Resveratrol: A Review on the Biological Activity and Applications

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Abstract

Resveratrol (RSV), a naturally occurring phytoalexin, is the most important stilbenoid synthesized by plants, as a defense mechanism, in response to microbial aggression, toxins or ultraviolet radiation. RSV came to the attention of researchers both as a potential chemopreventive agent and a possible explanation for the low incidence of cardiovascular disease (CVD) in French people with a high-fat diet. RSV is mainly administered as a food supplement, its properties being evaluated *in vitro* or *in vivo*, on various experimental models. RSV modulates signaling pathways that limit the spread of tumor cells, protects nerve cells from damage, is useful in the prevention of diabetes, and generally acts as an anti-aging natural compound. It was highlighted that RSV could ameliorate the consequences of an unhealthy lifestyle caused by an exaggerated caloric intake. This paper reviews the evidence supporting the beneficial effect of RSV for various pathological conditions, e.g., neoplastic diseases, neurodegeneration, metabolic syndrome, diabetes, obesity, CVDs, immune diseases, bacterial, viral, and fungal infections. The study also focused on the chromatographic analysis of *trans*-RSV (tRSV) in Romanian wine samples, providing a comprehensive overview of tRSV content across different types of wine.

Keywords: resveratrol; stilbenoids; grapes; wine; biological activity; applications.

1. Introduction

Stilbenes are natural secondary metabolites also known as phytoalexins. Stilbenoids, respectively the hydroxylated derivatives of stilbenes, have in their structure two benzene nuclei connected by an ethylene bridge and belong to the category of polyphenolic compounds that are biosynthesized in the same way as flavonoids. Due to their role as phytoalexins, stilbenoids are very important in the defense of plants against pathogens. Up to now, more than 1000 stilbenoids have been isolated and identified, of which the best known are the natural components resveratrol (RSV – 3,5,4'-trihydroxy-stilbene), piceid, piceatannol, pterostilbene, astringin, viniferin, pallidol, hopeaphenol. Grapes are the main source of natural stilbenoids. Stilbenoids are of special pharmacological interest due to the multitude of health benefits, especially regarding the prevention and potential treatment of some chronic diseases associated with aging, through anti-tumoral, antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antidiabetic action [Pawlus et al., 2012; Oh et al., 2021; Kaur et al., 2024].

The two natural isomers, *cis*-resveratrol (cRSV) and *trans*-RSV (tRSV), are biosynthesized almost entirely in grape skins; the highest concentrations of RSV were determined before the ripening of the grapes. tRSV has the highest biological activity, cRSV being occasionally identified only in some wines. It is believed that cRSV results from an enzymatic reaction during the wine fermentation process or by exposure of tRSV to ultraviolet (UV) radiation. tRSV is relatively stable and is preferred for chemical analyzes and syntheses [Kaur et al., 2024].

RSV has a higher lipophilicity compared to other phenolic compounds, which may lead to better cell permeability. Indeed, RSV shows better absorption compared to other polyphenolic derivatives. However, its bioavailability is relatively low due to rapid metabolism, so there is no correlation between *in vitro* and *in vivo* results [Pawlus et al., 2012; Oh et al., 2021].

RSV came to the attention of researchers approx. fifth decades, being both a potential chemopreventive agent and a possible explanation for the so-called "French paradox": the low incidence of cardiovascular disease (CVD) among the French, a people with a high-fat diet [Kaur et al., 2024].

RSV is mainly administered as a food supplement, its properties being evaluated *in vitro* or *in vivo*, on various

experimental models. RSV has potential beneficial effects in various diseases, e.g., diabetes, obesity, CVDs (hypertension), neoplastic diseases, Alzheimer's disease (AD). In particular, RSV has been found to affect the expression of several genes, including genes encoding cytokines, caspases, matrix metalloproteinases (MMPs), adhesion molecules, growth factors. Moreover, RSV can modulate the activity of several signaling pathways, such as phosphatidylinositol 3'-kinase (PI3K)/Akt, Wnt, nuclear factor-kappa B (NF-κB), Notch [Ghafouri-Fard et al., 2022; Kaur et al., 2024; Faisal et al., 2024].

RSV is a potential chemopreventive agent, both *in vivo* and *in vitro*, considering its inhibitory effects on cellular processes associated with cancer induction and progression. RSV inhibits cellular events associated with the three stages of carcinogenesis (initiation, promotion, progression), having antioxidant, antimutagenic, anti-inflammatory action. This polyphenolic compound prevents the promotion of cancer, inhibiting the activity of cyclooxygenase (COX)-1 and COX-2, enzymes that catalyze the conversion of arachidonic acid to proinflammatory substances that can stimulate tumor growth and suppress the immune response. The two COXs can activate carcinogens to reactive forms that produce cytogenetic damage. In addition to COX and hydroperoxidase inhibition, RSV induces the differentiation of human leukemic promyelocytes [Kaur et al., 2024; Faisal et al., 2024].

RSV induces the expression of phase II enzymes of the metabolism of active principles, the activity of quinone reductase (involved in detoxification) and inhibits ribonucleotide reductase [an enzyme complex that catalyzes the reduction of ribonucleotides to deoxyribonucleotides necessary for deoxyribonucleic acid (DNA) synthesis], cytochrome P450 CYP1A1, DNA polymerase, COX, and nicotinamide adenine dinucleotide reduced form (NADH)–ubiquinone oxidoreductase. The influence of RSV on these enzyme systems explains its antioxidant, antimutagenic and anticarcinogenic potential [Kaur et al., 2024; Faisal et al., 2024].

RSV has a structure similar to that of diethylstilbestrol and therefore could exhibit a phytoestrogenic effect. Phytoestrogens have numerous physiological effects in humans, the moderate consumption of red wine at meals being useful for protecting the body against diseases and improving the aging process [Calabrese, 1999]. In vegetarians, but also in the case of Asians, people with a diet rich in phytoestrogens, there is a low incidence of breast, endometrial, ovarian, and prostate cancer (PC). Phytoestrogens are natural non-steroidal plant components, structurally and functionally similar to estrogens produced by the human body. Studies have shown that these compounds alleviate menopause symptoms and have anticancer properties, conferring protection against osteoporosis and hormone-dependent cancers (breast, prostate). In addition, phytoestrogens inhibit angiogenesis and cell cycle progression [Huang et al., 2023]. Phytoestrogens bind and activate estrogen receptors (ERs) but are less effective than estrogens of endogenous origin. RSV exerts its antiestrogenic activity, competing with 17β-estradiol for binding to ERs. By antagonizing the stimulatory effect of estradiol, RSV inhibits the growth of ER-positive human breast cells, acting both at the cellular level (cell growth) and at the molecular level (gene activation) [Gehm et al., 1997; Alamolhodaei et al., 2017].

Research highlighted the fact that moderate intake of wine can have beneficial effects on human health, attributed especially to phenolic derivatives. In addition to flavonoids, polyphenolic acids (e.g., hydroxybenzoic acids, hydroxycinnamic acids) and stilbenes are important compounds present in grapes and wine. The remarkable properties of wines are due to polyphenolic compounds, mainly through their antioxidant activity and ability to eliminate free radicals. In addition, these compounds [(+)-catechol, (–)-epicatechol, proanthocyanidins, quercetin, kaempferol, RSV, gallic acid, caffeic acid] have been reported to exhibit a multitude of pharmacological actions, including cardioprotective, antiatherogenic, anti-inflammatory, antitumor, antibacterial, antiviral. From a phytochemical point of view, grapes represent a natural combination of polyphenols with a synergistic effect in the prevention of diseases and maintaining the health of the body. Epidemiological studies and clinical trials have shown that a regular and moderate consumption of red wine (1–2 glasses/day) is associated with a low incidence of CVDs, diabetes, and some types of cancer. The bioavailability of polyphenolic compounds varies within quite wide limits, so the most abundant polyphenols in wines are not necessarily the ones that determine the highest levels of active metabolites in the target tissues. Wine being a complex mixture, it is likely that a multitude of chemical constituents, mainly polyphenols and their metabolites, act synergistically on human health [Visioli et al., 2020; Rodríguez-Vaquero et al., 2020; Magrone et al., 2019].

This paper reviews the evidence supporting the beneficial effect of RSV for various pathological conditions, such as: neoplastic diseases, neurodegeneration, brain injury, metabolic syndrome, diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), CVDs, immune disorders, bacterial, viral, and fungal infections. In addition, the study focused on the ultra high-performance liquid chromatography–mass spectrometry (UHPLC–MS) analysis of tRSV in Romanian wine samples, both white and red varieties, providing a comprehensive overview of tRSV content across different types of wine.

2. Natural Occurrence of Resveratrol and Related Compounds

RSV has been identified in numerous natural resources of plant origin: e.g., grapevines, *Vitis vinifera* L. and *V. labrusca* L. (*Vitaceae*), the most important source; the roots of *Polygonum cuspidatum* Sieb., Japanese knotweed (*Polygonaceae*); the rhizomes and roots of *Holoschoenus vulgaris* Link. syn. *Scirpus holoschoenus* L., marsh cypress (*Cyperaceae*); the roots of *Veratrum grandiflorum* (Maxim. ex Baker) Loes., white sedge and *V. formosanum* O. Loes. (Liliaceae) – an endemic species in Taiwan; the leaves of *Eucalyptus globulus* Labill. and *E. accedens* W. Fitzg., eucalyptus (*Myrtaceae*); peanuts, *Arachis hypogaea* L. (*Fabaceae*) and peanut butter; spruce leaves, *Picea abies* L. (*Pinaceae*); the fruits of *Vaccinium myrtillus* L., blueberry, *V. corymbosum* L., American blueberry, and *V. macrocarpon* Ait., American

cranberry (*Ericaceae*); cocoa beans, *Theobroma cacao* L. (*Sterculiaceae*) and chocolate; blackberry, *Rubus fruticosus* L. (*Rosaceae*); tomatoes, *Lycopersicon esculentum* Mill. (*Solanaceae*); the aerial part of *Pterolobium hexapetallum* (Roth) Santapau & Wagh (*Fabaceae*); the fruits and leaves of *Cassia garrettiana* Caraib. and *C. quinquangulata* Rich. (*Fabaceae*); the wood of *Bauhinia racemosa* Lam. (*Fabaceae*); sweet almonds, *Prunus amygdalus* Bartock syn. *Prunus dulcis* (Mill.) D. A. Webb (*Rosaceae*); different varieties of hops used mainly in the beer industry (Amarillo, Cascade, Nugget, Simcoe, Sterling, Tomahawk, Vanguard, Warrior, Wilhamette), *Humulus lupulus* L. syn. *Lupulus amarus* Gilib. (*Cannabaceae*); apples, raspberries, plums, pistachios, hazelnuts; and also in the products derived from the processing of these raw materials (such as natural juices/syrups, various hydroalcoholic extracts, wines) [Oh et al., 2021; Pawlus et al., 2012; Ghafouri-Fard et al., 2022; Frémont, 2000; Jang et al., 1997; Kumar et al., 1988].

Spermatophytes, such as grapevines, generate RSV, which is the most important stilbenoid synthesized by plants, as a defense mechanism, in response to microbial attack, toxins or UV-irradiation, as a naturally occurring phytoalexin. *V. vinifera* L., mainly in the form of wine, is a valuable dietary source of stilbenoids, such as tRSV, which has the most important anti-aging biological effects in *in vitro* and *in vivo* studies. Hence, the compounds found in highly resistant strains are essential for the development of resistant crops, natural spray reagents and as novel nutritional supplements or phyto-pharmaceuticals [Pawlus et al., 2012].

RSV is found in large quantities especially in the skin, but not in the pulp of the grapes. RSV content in wines obtained from different grape varieties is extremely variable. Typically, white wines (those produced from the White Burgunder, Riesling, Ortega, and Gewürztraminer varieties) contain about 10 times less RSV than red wines (from the Cabernet Mitos, Cabernet Cubin, Syrah, Spätburgunder/Pinot noir, Cabernet Sauvignon and Merlot). In red wine, tRSV amounts generally vary between 0.1 and 15 mg/L. RSV concentration is influenced by several factors, such as: grape variety, genotype, climate zone, soil type, exposure to light, pest control, agrotechnical works, maturity, post-harvest treatment, storage, preservation [Oh et al., 2021; Frémont, 2000].

It was firstly reported the presence of RSV, as a bioactive compound, in eight Western Romanian propolis samples, along with kaempferol, quercetol, rosmarinic acid. The principal component analysis showed clustering of the propolis samples, according to the polyphenolic profile similarity [Duca et al., 2019].

The structure of phenanthrene, tri-O-methyl-RSV, methyl-tri-O-methyl-gallate, pterostilbene, RSV, methyl-gallate were determined by analytical and spectroscopic methods from the stems of *Pterolobium hexapetallum* [Kumar et al., 1988]. Bioassay-directed purification of the active compounds from an ethanol extract of *Psoralea corylifolia* led to the isolation of corylifolin and bakuchiol as DNA polymerase inhibitors and also, based on their structures, RSV was tested and demonstrated to be effective as a DNA polymerase inhibitor [Sun et al., 1998].

Viniferin is a derivative of RSV, which has several isomers: e.g., α-viniferin, β-viniferin, γ-viniferin, δ-viniferin, ε-viniferin, R-viniferin (vitisin A), R2-viniferin (vitisin B). δ-Viniferin is a dehydrodimer of RSV, respectively an isomer of ε-viniferin. It occurs *in vitro* by oxidative dimerization of RSV by plant peroxidases or fungal laccases. Also, δ-viniferin was recently identified in wines, in cell cultures and in grapevine leaves infected with *Plasmopara viticola* or irradiated with UVC. δ-Viniferin, identified in higher concentration than ε-viniferin, is one of the most important phytoalexins derived from RSV. Viniferins have a series of important biological activities, such as: anti-inflammatory, anti-psoriatic, anti-diabetic, anti-parasitic, anti-cancer, anti-angiogenic, antioxidant, anti-melanogenic, neuroprotective, antiviral, antibacterial, antifungal, anti-diarrheal, anti-obesity [Fuloria et al., 2022; Pezet et al., 2003].

Pallidol is a natural dimer of RSV, also identified in red wine, with antioxidant and antifungal properties. At low concentrations, pallidol has strong singlet oxygen inactivation effects, being ineffective in eliminating hydroxyl radicals or superoxide anions. Kinetic studies showed that the reaction of pallidol with singlet oxygen had a very high constant. Therefore, pallidol could be used as a pharmacological agent in singlet oxygen-mediated diseases, thus contributing to the beneficial health effects of red wine [He et al., 2009].

Hopeaphenol, identified for the first time in red wine, especially from the Merlot variety, has a stilbenoid tetramer structure. It was determined by reversed-phase high-performance liquid chromatography (RP–HPLC) analysis of wine samples from North Africa (Algeria), alongside the known stilbenoid components: tRES, *trans*-piceid, *trans*-ε-viniferin, pallidol [Guebailia et al., 2006].

3. Anti-Tumoral Properties

Chemoprevention by non-toxic agents, such as RSV, has been demonstrated to provide protection against various cancer types. Nevertheless, the molecular mechanisms responsible for anti-tumorigenic or chemopreventive actions of this phytochemical continue to be mostly unidentified [Aziz et al., 2003].

3.1. Leukemia and Lymphoma

RSV has been determined to inhibit carcinogenesis in murine models. Besides its chemopreventive action, it also induces apoptotic cell death in human leukemia cells, exhibiting specific involvement of the cluster of differentiation (CD)95-CD95L system in the anti-tumoral activity of RSV and emphasizing the chemotherapeutic ability of this natural compound [Clément et al., 1998]. It is a significant inhibitor of ribonucleotide reductase and DNA synthesis in mammalian cells, with possible utilizations as an antiproliferative and chemopreventive factor [Fontecave et al., 1998].

Studies demonstrate that RSV can inhibit every step of multistage carcinogenesis, by reducing viability and DNA synthesis ability of promyelocytic leukemia cells, inducing the apoptotic cell death, and decreasing the expression of anti-apoptotic B-cell lymphoma-2 (Bcl-2) [Surh et al., 1999]. In the concentration spectrum of 20 μM and higher, blocked the S-phase and caused apoptosis in the T-cell acute lymphoblastic leukemia (T-ALL), insufficient in functional

p53 and p16 [Bernhard et al., 2000]. Other studies had the same results in human histiocytic lymphoma cells, indicating that RSV is an important cell cycle blocker, in addition to being a chemopreventive agent [Park et al., 2001].

In the case of acute monocytic leukemia, researchers have shown that RSV inhibits the growth of THP-1 cells by inducing apoptosis, independent of the Fas/FasL signaling pathway and has no toxic effect on differentiated THP-1 cells [Tsan et al., 2000]. Other data established RSV and its correspondent, piceatannol, are powerful generators of apoptosis in BJAB Burkitt-like lymphoma cells, with a median effective dose of 25 μM, autonomous of the CD95/Fas signaling cascade [Wieder et al., 2001].

tRSV, ε-viniferin and vineatrol induced apoptosis in chronic leukemic B cells, by activating caspase-3, reducing the mitochondrial transmembrane potential, and inhibiting both the expressions of the Bcl-2 anti-apoptotic protein and the inducible nitric oxide (NO) synthase [Billard et al., 2002]. Some studies suggest the involvement of apoptosis signal-regulating kinase 1/c-Jun N-terminal kinase signaling in the regulation of FasL expression and following apoptosis induced by RSV in leukemia cells [Su et al., 2005].

The inhibitory effect on hydrogen peroxide (H_2O_2)-induced apoptosis is attributed to the antioxidant property of RSV, which, in small concentrations, can inhibit death signaling in human leukemia cells via nicotinamide adenine dinucleotide phosphate reduced form (NADPH) oxidase-dependent increase of intracellular superoxide that stops mitochondrial H_2O_2 synthesis [Ahmad et al., 2004].

Researchers determined that RSV has the ability to sensitize cancer cells to X-irradiation. The study involved cervix carcinoma, chronic myeloid leukemia and multiple myeloma and demonstrated that the addition of RSV alone induced apoptosis and inhibited cell growth, while concomitant treatment with either RSV or X-irradiation caused a synergical reaction [Baatout et al., 2004].

It has been discovered a plasma membrane receptor for RSV near the arginine–glycine–aspartate recognition site on integrin α(v)β₃ that participates in the proapoptotic mechanism of RSV in tumor cells, along with stimulating the intranuclear COX-2 accumulation, correlated to the activation of p53 [Lin et al., 2011].

The possible anti-tumour actions of RSV against the natural killer (NK) cell malignancies, especially aggressive NK cell leukemias and lymphomas include strong G0/G1 cell cycle blockage, substantially restriction of cell proliferation and apoptosis. Furthermore, RSV caused synergistic activity on the apoptotic and antiproliferative effects of L-asparaginase against cancer cells [Quoc Trung et al., 2013].

There are major distinctions in the anti-viability action of RSV among different types of human cancer cells. Some studies imply that RSV has the ability to cause apoptotic cell death in human leukemic cells considerably more than in human solid tumor cells, by reducing Akt activation due to Ras downregulation [Takashina et al., 2017].

3.2. Glioma, Glioblastoma and Neuroblastoma

Neuroblastoma is an aggressive type of tumor, which requires a more efficient and less cytotoxic treatment. Studies indicate that the activity of RSV in neuroblastoma cells can be mediated by functionally activated p53 [Liontas & Yeger, 2004]. RSV intervenes in the proliferation, apoptosis, and cell cycle modification of neuroblastoma cells, inducing important cytotoxicity and increased apoptosis. S-phase accumulation is connected to the downregulation of p21 and up-regulation of cyclin E [Chen et al., 2004].

During an investigation in rat gliomas, RSV exerted important glioma cell cytotoxicity and apoptosis, induced antitumor effects on the spinal cord and intracerebral gliomas and inhibited angiogenesis in spinal cord gliomas [Tseng et al., 2004]. RSV elevates cellular cytotoxicity and inhibits the proliferation of rat neuroblastoma cells, by activating mitochondria-mediated intrinsic caspase dependent pathway [Rahman et al., 2012].

Human glioma cells were utilized to comprehend the molecular mechanisms of the anticancer effect of RSV. The phytocompound caused apoptosis of glioma cells, as evaluated by lactate dehydrogenase release and internucleosomal DNA fragmentation analysis. RSV activated caspase-3, which lead to cytochrome c release from mitochondria to the cytoplasm and activation of caspase-9 [Jiang et al., 2005].

RSV has the ability to suppress the growth and proliferation of glioma and improve its apoptosis through upregulating the leucine repeat immunoglobulin-like protein 1 (LRIG1) gene expression, which stimulates antiglioma growth, suggesting that LRIG1 is a new biological objective in antiglioma cell proliferation and growth [Liu et al., 2018].

Researchers investigated autophagy induced by RSV in human glioma cells, which inhibited growth and induced cell apoptosis. Glioma cells firmly expressing green fluorescent protein (GFP) merged to LC3, engaged more GFP–LC3-labeled autophagosomes, and elevated the percentage of cells with GFP–LC3-labeled autophagosome. Also, RSV-induced autophagy was regulated by P38 and the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [Yamamoto et al., 2010].

Glioblastoma multiforme is the most destructive intracranial tumor that overexpresses the YKL-40 gene, related to the tumor stages of human primary astrocytomas and glioma cell proliferation. It was confirmed that RSV inhibits YKL-40 expression, by limiting the exertion of its supporter and decreasing messenger ribonucleic acid (mRNA) transcription and protein activity *in vitro*, involving the ERK1/2 pathway [Zhang et al., 2010].

Invasion and metastasis of glioblastoma-initiating cells are accountable for the evolution and recurrence of glioblastoma multiforme. *In vitro* and *in vivo* observations suggest that RSV inhibits the adhesion, invasion, and migration of glioblastoma-initiating cells. Furthermore, it suppresses the invasion of glioblastoma-initiating cells by the inhibition of PI3K/Akt/NF-κB signal transduction and the following suppression of MMP-2 expression [Jiao et al., 2015].

Recent findings exhibited the effect of RSV for the amelioration of glioblastoma inflammatory response by reducing NOD-like receptor protein 3 (NLRP3) inflammasome activation through inhibition of the Janus tyrosine kinase 2/signal

transducer and activator of the transcription 3 (JAK2/STAT3) pathway [Zhang et al., 2024].

3.3. Meningioma
RSV may be effective in meningioma cells because it decreases proliferation and stimulates apoptosis. It elevates the levels of cleaved caspase-3 protein, in addition to reducing the levels of pro-caspase-3 protein and Bcl-2 mRNA. The 3'-untranslated region (3'-UTR) of Bcl-2 includes binding sites for miR-34a-3p, which can regulate the expression of a luciferase reporter. Overexpression of miR-34a-3p decreases Bcl-2 protein levels in meningioma cells. To conclude, RSV inhibits proliferation and induces apoptosis in meningioma cells by upregulating miR-34a-3p, which consecutively downregulates Bcl-2 [Hu et al., 2019].

3.4. Estrogen-Dependent Pituitary Tumor
Phytoestrogens have been widely studied, due to their capacity to reduce the incidence of various estrogen-dependent tumors. Some of them were proven to be active in pituitary tumor cells, by binding to the ERs, stimulating growth and causing an estrogenic response, such as prolactin secretion. Nevertheless, RSV does not attach to the ERs. Zearalenone, genistein and coumestrol have been demonstrated to induce prolactin secretion and to encourage growth, while RSV exhibited prolactin secretion, but without growth stimulation [Stahl et al., 1998].

3.5. Breast Cancer
Breast cancer (BC) is one of the most prevalent tumors in females and is culpable for the principal cancer-related deaths after lung cancer. The anticancer mechanisms of RSV concerning BC involve the restriction of cell proliferation, decreasing of cell viability, invasion, and metastasis. However, its favorable therapeutic effects, it has limitations due to the reduced pharmacokinetics, stability, and poor water solubility, implying the help of nanodelivery systems to enhance its bioavailaha [Behroozaghdam et al., 2022; Quarta et al., 2021]. RSV-modified mesoporous silica nanoparticles (NPs) inhibit BC progression more efficiently, in comparison to the phytochemical alone, *via* suppressing the NF-κB signaling pathway, indicating that they are a novel and more secure method for applying in the complex therapeutics of BC [Gu & Fei, 2022].

Some research involved RSV-loaded solid lipid NPs that were properly designed to improve BC cells. The NPs presented a higher capacity than free RSV in suppresing the proliferation of tumor cells and displayed much better inhibitory actions on the incursion and migration of BC cells [Wang et al., 2017; Khazaei et al., 2024]. Additional data, important in the BC applications, established that transferrin–cathepsin B cleavable peptide modified mesoporous silica NPs encapsulated RSV substantially reduced cell viability and enhanced cell apoptosis [Li et al., 2023].

Studies have shown that RSV specifically stimulates the transcriptional activation of cytochrome P450 CYP1A1 and suppresses the formation of carcinogen-induced preneoplastic lesions in mouse mammary organ cultures. It also obstructs the development of mouse skin tumors in the two-stage models, it suppresses the enzymatic activities of COX-1 and COX-2 in cell-free models and inhibits COX-2 mRNA and tissue-type plasminogen activator (tPA)-induced activation of protein kinase C (PKC) and AP-1-mediated gene expressions in mammary epithelial cells [Bhat & Pezzuto, 2002].

