. RSV was appeared to invigorate the Nrf2 pathway in skin prompting an expansion in the GSH substance and improvement of skin quality [51].

- **The role of RSV in cancer prevention**

Jang reported in 1997 that topical treatments of RSV stopped the growth of skin cancer in mice treated with carcinogen10 [52]. Docensed tests of RSV's cancer development have been performed in animal models since then [53]. However, research tests evaluating impacts on colon cancer and melanoma (skin cancer) are currently being carried out on patients. No findings have been published for human cancer clinical trials [54]. In-vitro RSV interacts with different molecular targets and has affects breast, scalp, gastric, colon, oesophageal, prostate, and leukemia cells. However, studies on RSV pharmacokinetics in men concluded that even elevated levels of RSV could not be enough to avoid cancer systemically [55]. This is consistent with the

findings of animal cancer patterns that demonstrate that RSV's in vivo efficacy is limited by its low systemic bioavailability, which is the best proof of RSV anti-cancer action as it can come into close contact with tumors such as tumors of the skin and gastrointestinal [56]. The data remains unclear for other cancers even though large RSV doses are utilized.

Chemotherapy is frequently utilized as the cutting edge routine in the therapy of most disease types. Notwithstanding, the improvement of tumor protection from chemotherapy, alleged chemoresistance, is a significant obstacle in malignant growth treatment [56]. Chemosensitization is a compelling apparatus in defeating chemoresistance, whose instruments in tumors can be intrinsic or acquired [57]. These instruments may rely upon, for instance, drug flood and efflux, inactivation of chemotherapeutic specialists, changes in objective particles, improved DNA fix, development factor flagging, or potentially adjustments in the cell-passing guideline. RSV applies its sharpening impact by adjusting at least single or more mechanisms of resistance [58]. Recently reported discoveries show that RSV make the tumor cell sensitized to the chemotherapeutic agent by the cell endurance proteins modulation; for instance, to sharpen human disease cell lines to chemotherapeutic specialists, for example, doxorubicin cytarabine (AraC), actinomycin D, taxol, and methotrexate by down-regulation any survive indication and expanding apoptosis [59].Likewise, other studies have shown that chemotherapy agents such as cisplatin, paclitlexide and gefitinib in lung cancer cells cause induced apoptosis [60]. These cells are rather large and resistant to multiple drugs. Moreover, concentrating on the pharmacokinetics of RSV in people have presumed that even high RSV dosages may be deficient to accomplish the RSV fixation needed in vivo for the foundational anticipation of malignant growth. This perception is reliable with the discoveries made in creature malignancy models, which demonstrate that the in vivo viability of RSV is restricted by its poor fundamental bioavailability [61]. The most persuading proof regarding the anticancer impact of RSV has been acquired in tumors where direct contact with the atom was empowered, (for example, skin cancer and gastrointestinal tract). For different malignancies, the proof is dubious, regardless of whether gigantic dosages of RSV are utilized. The topical use of RSV in mice both prior to and after UVB treatment (Ultraviolet B or medium wave) inhibited the damage to the skin and minimized the occurrence of skin cancer. In treating mice inoculated with melanoma cells, oral RSV was, however, unsuccessful [62]. Injected intraperitoneally, however, RSV 2.5 or 10 mg/kg of RSV has delayed the development of Lewis metastatic lung carcinoma in mice. The impact of RSV injected in oral cancer is also not important [63]. The number of oesophageal tumors in rats treated with carcinogen was reduced by RSV (1 mg/kg orally). In a variety of experiments, the growth of intestinal and colon tumors in rats given various carcinogens has been decreased or prevented in small

doses of RSV prophylactically given (0.02– 8 mg/kg). Treatment with RSV seemed to inhibit mammary tumor production in animal modeling, but did not have an impact on tumor formation. Injecting RSV into mice in high doses, neuroblastomas delayed development. Paradoxically, high-dose therapy for pre-pubertal mice increased tumor development. Injecting RSV into mice in high doses, neuroblastoma development was delayed [64]. For example, colorectal cancer (CRC) is predominant cancer and one of the primary drivers of cancer mortality throughout the world. Some of the hereditary qualities to consume fewer calories are responsible for the occurrence of this danger. Its pathophysiology is heterogeneous which various molecules and signaling pathways involving oxidative stress, inflammation, and apoptosis are embroiled in its frequency and movement. A number of investigations have upheld the possible impacts of RSV in CRC treatment [3]. This polyphenol compound speaks to various properties including cancer prevention agent, mitigating, apoptosis inducer, and hostile to angiogenesis viability. Because of these huge impacts, RSV is recommended as a novel restorative specialist for cancers (see Fig. 6). In addition, a few investigations announced that RSV utilization in blend with other enemies of cancer medications can build their belongings and furthermore decline their results. Along these lines, this performing various tasks compound can be another up-and-comer in CRC treatment be that as it may, more human examinations are required [3].