There has been investigated a possible mechanism by which RSV could control the cell cycle and apoptosis, exploring the human BC MCF-7 cell line. The results showed a dose-dependent anti-proliferative effect of RSV, that was correlated with a notable inhibition of cyclin D and cyclin-dependent kinase (CDK)4 proteins and stimulation of p53 and CDK inhibitor p21$^{\text{WAF1/CIP}}$ [Kim et al., 2004; Kurzava Kendall et al., 2024]. Apoptosis caused by RSV was determined to happen exclusively in BC cells exhibiting wild-type p53, however not in mutant p53-expressing cells [Laux et al., 2004].

The growth factor heregulin-beta1 (HRG-β1) promotes the tumorigenicity and metastasis of human BC cells. MMP-9 is a crucial enzyme in the degeneration of extracellular matrices and has an altered expression in BC infiltration and metastasis. RSV showed anticarcinogenic activities in both *in vitro* and *in vivo* explorations that imply it suppresses the MMP-9 expression in BC cells, connected with the downregulation of the mitogen-activated protein kinase (MAPK)/ERK signaling pathway [Tang et al., 2008].

Metastasis is an important cause of decease in patients with BC. In the evolution of the tumor, epithelial–mesenchymal transition (EMT) is essential to supporting the invasion and migration of cancer cells. RSV suppresses the migration of human BC cells by invalidating the transforming growth factor-beta1 (TGF-β_1)-induced EMT and inhibits the lung metastasis in a xenograft-bearing mouse model [Sun et al., 2019]. The cytotoxic action of RSV on human BC cells may be correlated with its pro-oxidant effect, which inhibits casein kinase 2 activity, influencing cell viability and mitochondrial function [da Costa et al., 2022].

3.6. Hepatocellular Carcinoma
Many studies are designed to examine the chemopreventive action of various doses of RSV against hepatocellular carcinoma (HCC). It was demonstrated that a 100 mg/kg dose of RSV can be a suitable treatment for HCC produced by diethylnitrosamine in rats [Karabekir & Özgörgülü, 2020]. Other evidence revealed that RSV suppresses tumor necrosis factor-alpha (TNF-α)-regulated MMP-9 expression and progression of human HCC cells, which correlates with the inhibition of the NF-κB signaling axis [Yu et al., 2008]. RSV reduces cell proliferation, produces reactive oxygen species (ROS), and generates DNA single-strand breaks. Due to its ability to regulate the expression of proteins implicated in the redox pathways and apoptosis, RSV induces hepatic cancer cell death by inhibiting the expression of

antioxidant proteins [Choi et al., 2009].

It was demonstrated that several natural polyphenols stimulate the activity of telomerase. Recent studies show that silent information regulator 1 (SIRT1) and nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) are implicated in the modulation of human telomerase reverse transcriptase (hTERT). RSV, together with kuromanin chloride and gallic acid, stimulate the hTERT gene expression in the hepatocellular tumor cells, probably by activation of the SIRT1/Nrf2 signaling cascade. Accordingly, through addressing hTERT or this axis, the contra-tumor action of this class of phytochemicals might be increased [Moghadam et al., 2023].

When treated with a mixture of bioactive substances, RSV and berberine, human HCC cells, Hep-G2 and Hep-3B, with various p53 status, showed distinct reactions in cell viability by p53-reliant apoptosis pathway activation. An efficient concentration of berberine, combined with RSV, could be decreased even to 50% in tumor therapy and substantially decreases the viability of wild type p53 Hep-G2 and null p53-mutant Hep-3B. Therefore, p53 status in hepatocellular tumor cell lines regulates the reactions to phytotherapies [Skonieczna et al., 2022].

3.7. Pancreatic Carcinoma

Pancreatic tumor, one of the most frequent causes of cancer-connected mortality, has a weak outcome, brief survival rate and resistance to therapy. Studies have shown that RSV has chemopreventive and treatment action in pancreatic cancer: it reduces the propagation of pancreatic cancer cells; generates apoptosis and cell cycle arrest; prevents metastasis and infiltration of pancreatic cancer cells; obstructs the reproduction and viability of tumor stem cells; increases the chemoradiosensitization of cancer cells [Xu et al., 2015].

The examination of the mechanisms implicated in the *in vitro* antitumor activity of RSV revealed that it suppresses the proliferation of pancreatic cancer cells, which, after incubation with RSV, lead to cell apoptosis and cell cycle cessation. RSV generates the activation of caspases, modulates the activity of the contra-apoptotic proteins Bcl-xL, Bcl-2 and X-linked inhibitor of apoptosis protein (XIAP) and the proapoptotic protein Bax [Cui et al., 2010].

RSV performs dual functions in pancreatic tumors: as a cancer inhibitor by the up-regulation of Bax and as a carcinoma activator by the up-regulation of vascular endothelial growth factor-B (VEGF-B). However, the antitumor action of RSV is more powerful than the cancer stimulating one. As a result, the association of RSV with pharmacological inhibitor of VEGF-B can be a valuable clinical approach in the treatment of pancreatic cancer [Yang et al., 2014]. Moreover, polydopamine-based RSV–hyaluronidase nanomedicine inhibited pancreatic cancer cell invasive phenotype in hyaluronic acid enrichment tumor sphere model [Yu et al., 2024].

Hyperlipidemia acute pancreatitis is an important undercover threat concerning our health. Hence, researchers analyzed the preventive influence and the intrinsic mechanism of RSV in the hyperlipidemia acute pancreatitis in mice and discovered that the RSV pretreatment efficiently suppresses pancreatic pathological injury, inhibits inflammation and oxidative stress, by restraining the NF-κB signaling pathway and improving intestinal microbiota [Zhang et al., 2022c].

3.8. Esophageal Carcinoma

The purpose of several studies was to investigate the probability and possible mechanism of the inhibition of N-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis by RSV. It substantially reduces the up-regulated expression of COX-1 and COX-2 and the enhanced levels of prostaglandin (PG)E2 synthesis and for that reason it can be a promising natural anti-carcinogenesis factor for the prevention and therapy of human esophageal cancer [Li et al., 2002].

In vitro experiments were conducted to evaluate the RSV-induced apoptosis in esophageal cancer cells and its connection to the expressions of Bcl-2 and Bax. They concluded that RSV is capable of generating apoptosis in esophageal tumors by influencing the expressions of these two apoptosis-modulated genes: down-regulating Bcl-2 and up-regulating Bax [Zhou et al., 2003].

3.9. Gastric Cancer

Gastric cancer (GC) is one of the most frequent tumors with serious malignancy. Numerous studies have determined the implication of Wnt, Nrf2, MAPK, and PI3K/Akt signaling pathways in this type of cancer. RSV involves several signaling pathways to generate apoptotic cell death along with obstructing the migration and metastasis of GC cells [Ashrafizadeh et al., 2021].

Some observations showed that RSV is capable to decrease viability and generate apoptosis in GC cells by suppressing NF-κB activation [Wu et al., 2018]. Other studies established that RSV elevates superoxide dismutase (SOD) activity but reduces NF-κB transcriptional activity and heparanase enzymatic activity, which corresponds with the diminishing of invasion potential in GC cells [Rojo et al., 2022].

It has also been reported that RSV inhibits the proliferation, migration, and invasion of human gastric tumor cells through the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/micro-ribonucleic acid (miRNA)-383-5p/DNA damage-inducible transcript 4 pathway and generates apoptosis [Yang & Xia, 2022]. Overexpression of miRNA-155-5p, which generates oncogenesis in gastric tumors, is regulated by RSV, being one of the mechanisms that confirms the important antiproliferative activity of this phytochemical [Su et al., 2022b].

Chemotherapy toxicity is not principally caused by the medication itself, but is generated *via* cell-free chromatin particles, that are discharged from chemotherapy-induced decaying cells and are immediately internalized by healthy cells, at which point they produce double stranded DNA (dsDNA) breaks and stimulate inflammatory cytokines. It has been discovered that they can be inactivated by oxygen radicals that are induced after treatment with RSV and copper

and consequently curtail chemotherapy toxicity [Ostwal et al., 2022].

3.10. Colorectal Carcinoma

Chemotherapy is universally used for treating colorectal tumors. Because of the high toxicity to normal cells and the emerging cancer resistance, it is preferable to use chemotherapy combined with natural bioactive agents that can assuage the side effects, as coadjuvants. It was confirmed that the co-administration of RSV along with with chemotherapy has higher anti-proliferative effect, elevates chemotherapy-induced cytotoxicity, and synergistically has the ability to sensitize tumor cells to chemotherapy as a result of its oxidative, proapoptotic and anti-inflammatory action [Wu et al., 2023].

An RSV tetramer, vaticanol C, identified in the stem bark of *Vatica rassak*, subtsantially inhibits cell proliferation via initiation of apoptosis, which was represented by nuclear alterations and DNA ladder development, in several distinct human colon cancer cell lines [Ito et al., 2002]. Another phytocompound, tRSV, has antiproliferative effect without cytotoxicity and generates apoptosis in human colorectal carcinoma, through a ROS-dependent apoptosis pathway [Juan et al., 2008].

Certain articles submitted that the anti-tumor activity of RSV is viable by activating Hippo/YAP signaling and moderately perturbing the YAP–TEAD interaction, a very useful information in colon cancer therapy [Qin et al., 2022]. Reports documented that 0.5 g or 1.0 g of RSV *per os* every day generate efficient concentrations in the human digestive tube to induce antiproliferative activity, showing great potential as a colorectal cancer chemopreventive agent [Patel et al., 2010]. The anti-proliferative effect of a standardized combination of compounds: tRSV, quercetin, vitamin E and selenium (Neoplasmoxan) was reported in mouse colorectal carcinoma, suggesting that this preparation may be a synergic treatment in addition to standard chemotherapy or radiotherapy [Czapla et al., 2022].

When the comparative analysis of the anti-proliferative, proapoptotic and oxidative stress potential of RSV–zein NPs *versus* free RSV was performed against human colorectal carcinoma cells, the following observations were made: the NPs achieved cell cycle suppression promoted by enhanced cytotoxicity, response, and oxidative stress markers concentrations than RSV alone. These data suggests that the chemopreventive profile of RSV is expanded, as a result of the efficacious delivery system using histocompatible nano-dispersion [Khayat et al., 2022].

3.11. Lung Cancer

The anti-tumor effect of RSV has been connected to transformations in the sphingolipid metabolism. The analysis performed on the enzymes accountable for the aggregation of two most relevant sphingolipids, apoptosis-promoting ceramide, and proliferation-stimulating sphingosine-1-phosphate (S1P), in human lung adenocarcinoma cells, revealed that RSV administration enhanced apoptosis-promoting ceramide and sphingosine and reduced sphingomyelin and S1P [Momchilova et al., 2022].

Studies show that RSV generated apoptosis in lung cancer cells by precisely targeting phosphoAkt (pAkt) and cellular FLICE-like inhibitory protein (c-FLIP) downregulation, as a result of proteasomal degradation contingent to epidermal growth factor receptor (EGFR) [Wright et al., 2017]. Other data determined that inhibits lung tumor cells proliferation by suppressing COX-2 expression [Li et al., 2018b]. New mechanisms of RSV tumor suppression have been discovered, implying that this phytochemical has the ability to reprogram M2-like tumor-associated macrophages and tumor-infiltrating CD8T effector cells [Zhang et al., 2022b].

Further investigations reported the implication of autophagy in RSV-induced apoptosis and its possible molecular mechanisms *via* Ca^{2+}/adenosine-monophosphate activated-protein kinase (AMPK)–mammalian target of rapamycin (mTOR) signaling pathway in human lung adenocarcinoma cells [Zhang et al., 2013]. In a non-small-cell lung cancer assay, RSV-induced autophagy, and apoptosis at levels higher than 55 μM were mediated by the nerve growth factor receptor–AMPK–mTOR signaling pathway [Li et al., 2022b].

There are numerous indications that cancer stem cells are a crucial conductor of carcinogenesis and tumor reoccurrence, involving cytokines and chemokines – the cellular and soluble constituents of the tumor microenvironment. The expression level of interleukin (IL)-6 is interconnected to the existence of lung cancer stem-like cells in human lung carcinoma. RSV has the ability to multi-target lung cancer stem-like cells and IL-6 in the tumor microenvironment, being an innovative approach in the therapy and prevention of lung cancer [Xie et al., 2022].

Regarding the lung cancer metastasis of melanoma, the cytotoxicity of RSV was assessed in immunocompetent mice. The *in vitro* development of melanoma cells was substantially inhibited by RSV. The average survival rate of mice was improved, and the lung tumor proliferation was suppressed through *in vivo* intraperitoneal injection of 40 mg/kg RSV. The lung tumors exhibited enhanced interferon-gamma (IFN-γ) and C-X-C motif chemokine ligand 10 (CXCL10) levels and reduced angiogenesis and infiltration [Davoodvandi et al., 2020].

3.12. Bladder Cancer

Relevant information about the influence of RSV on human bladder carcinoma cells disclose that its effects are dose-dependent and may encourage the creation of impending chemoprevention approaches. Elevated doses of RSV produce apoptosis of bladder tumor cells, while reduced dosage provides protection, by regulating Bcl-2 protein, during oxidative stress condition [Stocco et al., 2012].

When the effects of RSV were evaluated in two human renal cell carcinoma cell lines, the findings indicated that it inhibits cell proliferation, migration, and infiltration, due to deactivation of the Akt and ERK1/2 signaling cascades, depending on concentration and time [Zhao et al., 2018].

Recent studies demonstrated the antiproliferative action of RSV in bladder tumor cells, mediated by the ROS production, intervention in the cell cycle and suppression of cell migration, regardless of their tumor protein p53 (TP53) status. The enhanced ROS formation after RSV administration was concluded by decreased cell viability and proliferation in all bladder cancer cell lines [Almeida et al., 2023].

3.13. Cervical Carcinoma
Cervical cancer is one of the most prevalent tumors in women, especially in developing countries. In order to find more affordable approaches in therapy, many studies included plant polyphenols, such as RSV or pterostilbene, which have presented antitumor and anti-human papillomavirus (HPV) effect opposed to cervical cancer cells. They reduce clonogenic survival, diminish cell migration, block cells at the S-phase and decrease the number of mitotic cells. The data confirmed a mechanism that concerns the downregulation of the HPV E6 oncoprotein, re-establishment of functional p53 protein and stimulation of apoptotic pathways, with pterostilbene being more effective comparative to RSV [Chatterjee et al., 2018].
RSV suppresses proliferation and generates apoptosis in human cervical cancer cells in a dose and time-relative process. The RSV-inflicted cell shrinkage and apoptosis is followed by the stimulation of caspase-3 and caspase-9, upregulation of the proapoptotic Bcl-2-associated X protein and downregulation of the contra-apoptotic genes Bcl-2 and Bcl-extra-large. Moreover, p53, an indispensable protein for cell survival and cell cycle continuity, presents RSV-induced increased expression levels in cervical carcinoma cells [Li et al., 2018a].
Currently, it was concluded that RSV causes the apoptosis and inhibition of the migration and invasion of cervical tumor cells by inhibiting the Hedgehog signal pathway. This natural compound downregulates the expression levels of Hedgehog signal pathway proteins (smoothened, zinc finger transcription factors and sonic hedgehog homolog). The Hedgehog agonist purmorphamine inverts the effects of RSV [Jiang et al., 2022].

3.14. Ovarian Cancer
Epithelial ovarian carcinoma constitutes the deadliest gynecological tumor and a considerable health problem, because of the serious mortality percentage. The potential antitumor action of RSV was appraised concurrently in *in vitro* and *in vivo* ovarian cancer. Even though it was efficient in inhibiting the *in vitro* cellular invasion of ovarian cancer cells, it was inactive in *in vivo* ovarian cancers in rats [Stakleff et al., 2012].
However, when the anti-cancer mechanism of RSV was evaluated in human ovarian cancer cells, it was validated that RSV generates ROS, which provokes autophagy and following apoptosis. RSV stimulates autophagy-related gene 5 (ATG5) expression and triggers LC3 cleavage. The RSV-induced apoptotic cell death was depreciated by pharmacological and also genetic suppression of autophagy, by silencing RNA (siRNA)-targeting of ATG5. Therefore, it was confirmed that autophagy and RSV-induced apoptosis are correlated in human ovarian cancer [Lang et al., 2015].

3.15. Osteosarcoma
Osteosarcoma is a high-degree bone neoplasm with serious invasive capacity. It was reported that RSV suppresses proliferation and glycolysis, generates apoptosis, and decreases the invasiveness of osteosarcoma cells *in vitro*. In addition to this, RSV downregulates the expression of interconnected Wnt/β-catenin signaling pathway target genes and enhances the level of E-cadherin. In an extended-time administration of RSV, the expression of connexin 43 (Cx43) was enhanced. Therefore, this data confirms that the anticancer influence of RSV on osteosarcoma cells is achieved *via* up-regulating Cx43 and E-cadherin and inhibiting the Wnt/β-catenin signaling pathway [Xie et al., 2017; Viegas et al., 2024].
Various studies invesigated the role of RSV on proliferation and apoptosis in osteosarcoma cell lines and associated it with the activation of the SIRT1/silent information regulator 2 (SIR2) family of nicotinamide dinucleotide oxidized form (NAD$^+$)-dependent deacetylases, which influences the calorie restriction-regulated tumor inhibition. SIRT1 protein has an increased expression in cancer cells than in normal osteoblasts. RSV generates apoptosis in osteosarcoma cells conditional to the dosage but has insignificant impact on normal osteoblasts. Moreover, the proapoptotic action of RSV may be stimulated by dietary limitation induced by L-asparaginase [Li et al., 2009].
Recent examinations certified that RSV prevents cell proliferation, migration, and invasion, initiating apoptotic cell termination in osteosarcoma cells. The mechanism might be the downregulation of NF-κB and Akt intracellular signaling transduction. Additionally, the association with pyrrolidine dithiocarbamate, an NF-κB inhibitor, determined combined inhibition of osteosarcoma evolution [Xu et al., 2020].

3.16. Epidermoid Carcinoma and Melanoma
Nonmelanoma skin cancer is the most frequent malignancy, caused by solar UV radiation, principally by its UVB segment (290–320 nm). RSV is a powerful antioxidant, known as "photochemopreventive agent" that can improve the damages provoked by UVB exposure to epidermis. In a study on hairless mice, the topical application of RSV suppressed the UVB-induced effects, such as: increase in bifold skin thickness, skin edema, induction of COX and ornithine decarboxylase (ODC) enzyme activities and protein expression of ODC, which are important factors in tumor development [Afaq et al., 2003; Synowiec-Wojtarowicz et al., 2023].
Regarding epidermoid carcinoma, the effect of RSV on transformed keratinocytes exhibiting mutant p53 was analyzed. It induced G1 cell cycle arrest, by significantly suppressing G1 cell cycle regulatory proteins, including cyclins A and D1, CDK6 and p53-independent induction of p21^{WAF1}. RSV also down-regulated activating protein 1 DNA-binding and

promoter activity, repressed MAPK/ERK1 or ERK1/2 signaling and inhibited c-Jun [Kim et al., 2006].

With reference to melanoma treatment, the aim of various surveys was to investigate the aptitude of RSV to complement chemotherapy. *In vitro* RSV substantially reduces melanoma cell viability, targeting only the cancer cells and exempting fibroblast cell lines. In comparison to the administration of temozolomide alone, the treatment of malignant cells with 50 μM RSV and temozolomide for 72 hours strongly augments cytotoxicity [Osmond et al., 2012]. Western blot analysis confirmed that RSV generates the apoptosis of human melanoma cells by increasing the expression of Bcl-2-associated X protein and Bcl-2, presumably through the p53 pathway and stimulation of caspase-9 and caspase-3 [Wu et al., 2015].

In a study intended to evaluate the chemopreventive and antimutagenic action of RSV against skin neoplasm *in vivo*, croton oil-induced increase of ODC effects of dorsal epidermis cells in mouse and mouse ear edema model were used to highlight the anti-promotion activity of RSV. Also, 7,12-dimenthylbenz[*a*]anthracene (DMBA)/croton oil was utilized to cause mouse skin cancer. Administration of RSV reduced ODC activity in croton oil-induced dorsal epidermis. It also was demonstrated that RSV could inhibit mouse skin papilloma produced by DMBA/croton oil, which involves expansion of cancer occurrence duration, reducing the prevalence of papilloma and decreasing tumor number per mouse [Fu et al., 2004].

3.17. Oral Carcinoma

Oral squamous cell carcinoma is the most typical tumor of the head and neck. Even though surgery, radiation, and chemotherapy are adequate therapeutic protocols, the medication tolerance and toxicity of oral cancer patients continue to be an issue. Various approaches on understanding the intrinsic mechanisms of RSV-induced apoptosis were conducted on this type of neoplasm. In the case of human tongue squamous cell carcinoma, the inhibitory effect of RSV was possible along the mitochondrial pathway and the suppression of cell invasion and migration by down-regulating the EMT-inducing transcription factors [Kim et al., 2014].

In vitro studies suggest that RSV influences the adhesion, migration, and infiltration of oral squamous cell carcinoma cells, therefore it has the ability to be a chemopreventive element for decreasing the invasion and metastasis [Shan et al., 2014]. Other data corroborated that RSV alone or in association with quercetin, in concentrations similar to red wines, are efficient inhibitors of oral squamous carcinoma cell evolution and proliferation [ElAttar & Virji, 1999].

In combination with copper, RSV can reduce tumor genome instability and inflammation, by inactivating the cell-free chromatin particles, with the help of oxygen radicals. Regarding the advanced squamous cell carcinoma of oral cavity, some results indicate that cell-free chromatin particles discharged into the tumor microenvironment from moribound malignant cells are universal generators for cancer manifestations and immune frontiers in remaining tumor cells. The capacity of this mixture to inactivate the chromatin particles, presents the possibility of an innovative and non-toxic therapeutic plan, which, instead of exterminating the cancer cells, provides treatment *via* inhibiting immune checkpoints and tumor hallmarks [Pilankar et al., 2022].

3.18. Nasopharyngeal Cancer

The underlying mechanism of RSV has been investigated in various tumors. Regarding human nasopharyngeal carcinoma cells, it inhibits cell proliferation by suppressing Ki67 and PCNA proteins and induces apoptosis by altering its analogous proteins, cleaved caspase-3 and cleaved caspase-9. RSV therapy diminishes the enhanced expression of Survivin that inactivates its reaction on cell growth and apoptosis. These results confirm that RSV can influence the cell proliferation and demise in nasopharyngeal carcinoma cells [Xiong et al., 2019].

Administration of RSV suppresses cell viability and generates apoptosis of the human nasopharyngeal carcinoma cells. Moreover, it was determined that RSV stimulates caspase-3 and modifies the Bax/Bcl-2 apoptotic signaling, due to the up-regulation of AMPK activity and inhibition of p70S6K and s6, succeeding components of AMPK [Cai et al., 2015].

3.19. Prostate Cancer

PC is one of the most frequent kinds of tumors in men, related to the unrestrained growth of the prostate gland. The evolution of androgen-independent PC implicates fundamental ERK1/2 activation, promoted by the epidermal growth factor/transforming growth factor-alpha/EGF receptor pathway. It was ascertained that RSV inhibits the ERK1/2 activation, by altering PKC, selectively its isozyme PKCα, in neoplastic human prostate epithelial cells *in vivo* [Stewart & O'Brian, 2004].

The antitumor effect of RSV in PC can be correlated to regulation of miRNAs, which are minuscule non-coding RNAs that antagonize gene expression. RSV down-regulates carcinogenic miRNAs and up-regulates cancer-inhibitor miRNAs in PC cells [Dhar et al., 2011]. This mechanism may be elucidated by its capacity to inactivate (ERK1/2), Akt and reduce the concentrations of estrogen and insulin growth factor-1 receptor, suppressing the Akt/miR-21 signaling pathway [Sheth et al., 2012].

New approaches support the benefit of RSV-loaded NPs for PC chemoprevention/ chemotherapy, due to the lack of adverse reactions on normal cells. Polymeric NPs encapsulating RSV were developed and they generated substantially higher cytotoxicity to PC cells than free RSV, whithout negative cytotoxic repercussions on murine macrophages, even at 200 μM [Nassir et al., 2018]. Similar results were obtained by the successful endeavor to expand systemic circulation and biological half-life of tRSV, utilizing solid lipid NPs, to raise its anti-tumor ability [Sharma et al., 2022].

The function of RSV as a radiosensitizer by targeting cancer stem cells in radioresistant PC cells was analyzed, employing stem cell markers and EMT markers, such as vimentin and E-cadherin. Association of RSV administration

with ionizing radiation, generated important decline in cell viability and stem cell markers genes and altered EMT markers [El-Benhawy et al., 2021].

Vasculogenic mimicry is specifically correlated to tumor progression and metastasis, being responsible for the poor prognosis of patients with PC. RSV decreases serum-induced invasion and vasculogenic mimicry formation in human PC cells. Blood-generated phosphorylation of erythropoiethin-producing hepatocellular A2 and the expression of vascular endothelial (VE)-cadherin at the mRNA and protein positions are reduced by RSV. Blood-induced AKT signaling cascade, as well as metalloproteinase-2 and laminin subunit 5 gamma-2, are damaged by this phytochemical [Han et al., 2022].

It is more and more aknowledged that the synergy of the glioma-associated oncogene axis and androgen receptor influences the evolution of PC. Recent *in vitro* and *in vivo* assyas on xenograft models in mice confirmed that RSV suppresses the hedgehog signals and tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) levels, to ameliorate PC progression. The mechanism of action involved EMT progression, reducing the tumor size and expressions of vimentin, VEGF and MMP-7, besides stimulating the expressions of E-cadherin and annexin 2 [Li et al., 2022c].

4. Neuroprotective Activity

4.1. Neurodegenerative Disorders

RSV, the polyphenol which can cross blood–brain barrier, has powerful neuroprotective effect on various neurodegenerative diseases by mitochondria modulation mechanism. Mitochondrial function alteration is the most frequent cause and pathological development in several neurodegenerative conditions, like amyotrophic lateral sclerosis, AD, Huntington's disease, or Parkinson's disease. The current accessible therapies for neurodegenerative disorders are only symptomatic treatments and have undeniable toxic reactions. In conclusion, there is a strong necessity for a safe, natural, and efficient therapy protocol [Yadav et al., 2022; Zhang et al., 2024; Shamsher et al., 2024].

AD is an escalating and neurodegenerative pathology of the cortex and hippocampus, which ultimately leads to cognitive deterioration. Despite its ambiguous etiology, the existence of β-amyloid peptides in the learning and memory areas is an indication of AD. It has been demonstrated that RSV has antioxidant, anti-inflammatory and neuroprotective effects and can reduce the toxicity and aggregation of β-amyloid peptides in the hippocampus, stimulate neurogenesis and avoid hippocampal impairment. Moreover, the antioxidant effect of RSV is very effective in neuronal differentiation, due to the activation of SIRT1. Because of the anti-inflammatory action, it inhibits M1 microglia activation, which plays a part in the induction of neurodegeneration and stimulates Th2 responses by enhancing anti-inflammatory cytokines and SIRT1 [Gomes et al., 2018; Bartra et al., 2024].

The mechanism and therapeutic action of RSV were explored in AD-like behavioral dysfunction caused by streptozotocin. The deteriorations in task-specific learning and memory provoked by the bilateral hippocampal microinjections of streptozotocin were improved by RSV. The mechanism is correlated to the modulation of brain-derived neurotrophic factor expression and synaptic plasticity-associated proteins in the hippocampus [Wei et al., 2022].

4.2. Chemical-Induced Neurotoxicity

The aqueous extract of RSV from methanol extracts of the roots of *Vitis thunbergii* var. *sinuata* (*Vitaceae*) showed substantial neuroprotection contra glutamate-caused neurotoxicity in primary cultured rat cortical cells. By using fractionation processes, five RSV derivatives [vitisinols A, B, C, (+)-vitisin A and (+)-vitisin C] were isolated. Three of them presented the most important neuroprotective effect opposite to the neurotoxicity produced by glutamate, as recorded by a cell viability of relatively 75–85%, at concentrations varying from 0.1 µM to 10 µM [Chung et al., 2011].

4.3. Scopolamine-Induced Cognitive Impairment

Researchers evaluated the role of RSV on cognitive disorder caused by scopolamine, a muscarinic antagonist, in mice. Scopolamine induced considerable extension of transfer latency on elevated plus maze, decrease in step-down latency on a passive avoidance apparatus and also escape latency in Morris' water maze test as well, demonstrating cognitive deterioration. Unfortunately, RSV administration did not annul the effects of scopolamine and, therefore, did not improve the loss in cognitive functions in mice [Gupta et al., 2012].

4.4. Resveratrol Against Brain Injury

Traumatic brain injury is the most frequent type of craniocerebral injury that generates neurological deterioration and cognitive impairment. RSV recovers cognitive activity in neurological dysfunctions and senescent prototypes as a result of its anti-inflammatory effect. Synapse creation is crucial for cognitive function and synaptophysin is one of the significant elements implicated in synapse induction. SIRT1 has a neuroprotective influence in several biological mechanisms, such as metabolism, inflammation, apoptosis, and autophagy. It was concluded that RSV enhances synaptophysin *via* activating the SIRT1/peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1) cascade and promotes the post-traumatic brain injury cognitive activity [Yu et al., 2022].

The influence of RSV against brain injury caused by radiation in rats was assessed. The radiation group of rats exhibited an important reduction in catalase (CAT), SOD, glutathione peroxidase and glutathione reductase functions, including glutathione contents. The administration of RSV substantially improved these benchmarks in the brain tissues

of the animals. This result is connected to the capacity of RSV to target the free radicals, stimulate the activity of the antioxidant enzymes, enhance glutathione content, and inhibit the inflammatory reactions and apoptosis markers [Zhang et al., 2020].

5. Metabolic Disturbances
5.1. Metabolic Syndrome
Metabolic syndrome is an important health issue, correlated with enhanced risk factors for hepatic steatosis, which is the most frequent liver disorder nowadays. The protective actions of RSV over metabolic dysfunctions influenced by a high-fat high-fructose diet were analyzed. The following observations were made on metabolic syndrome rats: hepatic dysfunction, increased body weight, dyslipidemia, hepatic oxidative and inflammatory stress conditions, hepatic insulin resistance, stimulation of mRNA expression of sterol regulatory element binding protein 1c (SREBP-1c) and inhibition of mRNA expressions of peroxisome proliferator activated receptor-alpha (PPAR-α) and insulin receptor substrate-2 (IRS2). Treatment with RSV diminished liver steatosis, inflammatory state, and oxidative stress. Moreover, it ameliorated lipid profile, together with insulin reactivity and regressed modifications in hepatic mRNA expression levels of the investigated genes [Reda et al., 2022].

5.2. Antidiabetic Properties
Diabetic complications, such as cataract and nephropathy, have numerous and complex mechanisms. RSV was investigated for its inhibitory effect versus rat lens and kidney aldose reductase *in vitro,* together with its capacity to block the generation of advanced glycation end products. The phytoalexin considerably amended glycaemic status and renal function in diabetic rats, with an important reduction in the production of advanced glycation end products in the kidneys. This evidence highlights the capability of RSV as a potential therapeutic factor opposed to long-term diabetic complications [Ciddi & Dodda, 2014].

Quercetin and RSV have well-known favorable actions on diabetes and diabetic complication; nevertheless, the results of mixed treatment of these phytochemicals on diabetes are not completely elucidated. The combined treatment guarded the functions of hepatic glucose metabolic enzymes and structure of pancreatic β-cells from the diabetes, and it is remarkable that this cotreatment exhibited the most beneficial action on the diabetic rats [Yang & Kang, 2018]. Other assays proved that the nutritional polyphenols RSV and piceatannol reduce postprandial hyperglycemia and suggest that suppression of intestinal α-glucosidase function can be a possible mechanism associated to their antidiabetic effect [Zhang et al., 2017].

5.3. Hyperlipidemia, Hepatic Steatosis, and Synaptic Impairment
In order to evaluate the impact of RSV on the lipid profile, dose-response meta-analysis of randomized controlled trials were conducted. The evidence showed that the intake of RSV may substantially reduce the total cholesterol, triglyceride, and low-density lipoprotein (LDL)-cholesterol levels, without modifying the level of high-density lipoprotein (HDL)-cholesterol. The decrease of LDL-cholesterol was more important in trials with an extended duration and in patients with type 2 diabetes mellitus, demonstrating that the dosage of the RSV treatment is a crucial element [Cao et al., 2022].

RSV produced *via* microorganism biotransformation exhibits better purity compared to the naturally obtained RSV, at a reduced expense than the chemically synthesized one. The beneficial actions of this novel product were examined in hamsters on a high-fat diet and substantially decreased liver enzymes, total cholesterol, triglycerides, serum glucose and liver weight. Moreover, HDL-cholesterol was also enhanced, while blood LDL-cholesterol was reduced. Triglycerides in liver tissue and fatty liver level were decreased and memory-associated proteins, phosphorylation of calmodulin-related protein kinase II and synaptophysin, were enhanced in the cerebrum of the hamsters. In conclusion, the microorganism-biotransformed RSV has the potential to defend patients from hyperlipidemia, hyperglycemia, hepatic steatosis, and synaptic alteration [Su et al., 2022a].

5.4. Anti-Obesity and Anti-Atherosclerotic Effects
Atherogenic or high lipid nutrition is recognized to generate CVDs and several studies explore the cardio-protective role of RSV. The treatment with RSV everted the anomalous blood lipid profile in a test involving atherogenic rats. Moreover, it improved the enzymatic and non-enzymatic antioxidants and stimulated the lipid metabolic proteins, demonstrating its beneficial role on lipid metabolism. Additionally, RSV repaired the tissue impairment and preserved the morphology of cardiac tissue. Therefore, RSV protects the cardiovascular system damaged by high lipid nutrition and is a favorable healthy lifestyle-adjuvant [Meng et al., 2014].

Red wines are considered a great nutritional provenience for tRSV, but also for its derivatives, such as ε-viniferin, a RSV dimer that has a better anti-adipogenesis role in metabolic disorders. Furthermore, ε-viniferin is more efficient than tRSV, due to its anti-obesity and anti-inflammatory actions in mice exposed to high-fat nutrition [Ohara et al., 2015]. Other studies highlight that RSV, together with its dimers, ε-viniferin and δ-viniferin, are beneficial in restraining atherosclerosis *via* a related molecular mechanism, with distinct capability and competence [Wu et al., 2020].

Atherosclerosis is a pathological fundament of cardiovascular and cerebrovascular disorders, which involves signal transduction in its development. It was determined that RSV is very efficient in different stages of atherosclerosis evolution through modulating lipid metabolism, suppressing inflammatory reactions and ameliorating oxidative stress, *via* regulating the transforming growth factor/extracellular regulated protein kinases signaling axis [Guo et al., 2022].

5.5. Polycystic Ovary Syndrome

Polycystic ovary syndrome is the most frequent endocrinopathy concerning women of reproductive age, especially involving hyperandrogenism. Assays on individualised ovarian theca-interstitial cells indicated that RSV decreases androgen formation, substantially inhibiting ovarian and adrenal androgens by stimulating insulin sensitivity and reducing the insulin level [Banaszewska et al., 2016]. Recent investigations assert that RSV presents valuable phytoestrogenic properties and induce hormonal regulation in rats with polycystic ovary syndrome. RSV treatment generates enhanced levels of plasma adiponectin and estradiol, recuperation of normal ovarian morphology and elevated ovarian expression of nesfatin-1 and aromatase at the RNA and protein levels [Zhang et al., 2021a].

The nutraceutical preparation mixture consisting in RSV, alpha-lipoic acid, folic acid, vitamin D and vitamin B provided favorable results for alleviating the metabolic profile of women with polycystic ovary syndrome. Following 12 weeks of therapy, body mass index, anthropometry and bioimpedance hallmarks were all decreased in the treated patients [Malvasi et al., 2022].

In a study participating one hundred and ten patients, the treatment with both RSV and myoinositol was substantially more efficient than metformin and pioglitazone in improving abnormal endocrine, metabolic markers and stress burden and has excellent potential in high-risk category of obese, oligo-anovulatory women with polycystic ovary syndrome [Hassan et al., 2023]. Another inquiry established that the protective actions of RSV on ovulation in rats with polycystic ovary syndrome is correlated to the modulation of glycolysis-dependent mediators, such as pyruvate kinase isozyme M2, lactate dehydrogenase A and SIRT1 [Huo et al., 2022].

5.6. Anti-Aging Properties

RSV and caloric restriction are very potent treatment alternatives for anti-aging and were compared *in vitro* and *in vivo*, regarding their activities in longevity-related gene silencing information regulator, SIRT1. Interestingly, 10 μM RSV *in vitro* and a higher dose *in vivo* exhibited superior anti-aging effects and SIRT1-stimulation degrees, compared to caloric restriction, implying the promising potential of the phytocompound as a caloric restriction-mimetic [Li et al., 2017].

RSV has a strong beneficial effect in lesion healing, regeneration and photoaging of the epidermis. Through the medium of complex mechanisms and pathways, it offers protection contra UV-B radiation, which is the principal element in skin aging development. Moreover, it increases collagen synthesis *via* stimulating the ERs and alleviates wrinkles. In deteriorated tissues, it expedites epidermis regeneration and healing by triggering VEGF. Undeniably, RSV is a valuable polyphenol in cosmetology, dermatology, and plastic surgery, being utilized in anti-aging products or administered topically on scars and lesions. Future approaches may involve RSV in the pharmacotherapy of various dermatoses [Leis et al., 2022].

6. Hepatoprotective Effect
6.1. Liver Ischemia–Reperfusion

Ischemia-reperfusion of the liver is a complex process that occurs during transplantation and surgery. The destructive repercussions of ischemia-reperfusion derive from the intense generation of ROS, which can provoke instantaneous tissue deterioration and numerous disastrous cellular reactions, including apoptosis, organ collapse and inflammation. The formation of ROS in the ischemia–reperfusion condition can impair the antioxidant system and produce liver depreciation. RSV has been demonstrated to possess antioxidant effects on liver lesion caused by ischemia-reperfusion in mice. The results revealed that hepatic ischemia happens after liver transplantation and that the administration of RSV in advance of reperfusion improves graft survival as a consequence of suppression of protein response signaling pathways, particularly protein kinase R-like ER kinase (PERK) and inositol-requiring enzyme 1alpha (IRE1α) [Totonchi et al., 2022].

6.2. Non-Alcoholic Fatty Liver Disease

NAFLD is a progressive disorder concerning the liver that compels efficient therapies to prevent liver damage. A micronized formulation of tRSV, with higher absorbtion and enhanced antioxidant action, proved to be more efficient than simple RSV preparations in humans. It was successful in decreasing the liver adipose tissue, including reducing insulin resistance and hepatic enzymes, such as serum glutamate pyruvic transaminase and gamma-glutamyl transpeptidase [Theodotou et al., 2019].

NAFLD is one of the most frequent origins of chronic liver disorder globally, associated with the escalation in body weight and obesity. The enlargement of lipids in patients with this condition causes insulin resistance, inflammatory reaction and oxidative stress in hepatocytes and modification of the circulating lipid and glycaemic profile. RSV might be effective in the management of NAFLD for its anti-inflammatory, antioxidant, and calorie restriction-like actions. *In vitro* and animal model assays have documented it decreases the hepatic conglomeration of lipids and promotes lipid and glycaemic metabolism, by initiation of the adenosine monophosphate (AMP)-activated protein kinase, SIRT1 and NF-κB signalling pathways [Tejada et al., 2021].

Polydatin is a natural precursor and glycosylated type of RSV, with different bioactivity. The responses of polydatin and RSV were measured against energy homeostasis disproportion in mice with a high-fructose nutrition. Overnourishment-activated ROS stimulate AMPK inhibition and metabolic dysfunction. In conclusion, it was firstly validated that polydatin treatment enhances the fecal concentrations of valeric and caproic acids, by altering gut microbiota; therefore, stimulating AMPK activation might be the intrinsic mechanism that polydatin is preferable to

RSV in ameliorating the lipid dysmetabolism [Zhao et al., 2022].

6.3. Anti-Hepatotoxic Activity

The liver is a crucial organ in the body and operates essential functions. RSV has favorable pharmacological effects in the therapy of several liver pathologies, such as fatty hepatitis, liver steatosis, liver carcinoma and liver fibrosis through its anti-inflammatory, anti-apoptotic, antioxidative and hepatoprotective actions. RSV reduces liver inflammation by inhibiting numerous proinflammatory cytokines. Additionally, it suppresses the NF-κB transcription factor, which initiates the inflammatory pathway and deactivates the PI3K/Akt/mTOR axis to inflict apoptosis. Furthermore, it decreases oxidative stress in hepatocytes by substantially diminishing malondialdehyde and NO and enhancing CAT and SOD. Because of its antioxidant, anti-inflammatory and anti-fibrotic effects, RSV curtails liver injury indicators. It is also a reliable natural antioxidant that improves the hepatotoxicity of noxious chemicals [Chupradit et al., 2022].

The hepatoprotective effect of RSV against ethanol-induced oxidative stress was examined *in vivo*. The fundamental mechanisms by which RSV exhibits its anti-oxidative activity on hepatic cells is explained through the generation of SOD activity and gene expression [Chen et al., 2016].

Recent investigations targeted the protective actions of RSV and avocado oil against paracetamol-generated hepatotoxicity in rats. The outcome illustrated that the total oxidant status was enlarged in the paracetamol lot, while the total antioxidant status was enhanced in the RSV and RSV plus avocado oil groups. The histopathological analysis determined necrotic regions in the livers of the rats. The administration of both RSV and avocado oil in advance, inverted the oxidative stress parameters, DNA deterioration and necrosis caused by paracetamol [Gokkaya et al., 2022].

7. Cardioprotective Properties

7.1. Coronary Heart Disease

Red wine is the most beneficial alcoholic beverage in reducing the incidence of coronary heart disease (CHD). There have been investigations of the mechanism of tRSV on human platelet aggregation and synthesis of eicosanoids from arachidonate by platelets. Numerous wine phenolic compounds and antioxidants were compared, tRSV and quercetin showing a dose-related reduction of platelet aggregation caused by thrombin and adenosine diphosphate (ADP). Moreover, tRSV suppressed the formation of thromboxane B2, hydroxyheptadecatrienoate and 12-hydroxyeicosatetraenoate, from arachidonate, conditioned by the dosage. This information emphasized the protective effect of red wine against atherosclerosis and CHD, due to tRSV [Pace-Asciak et al., 1995].

7.2. Myocardial Ischemia–Reperfusion

The preadministration of RSV has a benefic influence in mitochondrial activity and myocardial ischemia–reperfusion damage, due to the suppression of stromal interaction molecule 2 (STIM2), through the medium of miRNA-20b-5p. This data has been recently verified in a study on ninety rats, involving assyas to identify the expressions of Bcl-2, Bcl-2-associated X protein and cleaved-cysteine proteinase 3, together with the levels of mitochondrial membrane potential, ROS and adenosine triphosphate (ATP) [Li et al., 2022a].

7.3. Resveratrol as Vascular Protective Natural Compound

Vascular metabolic dysfunction is exhibited in numerous recurrent disorders, such as atherosclerosis, hypertension, and diabetes mellitus. Current appraisals have determined that RSV has valuable influence on repairing metabolism in endothelial cells and vascular smooth muscle cells. The regulation of cell metabolism activity is connected to the suppression of glucose uptake, inhibition of glycolysis, prevention against damages caused by fatty acids through stimulation of fatty acid oxidation, reduction of lipogenesis by increasing lipolysis and elevation of glutamine uptake and synthesis [Fan et al., 2022]. Vascular smooth muscle cells senescence is a critical element that stimulates the progression of CVDs. RSV has the ability to prevent vascular senescence *via* inhibiting oxidative stress and mitochondrial alteration by activating E2F1/SOD2 pathway [Liu et al., 2022].

7.4. Resveratrol and Calcium Fructoborate Supplementation in Subjects with Stable Angina Pectoris

The clinical and biological conditions of humans diagnosed with stable angina pectoris were investigated in a study that proposed to assess the results of *per os* treatment with calcium fructoborate (CaFB) and RSV. The following observations were highlighted: high-sensitivity C-reactive protein, an inflammation biomarker, was seriously reduced; the N-terminal prohormone of brain natriuretic peptide, a left ventricular function marker, was substantially decreased; the lipid markers were also influenced. The findings determined that the association of RSV with CaFB has favorable consequences in patients diagnosed with angina pectoris, improving their quality of life [Militaru et al., 2013].

8. Immunostimulatory Activity

The obstructive effects of RSV on the release of mediators from bone marrow-derived mouse mast cells were verified *in vitro*. Regulated by immunoglobulin E (IgE), the discharge of histamine, TNF-α, leukotrienes, and PGD2 were seriously suppressed by RSV; in addition, A23187-modulated release of histamine and leukotrienes was also actively decreased. RSV did not exhibit cytotoxic effect against mast cells and can, therefore, be an important non-selective blocker of mediator release from activated mast cells [Baolin et al., 2004].

The study of the influence of RSV alone and combined with cyclosporin A on the propagation of human peripheral blood T-lymphocytes, conversion into lymphoblasts, as well as IL-2 and INF-γ generation revealed that RSV can

significantly inhibit the proliferation and transformation of lymphocytes and the synergic mixture of RSV and cyclosporine A can stimulate immune suppression [Yu et al., 2003].

9. Antioxidant Effect

RSV has been determined to defend LDLs against peroxidative degeneration. Being a tyrosine kinase suppressor, it also has the capacity to inhibit intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 expressions and to stop the attachment of monocytes and granulocytes to endothelial cells. This mechanism is autonomous from its antioxidant action and provides a different interpretation [Ferrero et al., 1998].

Nutritional addition of RSV inhibits lipid peroxidation, the critical consequence of oxidative stress caused by chronic ethanol treatment. During a study on ethanol treated rats, RSV substantially counteracted the elevation in malondialdehyde, a marker of oxidative damage, concentrations in the liver, heart, brain and testi, demonstrating its protective effect [Kasdallah-Grissa et al., 2006]. Numerous assays evaluated the inhibitory effect of RSV in oxidative stress. However, the association of RSV and vitamins C and E is more efficient in protecting the cells than any of these antioxidants alone [Chanvitayapongs et al., 1997].

10. Bone Protection

Nutritional supplementation of RSV has beneficial effects against hip fracture risk in elderly patients. This information was documented by research involving recently diagnosed patients of hip fracture. The investigations included the administration of RSV and piceid, in addition to RSV-rich foods, such as grapes, apples and nuts. The results were more conspicuous in female and non-obese subjects and highlighted that alimentation with RSV correlates with decreased risk of hip fracture [Liu et al., 2023].

11. Wound Healing Properties

The role of local and systemic injections of RSV on open cutaneous wound healing was compared in rats. Both of them elevated the histological scores for collagen deposition, chronic inflammation, and granulation. Neovascularization rates were substantially higher in the subcutaneous RSV treatment category than in the intraperitoneal one. Both systemic and local administrations importantly boosted wound healing and enhanced the tensile strength of the epidermis. Local subcutaneous injection of RSV emerged to be a better therapeutic approach, compared to the systemic treatment, due to the neovascularization to help wound healing [Bilgic, 2021]. On the other hand, topical administration of 5% RSV ointment demonstrated to stimulate burn wound healing, by enhancing the progress of wound contraction, via collagen fibre synthesis, granulation tissue creation and epithelial regeneration in rats [Yoksa et al., 2022].

Diabetic injuries are problematic to heal because of constant inflammation and reduced angiogenesis. Platelet-derived extracellular vesicles are abundant in growth factors and cytokines that stimulate proliferation and angiogenesis. Nevertheless, individual medication therapy has reduced potency and release ability that can be improved by bioengineering, which combines active substances and materials to obtain synergic medication. A composite hydrogel was used as a wound cover for continuous RSV delivery from mesoporous silica NPs, combined with platelet-derived extracellular vesicles, and showed promising effects in modulating inflammation and angiogenesis of diabetic injuries and accelerating wound restoration [Zhu et al., 2022; Liu et al., 2024].

12. Anti-Inflammatory Effect

Oxaliplatin is an average chemotherapy medication that causes neurotoxicity. To examine possible treatment variants for the neuropathic pain and inflammatory reaction induced by oxaliplatin, RSV was intrathecally injected into the spinal cord of rats. The findings revealed that RSV administration decreased COX-2 expression and obstructed ROS generation. The anti-inflammatory mechanism of RSV inhibited astrocytic activation and induced an antinociception effect that relieved the neuropathic pain [Dong et al., 2022].

Assays of the significance of RSV in diabetic peripheral neuropathy emphasized the following results: the discomfort and temperature responses of diabetic mice were ameliorated; Nrf2 level was enhanced in the diabetic peripheral nerves and NF-κB axis suppression preserved nerves; RSV regulated the anti-inflammatory microenvironment of peripheral nerves through stimulating Nrf2 activation and the expression of phospho-p65 [Zhang et al., 2021b].

Due to its reduced bioavailability, the RSV NPs are a better solution and have higher neuroprotective role in a study involving rats with middle cerebral artery occlusion. Animals were tested for infarct volume, oxidative, inflammatory, and apoptotic markers. The mechanism of RSV involved the increased expressions of caspase-3 and caspase-9, and IL-1, IL-6 and TNF-α cytokines. Therefore, these findings show that suppression by RSV NPs has therapeutic effect in the ischemic stroke [Ashafaq et al., 2021].

Recent explorations presented that the treatment with either monomeric tRSV or RSV dimer (gnetin C from *Gnetum gnemon* seed extract) limits periodontitis, with higher decrease of bone loss being exhibited in the dimer lot than the monomer batch and that these effects are connected to reduced oxidative stress and consequently minimization of local inflammation by downregulation of IL-1β, a proinflammatory cytokine [Ikeda et al., 2022]. Another finding suggests that RSV suppresses systemic local inflammatory markers and systemic endotoxin and implies that 500 mg per day of RSV is the optimal dosage for patients with periodontitis [Zhang et al., 2022a].