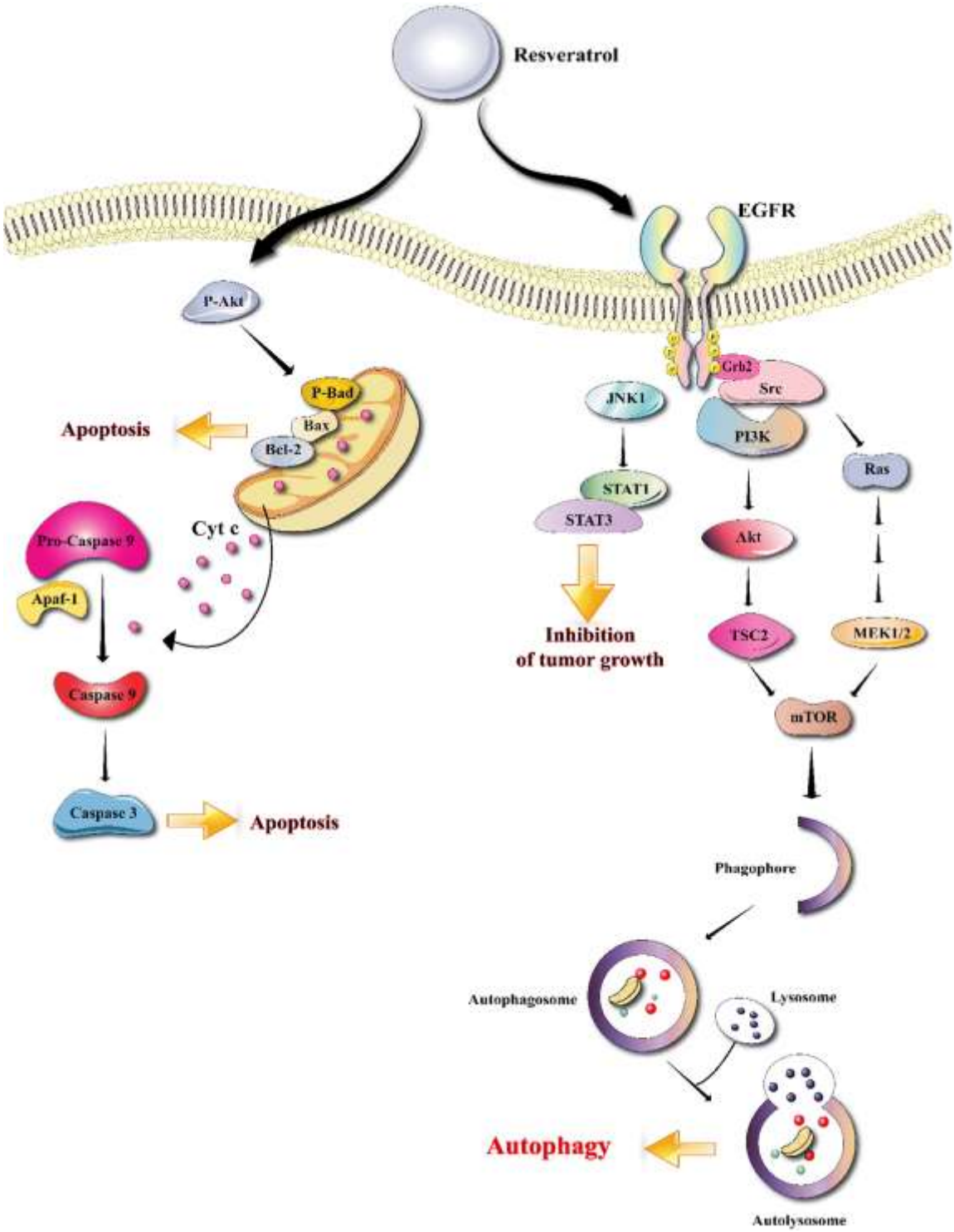


Figure 6. Scheme for targeting different signaling pathways using RSV as a colon cancer treatment [3].

- **The roles of RSV in lower blood pressure**

RSV may be a promising supplement to relieve blood pressure because of its antioxidant effects [65]. In a study in 2015, large doses could help to minimize strain on walls of the artery as the heartbeats. This is known as systolic blood pressure and is the top number of readings of blood pressure. Typically, systolic blood pressure is raised with age as the arteries rise. Highly, it's a cardiac risk factor. The effect of RSV can be minimized by helping to create more nitric oxide that relaxes blood vessels. But further study is required before clear recommendations on the right dosage of RSV can be made to optimize the gain of blood pressure [66].

In a recent study [67], resveratrol was evaluated in the isolated rat aortic smooth muscle cells to oxidize cGMP-dependent PKG1α (protein kinase 1α). Mice became hypertensive, through the use of osmotic mini-pumps and blood pressure after 15 days of vehicle- or resveratrol-containing chow diet. Mice were treated with angiotensin II. Phenolic ring oxidization of resveratrol paradoxically contributes to oxidative changes in proteins, explained by the creation of reactive quinone, oxidizing the thiolate cysteine residue side chain; activities which have been exacerbated by oxidative stress cells. Therefore resveratrol mediated PKG1α oxidative activations in hypertensive wild-type mice and reduced blood pressure, but not disulfide-resistible C42S PKG1α knock in mice.