13. Antimicrobial Activity

RSV manifests antimicrobial action opposite to a remarkably extensive spectrum of bacterial and fungal species. It has

the ability to modify bacterial expression of virulence nature, promoting decreased toxin formation, suppression of biofilm generation, limited motility and influencing the quorum sensing. In association with regular antibiotics, RSV stimulates the activity of aminoglycosides contra *Staphylococcus aureus*, while it inhibits the noxious activity of fluoroquinolones against *S. aureus* and *Escherichia coli*. Moreover, topical administration of this nutraceutical has proven beneficial in acne lesions provoked by the bacterium *Propionibacterium acnes*. Recent data illustrates that the synergic combination of RSV with specific antibiotics may increase their antimicrobial potency, alleviating the crescent issue of antimicrobial resistance [Vestergaard M, Ingmer, 2019].

Candida albicans is the principal candidosis-inducing fungal pathogen in humans and one of its most critical virulence elements is the capacity to synthesize biofilms. The antifungal effects of RSV alter the morphological transition of *C. albicans* following several hypha-inducing circumstances and reduce growth of the yeast-form and mycelia. Therefore, RSV has promising anti-*Candida* actions via suppressing existing or in the formation process *C. albicans* biofilms [Okamoto-Shibayama et al., 2021].

Topical bacterial infection produced by multidrug-resistant *Pseudomonas aeruginosa* is very difficult to treat, using polymyxins as the last alternative therapy, with unfavorable pharmacodynamics and pharmacokinetics, improbable to attain effective blood levels. Well-tolerated RSV had a synergic effect combined with polymyxin B therapy, when analyzed *in vitro* on antibacterial and anti-biofilm activities [Qi et al., 2022]. There was also established that Chilean red wines have antibacterial effect against *Helicobacter pylori*, due to the existence of RSV in their composition [Daroch et al., 2001; Spósito et al., 2024].

14. Antiviral Properties

Several scrutinies described that RSV has a cooperative effect in association with the nucleoside analogues, such as zidovudine, zalcitabine and didanosine, stimulating their activity against human immunodeficiency virus type 1 (HIV-1). Individual RSV did not produce cell toxicity and inhibited viral replication, while in peripheral blood mononuclear cells infected with human T-cell lymphotropic virus-IIIB (HTLV-IIIB) isolate of HIV, it decreased the inhibitory concentration of the nucleoside analogues. Identical antiviral effect was documented when didanosine was merged with RSV in peripheral blood mononuclear cells infected with HIV-1. The inclusion of RSV determined a 10-time amplification of the antiviral action of didanosine in infected monocyte-derived macrophages. In a test on HTLV-IIIB-infected T-lymphocytes, the RSV–didanosine mixture, but not independently, inhibited the viral infection [Heredia et al., 2000].

RSV has been demonstrated to have anti-herpes simplex virus (HSV) effect *in vitro*. To examine its activity *in vivo*, the abraded skin of mice was infected with HSV-1 and RSV cream was applied locally. The following findings were made: 25% RSV cream successfully inhibited lesion progression, while 12.5% RSV cream had the same effect only if applied one hour after infection; neither one was effective if applied twelve hours after infection. In addition, RSV cream, 10% docosanol cream and 5% acyclovir ointment were compared. RSV and acyclovir substantially obstructed the progression of HSV-1-caused epidermis lesions, while docosanol had no influence. The application of RSV provoked no dermal toxicity, such as erythema, scaling, crusting, lichenification or excoriation [Docherty et al., 2004].

Regarding human cytomegalovirus replication, extremely high concentrations of RSV were necessary to generate cytotoxicity opposed to developing or stagnant human embryonic lung fibroblasts. RSV obstructed the virus-activated epidermal growth factor receptor and PI3K signal transduction as well as NF-κB and Sp1 transcription factor activation, immediately post-infection. The mechanisms of the cytomegalovirus, such as DNA replication, PI3K signaling and transcription factor activation, were all suppressed by RSV. However, the virucidal action was incompatibile and also the antiviral effect of RSV was significantly reduced when administered four hours after infecton. As a result, this phytocompound engaged amid attachment and entry, *via* arrest of epidermal growth factor receptor activation and its succeeding effectors [Evers et al., 2004].

Worldwide, rotavirus is the principal originator for viral gastroenteritis in children, with no efficient therapy. The anti-rotavirus impact of RSV was inspected *in vitro*, including production of virion descendants, viral polyprotein expression, genomic RNA synthesis, antigen clearance and alterations in proinflammatory cytokines/chemokines in infant mouse cells. The assays concluded that RSV strongly limited rotavirus replication by inhibiting RNA formation, protein expression, viroplasm plaque generation, progeny virion synthesis and cytopathy. RSV treatment ameliorated the gravity of diarrhea, reduced viral titers and alleviated correlated symptoms [Huang et al., 2020].

The high-occurence hepatitis B virus infection requires successful therapeutics. A recent study prospected the influence of RSV on hepatitis B virus replication, utilizing *in vitro* and *in vivo* analysis, confirmed it suppresses cytotoxicity and virus replication. Through its mechanism of action via reducing miR-155 expression and stimulating autophagy, RSV proved to be a promising novel approach for the treatment of hepatitis B virus infection [Pan et al., 2022].

15. UHPLC–MS Analysis of *trans*-Resveratrol in Romanian Wines
15.1. Chemicals and Reagents

For the analysis of tRSV in wine samples through UHPLC–MS, the following chemicals and reagents were used: tRSV was purchased from Sigma-Aldrich (Taufkirchen, Germany) and utilized as a reference for identification and quantification processes. Acetonitrile, obtained from Merck (Darmstadt, Germany), served as one of the mobile phase components due to its excellent solvent properties and compatibility with MS. Formic acid, also sourced from Merck, was employed as a mobile phase modifier to enhance the ionization of tRSV during the MS detection phase. Ultrapure water was produced locally in our laboratory using the HALIOS 6 (Neptec, Montabaur, Germany) ultrapure water

system and was utilized as the aqueous component of the mobile phase and for all preparations requiring solvent. All reagents were of analytical grade and were used without further purification to ensure the integrity and reproducibility of the results, ensuring optimal separation, identification, and quantification of tRSV in the studied wine samples.

15.2. Calibration Curve for trans-Resveratrol Quantification

A stock solution of tRSV was prepared at a concentration of 1 mg/mL. From this stock solution, serial dilutions were made to create calibration standards at the following concentrations: 244.141 ng/mL, 122.070 ng/mL, 61.035 ng/mL, 30.518 ng/mL, and 15.259 ng/mL. These standards were prepared by diluting the stock solution with the initial mobile phase to achieve the precise concentrations needed. These diluted standards were then analyzed using the UHPLC–MS system under identical conditions to those of the wine samples. The resulting peak areas for tRSV at m/z 227 were plotted against their respective concentrations to construct the calibration curve. The linearity of the calibration curve was validated by the correlation coefficient (R^2) obtained from the linear regression of the data. This curve was crucial for quantifying the concentration of tRSV in the wine samples by interpolating the sample peak areas against the calibration data. Measurements were made in triplicate to ensure the accuracy and reliability of the data. The limits of detection (LOD) and quantification (LOQ) for tRSV were determined based on the standard deviation (SD) of the response and the slope of the calibration curve, ensuring precise and reliable quantification [Vlase et al., 2009; Svilar et al., 2019; Li et al., 2024].

15.3. Wine Samples

The study focused on the analysis of tRSV in four wine samples, all sourced from local Romanian vineyards to represent both white and red varieties, providing a comprehensive overview of tRSV content across different types of wine. The white wine samples included a Fetească Regală (W1), a traditional Romanian grape variety known for its aromatic profile and high acidity, and a Dry Muscat (W3), noted for its sweet floral aromas and dry finish. The red wine samples consisted of a Fetească Neagră (W2), an indigenous Romanian variety valued for its deep color, medium tannins, and berry flavors, and a Cabernet Sauvignon (W4), a globally recognized grape chosen for its robust structure and potential for aging. Each wine sample was stored and handled under controlled conditions to preserve its chemical integrity until analysis, aiming to explore the influence of grape type and wine style on the levels of tRSV and enhancing our understanding of how this phenolic compound varies within Romanian wines [Crăciun & Gutt, 2023].

15.4. UHPLC–MS Analysis

The UHPLC–MS analysis of tRSV in wine samples was conducted using a Waters Arc System coupled with a Waters QDa detector. Initially, all samples were diluted five-fold and then filtered through 0.2 μm filters before being injected into the system, with an injection volume set at 5 μL. The mobile phase comprised two components: (A) was 0.1% formic acid in water, and (B) was 0.1% formic acid in acetonitrile. The flow rate was maintained at 0.8 mL/min. The gradient program was as follows: from 0 to 1.8 minutes, (B) increased from 2% to 9%; from 1.8 to 4 minutes, (B) held steady at 9%; from 4 to 10 minutes, (B) rose from 9% to 30%; from 10 to 15 minutes, (B) escalated from 30% to 90% and was maintained at 90% until 16 minutes; from 16 to 17 minutes, (B) rapidly decreased back to 2% for re-equilibration. The column used was a Waters CORTECS C18 (4.6×50 mm, 2.7 μm), with the temperature controlled at 28℃ and samples maintained at 10℃. A 15-minute equilibration period was allowed between each injection to ensure consistent performance. The QDa mass spectrometer operated in negative mode, with the capillary voltage set at 0.8 kV and the cone voltage at 15 V. Mass spectra were acquired in the range of m/z 100–400, with selected ion recording (SIR) at m/z 227 for the specific quantification of tRSV, providing a robust and sensitive method for analyzing the presence and concentration of this compound in the wine samples [Vlase et al., 2009; Svilar et al., 2019; Li et al., 2024].

Our study included both white (W1 and W3) and red (W2 and W4) varieties, to evaluate the presence and concentration of tRSV. The calibration curve parameters, indicative of the method's current performance, are detailed, providing insight into the potential for precise quantification. It is important to note that while this analysis offers valuable initial data, the method is undergoing further validation to refine its accuracy and reliability. The results herein serve as a foundation for subsequent validation efforts and offer an early look at tRSV levels in these wines, contributing to the broader understanding of its distribution in Romanian viniculture.

The calibration curve (Figure 1) parameters presented in Table 1 demonstrate a robust analytical method for the quantification of tRSV. The wide linearity range of 15.259 to 244.141 ng/mL indicates that the method is capable of accurately measuring tRSV across a range of concentrations that are relevant for wine samples. This range comfortably exceeds the expected concentration levels in typical wine samples, allowing for precise quantification even in wines with lower tRSV content.
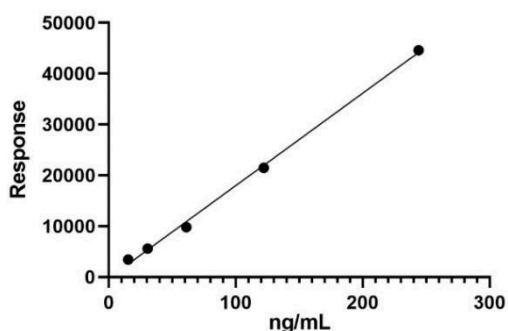
Figure 1. Calibration curve of *trans*-resveratrol displaying the detector response across a range of standard concentrations.

Table 1. Summary of calibration curve parameters for *trans*-resveratrol quantification.

Parameter	Values
Linearity range [ng/mL]	15.259–244.141
R^2	0.9979
Equation	$Y = 181.7X - 197.6$
LOD [ng/mL]	16.197
LOQ [ng/mL]	49.081

LOD: Limit of detection; LOQ: Limit of quantification; R^2: Correlation coefficient.

R^2 of 0.9979 reflects a high degree of linearity, suggesting that the response is directly proportional to the concentration over the range tested. This is critical for ensuring that the quantification is reliable, and that the method can be used confidently for routine analysis.

The equation of the calibration curve, $Y = 181.7X - 197.6$, provides the relationship between the instrument's response and the concentration of tRSV. The positive slope (181.7) signifies a strong response to increasing concentrations, while the intercept (-197.6) is relatively small compared to the slope, indicating minimal background noise or interference.

LOD and LOQ are also indicators of the method's sensitivity. With a LOD of 16.197 ng/mL and a LOQ of 49.081 ng/mL, the method is sensitive enough to detect and quantify even small amounts of tRSV. This is particularly important for scientific and regulatory purposes where it is necessary to detect all ranges of concentrations present in various wine samples.

The UHPLC chromatogram presents a distinct peak corresponding to the pure tRSV reference sample. The specificity of the peak is enhanced by the mass spectrometer's detection of the *m/z* 227 molecular ion, characteristic of tRSV. This suggests that the UHPLC–MS method provides high specificity, primarily due to the mass detection at *m/z* 227, ensuring that the observed peak can be confidently attributed to tRSV without interference from other substances. Such specificity is critical for accurate quantification in complex matrices like wine (Figure 2).
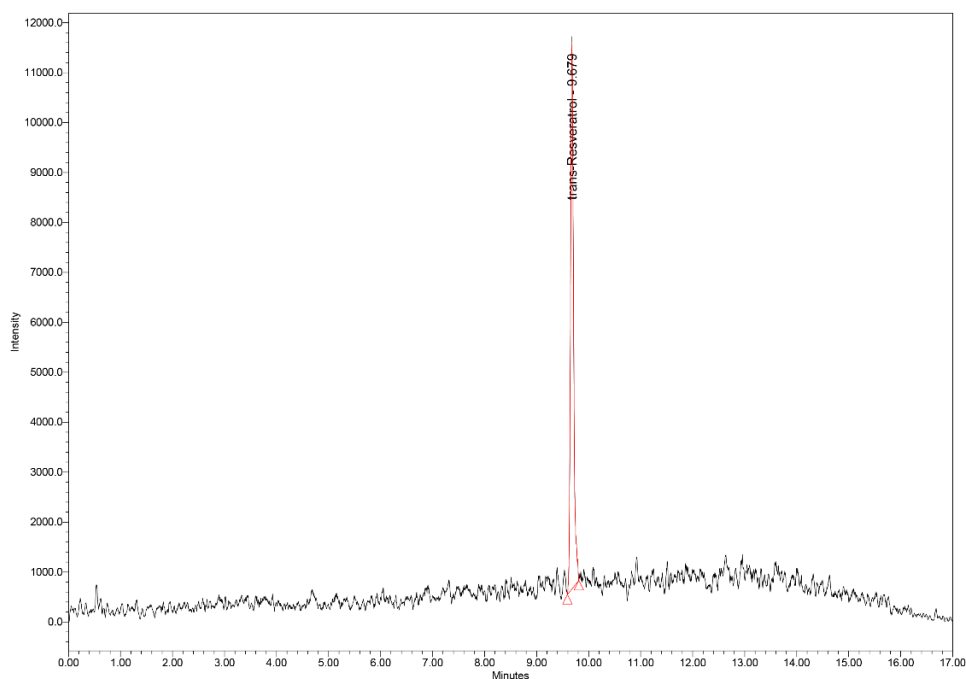
Figure 2. Chromatogram of a *trans*-resveratrol standard showing a prominent peak at 9.67 minutes, indicative of its purity and concentration in the reference sample.

In addition to the distinct peak at the specific retention time (RT), the confirmation of tRSV in the samples was further substantiated by comparing the mass spectrum obtained between *m/z* 100–400. This range was meticulously examined to match the ionization pattern of the tRSV reference with the sample peaks. By ensuring that the spectra of the samples aligned with that of the reference tRSV, particularly the peak at *m/z* 227, the presence of tRSV could be confirmed with greater certainty. This comparative approach across the broad mass range enhances the reliability of the identification, ruling out the possibility of coincidental matches or false positives that might arise from other compounds eluting at similar RTs (Figure 3).
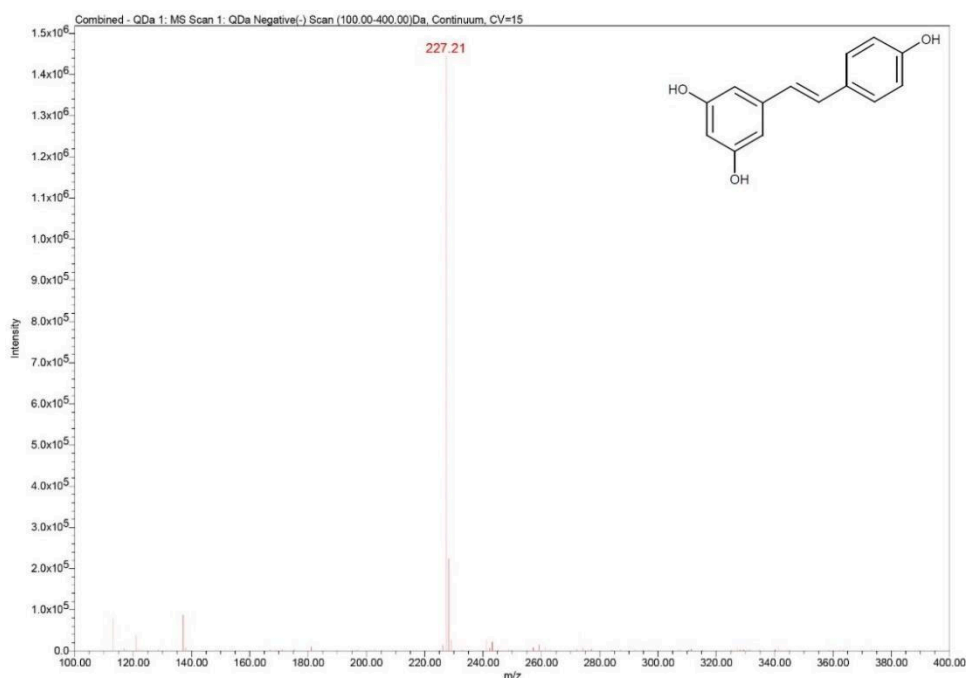
Figure 3. Mass spectrum of *trans*-resveratrol illustrating the quantification of molecular ion peak at *m/z* 227, used for both confirmation and quantification of the analyte.

In Figure 4, we observe the elution profiles of four different wine samples labeled W1 through W4. Each chromatogram is overlaid to facilitate comparison, particularly focusing on the tRSV peak. For all samples, the tRSV peak was identified at the same RT, which is consistent with the reference peak, suggesting successful identification of tRSV in

each wine. The peak intensities vary among the wine samples, which may reflect the different concentrations of tRSV in each type of wine. The RT's consistency across all samples is a good indicator of the method's reproducibility. Furthermore, the distinct peaks observed for tRSV in each sample, without interference from other peaks, confirm the specificity of the method, especially considering the mass detection confirmation at *m/z* 227. This comparative display allows for a visual assessment of the presence and relative quantity of tRSV across the different wine samples, providing an at-a-glance understanding of how tRSV concentrations may differ between white and red wines, as well as among different varieties. The clean baselines and sharp peak shapes are indicative of a well-optimized UHPLC method, essential for accurate quantification and comparison between samples (Figure 4).
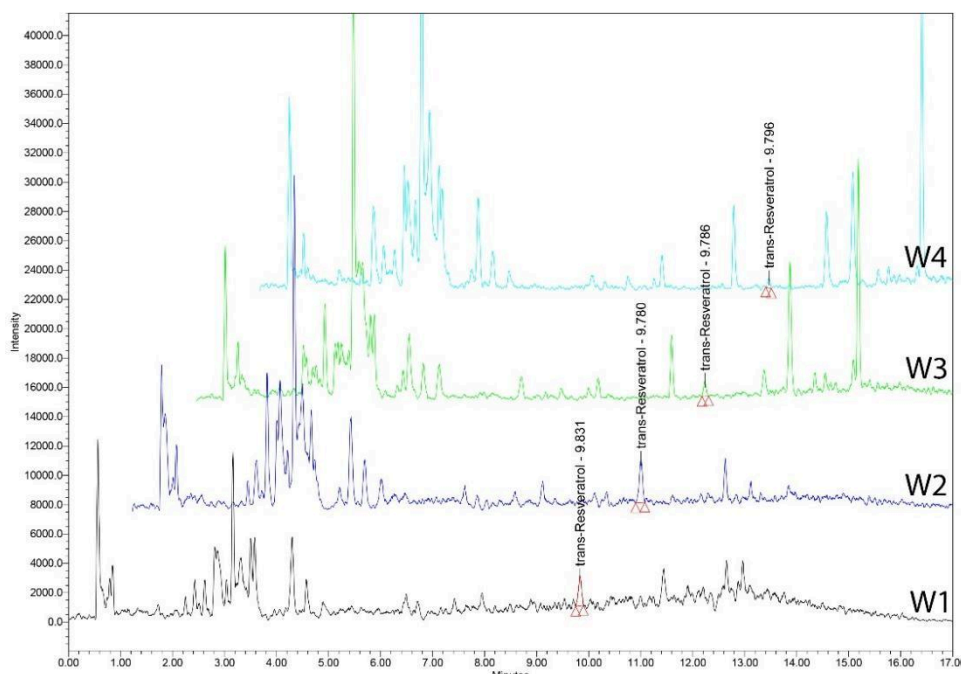
Figure 4. Overlay of UHPLC chromatograms for Romanian wine samples, with the *trans*-resveratrol peak identified at the specific retention time across all samples. UHPLC: Ultra high-performance liquid chromatography; W1: Fetească Regală; W2: Fetească Neagră; W3: Dry Muscat; W4: Cabernet Sauvignon.

Sample W1 (Fetească Regală variety) registers the highest concentration of tRSV among the white wines, suggesting that this varietal may naturally accumulate more of this compound, or that the vinification methods have been conducive to its retention. Moving to W3 (Dry Muscat variety), we can see that the tRSV content is significantly lower, which may reflect inherent varietal differences or distinct processing techniques affecting the final tRSV levels. When looking at the red wines, W2 (Fetească Neagră variety) contains the highest concentration of tRSV in the selection, aligning with the general observation that red wines often have higher levels of tRSV due to the extended contact with grape skins during fermentation, which typically enriches the wine with more phenolic compounds. W4 (Cabernet Sauvignon variety), however, has a notably lower level of tRSV, which might be influenced by a myriad of factors including viticultural conditions, grape harvesting parameters, or the specific methodologies employed during the winemaking process (Table 2).

Table 2. *trans*-Resveratrol amounts detected in Romanian wine samples.

Sample	*trans*-Resveratrol amount [ng/mL]
W1	243.291±2.51
W2	372.042±2.75
W3	108.487±1.98
W4	69.166±1.05

White wine samples: W1: Fetească Regală; W3: Dry Muscat. Red wine samples: W2: Fetească Neagră; W4: Cabernet Sauvignon.

The low SD associated with each measurement implies that the method used for quantification is both precise and reliable. This data provides valuable insights for winemaking strategies, could inform consumer choices regarding healthful components in wine, and may stimulate additional research into the beneficial properties of wine polyphenols.

16. Conclusions
Stilbenoids are natural compounds of the C6–C2–C6 type, consisting of two benzene nuclei linked together by an

ethylene bridge. The double bond between the two benzene nuclei can have *E* (*trans*) or *Z* (*cis*) configuration. The *trans* configuration is the predominant form, much more pharmacologically active. For their role as phytoalexins, respectively hormones that trigger defense mechanisms, stilbenoids are synthesized by the plant kingdom in response to external stimuli, such as infection or UV radiation. More than 1000 stilbenoids have been isolated and identified, the best known of which are the natural components RSV, piceid, piceatannol, pterostilbene, astringin, rapontigenol, viniferin, pallidol, hopeaphenol. Grapes are the main source of natural stilbenoids. RSV is a potential chemopreventive agent, both *in vivo* and *in vitro*, considering its inhibitory effects on cellular processes associated with cancer induction and progression. The influence of RSV on numerous enzyme systems explains its antioxidant, antimutagenic and anticarcinogenic potential. In some bioassay systems, RSV has been shown to provide protection against several types of cancer. RSV has an antioxidant effect, but also numerous pharmacological actions useful for maintaining cardiovascular health and protection against aging, especially against diseases associated with aging, neurodegeneration, inflammatory, metabolic, or immune diseases and some types of cancer. RSV modulates signaling pathways that limit the spread of tumor cells, protects nerve cells from damage, is useful in the prevention of diabetes, and generally acts as an anti-aging agent that alleviates the symptoms of aging. It was highlighted that RSV could ameliorate the consequences of an unhealthy lifestyle caused by an exaggerated caloric intake. A moderate consumption of red wine, over a long period of time, protects the body against CHDs and could be the main factor responsible for the so-called "French paradox". tRSV from the Romanian wine samples, both white and red varieties, can be identified and quantified by UHPLC–MS.

References

Adhami, V.M.; Afaq, F.; Ahmad, N. Suppression of ultraviolet B exposure-mediated activation of NF-κB in normal human keratinocytes by resveratrol. Neoplasia 2003, 5, 74–82. [https://doi.org/10.1016/s1476-5586(03)80019-2] [https://pubmed.ncbi.nlm.nih.gov/12659672/]

Adlercreutz, H.; Markkanen, H.; Watanabe, S. Plasma concentrations of phyto-oestrogens in Japanese men. Lancet 1993, 342, 1209–1210. [https://doi.org/10.1016/0140-6736(93)92188-y] [https://pubmed.ncbi.nlm.nih.gov/7901532/]

Afaq, F.; Adhami, V.M.; Ahmad, N. Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. Toxicol. Appl. Pharmacol. 2003, 186, 28–37. [https://doi.org/10.1016/s0041-008x(02)00014-5] [https://pubmed.ncbi.nlm.nih.gov/12583990/]

Ahmad, K.A.; Clement, M.V.; Hanif, I.M.; Pervaiz, S. Resveratrol inhibits drug-induced apoptosis in human leukemia cells by creating an intracellular milieu nonpermissive for death execution. Cancer Res. 2004, 64, 1452–1459. [https://doi.org/10.1158/0008-5472.can-03-2414] [https://pubmed.ncbi.nlm.nih.gov/14973069/]

Alamolhodaei, N.S.; Tsatsakis, A.M.; Ramezani, M.; Hayes, A.W.; Karimi, G. Resveratrol as MDR reversion molecule in breast cancer: An overview. Food Chem. Toxicol. 2017, 103, 223–232. [https://doi.org/10.1016/j.fct.2017.03.024] [https://pubmed.ncbi.nlm.nih.gov/28315369/]

Almeida, T.C.; Melo, A.S.; Lima, A.P.B.; Branquinho, R.T.; da Silva, G.N. Resveratrol induces the production of reactive oxygen species, interferes with the cell cycle, and inhibits the cell migration of bladder tumour cells with different *TP53* status. Nat. Prod. Res. 2023, 37, 3838–3843. [https://doi.org/10.1080/14786419.2022.2151007] [https://pubmed.ncbi.nlm.nih.gov/36441214/]

Aquilano, K.; Baldelli, S.; Rotilio, G.; Ciriolo, M.R. *trans*-Resveratrol inhibits H_2O_2-induced adenocarcinoma gastric cells proliferation *via* inactivation of MEK1/2-ERK1/2-c-Jun signalling axis. Biochem. Pharmacol. 2009, 77, 337–347. [https://doi.org/10.1016/j.bcp.2008.10.034] [https://pubmed.ncbi.nlm.nih.gov/19038233/]

Ashafaq, M.; Intakhab Alam, M.; Khan, A.; Islam, F.; Khuwaja, G.; Hussain, S.; Ali, R.; Alshahrani, S.; Antar Makeen, H.; Alhazmi, H.A.; et al. Nanoparticles of resveratrol attenuates oxidative stress and inflammation after ischemic stroke in rats. Int. Immunopharmacol. 2021, 94, 107494. [https://doi.org/10.1016/j.intimp.2021.107494] [https://pubmed.ncbi.nlm.nih.gov/33676175/]

Ashrafizadeh, M.; Rafiei, H.; Mohammadinejad, R.; Farkhondeh, T.; Samarghandian, S. Anti-tumor activity of resveratrol against gastric cancer: A review of recent advances with an emphasis on molecular pathways. Cancer Cell Int. 2021, 21, 66. [https://doi.org/10.1186/s12935-021-01773-7]

[https://pubmed.ncbi.nlm.nih.gov/33478512/]

Atten, M.J.; Attar, B.M.; Milson, T.; Holian, O. Resveratrol-induced inactivation of human gastric adenocarcinoma cells through a protein kinase C-mediated mechanism. Biochem. Pharmacol. 2001, 62, 1423–1432. [https://doi.org/10.1016/s0006-2952(01)00788-2] [https://pubmed.ncbi.nlm.nih.gov/11709203/]

Aziz, M.H.; Kumar, R.; Ahmad, N. Cancer chemoprevention by resveratrol: In vitro and in vivo studies and the underlying mechanisms (review). Int. J. Oncol. 2003, 23, 17–28. [https://doi.org/10.3892/ijo.23.1.17] [https://pubmed.ncbi.nlm.nih.gov/12792772/]

Baatout, S.; Derradji, H.; Jacquet, P.; Ooms, D.; Michaux, A.; Mergeay, M. Enhanced radiation-induced apoptosis of cancer cell lines after treatment with resveratrol. Int. J. Mol. Med. 2004, 13, 895–902. [https://doi.org/10.3892/ijmm.13.6.895] [https://pubmed.ncbi.nlm.nih.gov/15138632/]

Banaszewska, B.; Wrotyńska-Barczyńska, J.; Spaczynski, R.Z.; Pawelczyk, L.; Duleba, A.J. Effects of resveratrol on polycystic ovary syndrome: A double-blind, randomized, placebo-controlled trial. J. Clin. Endocrinol. Metab. 2016, 101, 4322–4328. [https://doi.org/10.1210/jc.2016-1858] [https://pubmed.ncbi.nlm.nih.gov/27754722/]

Banerjee, S.; Bueso-Ramos, C.; Aggarwal, B.B. Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: Role of nuclear factor-κB, cyclooxygenase 2, and matrix metalloprotease 9. Cancer Res. 2002, 62, 4945–4954. [https://pubmed.ncbi.nlm.nih.gov/12208745/]

Baolin, L.; Inami, Y.; Tanaka, H.; Inagaki, N.; Iinuma, M.; Nagai, H. Resveratrol inhibits the release of mediators from bone marrow-derived mouse mast cells in vitro. Planta Med. 2004, 70, 305–309. [https://doi.org/10.1055/s-2004-818940] [https://pubmed.ncbi.nlm.nih.gov/15095144/]

Bartra, C.; Yuan, Y.; Vuraić, K.; Valdés-Quiroz, H.; Garcia-Baucells, P.; Slevin, M.; Pastorello, Y.; Suñol, C.; Sanfeliu, C. Resveratrol activates antioxidant protective mechanisms in cellular models of Alzheimer's disease inflammation. Antioxidants (Basel) 2024, 13, 177. [https://doi.org/10.3390/antiox13020177] [https://pubmed.ncbi.nlm.nih.gov/38397775/]

Behroozaghdam, M.; Dehghani, M.; Zabolian, A.; Kamali, D.; Javanshir, S.; Hasani Sadi, F.; Hashemi, M.; Tabari, T.; Rashidi, M.; Mirzaei, S.; et al. Resveratrol in breast cancer treatment: From cellular effects to molecular mechanisms of action. Cell. Mol. Life Sci. 2022, 79, 539. [https://doi.org/10.1007/s00018-022-04551-4] [https://pubmed.ncbi.nlm.nih.gov/36194371/]

Berge, G.; Øvrebø, S.; Botnen, I.V.; Hewer, A.; Phillips, D.H.; Haugen, A.; Mollerup, S. Resveratrol inhibits benzo[a]pyrene–DNA adduct formation in human bronchial epithelial cells. Br. J. Cancer 2004, 91, 333–338. [https://doi.org/10.1038/sj.bjc.6601898] [https://pubmed.ncbi.nlm.nih.gov/15162144/]

Bernhard, D.; Tinhofer, I.; Tonko, M.; Hübl, H.; Ausserlechner, M.J.; Greil, R.; Kofler, R.; Csordas, A. Resveratrol causes arrest in the S-phase prior to Fas-independent apoptosis in CEM-C7H2 acute leukemia cells. Cell Death Differ. 2000, 7, 834–842. [https://doi.org/10.1038/sj.cdd.4400719] [https://pubmed.ncbi.nlm.nih.gov/11042678/]

Bhat, K.P.L.; Pezzuto, J.M. Cancer chemopreventive activity of resveratrol. Ann. N. Y. Acad. Sci. 2002, 957, 210–229. [https://doi.org/10.1111/j.1749-6632.2002.tb02918.x] [https://pubmed.ncbi.nlm.nih.gov/12074974/]

Bilgic, T. Comparison of the effect of local and systemic injection of resveratrol on cutaneous wound healing in rats. Int. J. Low. Extrem. Wounds 2021, 20, 55–59. [https://doi.org/10.1177/1534734620938168] [https://pubmed.ncbi.nlm.nih.gov/32734786/]

Billard, C.; Izard, J.C.; Roman, V.; Kern, C.; Mathiot, C.; Mentz, F.; Kolb, J.P. Comparative antiproliferative and apoptotic effects of resveratrol, ε-viniferin and vine-shots derived polyphenols (vineatrols) on chronic B lymphocytic leukemia cells and normal human lymphocytes. Leuk. Lymphoma 2002, 43, 1991–2002. [https://doi.org/10.1080/1042819021000015952] [https://pubmed.ncbi.nlm.nih.gov/12481898/]

Buhrmann, C.; Shayan, P.; Goel, A.; Shakibaei, M. Resveratrol regulates colorectal cancer cell invasion by modulation of focal adhesion molecules. Nutrients 2017, 9, 1073. [https://doi.org/10.3390/nu9101073] [https://pubmed.ncbi.nlm.nih.gov/28953264/]

Cai, Y.; Zhao, L.; Qin, Y.; Zhang, M.; He, Y. Resveratrol inhibits proliferation and induces apoptosis of nasopharyngeal carcinoma cell line C666-1 through AMPK activation. Pharmazie 2015, 70, 399–403. [https://doi.org/10.1691/ph.2015.4815] [https://pubmed.ncbi.nlm.nih.gov/26189302/]

Calabrese, G. Nonalcoholic compounds of wine: the phytoestrogen resveratrol and moderate red wine consumption during menopause. Drugs Exp. Clin. Res. 1999, 25, 111–114. [https://pubmed.ncbi.nlm.nih.gov/10370872/]

Cao, X.; Liao, W.; Xia, H.; Wang, S.; Sun, G. The effect of resveratrol on blood lipid profile: a dose-response meta-analysis of randomized controlled trials. Nutrients 2022, 14, 3755. [https://doi.org/10.3390/nu14183755] [https://pubmed.ncbi.nlm.nih.gov/36145131/]

Chalons, P.; Amor, S.; Courtaut, F.; Cantos-Villar, E.; Richard, T.; Auger, C.; Chabert, P.; Schni-Kerth, V.; Aires, V.; Delmas, D. Study of potential anti-inflammatory effects of red wine extract and resveratrol through a modulation of interleukin-1-beta in macrophages. Nutrients 2018, 10, 1856. [https://doi.org/10.3390/nu10121856] [https://pubmed.ncbi.nlm.nih.gov/30513737/]

Chanvitayapongs, S.; Draczynska-Lusiak, B.; Sun, A.Y. Amelioration of oxidative stress by antioxidants and resveratrol in PC12 cells. Neuroreport 1997, 8, 1499–1502. [https://doi.org/10.1097/00001756-199704140-00035] [https://pubmed.ncbi.nlm.nih.gov/9172162/]

Chatterjee, K.; AlSharif, D.; Mazza, C.; Syar, P.; Al Sharif, M.; Fata, J.E. Resveratrol and pterostilbene exhibit anticancer properties involving the downregulation of HPV oncoprotein E6 in cervical cancer cells. Nutrients 2018, 10, 243. [https://doi.org/10.3390/nu10020243] [https://pubmed.ncbi.nlm.nih.gov/29485619/]

Chen, W.M.; Shaw, L.H.; Chang, P.J.; Tung, S.Y.; Chang, T.S.; Shen, C.H.; Hsieh, Y.Y.; Wei, K.L. Hepatoprotective effect of resveratrol against ethanol-induced oxidative stress through induction of superoxide dismutase *in vivo* and *in vitro*. Exp. Ther. Med. 2016, 11, 1231–1238. [https://doi.org/10.3892/etm.2016.3077] [https://pubmed.ncbi.nlm.nih.gov/27073428/]

Chen, Y.; Tseng, S.H.; Lai, H.S.; Chen, W.J. Resveratrol-induced cellular apoptosis and cell cycle arrest in neuroblastoma cells and antitumor effects on neuroblastoma in mice. Surgery 2004, 136, 57–66. [https://doi.org/10.1016/j.surg.2004.01.017] [https://pubmed.ncbi.nlm.nih.gov/15232540/]

Choi, H.Y.; Chong, S.A.; Nam, M.J. Resveratrol induces apoptosis in human SK-HEP-1 hepatic cancer cells. Cancer Genomics Proteomics 2009, 6, 263–268. [https://pubmed.ncbi.nlm.nih.gov/19996131/]

Chung, I.M.; Yeo, M.A.; Kim, S.J.; Moon, H.I. Neuroprotective effects of resveratrol derivatives from the roots of *Vitis thunbergii* var. *sinuata* against glutamate-induced neurotoxicity in primary cultured rat cortical cells. Hum. Exp. Toxicol. 2011, 30, 1404–1408. [https://doi.org/10.1177/0960327110390065] [https://pubmed.ncbi.nlm.nih.gov/21084527/]

Chupradit, S.; Bokov, D.; Zamanian, M.Y.; Heidari, M.; Hakimizadeh, E. Hepatoprotective and therapeutic effects of resveratrol: A focus on anti-inflammatory and antioxidative activities. Fundam. Clin. Pharmacol. 2022, 36, 468–485. [https://doi.org/10.1111/fcp.12746] [https://pubmed.ncbi.nlm.nih.gov/34935193/]

Ciddi, V.; Dodda, D. Therapeutic potential of resveratrol in diabetic complications: *In vitro* and *in vivo* studies. Pharmacol. Rep. 2014, 66, 799–803. [https://doi.org/10.1016/j.pharep.2014.04.006] [https://pubmed.ncbi.nlm.nih.gov/25149983/]

Ciolino, H.P.; Daschner, P.J.; Yeh, G.C. Resveratrol inhibits transcription of CYP1A1 *in vitro* by preventing activation of the aryl hydrocarbon receptor. Cancer Res. 1998, 58, 5707–5712. [https://pubmed.ncbi.nlm.nih.gov/9865727/]

Clément, M.V.; Hirpara, J.L.; Chawdhury, S.H.; Pervaiz, S. Chemopreventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. Blood 1998, 92, 996–1002. [https://doi.org/10.1182/blood.V92.3.996] [https://pubmed.ncbi.nlm.nih.gov/9680369/]

Crăciun, A.L.; Gutt, G. Optimization of experimental parameters in the solvent extraction of *trans*-resveratrol from pruning waste of *Vitis vinifera*, Fetească Neagră variety. Appl. Sci. 2023, 13, 823. [https://doi.org/10.3390/app13020823]

Cui, J.; Sun, R.; Yu, Y.; Gou, S.; Zhao, G.; Wang, C. Antiproliferative effect of resveratrol in pancreatic cancer cells. Phytother. Res. 2010, 24, 1637–1644. [https://doi.org/10.1002/ptr.3157] [https://pubmed.ncbi.nlm.nih.gov/21031621/]

Czapla, J.; Drzyzga, A.; Matuszczak, S.; Pilny, E.; Cichoń, T.; Stojecki, K.; Smolarczyk, R. The complex composition of *trans*-resveratrol, quercetin, vitamin E and selenium inhibits the growth of colorectal carcinoma. Anticancer Res. 2022, 42, 4763–4772. [https://doi.org/10.21873/anticanres.15981] [https://pubmed.ncbi.nlm.nih.gov/36191991/]

da Costa, P.S.; Ramos, P.S.; Ferreira, C.; Silva, J.L.; El-Bacha, T.; Fialho, E. Pro-oxidant effect of resveratrol on human breast cancer MCF-7 cells is associated with CK2 inhibition. Nutr. Cancer 2022, 74, 2142–2151. [https://doi.org/10.1080/01635581.2021.1977834] [https://pubmed.ncbi.nlm.nih.gov/34519606/]

Daroch, F.; Hoeneisen, M.; González, C.L.; Kawaguchi, F.; Salgado, F.; Solar, H.; García, A. *In vitro* antibacterial activity of Chilean red wines against *Helicobacter pylori*. Microbios 2001, 104, 79–85. [https://pubmed.ncbi.nlm.nih.gov/11297014/]

Davoodvandi, A.; Darvish, M.; Borran, S.; Nejati, M.; Mazaheri, S.; Reza Tamtaji, O.; Hamblin, M.R.; Masoudian, N.; Mirzaei, H. The therapeutic potential of resveratrol in a mouse model of melanoma lung metastasis. Int. Immunopharmacol. 2020, 88, 106905. [https://doi.org/10.1016/j.intimp.2020.106905] [https://pubmed.ncbi.nlm.nih.gov/32905970/]

De Lédinghen, V.; Monvoisin, A.; Neaud, V.; Krisa, S.; Payrastre, B.; Bedin, C.; Desmoulière, A.; Bioulac-Sage, P.; Rosenbaum, J. *Trans*-resveratrol, a grapevine-derived polyphenol, blocks hepatocyte growth factor-induced invasion of hepatocellular carcinoma cells. Int. J. Oncol. 2001, 19, 83–88. [https://doi.org/10.3892/ijo.19.1.83] [https://pubmed.ncbi.nlm.nih.gov/11408926/]

Delmas, D.; Jannin, B.; Cherkaoui Malki, M.; Latruffe, N. Inhibitory effect of resveratrol on the proliferation of human and rat hepatic derived cell lines. Oncol. Rep. 2000, 7, 847–852. [https://doi.org/10.3892/or.7.4.847] [https://pubmed.ncbi.nlm.nih.gov/10854556/]

Dhar, S.; Hicks, C.; Levenson, A.S. Resveratrol and prostate cancer: Promising role for microRNAs. Mol. Nutr. Food Res. 2011, 55, 1219–1229. [https://doi.org/10.1002/mnfr.201100141] [https://pubmed.ncbi.nlm.nih.gov/21714127/]

Docherty, J.J.; Smith, J.S.; Fu, M.M.; Stoner, T.; Booth, T. Effect of topically applied resveratrol on cutaneous herpes simplex virus infections in hairless mice. Antiviral Res. 2004, 61, 19–26. [https://doi.org/10.1016/j.antiviral.2003.07.001] [https://pubmed.ncbi.nlm.nih.gov/14670590/]

Dong, Z.B.; Wang, Y.J.; Wan, W.J.; Wu, J.; Wang, B.J.; Zhu, H.L.; Xie, M.; Liu, L. Resveratrol ameliorates oxaliplatin-induced neuropathic pain *via* anti-inflammatory effects in rats. Exp. Ther. Med. 2022, 24, 586. [https://doi.org/10.3892/etm.2022.11523] [https://pubmed.ncbi.nlm.nih.gov/35949346/]

Donnelly, L.E.; Newton, R.; Kennedy, G.E.; Fenwick, P.S.; Leung R.H.F.; Ito, K.; Russell, R.E.K.; Barnes, P.J. Anti-inflammatory effects of resveratrol in lung epithelial cells: Molecular mechanisms. Am. J. Physiol. Lung Cell. Mol. Physiol. 2004, 287, L774–L783. [https://doi.org/10.1152/ajplung.00110.2004]

[https://pubmed.ncbi.nlm.nih.gov/15180920/]

Duca, A.; Sturza, A.; Moacă, E.A.; Negrea, M.; Lalescu, V.D.; Lungeanu, D.; Dehelean, C.A.; Muntean, D.M.; Alexa, E. Identification of resveratrol as bioactive compound of propolis from Western Romania and characterization of phenolic profile and antioxidant activity of ethanolic extracts. Molecules 2019, 24, 3368. [https://doi.org/10.3390/molecules24183368] [https://pubmed.ncbi.nlm.nih.gov/31527469/]

ElAttar, T.M.; Virji, A.S. Modulating effect of resveratrol and quercetin on oral cancer cell growth and proliferation. Anticancer Drugs 1999, 10, 187–193. [https://doi.org/10.1097/00001813-199902000-00007] [https://pubmed.ncbi.nlm.nih.gov/10211549/]

El-Benhawy, S.A.; Morsi, M.I.; Fahmy, E.I.; Soula, M.A.; Khalil, F.A.Z.F.; Arab, A.R. Role of resveratrol as radiosensitizer by targeting cancer stem cells in radioresistant prostate cancer cells (PC-3). Asian Pac. J. Cancer Prev. 2021, 22, 3823–3837. [https://doi.org/10.31557/APJCP.2021.22.12.3823] [https://pubmed.ncbi.nlm.nih.gov/34967561/]

Evers, D.L.; Wang, X.; Huong, S.M.; Huang, D.Y.; Huang, E.S. 3,4',5-Trihydroxy-*trans*-stilbene (resveratrol) inhibits human cytomegalovirus replication and virus-induced cellular signaling. Antiviral Res. 2004, 63, 85–95. [https://doi.org/10.1016/j.antiviral.2004.03.002] [https://pubmed.ncbi.nlm.nih.gov/15302137/]

Faisal, Z.; Mazhar, A.; Batool, S.A.; Akram, N.; Hassan, M.; Khan, M.U.; Afzaal, M.; Hassan, U.U.; Shah, Y.A.; Desta, D.T. Exploring the multimodal health-promoting properties of resveratrol: A comprehensive review. Food Sci. Nutr. 2024, 12, 2240–2258. [https://doi.org/10.1002/fsn3.3933] [https://pubmed.ncbi.nlm.nih.gov/38628180/]

Fan, D.; Liu, C.; Zhang, Z.; Huang, K.; Wang, T.; Chen, S.; Li, Z. Progress in the preclinical and clinical study of resveratrol for vascular metabolic disease. Molecules 2022, 27, 7524. [https://doi.org/10.3390/molecules27217524] [https://pubmed.ncbi.nlm.nih.gov/36364370/]

Ferrero, M.E.; Bertelli, A.E.; Fulgenzi, A.; Pellegatta, F.; Corsi, M.M.; Bonfrate, M.; Ferrara, F.; De Caterina, R.; Giovannini, L.; Bertelli, A. Activity *in vitro* of resveratrol on granulocyte and monocyte adhesion to endothelium. Am. J. Clin. Nutr. 1998, 68, 1208–1214. [https://doi.org/10.1093/ajcn/68.6.1208] [https://pubmed.ncbi.nlm.nih.gov/9846848/]

Fontecave, M.; Lepoivre, M.; Elleingand, E.; Gerez, C.; Guittet, O. Resveratrol, a remarkable inhibitor of ribonucleotide reductase. FEBS Lett. 1998, 421, 277–279. [https://doi.org/10.1016/s0014-5793(97)01572-x] [https://pubmed.ncbi.nlm.nih.gov/9468322/]

Frémont, L. Biological effects of resveratrol. Life Sci. 2000, 66, 663–673. [https://doi.org/10.1016/s0024-3205(99)00410-5] [https://pubmed.ncbi.nlm.nih.gov/10680575/]

Freyssin, A.; Rioux Bilan, A.; Fauconneau, B.; Galineau, L.; Serrière, S.; Tauber, C.; Perrin, F.; Guillard, J.; Chalon, S.; Page, G. *Trans ε*-viniferin decreases amyloid deposits with greater efficiency than resveratrol in an Alzheimer's mouse model. Front. Neurosci. 2022, 15, 803927. [https://doi.org/10.3389/fnins.2021.803927] [https://pubmed.ncbi.nlm.nih.gov/35069106/]

Fu, Z.D.; Cao, Y.; Wang, K.F.; Xu, S.F.; Han, R. [Chemopreventive effect of resveratrol to cancer]. Ai Zheng 2004, 23, 869–873. [https://pubmed.ncbi.nlm.nih.gov/15301705/]

Fuggetta, M.P.; D'Atri, S.; Lanzilli, G.; Tricarico, M.; Cannavò, E.; Zambruno, G.; Falchetti, R.; Ravagnan, G. *In vitro* antitumour activity of resveratrol in human melanoma cells sensitive or resistant to temozolomide. Melanoma Res. 2004, 14, 189–196. [https://doi.org/10.1097/01.cmr.0000130007.54508.b2] [https://pubmed.ncbi.nlm.nih.gov/15179187/]

Fuloria, S.; Sekar, M.; Khattulanuar, F.S.; Gan, S.H.; Rani, N.N.I.M.; Ravi, S.; Subramaniyan, V.; Jeyabalan, S.; Begum, M.Y.; Chidambaram, K.; et al. Chemistry, biosynthesis and pharmacology of viniferin: Potential resveratrol-derived molecules for new drug discovery, development and therapy. Molecules 2022, 27, 5072. [https://doi.org/10.3390/molecules27165072] [https://pubmed.ncbi.nlm.nih.gov/36014304/]

Gehm, B.D.; McAndrews, J.M.; Chien, P.Y.; Jameson, J.L. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. Proc. Natl. Acad. Sci. U. S. A. 1997, 94, 14138–14143. [https://doi.org/10.1073/pnas.94.25.14138] [https://pubmed.ncbi.nlm.nih.gov/9391166/]

Ghafouri-Fard, S.; Bahroudi, Z.; Shoorei, H.; Hussen, B.M.; Talebi, S.F.; Baig, S.G.; Taheri, M.; Ayatollahi, S.A. Disease-associated regulation of gene expression by resveratrol: Special focus on the PI3K/AKT signaling pathway. Cancer Cell Int. 2022, 22, 298. [https://doi.org/10.1186/s12935-022-02719-3] [https://pubmed.ncbi.nlm.nih.gov/36180892/]

Gokkaya, E.O.; Yesilot, S.; Ozgocmen, M.; Aslankoc, R.; Aydin Acar, C. Protective effects of resveratrol and avocado oil against paracetamol-induced hepatotoxicity in rats. Drug Chem. Toxicol. 2022, 45, 2131–2139. [https://doi.org/10.1080/01480545.2021.1908716] [https://pubmed.ncbi.nlm.nih.gov/33832400/]