- **RSV as brain supportive**

Several studies have found that age-related cognition can be slowed by drinking red wine. The antioxidant and anti-inflammatory function of RSV can be partly responsible. The protein fragments called beta-amyloid tend to interact with the creation of placards that are central to the progression of Alzheimer's disease. Besides, the compound may cause a sequence of events that avoid damage to the brain cells. While this study is interesting, scientists also wonder how effectively the human body can use supplementary RSV, restricting the immediate use of it as a brain defense supplement [68].

Mediterranean diet (MD), also called Cretan diet, has been proven to prevent diseases including cardiovascular pathologies, cancer, and to prevent aging. Interestingly, the grape and more precisely in grape skin contains the highest concentration of RSV. In consequence, red wine it is the most concentrated food source of RSV found in human diet. A recent study accomplished by Silva et al. dealt with how efficient is RSV towards alterations during the aging process [69]; obtained from recent data of clinical trials, pre-clinical studies and cell culture approach; expecially RSV protecting effect on brain aging of elderly; its role on the microglial cells playing a central role in the neuro-inflammation; and in its anti-inflammatory effects on ocular diseases.

- **The roles of RSV Diabetes patient**

Here are a few extra advantages for diabetes people, such as its antioxidant activity will help protect against oxidant stress causing a range of diabetes complications. Helps suppress inflammation, it is believed that RSV decreases inflammation, which is a vital contributor to chronic disorders such as diabetes. Activated AMPK helps sustain low levels of blood sugar. RSV can give people with diabetes even more advantages than people who don't. In one animal study, red wine and RSV in rats with diabetes were actually more effective antioxidants than rats without it. Researchers suggest that this compound could be used in the future to treat diabetes and its complications, but more study is necessary [70].

- **Improvement of insulin resistance**

Diabetic patients are less glucose and more insulin responsiveness in human clinical trials or RES single-dose oral dosing (5 mg5 g) over 12 months [71]. In addition, in patients with glucose tolerance, the insulin-sensitizing effects of RES were found. These findings indicate that after-prandial glucose levels are lowered considerably without an increase in insulin output and thus confirm an increase in insulin sensitivity after RES [72] administration. Furthermore, findings indicate that the RES will recover the insular, IGF and blood glycémy abnormally due to AMP-dependent protein kinase (AMPK) and sirtuin (SIRT) activations [73]. The nucleus and mitochondriamays are both SIRT1 and SIRT3 and play a key role in the control of irregular metabolism, such as diabetes and obesity [74].

- **Enhancement of glucose uptake and metabolism**

Normal metabolism of glucose plays a crucial part in ensuring the stability of blood sugar. The use of insulin-stimulated glucose is largely due to accelerated absorption in the skeletal muscle of glucose [75]. Reduced GLUT4 expression, the main regulatory protein in diabetic animals was confirmed, while the levels of RES (3 mg/kg 7 days) in livers of diabetic rats may increase GLUT4 and GLUT2 [76]. In addition, in the absence of insulin RES promotes the uptake or use of glucose in isolated cells leading to an increased expression of GLUT4 in the plasma membrane. In another word, RES enhances glucose absorption into muscle cells through a rapid stimulation of endogenous GLUT4 translocations and improves the phosphorylation of the signal pathways PI3K/Akt or AMPK/Akt [77]. Sin's team also reported that RES has a major hypoglycemic role in speeding deacetylase SIRT1 as an anti-diabetic candidate drug and prevents phosphorylation of Foxo1. These results may be important for increasing the conversion of glucose and metabolism. Modifications in the action of enzymes can support skeletal muscle glycolysis and glycogen synthesis [78]. All the above-mentioned studies show that RES decreases blood sugar by disrupting the uptake and metabolism of glucose. But the role of RES on the metabolism of glucose or insulin in elderly people remains unknown and should be further examined.

Conclusion

RSV is an essential polyphenol with many established health advantages. RSV is an antioxidant and a treatment for oxidative damage that causes damage in vivo, such as diabetes, neurodegeneration, heart disease, cancer and aging. RSV has great potential as a topical component in skin treatment and the clinical symptoms of aging can be both avoided and strengthened. However, studies on RSV pharmacokinetics in men concluded that even elevated levels of RSV could not be enough to avoid cancer systemically. On the other hand, recently reported discoveries show that RSV makes the tumor cell sensitized to the chemotherapeutic agent by the cell endurance proteins modulation. RSV may be a promising supplement to relieve blood pressure because of its antioxidant effects due to RSV create more nitric oxide that relaxes blood vessels. Finally, with all the threputic properties of RSV researchers suggest that this compound could be used in the future to as a threputic substance, but more study is necessary.

Conflict of interests.

There are non-conflicts of interest.

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