Gomes, B.A.Q.; Silva, J.P.B.; Romeiro, C.F.R.; Dos Santos, S.M.; Rodrigues, C.A.; Gonçalves, P.R.; Sakai, J.T.; Mendes, P.F.S.; Varela, E.L.P.; Monteiro, M.C. Neuroprotective mechanisms of resveratrol in Alzheimer's disease: Role of SIRT1. Oxid. Med. Cell. Longev. 2018, 2018, 8152373. [https://doi.org/10.1155/2018/8152373] [https://pubmed.ncbi.nlm.nih.gov/30510627/]

Gong, W.H.; Zhao, N.; Zhang, Z.M.; Zhang, Y.X.; Yan, L.; Li, J.B. The inhibitory effect of resveratrol on COX-2 expression in human colorectal cancer: A promising therapeutic strategy. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 1136–1143. [https://pubmed.ncbi.nlm.nih.gov/28338176/]

Gu, Y.; Fei, Z. Mesoporous silica nanoparticles loaded with resveratrol are used for targeted breast cancer therapy. J. Oncol. 2022, 2022, 8471331. [https://doi.org/10.1155/2022/8471331]

[https://pubmed.ncbi.nlm.nih.gov/36245986/]

Guebailia, H.A.; Chira, K.; Richard, T.; Mabrouk, T.; Furiga, A.; Vitrac, X.; Monti, J.P.; Delaunay, J.C.; Mérillon, J.M. Hopeaphenol: The first resveratrol tetramer in wines from North Africa. J. Agric. Food Chem. 2006, 54, 9559–9564. [https://doi.org/10.1021/jf062024g] [https://pubmed.ncbi.nlm.nih.gov/17147446/]

Guo, S.; Zhou, Y.; Xie, X. Resveratrol inhibiting TGF/ERK signaling pathway can improve atherosclerosis: Backgrounds, mechanisms and effects. Biomed. Pharmacother. 2022, 155, 113775. [https://doi.org/10.1016/j.biopha.2022.113775] [https://pubmed.ncbi.nlm.nih.gov/36271557/]

Gupta, R.; Gupta, L.K.; Mediratta, P.K.; Bhattacharya, S.K. Effect of resveratrol on scopolamine-induced cognitive impairment in mice. Pharmacol. Rep. 2012, 64, 438–444. [https://doi.org/10.1016/s1734-1140(12)70785-5] [https://pubmed.ncbi.nlm.nih.gov/22661196/]

Han, D.S.; Lee, H.J.; Lee, E.O. Resveratrol suppresses serum-induced vasculogenic mimicry through impairing the EphA2/twist-VE-cadherin/AKT pathway in human prostate cancer PC-3 cells. Sci. Rep. 2022, 12, 20125. [https://doi.org/10.1038/s41598-022-24414-z] [https://pubmed.ncbi.nlm.nih.gov/36418859/]

Han, Y.N.; Ryu, S.Y.; Han, B.H. Antioxidant activity of resveratrol closely correlates with its monoamine oxidase-A inhibitory activity. Arch. Pharm. Res. 1990, 13, 132–135. [https://doi.org/10.1007/BF02857789]

Hassan, S.; Shah, M.; Malik, M.O.; Ehtesham, E.; Habib, S.H.; Rauf, B. Treatment with combined resveratrol and myoinositol ameliorates endocrine, metabolic alterations and perceived stress response in women with PCOS: A double-blind randomized clinical trial. Endocrine 2023, 79, 208–220. [https://doi.org/10.1007/s12020-022-03198-2] [https://pubmed.ncbi.nlm.nih.gov/36169918/]

He, S.; Jiang, L.; Wu, B.; Pan, Y.; Sun, C. Pallidol, a resveratrol dimer from red wine, is a selective singlet oxygen quencher. Biochem. Biophys. Res. Commun. 2009, 379, 283–287. [https://doi.org/10.1016/j.bbrc.2008.12.039] [https://pubmed.ncbi.nlm.nih.gov/19101516/]

Heebøll, S.; Thomsen, K.L.; Clouston, A.; Sundelin, E.I.; Radko, Y.; Christensen, L.P.; Ramezani-Moghadam, M.; Kreutzfeldt, M.; Pedersen, S.B.; Jessen, N.; et al. Effect of resveratrol on experimental non-alcoholic steatohepatitis. Pharmacol. Res. 2015, 95–96, 34–41. [https://doi.org/10.1016/j.phrs.2015.03.005] [https://pubmed.ncbi.nlm.nih.gov/25814186/]

Heredia, A.; Davis, C.; Redfield, R. Synergistic inhibition of HIV-1 in activated and resting peripheral blood mononuclear cells, monocyte-derived macrophages, and selected drug-resistant isolates with nucleoside analogues combined with a natural product, resveratrol. J. Acquir. Immune Defic. Syndr. 2000, 25, 246–255. [https://doi.org/10.1097/00126334-200011010-00006] [https://pubmed.ncbi.nlm.nih.gov/11115955/]

Holian, O.; Wahid, S.; Atten, M.J.; Attar, B.M. Inhibition of gastric cancer cell proliferation by resveratrol: Role of nitric oxide. Am. J. Physiol. Gastrointest. Liver Physiol. 2002, 282, G809–G816. [https://doi.org/10.1152/ajpgi.00193.2001] [https://pubmed.ncbi.nlm.nih.gov/11960777/]

Hu, S.A.; Wei, W.; Yuan, J.; Cheng, J. Resveratrol inhibits proliferation in HBL-52 meningioma cells. Onco Targets Ther. 2019, 12, 11579–11586. [https://doi.org/10.2147/OTT.S228513] [https://pubmed.ncbi.nlm.nih.gov/31920345/]

Huang, H.; Liao, D.; Zhou, G.; Zhu, Z.; Cui, Y.; Pu, R. Antiviral activities of resveratrol against rotavirus in vitro and in vivo. Phytomedicine 2020, 77, 153230. [https://doi.org/10.1016/j.phymed.2020.153230] [https://pubmed.ncbi.nlm.nih.gov/32682225/]

Huang, S.; Qi, B.; Yang, L.; Wang, X.; Huang, J.; Zhao, Y.; Hu, Y.; Xiao, W. Phytoestrogens, novel dietary supplements for breast cancer. Biomed. Pharmacother. 2023, 160, 114341. [https://doi.org/10.1016/j.biopha.2023.114341] [https://pubmed.ncbi.nlm.nih.gov/36753952/]

Huo, P.; Li, M.; Le, J.; Zhu, C.; Yao, J.; Zhang, S. Resveratrol improves follicular development of PCOS rats via regulating glycolysis pathway and targeting SIRT1. Syst. Biol. Reprod. Med. 2023, 69, 153–165. [https://doi.org/10.1080/19396368.2022.2125855] [https://pubmed.ncbi.nlm.nih.gov/36268996/]

Ikeda, E.; Tanaka, D.; Glogauer, M.; Tenenbaum, H.C.; Ikeda, Y. Healing effects of monomer and dimer resveratrol in a mouse periodontitis model. BMC Oral Health 2022, 22, 460. [https://doi.org/10.1186/s12903-022-02499-2] [https://pubmed.ncbi.nlm.nih.gov/36319994/]

Ito, T.; Akao, Y.; Tanaka, T.; Iinuma, M.; Nozawa, Y. Vaticanol C, a novel resveratrol tetramer, inhibits cell growth through induction of apoptosis in colon cancer cell lines. Biol. Pharm. Bull. 2002, 25, 147–148. [https://doi.org/10.1248/bpb.25.147] [https://pubmed.ncbi.nlm.nih.gov/11824549/]

Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.; Fong, H.H.; Farnsworth, N.R.; Kinghorn, A.D.; Mehta, R.G.; et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997, 275, 218–220. [https://doi.org/10.1126/science.275.5297.218] [https://pubmed.ncbi.nlm.nih.gov/8985016/]

Jeong, W.S.; Kim, I.W.; Hu, R.; Kong, A.N.T. Modulation of AP-1 by natural chemopreventive compounds in human colon HT-29 cancer cell line. Pharm. Res. 2004, 21, 649–660. [https://doi.org/10.1023/b:pham.0000022412.69380.d7] [https://pubmed.ncbi.nlm.nih.gov/15139522/]

Jiang, H.; Zhang, L.; Kuo, J.; Kuo, K.; Gautam, S.C.; Groc, L.; Rodriguez, A.I.; Koubi, D.; Hunter, T.J.; Corcoran, G.B.; et al. Resveratrol-induced apoptotic death in human U251 glioma cells. Mol. Cancer Ther. 2005, 4, 554–561. [https://doi.org/10.1158/1535-7163.MCT-04-0056] [https://pubmed.ncbi.nlm.nih.gov/15827328/]

Jiang, J.; Liu, Z.; Zhou, X.; Peng, F.; Wang, Z.; Li, F.; Li, M. Resveratrol induces apoptosis, suppresses migration, and invasion of cervical cancer cells by inhibiting the hedgehog signaling pathway. Biomed Res. Int. 2022, 2022,

8453011. [https://doi.org/10.1155/2022/8453011] [https://pubmed.ncbi.nlm.nih.gov/36246980/]

Jiang, L.; Gu, Y.; Ye, J.; Liu, F.; Zhao, Y.; Wang, C.; Xu, Y.; Cao, X.; Zhang, L.; Dong, W.; et al. Resveratrol prevents hepatic steatosis induced by hepatitis C virus core protein. Biotechnol. Lett. 2012, 34, 2205–2212. [https://doi.org/10.1007/s10529-012-1034-0] [https://pubmed.ncbi.nlm.nih.gov/22941371/]

Jiao, Y.; Li, H.; Liu, Y.; Guo, A.; Xu, X.; Qu, X.; Wang, S.; Zhao, J.; Li, Y.; Cao, Y. Resveratrol inhibits the invasion of glioblastoma-initiating cells via down-regulation of the PI3K/Akt/NF-κB signaling pathway. Nutrients 2015, 7, 4383–4402. [https://doi.org/10.3390/nu7064383] [https://pubmed.ncbi.nlm.nih.gov/26043036/]

Jin, F.; Wu, Q.; Lu, Y.F.; Gong, Q.H.; Shi, J.S. Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. Eur. J. Pharmacol. 2008, 600, 78–82. [https://doi.org/10.1016/j.ejphar.2008.10.005] [https://pubmed.ncbi.nlm.nih.gov/18940189/]

Juan, M.E.; Wenzel, U.; Daniel, H.; Planas, J.M. Resveratrol induces apoptosis through ROS-dependent mitochondria pathway in HT-29 human colorectal carcinoma cells. J. Agric. Food Chem. 2008, 56, 4813–4818. [https://doi.org/10.1021/jf800175a] [https://pubmed.ncbi.nlm.nih.gov/18522405/]

Karabekir, S.C.; Özgörgülü, A. Possible protective effects of resveratrol in hepatocellular carcinoma. Iran. J. Basic Med. Sci. 2020, 23, 71–78. [https://doi.org/10.22038/IJBMS.2019.36821.8774] [https://pubmed.ncbi.nlm.nih.gov/32405350/]

Kasdallah-Grissa, A.; Mornagui, B.; Aouani, E.; Hammami, M.; Gharbi, N.; Kamoun, A.; El-Fazaa, S. Protective effect of resveratrol on ethanol-induced lipid peroxidation in rats. Alcohol Alcohol. 2006, 41, 236–239. [https://doi.org/10.1093/alcalc/agh256] [https://pubmed.ncbi.nlm.nih.gov/16517551/]

Kaur, G.; Kaur, R.; Sodhi, G.K.; George, N.; Rath, S.K.; Walia, H.K.; Dwibedi, V.; Saxena S. Stilbenes: A journey from folklore to pharmaceutical innovation. Arch. Microbiol. 2024, 206, 229. [https://doi.org/10.1007/s00203-024-03939-z] [https://pubmed.ncbi.nlm.nih.gov/38647675/]

Khayat, M.T.; Zarka, M.A.; El-Telbany, D.F.A.; El-Halawany, A.M.; Kutbi, H.I.; Elkhatib, W.F.; Noreddin, A.M.; Khayyat, A.N.; El-Telbany, R.F.A.; Hammad, S.F.; et al. Intensification of resveratrol cytotoxicity, pro-apoptosis, oxidant potentials in human colorectal carcinoma HCT-116 cells using zein nanoparticles. Sci. Rep. 2022, 12, 15235. [https://doi.org/10.1038/s41598-022-18557-2] [https://pubmed.ncbi.nlm.nih.gov/36075939/]

Khazaei, M.R.; Bozorgi, M.; Khazaei, M.; Aftabi, M.; Bozorgi, A. Resveratrol nanoformulation inhibits invasive breast cancer cell growth through autophagy induction: An in vitro study. Cell J. 2024, 26, 112–120. [https://doi.org/10.22074/cellj.2024.2016930.1458] [https://pubmed.ncbi.nlm.nih.gov/38459728/]

Kim, A.L.; Zhu, Y.; Zhu, H.; Han, L.; Kopelovich, L.; Bickers, D.R.; Athar, M. Resveratrol inhibits proliferation of human epidermoid carcinoma A431 cells by modulating MEK1 and AP-1 signalling pathways. Exp. Dermatol. 2006, 15, 538–546. [https://doi.org/10.1111/j.1600-0625.2006.00445.x] [https://pubmed.ncbi.nlm.nih.gov/16761963/]

Kim, S.E.; Shin, S.H.; Lee, J.Y.; Kim, C.H.; Chung, I.K.; Kang, H.M.; Park, H.R.; Park, B.S.; Kim, I.R. Resveratrol induces mitochondrial apoptosis and inhibits epithelial–mesenchymal transition in oral squamous cell carcinoma cells. Nutr. Cancer 2018, 70, 125–135. [https://doi.org/10.1080/01635581.2018.1397708] [https://pubmed.ncbi.nlm.nih.gov/29148840/]

Kim, Y.A.; Choi, B.T.; Lee, Y.T.; Park, D.I.; Rhee, S.H.; Park, K.Y.; Choi, Y.H. Resveratrol inhibits cell proliferation and induces apoptosis of human breast carcinoma MCF-7 cells. Oncol. Rep. 2004, 11, 441–446. [https://doi.org/10.3892/or.11.2.441] [https://pubmed.ncbi.nlm.nih.gov/14719081/]

Kim, Y.A.; Lee, W.H.; Choi, T.H.; Rhee, S.H.; Park, K.Y.; Choi, Y.H. Involvement of p21$^{\text{WAF1/CIP1}}$, pRB, Bax and NF-κB in induction of growth arrest and apoptosis by resveratrol in human lung carcinoma A549 cells. Int. J. Oncol. 2003a, 23, 1143–1149. [https://doi.org/10.3892/ijo.23.4.1143] [https://pubmed.ncbi.nlm.nih.gov/12963997/]

Kim, Y.A.; Rhee, S.H.; Park, K.Y.; Choi, Y.H. Antiproliferative effect of resveratrol in human prostate carcinoma cells. J. Med. Food. 2003b, 6, 273–280. [https://doi.org/10.1089/109662003772519813] [https://pubmed.ncbi.nlm.nih.gov/14977434/]

Kimura, Y.; Okuda, H. Effects of naturally occurring stilbene glucosides from medicinal plants and wine, on tumour growth and lung metastasis in Lewis lung carcinoma-bearing mice. J. Pharm. Pharmacol. 2000, 52, 1287–1295. [https://doi.org/10.1211/0022357001777270] [https://pubmed.ncbi.nlm.nih.gov/11092574/]

Kong, D.; Yan, Y.; He, X.Y.; Yang, H.; Liang, B.; Wang, J.; He, Y.; Ding, Y.; Yu, H. Effects of resveratrol on the mechanisms of antioxidants and estrogen in Alzheimer's disease. Biomed Res. Int. 2019, 2019, 8983752. [https://doi.org/10.1155/2019/8983752] [https://pubmed.ncbi.nlm.nih.gov/31016201/]

Kubota, T.; Uemura, Y.; Kobayashi, M.; Taguchi, H. Combined effects of resveratrol and paclitaxel on lung cancer cells. Anticancer Res. 2003, 23, 4039–4046. [https://pubmed.ncbi.nlm.nih.gov/14666716/]

Kumar, R.J.; Jyostna, D.; Krupadanam, G.L.D.; Srimannarayana, G. Phenanthrene and stilbenes from Pterolobium hexapetallum. Phytochemistry 1988, 27, 3625–3626. [https://doi.org/10.1016/0031-9422(88)80779-9]

Kurzava Kendall, L.; Ma, Y.; Yang, T.; Lubecka, K.; Stefanska, B. Epigenetic effects of resveratrol on oncogenic signaling in breast cancer. Nutrients 2024, 16, 699. [https://doi.org/10.3390/nu16050699] [https://pubmed.ncbi.nlm.nih.gov/38474826/]

Lang, F.; Qin, Z.; Li, F.; Zhang, H.; Fang, Z.; Hao, E. Apoptotic cell death induced by resveratrol is partially mediated by the autophagy pathway in human ovarian cancer cells. PLoS One 2015, 10, e0129196. [https://doi.org/10.1371/journal.pone.0129196] [https://pubmed.ncbi.nlm.nih.gov/26067645/]

Larrosa, M.; Tomás-Barberán, F.A.; Espín, J.C. Grape polyphenol resveratrol and the related molecule

4-hydroxystilbene induce growth inhibition, apoptosis, S-phase arrest, and upregulation of cyclins A, E, and B1 in human SK-Mel-28 melanoma cells. J. Agric. Food Chem. 2003, 51, 4576–4584. [https://doi.org/10.1021/jf030073c] [https://pubmed.ncbi.nlm.nih.gov/14705880/]

Laux, M.T.; Aregullin, M.; Berry, J.P.; Flanders, J.A.; Rodriguez, E. Identification of a p53-dependent pathway in the induction of apoptosis of human breast cancer cells by the natural product, resveratrol. J. Altern. Complement. Med. 2004, 10, 235–239. [https://doi.org/10.1089/107555304323062211] [https://pubmed.ncbi.nlm.nih.gov/15165403/]

Le Corre, L.; Fustier, P.; Chalabi, N.; Bignon, Y.J.; Bernard-Gallon, D. Effects of resveratrol on the expression of a panel of genes interacting with the BRCA1 oncosuppressor in human breast cell lines. Clin. Chim. Acta 2004, 344, 115–121. [https://doi.org/10.1016/j.cccn.2004.02.024] [https://pubmed.ncbi.nlm.nih.gov/15149879/]

Lee, J.H.; Kim, Y.G.; Ryu, S.Y.; Cho, M.H.; Lee, J. Resveratrol oligomers inhibit biofilm formation of Escherichia coli O157:H7 and Pseudomonas aeruginosa. J. Nat. Prod. 2014, 77, 168–172. [https://doi.org/10.1021/np400756g] [https://pubmed.ncbi.nlm.nih.gov/24456071/]

Lee, K.A.; Lee, Y.J.; Ban, J.O.; Lee, Y.J.; Lee, S.H.; Cho, M.K.; Nam, H.S.; Hong, J.T.; Shim, J.H. The flavonoid resveratrol suppresses growth of human malignant pleural mesothelioma cells through direct inhibition of specificity protein 1. Int. J. Mol. Med. 2012, 30, 21–27. [https://doi.org/10.3892/ijmm.2012.978] [https://pubmed.ncbi.nlm.nih.gov/22552784/]

Leis, K.; Pisanko, K.; Jundziłł, A.; Mazur, E.; Mêcińska-Jundziłł, K.; Witmanowski, H. Resveratrol as a factor preventing skin aging and affecting its regeneration. Postepy Dermatol. Alergol. 2022, 39(3):439–445. [https://doi.org/10.5114/ada.2022.117547] [https://pubmed.ncbi.nlm.nih.gov/35950117/]

Li, D.; Song, C.; Zhang, J.; Zhao, X. Targeted delivery and apoptosis induction activity of peptide-transferrin targeted mesoporous silica encapsulated resveratrol in MCF-7 cells. J. Pharm. Pharmacol. 2023, 75, 49–56. [https://doi.org/10.1093/jpp/rgac028] [https://pubmed.ncbi.nlm.nih.gov/36173891/]

Li, D.; Wang, G.; Jin, G.; Yao, K.; Zhao, Z.; Bie, L.; Guo, Y.; Li, N.; Deng, W.; Chen, X.; et al. Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway. Int. J. Mol. Med. 2019, 43, 630–640. [https://doi.org/10.3892/ijmm.2018.3969] [https://pubmed.ncbi.nlm.nih.gov/30387805/]

Li, J.; Duan, Q.J.; Shen, J. [Resveratrol pretreatment improves mitochondrial function and alleviates myocardial ischemia–reperfusion injury by up-regulating mi R-20b-5p to inhibit STIM2]. Zhongguo Zhong Yao Za Zhi, 2022a, 47, 4987–4995. [https://doi.org/10.19540/j.cnki.cjcmm.20220314.401] [https://pubmed.ncbi.nlm.nih.gov/36164909/]

Li, J.; Fan, Y.; Zhang, Y.; Liu, Y.; Yu, Y.; Ma, M. Resveratrol induces autophagy and apoptosis in non-small-cell lung cancer cells by activating the NGFR-AMPK-mTOR pathway. Nutrients 2022b, 14, 2413. [https://doi.org/10.3390/nu14122413] [https://pubmed.ncbi.nlm.nih.gov/35745143/]

Li, J.; Wang, Z.; Li, H.; Cao, J.; Nan, N.; Zhai, X.; Liu, Y.; Chong, T. Resveratrol inhibits TRAF6/PTCH/SMO signal and regulates prostate cancer progression. Cytotechnology 2022c, 74, 549–558. [https://doi.org/10.1007/s10616-022-00544-0] [https://pubmed.ncbi.nlm.nih.gov/36238265/]

Li, J.; Zhang, C.X.; Liu, Y.M.; Chen, K.L.; Chen, G. A comparative study of anti-aging properties and mechanism: Resveratrol and caloric restriction. Oncotarget 2017, 8, 65717–65729. [https://doi.org/10.18632/oncotarget.20084] [https://pubmed.ncbi.nlm.nih.gov/29029466/]

Li, L.; Qiu, R.L.; Lin, Y.; Cai, Y.; Bian, Y.; Fan, Y.; Gao, X.J. Resveratrol suppresses human cervical carcinoma cell proliferation and elevates apoptosis via the mitochondrial and p53 signaling pathways. Oncol. Lett. 2018a, 15, 9845–9851. [https://doi.org/10.3892/ol.2018.8571] [https://pubmed.ncbi.nlm.nih.gov/29928358/]

Li, W.; Yuan, H.; Liu, Y.; Wang, B.; Xu, X.; Xu, X.; Hussain, D.; Ma, L.; Chen, D. Current analytical strategies for the determination of resveratrol in foods. Food Chem. 2024, 431, 137182. [https://doi.org/10.1016/j.foodchem.2023.137182] [https://pubmed.ncbi.nlm.nih.gov/37603999/]

Li, X.; Li, F.; Wang, F.; Li, J.; Lin, C.; Du, J. Resveratrol inhibits the proliferation of A549 cells by inhibiting the expression of COX-2. Onco Targets Ther. 2018b, 11, 2981–2989. [https://doi.org/10.2147/OTT.S157613] [https://pubmed.ncbi.nlm.nih.gov/29872310/]

Li, Y.; Bäckesjö, C.M.; Haldosén, L.A.; Lindgren, U. Resveratrol inhibits proliferation and promotes apoptosis of osteosarcoma cells. Eur. J. Pharmacol. 2009, 609, 13–18. [https://doi.org/10.1016/j.ejphar.2009.03.004] [https://pubmed.ncbi.nlm.nih.gov/19285066/]

Li, Z.G.; Hong, T.; Shimada, Y.; Komoto, I.; Kawabe, A.; Ding, Y.; Kaganoi, J.; Hashimoto, Y.; Imamura, M. Suppression of N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. Carcinogenesis 2002, 23, 1531–1536. [https://doi.org/10.1093/carcin/23.9.1531] [https://pubmed.ncbi.nlm.nih.gov/12189197/]

Liang, Y.C.; Tsai, S.H.; Chen, L.; Lin-Shiau, S.Y.; Lin, J.K. Resveratrol-induced G_2 arrest through the inhibition of CDK7 and p34^{CDC2} kinases in colon carcinoma HT29 cells. Biochem. Pharmacol. 2003, 65, 1053–1060. [https://doi.org/10.1016/s0006-2952(03)00011-x] [https://pubmed.ncbi.nlm.nih.gov/12663041/]

Lin, H.Y.; Tang, H.Y.; Davis, F.B.; Davis, P.J. Resveratrol and apoptosis. Ann. N. Y. Acad. Sci. 2011, 1215, 79–88. [https://doi.org/10.1111/j.1749-6632.2010.05846.x] [https://pubmed.ncbi.nlm.nih.gov/21261644/]

Liontas, A.; Yeger, H. Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. Anticancer Res. 2004, 24, 987–998. [https://pubmed.ncbi.nlm.nih.gov/15161054/]

Liu, L.; Yang, X.; Liao, Y.; Wang, C.; Wang, Y. Resveratrol alleviates Ang II-induced vascular smooth muscle cell

senescence by upregulating E2F1/SOD2 axis. Toxicol. Res. (Camb.) 2022, 11, 831–840. [https://doi.org/10.1093/toxres/tfac051] [https://pubmed.ncbi.nlm.nih.gov/36337239/]

Liu, L.; Zhang, Y.; Zhu, K.; Song, L.; Tao, M.; Huang, P.; Pan, Y. Resveratrol inhibits glioma cell growth *via* targeting LRIG1. J. BUON 2018, 23, 403–409. [https://pubmed.ncbi.nlm.nih.gov/29745084/]

Liu, Y.; Zheng, B.; Zheng, H.; Xu, G.; Jiang, H. Resveratrol promotes diabetic wound healing by inhibiting Notch pathway. J. Surg. Res. 2024, 297, 63–70. [https://doi.org/10.1016/j.jss.2024.02.004] [https://pubmed.ncbi.nlm.nih.gov/38447337/]

Liu, Z.M.; Li, S.Y.; Huang, Q.; Zeng, F.F.; Li, B.L.; Cao, W.T.; Chen, Y.M. Greater habitual resveratrol intakes were associated with lower risk of hip fracture – a 1:1 matched case-control study in Chinese elderly. Phytother. Res. 2023, 37, 672–678. [https://doi.org/10.1002/ptr.7645] [https://pubmed.ncbi.nlm.nih.gov/36205605/]

Lucas, I.K.; Kolodziej, H. *trans*-Resveratrol induces apoptosis through ROS-triggered mitochondria-dependent pathways in A549 human lung adenocarcinoma epithelial cells. Planta Med. 2015, 81, 1038–1044. [https://doi.org/10.1055/s-0035-1546129] [https://pubmed.ncbi.nlm.nih.gov/26085046/]

Ma, C.; Wang, Y.; Dong, L.; Li, M.; Cai, W. Anti-inflammatory effect of resveratrol through the suppression of NF-κB and JAK/STAT signaling pathways. Acta Biochim. Biophys. Sin. (Shanghai) 2015, 47, 207–213. [https://doi.org/10.1093/abbs/gmu135] [https://pubmed.ncbi.nlm.nih.gov/25651848/]

Magrone, T.; Magrone, M.; Russo, M.A.; Jirillo, E. Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: *In vitro* and *in vivo* studies. Antioxidants (Basel) 2019, 9, 35. [https://doi.org/10.3390/antiox9010035] [https://pubmed.ncbi.nlm.nih.gov/31906123/]

Malvasi, A.; Tinelli, A.; Lupica, G.; Vimercati, A.; Spyropoulou, K.; Dellino, M.; Mynbaev, O. Effects of a combination of resveratrol and alpha-lipoic acid on body weight and adipose composition in women with PCOS: A preliminary pilot study. Eur. Rev. Med. Pharmacol. Sci. 2022, 26, 6578–6582. [https://doi.org/10.26355/eurrev_202209_29757] [https://pubmed.ncbi.nlm.nih.gov/36196707/]

Martín, A.R.; Villegas, I.; La Casa, C.; de la Lastra, C.A. Resveratrol, a polyphenol found in grapes, suppresses oxidative damage and stimulates apoptosis during early colonic inflammation in rats. Biochem. Pharmacol. 2004, 67, 1399–1410. [https://doi.org/10.1016/j.bcp.2003.12.024] [https://pubmed.ncbi.nlm.nih.gov/15013856/]

Meng, C.; Liu, J.L.; Du, A.L. Cardioprotective effect of resveratrol on atherogenic diet-fed rats. Int. J. Clin. Exp. Pathol. 2014, 7, 7899–7906. [https://pubmed.ncbi.nlm.nih.gov/25550830/]

Mgbonyebi, O.P.; Russo, J.; Russo, I.H. Antiproliferative effect of synthetic resveratrol on human breast epithelial cells. Int. J. Oncol. 1998, 12, 865–869. [https://doi.org/10.3892/ijo.12.4.865] [https://pubmed.ncbi.nlm.nih.gov/9499448/]

Militaru, C.; Donoiu, I.; Craciun, A.; Scorei, I.D.; Bulearca, A.M.; Scorei, R.I. Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: Effects on lipid profiles, inflammation markers, and quality of life. Nutrition 2013, 29, 178–183. [https://doi.org/10.1016/j.nut.2012.07.006] [https://pubmed.ncbi.nlm.nih.gov/23153742/]

Miura, D.; Miura, Y.; Yagasaki, K. Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. Life Sci. 2003, 73, 1393–1400. [https://doi.org/10.1016/s0024-3205(03)00469-7] [https://pubmed.ncbi.nlm.nih.gov/12850500/]

Mizutani, K.; Ikeda, K.; Kawai, Y.; Yamori, Y. Resveratrol stimulates the proliferation and differentiation of osteoblastic MC3T3-E1 cells. Biochem. Biophys. Res. Commun. 1998, 253, 859–863. [https://doi.org/10.1006/bbrc.1998.9870] [https://pubmed.ncbi.nlm.nih.gov/9918820/]

Moghadam, D.; Zarei, R.; Vakili, S.; Ghojoghi, R.; Zarezade, V.; Veisi, A.; Sabaghan, M.; Azadbakht, O.; Behrouj, H. The effect of natural polyphenols Resveratrol, Gallic acid, and Kuromanin chloride on human telomerase reverse transcriptase (hTERT) expression in HepG2 hepatocellular carcinoma: Role of SIRT1/Nrf2 signaling pathway and oxidative stress. Mol. Biol. Rep. 2023, 50, 77–84. [https://doi.org/10.1007/s11033-022-08031-7] [https://pubmed.ncbi.nlm.nih.gov/36307623/]

Momchilova, A.; Pankov, R.; Staneva, G.; Pankov, S.; Krastev, P.; Vassileva, E.; Hazarosova, R.; Krastev, N.; Robev, B.; Nikolova, B.; et al. Resveratrol affects sphingolipid metabolism in A549 lung adenocarcinoma cells. Int. J. Mol. Sci. 2022, 23, 10870. [https://doi.org/10.3390/ijms231810870] [https://pubmed.ncbi.nlm.nih.gov/36142801/]

Nassir, A.M.; Shahzad, N.; Ibrahim, I.A.A.; Ahmad, I.; Md, S.; Ain, M.R. Resveratrol-loaded PLGA nanoparticles mediated programmed cell death in prostate cancer cells. Saudi Pharm. J. 2018, 26, 876–885. [https://doi.org/10.1016/j.jsps.2018.03.009] [https://pubmed.ncbi.nlm.nih.gov/30202231/]

Niles, R.M.; McFarland, M.; Weimer, M.B.; Redkar, A.; Fu, Y.M.; Meadows, G.G. Resveratrol is a potent inducer of apoptosis in human melanoma cells. Cancer Lett. 2003, 190, 157–163. [https://doi.org/10.1016/s0304-3835(02)00676-6] [https://pubmed.ncbi.nlm.nih.gov/12565170/]

Oh, W.Y.; Gao, Y.; Shahidi, F. Stilbenoids: Chemistry, occurrence, bioavailability and health effects – a review. J. Food Bioact. 2021, 13, 20–31. [https://doi.org/10.31665/JFB.2020.13256]

Ohara, K.; Kusano, K.; Kitao, S.; Yanai, T.; Takata, R.; Kanauchi, O. ε-Viniferin, a resveratrol dimer, prevents diet-induced obesity in mice. Biochem. Biophys. Res. Commun. 2015, 468, 877–882. [https://doi.org/10.1016/j.bbrc.2015.11.047] [https://pubmed.ncbi.nlm.nih.gov/26596701/]

Okamoto-Shibayama, K.; Yoshida, A.; Ishihara, K. Inhibitory effect of resveratrol on *Candida albicans* biofilm formation. Bull. Tokyo Dent. Coll. 2021, 62, 1–6. [https://doi.org/10.2209/tdcpublication.2020-0023]

[https://pubmed.ncbi.nlm.nih.gov/33583879/]

Osmond, G.W.; Augustine, C.K.; Zipfel, P.A.; Padussis, J.; Tyler, D.S. Enhancing melanoma treatment with resveratrol. J. Surg. Res. 2012, 172, 109–115. [https://doi.org/10.1016/j.jss.2010.07.033] [https://pubmed.ncbi.nlm.nih.gov/20855085/]

Ostwal, V.; Ramaswamy, A.; Bhargava, P.; Srinivas, S.; Mandavkar, S.; Chaugule, D.; Peelay, Z.; Baheti, A.; Tandel, H.; Jadhav, V.K.; et al. A pro-oxidant combination of resveratrol and copper reduces chemotherapy-related non-haematological toxicities in advanced gastric cancer: Results of a prospective open label phase II single-arm study (RESCU III study). Med. Oncol. 2022, 40, 17. [https://doi.org/10.1007/s12032-022-01862-1] [https://pubmed.ncbi.nlm.nih.gov/36372825/]

Pace-Asciak, C.R.; Hahn, S.; Diamandis, E.P.; Soleas, G.; Goldberg, D.M. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: Implications for protection against coronary heart disease. Clin. Chim. Acta 1995, 235, 207–219. [https://doi.org/10.1016/0009-8981(95)06045-1] [https://pubmed.ncbi.nlm.nih.gov/7554275/]

Pan, P.; Li, J.; Lin, W.; Long, G. Effects of resveratrol on hepatitis B virus replication: In vitro and in vivo experiments. Intervirology 2022, 65, 206–214. [https://doi.org/10.1159/000525807] [https://pubmed.ncbi.nlm.nih.gov/36088911/]

Park, J.W.; Choi, Y.J.; Jang, M.A.; Lee, Y.S.; Jun, D.Y.; Suh, S.I.; Baek, W.K.; Suh, M.H.; Jin, I.N.; Kwon, T.K. Chemopreventive agent resveratrol, a natural product derived from grapes, reversibly inhibits progression through S and G2 phases of the cell cycle in U937 cells. Cancer Lett. 2001, 163, 43–49. [https://doi.org/10.1016/s0304-3835(00)00658-3] [https://pubmed.ncbi.nlm.nih.gov/11163107/]

Patel, K.R.; Brown, V.A.; Jones, D.J.L.; Britton, R.G.; Hemingway, D.; Miller, A.S.; West, K.P.; Booth, T.D.; Perloff, M.; Crowell, J.A.; et al. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res. 2010, 70, 7392–7399. [https://doi.org/10.1158/0008-5472.CAN-10-2027] [https://pubmed.ncbi.nlm.nih.gov/20841478/]

Pawlus, A.D.; Waffo-Téguo, P.; Shaver, J.; Mérillon, J.M. Stilbenoid chemistry from wine and the genus Vitis, a review. OENO One 2012, 46, 57–111. [https://doi.org/10.20870/oeno-one.2012.46.2.1512]

Pezet, R.; Perret, C.; Jean-Denis, J.B.; Tabacchi, R.; Gindro, K.; Viret, O. Delta-viniferin, a resveratrol dehydrodimer: One of the major stilbenes synthesized by stressed grapevine leaves. J. Agric. Food Chem. 2003, 51, 5488–5492. [https://doi.org/10.1021/jf030227o] [https://pubmed.ncbi.nlm.nih.gov/12926902/]

Pilankar, A.; Singhavi, H.; Raghuram, G.V.; Siddiqui, S.; Khare, N.K.; Jadhav, V.; Tandel, H.; Pal, K.; Bhattacharjee, A.; Chaturvedi, P.; et al. A pro-oxidant combination of resveratrol and copper down-regulates hallmarks of cancer and immune checkpoints in patients with advanced oral cancer: Results of an exploratory study (RESCU 004). Front. Oncol. 2022, 12, 1000957. [https://doi.org/10.3389/fonc.2022.1000957] [https://pubmed.ncbi.nlm.nih.gov/36185249/]

Qi, L.; Liang, R.; Duan, J.; Song, S.; Pan, Y.; Liu, H.; Zhu, M.; Li, L. Synergistic antibacterial and anti-biofilm activities of resveratrol and polymyxin B against multidrug-resistant Pseudomonas aeruginosa. J. Antibiot. (Tokyo) 2022, 75, 567–575. [https://doi.org/10.1038/s41429-022-00555-1] [https://pubmed.ncbi.nlm.nih.gov/35999263/]

Qin, X.; Luo, H.; Deng, Y.; Yao, X.; Zhang, J.; He, B. Resveratrol inhibits proliferation and induces apoptosis via the Hippo/YAP pathway in human colon cancer cells. Biochem. Biophys. Res. Commun. 2022, 636, 197–204. [https://doi.org/10.1016/j.bbrc.2022.10.077] [https://pubmed.ncbi.nlm.nih.gov/36335870/]

Quarta, A.; Gaballo, A.; Pradhan, B.; Patra, S.; Jena, M.; Ragusa, A. Beneficial oxidative stress-related trans-resveratrol effects in the treatment and prevention of breast cancer. Appl. Sci. 2021, 11, 11041. [https://doi.org/10.3390/app112211041]

Quoc Trung, L.; Espinoza, J.L.; Takami, A.; Nakao, S. Resveratrol induces cell cycle arrest and apoptosis in malignant NK cells via JAK2/STAT3 pathway inhibition. PLoS One 2013, 8, e55183. [https://doi.org/10.1371/journal.pone.0055183] [https://pubmed.ncbi.nlm.nih.gov/23372833/]

Rahman, M.A.; Kim, N.H.; Kim, S.H.; Oh, S.M.; Huh, S.O. Antiproliferative and cytotoxic effects of resveratrol in mitochondria-mediated apoptosis in rat b103 neuroblastoma cells. Korean J. Physiol. Pharmacol. 2012, 16, 321–326. [https://doi.org/10.4196/kjpp.2012.16.5.321] [https://pubmed.ncbi.nlm.nih.gov/23118555/]

Reda, D.; Elshopakey, G.E.; Mahgoub, H.A.; Risha, E.F.; Khan, A.A.; Rajab, B.S.; El-Boshy, M.E.; Abdelhamid, F.M. Effects of resveratrol against induced metabolic syndrome in rats: Role of oxidative stress, inflammation, and insulin resistance. Evid. Based Complement. Alternat. Med. 2022, 2022, 3362005. [https://doi.org/10.1155/2022/3362005] [https://pubmed.ncbi.nlm.nih.gov/35990819/]

Ren, C.P.; Zhang, Y.N.; Wu, Y.L.; Du, X.X.; Cui, X.L. [Effects of resveratrol on inhibiting pyroptosis of intestinal cancer cells]. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2022, 38, 326–331. [https://doi.org/10.12047/j.cjap.6303.2022.062] [https://pubmed.ncbi.nlm.nih.gov/36414556/]

Revel, A.; Raanani, H.; Younglai, E.; Xu, J.; Rogers, I.; Han, R.; Savouret, J.F.; Casper, R.F. Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects lung from DNA damage and apoptosis caused by benzo[a]pyrene. J. Appl. Toxicol. 2003, 23, 255–261. [https://doi.org/10.1002/jat.916] [https://pubmed.ncbi.nlm.nih.gov/12884409/]

Rodríguez-Vaquero, M.J.; Vallejo, C.V.; Aredes-Fernández, P.A. Antibacterial, antioxidant and antihypertensive properties of polyphenols from Argentinean red wines varieties. Open J. Pharmacol. Pharmacother. 2020, 5, 1–6. [https://doi.org/10.17352/ojpp.000010]

Rojo, D.; Madrid, A.; Martín, S.S.; Párraga, M.; Silva Pinhal, M.A.; Villena, J.; Valenzuela-Valderrama, M. Resveratrol decreases the invasion potential of gastric cancer cells. Molecules 2022, 27, 3047. [https://doi.org/10.3390/molecules27103047] [https://pubmed.ncbi.nlm.nih.gov/35630523/]

Samsami-Kor, M.; Daryani, N.E.; Asl, P.R.; Hekmatdoost, A. Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: A randomized, double-blind, placebo-controlled pilot study. Arch. Med. Res. 2015, 46, 280–285. [https://doi.org/10.1016/j.arcmed.2015.05.005] [https://pubmed.ncbi.nlm.nih.gov/26002728/]

Schneider, Y.; Duranton, B.; Gossé, F.; Schleiffer, R.; Seiler, N.; Raul, F. Resveratrol inhibits intestinal tumorigenesis and modulates host-defense-related gene expression in an animal model of human familial adenomatous polyposis. Nutr. Cancer 2001, 39, 102–107. [https://doi.org/10.1207/s15327914nc391_14] [https://pubmed.ncbi.nlm.nih.gov/11588890/]

Schneider, Y.; Vincent, F.; Duranton, B.; Badolo, L.; Gossé, F.; Bergmann, C.; Seiler, N.; Raul, F. Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. Cancer Lett. 2000, 158, 85–91. [https://doi.org/10.1016/s0304-3835(00)00511-5] [https://pubmed.ncbi.nlm.nih.gov/10940513/]

Shamsher, E.; Khan, R.S.; Davis, B.M.; Dine, K.; Luong, V.; Cordeiro, M.F.; Shindler, K.S. Intranasal resveratrol nanoparticles enhance neuroprotection in a model of multiple sclerosis. Int. J. Mol. Sci. 2024, 25, 4047. [https://doi.org/10.3390/ijms25074047] [https://pubmed.ncbi.nlm.nih.gov/38612856/]

Shan, Z.; Yang, G.; Xiang, W.; Pei-Jun, W.; Bin, Z. Effects of resveratrol on oral squamous cell carcinoma (OSCC) cells in vitro. J. Cancer Res. Clin. Oncol. 2014, 140, 371–374. [https://doi.org/10.1007/s00432-013-1575-1] [https://pubmed.ncbi.nlm.nih.gov/24384874/]

Sharma, A.N.; Upadhyay, P.K.; Dewangan, H.K. Development, evaluation, pharmacokinetic and biodistribution estimation of resveratrol loaded solid lipid nanoparticles for prostate cancer targeting. J. Microencapsul. 2022, 39, 563–574. [https://doi.org/10.1080/02652048.2022.2135785] [https://pubmed.ncbi.nlm.nih.gov/36222429/]

She, Q.B.; Bode, A.M.; Ma, W.Y.; Chen, N.Y.; Dong, Z. Resveratrol-induced activation of p53 and apoptosis is mediated by extracellular-signal-regulated protein kinases and p38 kinase. Cancer Res. 2001, 61, 1604–1610. [https://pubmed.ncbi.nlm.nih.gov/11245472/]

Sheth, S.; Jajoo, S.; Kaur, T.; Mukherjea, D.; Sheehan, K.; Rybak, L.P.; Ramkumar, V. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. PLoS One 2012, 7, e51655. [https://doi.org/10.1371/journal.pone.0051655] [https://pubmed.ncbi.nlm.nih.gov/23272133/]

Singh, B.; Shoulson, R.; Chatterjee, A.; Ronghe, A.; Bhat, N.K.; Dim, D.C.; Bhat, H.K. Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways. Carcinogenesis 2014, 35, 1872–1880. [https://doi.org/10.1093/carcin/bgu120] [https://pubmed.ncbi.nlm.nih.gov/24894866/]

Skonieczna, M.; Adamiec-Organisciok, M.; Hudy, D.; Dziedzic, A.; Los, L.; Skladany, L.; Grgurevic, I.; Filipec-Kanizaj, T.; Jagodzinski, M.; Kukla, M.; et al. Hepatocellular cancer cell lines, Hep-3B and Hep-G2 display the pleiotropic response to resveratrol and berberine. Adv. Med. Sci. 2022, 67, 379–385. [https://doi.org/10.1016/j.advms.2022.09.003] [https://pubmed.ncbi.nlm.nih.gov/36191360/]

Soleas, G.J.; Grass, L.; Josephy, P.D.; Goldberg, D.M.; Diamandis, E.P. A comparison of the anticarcinogenic properties of four red wine polyphenols. Clin. Biochem. 2002, 35, 119–124. [https://doi.org/10.1016/s0009-9120(02)00275-8] [https://pubmed.ncbi.nlm.nih.gov/11983346/]

Spósito, L.; Fonseca, D.; Gonçalves Carvalho, S.; Miguel Sábio, R.; Marena, G.D.; Maria Bauab, T.; Bagliotti Meneguin, A.; Parreira, P.; Martins, M.C.L.; Chorilli, M. Engineering resveratrol-loaded chitosan nanoparticles for potential use against Helicobacter pylori infection. Eur. J. Pharm. Biopharm. 2024, 199, 114280. [https://doi.org/10.1016/j.ejpb.2024.114280] [https://pubmed.ncbi.nlm.nih.gov/38588828/]

Stahl, S.; Chun, T.Y.; Gray, W.G. Phytoestrogens act as estrogen agonists in an estrogen-responsive pituitary cell line. Toxicol. Appl. Pharmacol. 1998, 152, 41–48. [https://doi.org/10.1006/taap.1998.8500] [https://pubmed.ncbi.nlm.nih.gov/9772198/]

Stakleff, K.S.; Sloan, T.; Blanco, D.; Marcanthony, S.; Booth, T.D.; Bishayee, A. Resveratrol exerts differential effects in vitro and in vivo against ovarian cancer cells. Asian Pac. J. Cancer Prev. 2012, 13, 1333–1340. [https://doi.org/10.7314/apjcp.2012.13.4.1333] [https://pubmed.ncbi.nlm.nih.gov/22799328/]

Stewart, J.R.; O'Brian, C.A. Resveratrol antagonizes EGFR-dependent Erk1/2 activation in human androgen-independent prostate cancer cells with associated isozyme-selective PKC alpha inhibition. Invest. New Drugs 2004, 22, 107–117. [https://doi.org/10.1023/b:drug.0000011787.75522.ec] [https://pubmed.ncbi.nlm.nih.gov/14739659/]

Stocco, B.; Toledo, K.; Salvador, M.; Paulo, M.; Koyama, N.; Torqueti Toloi, M.R. Dose-dependent effect of resveratrol on bladder cancer cells: Chemoprevention and oxidative stress. Maturitas 2012, 72, 72–78. [https://doi.org/10.1016/j.maturitas.2012.02.004] [https://pubmed.ncbi.nlm.nih.gov/22386766/]

Su, C.H.; Wang, H.L.; Tsai, M.L.; Lin, Y.C.; Liao, J.M.; Yen, C.C.; Ting, H.C.; Yu, C.H. Protective effect of microorganism biotransformation-produced resveratrol on the high fat diet-induced hyperlipidemia, hepatic steatosis and synaptic impairment in hamsters. Int. J. Med. Sci. 2022a, 19, 1586–1595. [https://doi.org/10.7150/ijms.59018] [https://pubmed.ncbi.nlm.nih.gov/36185335/]

Su, J.L.; Lin, M.T.; Hong, C.C.; Chang, C.C.; Shiah, S.G.; Wu, C.W.; Chen, S.T.; Chau, Y.P.; Kuo, M.L. Resveratrol induces FasL-related apoptosis through Cdc42 activation of ASK1/JNK-dependent signaling pathway in human leukemia HL-60 cells. Carcinogenesis 2005, 26, 1–10. [https://doi.org/10.1093/carcin/bgh220]

[https://pubmed.ncbi.nlm.nih.gov/15217905/]

Su, N.; Li, L.; Zhou, E.; Li, H.; Wu, S.; Cao, Z. Resveratrol downregulates miR-155-5p to block the malignant behavior of gastric cancer cells. Biomed Res. Int. 2022b, 2022, 6968641. [https://doi.org/10.1155/2022/6968641] [https://pubmed.ncbi.nlm.nih.gov/35789645/]

Sun, N.J.; Woo, S.H.; Cassady, J.M.; Snapka, R.M. DNA polymerase and topoisomerase II inhibitors from *Psoralea corylifolia*. J. Nat. Prod. 1998, 61, 362–366. [https://doi.org/10.1021/np970488q] [https://pubmed.ncbi.nlm.nih.gov/9544566/]

Sun, Y.; Zhou, Q.M.; Lu, Y.Y.; Zhang, H.; Chen, Q.L.; Zhao, M.; Su, S.B. Resveratrol inhibits the migration and metastasis of MDA-MB-231 human breast cancer by reversing TGF-β1-induced epithelial–mesenchymal transition. Molecules 2019, 24, 1131. [https://doi.org/10.3390/molecules24061131] [https://pubmed.ncbi.nlm.nih.gov/30901941/]

Surh, Y.J.; Hurh, Y.J.; Kang, J.Y.; Lee, E.; Kong, G.; Lee, S.J. Resveratrol, an antioxidant present in red wine, induces apoptosis in human promyelocytic leukemia (HL-60) cells. Cancer Lett. 1999, 140, 1–10. [https://doi.org/10.1016/s0304-3835(99)00039-7] [https://pubmed.ncbi.nlm.nih.gov/10403535/]

Svilar, L.; Martin, J.C.; Defoort, C.; Paut, C.; Tourniaire, F.; Brochot, A. Quantification of *trans*-resveratrol and its metabolites in human plasma using ultra-high performance liquid chromatography tandem quadrupole–orbitrap mass spectrometry. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2019, 1104, 119–129. [https://doi.org/10.1016/j.jchromb.2018.11.016] [https://pubmed.ncbi.nlm.nih.gov/30453129/]

Synowiec-Wojtarowicz, A.; Krawczyk, A.; Kimsa-Dudek, M. The effect of resveratrol and static magnetic field interactions on the oxidation–reduction parameters of melanoma malignant cells. Appl. Sci. 2023, 13, 8042. [https://doi.org/10.3390/app13148042]

Tabata, Y.; Takano, K.; Ito, T.; Iinuma, M.; Yoshimoto, T.; Miura, H.; Kitao, Y.; Ogawa, S.; Hori, O. Vaticanol B, a resveratrol tetramer, regulates endoplasmic reticulum stress and inflammation. Am. J. Physiol. Cell Physiol. 2007, 293, C411–C418. [https://doi.org/10.1152/ajpcell.00095.2007] [https://pubmed.ncbi.nlm.nih.gov/17475668/]

Takashina, M.; Inoue, S.; Tomihara, K.; Tomita, K.; Hattori, K.; Zhao, Q.L.; Suzuki, T.; Noguchi, M.; Ohashi, W.; Hattori, Y. Different effect of resveratrol to induction of apoptosis depending on the type of human cancer cells. Int. J. Oncol. 2017, 50, 787–797. [https://doi.org/10.3892/ijo.2017.3859] [https://pubmed.ncbi.nlm.nih.gov/28197625/]

Tang, F.Y.; Chiang, E.P.I.; Sun, Y.C. Resveratrol inhibits heregulin-β_1-mediated matrix metalloproteinase-9 expression and cell invasion in human breast cancer cells. J. Nutr. Biochem. 2008, 19, 287–294. [https://doi.org/10.1016/j.jnutbio.2007.03.003] [https://pubmed.ncbi.nlm.nih.gov/17651959/]

Tao, K.; Bai, X.; Jia, W.; Liu, Y.; Zhu, X.; Han, J.; Dong, M.; Li, J.; Chen, D.; Hu, D. Effects of resveratrol on the treatment of inflammatory response induced by severe burn. Inflammation 2015, 38, 1273–1280. [https://doi.org/10.1007/s10753-014-0097-6] [https://pubmed.ncbi.nlm.nih.gov/25586484/]

Tejada, S.; Capó, X.; Mascaró, C.M.; Monserrat-Mesquida, M.; Quetglas-Llabrés, M.M.; Pons, A.; Tur, J.A.; Sureda, A. Hepatoprotective effects of resveratrol in non-alcoholic fatty live disease. Curr. Pharm. Des. 2021, 27, 2558–2570. [https://doi.org/10.2174/1381612826666200417165801] [https://pubmed.ncbi.nlm.nih.gov/32303170/]

Tessitore, L.; Davit, A.; Sarotto, I.; Caderni, G. Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21$^{\text{CIP}}$ expression. Carcinogenesis 2000, 21, 1619–1622. [https://doi.org/10.1093/carcin/21.8.1619] [https://pubmed.ncbi.nlm.nih.gov/10910967/]

Theodotou, M.; Fokianos, K.; Moniatis, D.; Kadlenic, R.; Chrysikou, A.; Aristotelous, A.; Mouzouridou, A.; Diakides, J.; Stavrou, E. Effect of resveratrol on non-alcoholic fatty liver disease. Exp. Ther. Med. 2019, 18, 559–565. [https://doi.org/10.3892/etm.2019.7607] [https://pubmed.ncbi.nlm.nih.gov/31316594/]

Totonchi, H.; Mokarram, P.; Karima, S.; Rezaei, R.; Dastghaib, S.; Koohpeyma, F.; Noori, S.; Azarpira, N. Resveratrol promotes liver cell survival in mice liver-induced ischemia-reperfusion through unfolded protein response: A possible approach in liver transplantation. BMC Pharmacol. Toxicol. 2022, 23, 74. [https://doi.org/10.1186/s40360-022-00611-4] [https://pubmed.ncbi.nlm.nih.gov/36175937/]

Tredici, G.; Miloso, M.; Nicolini, G.; Galbiati, S.; Cavaletti, G.; Bertelli, A. Resveratrol, MAP kinases and neuronal cells: Might wine be a neuroprotectant? Drugs Exp. Clin. Res. 1999, 25, 99–103. [https://pubmed.ncbi.nlm.nih.gov/10370870/]

Tsan, M.F.; White, J.E.; Maheshwari, J.G.; Bremner, T.A.; Sacco, J. Resveratrol induces Fas signalling-independent apoptosis in THP-1 human monocytic leukaemia cells. Br. J. Haematol. 2000, 109, 405–412. [https://doi.org/10.1046/j.1365-2141.2000.01980.x] [https://pubmed.ncbi.nlm.nih.gov/10848832/]

Tsang, S.W.; Zhang, H.; Lin, Z.; Mu, H.; Bian, Z.X. Anti-fibrotic effect of *trans*-resveratrol on pancreatic stellate cells. Biomed. Pharmacother. 2015, 71, 91–97. [https://doi.org/10.1016/j.biopha.2015.02.013] [https://pubmed.ncbi.nlm.nih.gov/25960221/]

Tseng, S.H.; Lin, S.M.; Chen, J.C.; Su, Y.H.; Huang, H.Y.; Chen, C.K.; Lin, P.Y.; Chen, Y. Resveratrol suppresses the angiogenesis and tumor growth of gliomas in rats. Clin. Cancer Res. 2004, 10, 2190–2202. [https://doi.org/10.1158/1078-0432.ccr-03-0105] [https://pubmed.ncbi.nlm.nih.gov/15041740/]

Tung, B.T.; Rodríguez-Bies, E.; Talero, E.; Gamero-Estévez, E.; Motilva, V.; Navas, P.; López-Lluch, G. Anti-inflammatory effect of resveratrol in old mice liver. Exp. Gerontol. 2015, 64, 1–7.

[https://doi.org/10.1016/j.exger.2015.02.004] [https://pubmed.ncbi.nlm.nih.gov/25687021/]

Vestergaard, M.; Ingmer, H. Antibacterial and antifungal properties of resveratrol. Int. J. Antimicrob. Agents 2019, 53, 716–723. [https://doi.org/10.1016/j.ijantimicag.2019.02.015] [https://pubmed.ncbi.nlm.nih.gov/30825504/]

Viegas, S.; Marinheiro, D.; Bastos, V.; Daniel-da-Silva, A.L.; Vieira, R.; Oliveira, H.; Almeida, J.C.; Ferreira, B.J.M.L. Resveratrol-loaded polydimethylsiloxane–silica hybrid materials: Synthesis, characterization, and antitumoral activity. Polymers (Basel) 2024, 16, 879. [https://doi.org/10.3390/polym16070879] [https://pubmed.ncbi.nlm.nih.gov/38611137/]

Visioli, F.; Panaite, S.A.; Tomé-Carneiro, J. Wine's phenolic compounds and health: A Pythagorean view. Molecules 2020, 25, 4105. [https://doi.org/10.3390/molecules25184105] [https://pubmed.ncbi.nlm.nih.gov/32911765/]

Vlase, L.; Kiss, B.; Leucuta, S.E.; Gocan, S. A rapid method for determination of resveratrol in wines by HPLC-MS. J. Liq. Chromatogr. Relat. Technol. 2009, 32, 2105–2121. [https://doi.org/10.1080/10826070903126989]

Wang, W.; Zhang, L.; Chen, T.; Guo, W.; Bao, X.; Wang, D.; Ren, B.; Wang, H.; Li, Y.; Wang, Y.; et al. Anticancer effects of resveratrol-loaded solid lipid nanoparticles on human breast cancer cells. Molecules 2017, 22, 1814. [https://doi.org/10.3390/molecules22111814] [https://pubmed.ncbi.nlm.nih.gov/29068422/]

Wei, Y.D.; Chen, X.X.; Yang, L.J.; Gao, X.R.; Xia, Q.R.; Qi, C.C.; Ge, J.F. Resveratrol ameliorates learning and memory impairments induced by bilateral hippocampal injection of streptozotocin in mice. Neurochem. Int. 2022, 159, 105385. [https://doi.org/10.1016/j.neuint.2022.105385] [https://pubmed.ncbi.nlm.nih.gov/35843421/]

Wieder, T.; Prokop, A.; Bagci, B.; Essmann, F.; Bernicke, D.; Schulze-Osthoff, K.; Dörken, B.; Schmalz, H.G.; Daniel, P.T.; Henze, G. Piceatannol, a hydroxylated analog of the chemopreventive agent resveratrol, is a potent inducer of apoptosis in the lymphoma cell line BJAB and in primary, leukemic lymphoblasts. Leukemia 2001, 15, 1735–1742. [https://doi.org/10.1038/sj.leu.2402284] [https://pubmed.ncbi.nlm.nih.gov/11681415/]

Wolter, F.; Akoglu, B.; Clausnitzer, A.; Stein, J. Downregulation of the cyclin D1/Cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines. J. Nutr. 2001, 131, 2197–2203. [https://doi.org/10.1093/jn/131.8.2197] [https://pubmed.ncbi.nlm.nih.gov/11481417/]

Wright, C.; Iyer, A.K.V.; Yakisich, J.S.; Azad, N. Anti-tumorigenic effects of resveratrol in lung cancer cells through modulation of c-FLIP. Curr. Cancer Drug Targets 2017, 17, 669–680. [https://doi.org/10.2174/1568009617666170315162932] [https://pubmed.ncbi.nlm.nih.gov/28302032/]

Wu, C.W.; Nakamoto, Y.; Hisatome, T.; Yoshida, S.; Miyazaki, H. Resveratrol and its dimers ε-viniferin and δ-viniferin in red wine protect vascular endothelial cells by a similar mechanism with different potency and efficacy. Kaohsiung J. Med. Sci. 2020, 36, 535–542. [https://doi.org/10.1002/kjm2.12199] [https://pubmed.ncbi.nlm.nih.gov/32118360/]

Wu, X.; Xu, Y.; Zhu, B.; Liu, Q.; Yao, Q.; Zhao, G. Resveratrol induces apoptosis in SGC-7901 gastric cancer cells. Oncol. Lett. 2018, 16, 2949–2956. [https://doi.org/10.3892/ol.2018.9045] [https://pubmed.ncbi.nlm.nih.gov/30127883/]

Wu, X.Y.; Zhai, J.; Huan. X.K.; Xu, W.W.; Tian, J.; Farhood, B. A systematic review of the therapeutic potential of resveratrol during colorectal cancer chemotherapy. Mini Rev. Med. Chem. 2023, 23, 1137–1152. [https://doi.org/10.2174/1389557522666220907145153] [https://pubmed.ncbi.nlm.nih.gov/36173048/]

Wu, Z.; Liu, B.; E, C.; Liu, J.; Zhang, Q.; Liu, J.; Chen, N.; Chen, R.; Zhu, R. Resveratrol inhibits the proliferation of human melanoma cells by inducing G1/S cell cycle arrest and apoptosis. Mol. Med. Rep. 2015, 11, 400–404. [https://doi.org/10.3892/mmr.2014.2716] [https://pubmed.ncbi.nlm.nih.gov/25333673/]

Xie, C.; Liang, C.; Wang, R.; Yi, K.; Zhou, X.; Li, X.; Chen, Y.; Miao, D.; Zhong, C.; Zhu, J. Resveratrol suppresses lung cancer by targeting cancer stem-like cells and regulating tumor microenvironment. J. Nutr. Biochem. 2022, 112, 109211. [https://doi.org/10.1016/j.jnutbio.2022.109211] [https://pubmed.ncbi.nlm.nih.gov/36370924/]

Xie, D.; Zheng, G.Z.; Xie, P.; Zhang, Q.H.; Lin, F.X.; Chang, B.; Hu, Q.X.; Du, S.X.; Li, X.D. Antitumor activity of resveratrol against human osteosarcoma cells: A key role of Cx43 and Wnt/β-catenin signaling pathway. Oncotarget 2017, 8, 111419–111432. [https://doi.org/10.18632/oncotarget.22810] [https://pubmed.ncbi.nlm.nih.gov/29340064/]

Xiong, H.; Cheng, J.; Jiang, S.; Wen, J.; Jian, Y.; Wei, L.; Zhe, Z.; Fu-Qiang, J.; Peng, X. The antitumor effect of resveratrol on nasopharyngeal carcinoma cells. Front. Biosci. (Landmark Ed.) 2019, 24, 961–970. [https://doi.org/10.2741/4761] [https://pubmed.ncbi.nlm.nih.gov/30844723/]

Xu, F.; Du, H.; Hou, J.; Liu, J.; Li, N. Anti-inflammation properties of resveratrol in the detrusor smooth muscle of the diabetic rat. Int. Urol. Nephrol. 2022, 54, 2833–2843. [https://doi.org/10.1007/s11255-022-03334-x] [https://pubmed.ncbi.nlm.nih.gov/35943662/]

Xu, N.; Wang, L.; Fu, S.; Jiang, B. Resveratrol is cytotoxic and acts synergistically with NF-κB inhibition in osteosarcoma MG-63 cells. Arch. Med. Sci. 2020, 17, 166–176. [https://doi.org/10.5114/aoms.2020.100777] [https://pubmed.ncbi.nlm.nih.gov/33488869/]

Xu, Q.; Zong, L.; Chen, X.; Jiang, Z.; Nan, L.; Li, J.; Duan, W.; Lei, J.; Zhang, L.; Ma, J.; et al. Resveratrol in the treatment of pancreatic cancer. Ann. N. Y. Acad. Sci. 2015, 1348, 10–19. [https://doi.org/10.1111/nyas.12837] [https://pubmed.ncbi.nlm.nih.gov/26284849/]

Yadav, E.; Yadav, P.; Khan, M.M.U.; Singh, H.; Verma, A. Resveratrol: A potential therapeutic natural polyphenol for neurodegenerative diseases associated with mitochondrial dysfunction. Front. Pharmacol. 2022, 13, 922232. [https://doi.org/10.3389/fphar.2022.922232] [https://pubmed.ncbi.nlm.nih.gov/36188541/]

Yamamoto, M.; Suzuki, S.O.; Himeno, M. Resveratrol-induced autophagy in human U373 glioma cells. Oncol. Lett.

2010, 1, 489–493. [https://doi.org/10.3892/ol_00000086] [https://pubmed.ncbi.nlm.nih.gov/22966330/]

Yang, D.K.; Kang, H.S. Anti-diabetic effect of cotreatment with quercetin and resveratrol in streptozotocin-induced diabetic rats. Biomol. Ther. (Seoul) 2018, 26, 130–138. [https://doi.org/10.4062/biomolther.2017.254] [https://pubmed.ncbi.nlm.nih.gov/29462848/]

Yang, L.; Yang, L.; Tian, W.; Li, J.; Liu, J.; Zhu, M.; Zhang, Y.; Yang, Y.; Liu, F.; Zhang, Q.; et al. Resveratrol plays dual roles in pancreatic cancer cells. J. Cancer Res. Clin. Oncol. 2014, 140, 749–755. [https://doi.org/10.1007/s00432-014-1624-4] [https://pubmed.ncbi.nlm.nih.gov/24604347/]

Yang, S.; Li, W.; Sun, H.; Wu, B.; Ji, F.; Sun, T.; Chang, H.; Shen, P.; Wang, Y.; Zhou, D. Resveratrol elicits anti-colorectal cancer effect by activating miR-34c-KITLG in vitro and in vivo. BMC Cancer 2015, 15, 969. [https://doi.org/10.1186/s12885-015-1958-6] [https://pubmed.ncbi.nlm.nih.gov/26674205/]

Yang, Z.; Xia, L. Resveratrol inhibits the proliferation, invasion, and migration, and induces the apoptosis of human gastric cancer cells through the MALAT1/miR-383-5p/DDIT4 signaling pathway. J. Gastrointest. Oncol. 2022, 13, 985–996. [https://doi.org/10.21037/jgo-22-307] [https://pubmed.ncbi.nlm.nih.gov/35837196/]

Yoksa, D.T.; Abba, Y.; Shamaki, B.U.; Satumari, N.A. Effects of resveratrol topical ointment on wound healing of full-thickness cutaneous burns in albino rats. J. Wound Care 2022, 31, 780–791. [https://doi.org/10.12968/jowc.2022.31.9.780] [https://pubmed.ncbi.nlm.nih.gov/36113542/]

Yoo, K.M.; Kim, S.; Moon, B.K.; Kim, S.S.; Kim, K.T.; Kim, S.Y.; Choi, S.Y. Potent inhibitory effects of resveratrol derivatives on progression of prostate cancer cells. Arch. Pharm. (Weinheim) 2006, 339, 238–241. [https://doi.org/10.1002/ardp.200500228] [https://pubmed.ncbi.nlm.nih.gov/16619281/]

Yu, D.; Zhao, X.Y.; Meng, Q.P.; Teng, D.; Deng, K.; Lin, N. Resveratrol activates the SIRT1/PGC-1 pathway in mice to improve synaptic-related cognitive impairment after TBI. Brain Res. 2022, 1796, 148109. [https://doi.org/10.1016/j.brainres.2022.148109] [https://pubmed.ncbi.nlm.nih.gov/36183792/]

Yu, H.; Pan, C.; Zhao, S.; Wang, Z.; Zhang, H.; Wu, W. Resveratrol inhibits tumor necrosis factor-alpha-mediated matrix metalloproteinase-9 expression and invasion of human hepatocellular carcinoma cells. Biomed. Pharmacother. 2008, 62, 366–372. [https://doi.org/10.1016/j.biopha.2007.09.006] [https://pubmed.ncbi.nlm.nih.gov/17988825/]

Yu, L.; Wu, S.L.; Zhang, M.; Pan, C.E. [Effect of resveratrol alone and its combination with cyclosporin A on the immune function of human peripheral blood T lymphocytes]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2003, 19, 549–551. [https://pubmed.ncbi.nlm.nih.gov/15182646/]

Yu, S.; Zhang, L.; Yang, Y.; Wang, M.; Liu, T.; Ji, W.; Liu, Y.; Lv, H.; Zhao, Y.; Chen, X.; et al. Polydopamine-based resveratrol–hyaluronidase nanomedicine inhibited pancreatic cancer cell invasive phenotype in hyaluronic acid enrichment tumor sphere model. ACS Pharmacol. Transl. Sci. 2024, 7, 1013–1022. [https://doi.org/10.1021/acsptsci.3c00304] [https://pubmed.ncbi.nlm.nih.gov/38633596/]

Zhang, A.J.; Rimando, A.M.; Mizuno, C.S.; Mathews, S.T. α-Glucosidase inhibitory effect of resveratrol and piceatannol. J. Nutr. Biochem. 2017, 47, 86–93. [https://doi.org/10.1016/j.jnutbio.2017.05.008] [https://pubmed.ncbi.nlm.nih.gov/28570943/]

Zhang, C.; Peng, Q.; Tang, Y.; Wang, C.; Wang, S.; Yu, D.; Hou, S.; Wang, Y.; Zhang, L.; Lin, N. Resveratrol ameliorates glioblastoma inflammatory response by reducing NLRP3 inflammasome activation through inhibition of the JAK2/STAT3 pathway. J. Cancer Res. Clin. Oncol. 2024, 150, 168. [https://doi.org/10.1007/s00432-024-05625-5] [https://pubmed.ncbi.nlm.nih.gov/38546908/]

Zhang, J.; Chiu, J.; Zhang, H.; Qi, T.; Tang, Q.; Ma, K.; Lu, H.; Li, G. Autophagic cell death induced by resveratrol depends on the Ca^{2+}/AMPK/mTOR pathway in A549 cells. Biochem. Pharmacol. 2013, 86, 317–328. [https://doi.org/10.1016/j.bcp.2013.05.003] [https://pubmed.ncbi.nlm.nih.gov/23680031/]

Zhang, N.; Zhuang, L.; Gai, S.; Shan, Y.; Wang, S.; Li, F.; Chen, L.; Zhao, D.; Liu, X. Beneficial phytoestrogenic effects of resveratrol on polycystic ovary syndrome in rat model. Gynecol. Endocrinol. 2021a, 37, 337–341. [https://doi.org/10.1080/09513590.2020.1812569] [https://pubmed.ncbi.nlm.nih.gov/32851887/]

Zhang, Q.; Xu, S.; Xu, W.; Zhou, Y.; Luan, H.; Wang, D. Resveratrol decreases local inflammatory markers and systemic endotoxin in patients with aggressive periodontitis. Medicine (Baltimore) 2022a, 101, e29393. [https://doi.org/10.1097/md.0000000000029393] [https://pubmed.ncbi.nlm.nih.gov/35758374/]

Zhang, W.; Murao, K.; Zhang, X.; Matsumoto, K.; Diah, S.; Okada, M.; Miyake, K.; Kawai, N.; Fei, Z.; Tamiya, T. Resveratrol represses YKL-40 expression in human glioma U87 cells. BMC Cancer 2010, 10, 593. [https://doi.org/10.1186/1471-2407-10-593] [https://pubmed.ncbi.nlm.nih.gov/21029458/]

Zhang, W.; Yu, H.; Lin, Q.; Liu, X.; Cheng, Y.; Deng, B. Anti-inflammatory effect of resveratrol attenuates the severity of diabetic neuropathy by activating the Nrf2 pathway. Aging (Albany N.Y.) 2021b, 13, 10659–10671. [https://doi.org/10.18632/aging.202830] [https://pubmed.ncbi.nlm.nih.gov/33770763/]

Zhang, W.; Zhang, R.; Chang, Z.; Wang, X. Resveratrol activates CD8+ T cells through IL-18 bystander activation in lung adenocarcinoma. Front. Pharmacol. 2022b, 13, 1031438. [https://doi.org/10.3389/fphar.2022.1031438] [https://pubmed.ncbi.nlm.nih.gov/36339614/]

Zhang, X.; Yang, G.; Chen, Y.; Mu, Z.; Zhou, H.; Zhang, L. Resveratrol pre-treatment alleviated caerulein-induced acute pancreatitis in high-fat diet-feeding mice via suppressing the NF-κB proinflammatory signaling and improving the gut microbiota. BMC Complement. Med. Ther. 2022c, 22, 189. [https://doi.org/10.1186/s12906-022-03664-4] [https://pubmed.ncbi.nlm.nih.gov/35842665/]

Zhang, Y.; Guo, H.; Fu, H. Protective effect of resveratrol combined with levodopa against oxidative damage in

dopaminergic neurons. Cell Biochem. Biophys. 2024, Apr 15. [https://doi.org/10.1007/s12013-024-01233-9] [https://pubmed.ncbi.nlm.nih.gov/38619644/]

Zhang, Y.; Li, Y.; Wang, Y.; Wang, G.; Mao, L.; Zhang, D.; Wang, J. Effects of resveratrol on learning and memory in rats with vascular dementia. Mol. Med. Rep. 2019, 20, 4587–4593. [https://doi.org/10.3892/mmr.2019.10723] [https://pubmed.ncbi.nlm.nih.gov/31702039/]

Zhang, Y.; Zhu, X.B.; Zhao, J.C.; Gao, X.F.; Zhang, X.N.; Hou, K. Neuroprotective effect of resveratrol against radiation after surgically induced brain injury by reducing oxidative stress, inflammation, and apoptosis through NRf2/HO-1/NF-κB signaling pathway. J. Biochem. Mol. Toxicol. 2020, 34, e22600. [https://doi.org/10.1002/jbt.22600] [https://pubmed.ncbi.nlm.nih.gov/32815255/]

Zhao, G.; Yang, L.; Zhong, W.; Hu, Y.; Tan, Y.; Ren, Z.; Ban, Q.; Yang, C.S.; Wang, Y.; Wang, Z. Polydatin, a glycoside of resveratrol, is better than resveratrol in alleviating non-alcoholic fatty liver disease in mice fed a high-fructose diet. Front. Nutr. 2022, 9, 857879. [https://doi.org/10.3389/fnut.2022.857879] [https://pubmed.ncbi.nlm.nih.gov/35651514/]

Zhao, Y.; Tang, H.; Zeng, X.; Ye, D.; Liu, J. Resveratrol inhibits proliferation, migration and invasion *via* Akt and ERK1/2 signaling pathways in renal cell carcinoma cells. Biomed. Pharmacother. 2018, 98, 36–44. [https://doi.org/10.1016/j.biopha.2017.12.029] [https://pubmed.ncbi.nlm.nih.gov/29241073/]

Zhou, H.B.; Yan, Y.; Sun, Y.N.; Zhu, J.R. Resveratrol induces apoptosis in human esophageal carcinoma cells. World J. Gastroenterol. 2003, 9, 408–411. [https://doi.org/10.3748/wjg.v9.i3.408] [https://pubmed.ncbi.nlm.nih.gov/12632486/]

Zhu, W.; Dong, Y.; Xu, P.; Pan, Q.; Jia, K.; Jin, P.; Zhou, M.; Xu, Y.; Guo, R.; Cheng, B. A composite hydrogel containing resveratrol-laden nanoparticles and platelet-derived extracellular vesicles promotes wound healing in diabetic mice. Acta Biomater. 2022, 154, 212–230. [https://doi.org/10.1016/j.actbio.2022.10.038] [https://pubmed.ncbi.nlm.nih.gov/36309190/]