Oncology
and Radiotherapy ©
Vol.15 Iss.12:1-12 • Review Article

Resveratrol as anti-cancer and cardio protective agent: a review

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SUMMARY

This review aims to summarize the major therapeutic roles played by resveratrol and their associated pathways. Aspects of this ingredient with potential therapeutic applications have also been highlighted in the review. Various studies concerning resveratrol's health benefits are discussed in the article. Various cardiovascular diseases and cancer therapies are linked to oxidative stress, which is a probable pathophysiological factor. It has been proven that resveratrol, with its powerful antioxidant and free radical scavenging properties, restores the normal function of the heart and also protects against cancer. Resveratrol has also been shown to reduce the risk of coronary heart disease, hypertension, stroke, and complications. Resveratrol is also shown to be a significant cancer-fighting ingredient. According to the review, resveratrol could be useful for coronary heart disease and cancer chemotherapy as it lessens Endoplasmic Reticulum (ER) stress.

Key words: resveratrol, oxidative stress, cancer therapy, endoplasmic reticulum stress, cardiovascular diseases, coronary artery diseases

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Word count: 11445 **Table:** 01 **Figures:** 02 **References:** 124

Received: - 04 October, 2021

Accepted: - 21 December, 2021

Published: - 27 December, 2021

INTRODUCTION

The world's leading cause of death continues to be cardiovascular complications. A CDC (Centres for Disease Control and Prevention) report indicates that about half a million Americans die every year from heart disease or about one death for every four [1]. Increasing cardiovascular and type 2 diabetes rates are linked to obesity, inflammation, and oxidative stress, which have significantly increased worldwide [2, 3]. Weight loss is one of the most effective ways to reduce these conditions [4], and long term dietary strategies may be used to keep the weight off and improve health [5]. Resveratrol is one of the well-known natural products which fall under this category of non-pharmacological approaches that can reduce cardiovascular risks.

Cancer occurs when abnormal cells grow unchecked in the body, resulting in malignant tumours that invade nearby tissues. Most benign tumours are those that remain in one place and do not progress. It is alleged that a tumour has metastasized when it has spread to other parts of the body, become invasive and eradicated further healthy tissue systems. Activation of certain specialized genes-proto-oncogenes in oncogenes occurs when chemicals, physical agents, or viruses trigger abnormal behaviour [6]. Approximately 11.5 million cancer deaths are expected worldwide by 2030. Old and damaged cells die and new cells invade their space when they become old and injured. These progressions can sometimes lead to errors. Injured or old cells do not perish as they should since new cells are fashioned when the physiology does not want them. An accumulation of extra cells may cause a lump, nodule, growth, or tumour to form. Palliative care [7], early detection [8], and treatment of cancer [9] are all needed to reduce cancer incidence, especially by taking the advantages of nanotechnology-based advances.

Resveratrol is chemically trans-3,5,4'-trihydroxystilbene. It is a polyphenol phytoalexin compound abundant naturally in a variety of plant species, including white hellebore (Veratrumgrandiflorum O. Loes), Polygonumcuspidatum, grapes, blueberries, peanuts, wine and mulberries [10,11]. Resveratrol comes to the attention following the discovery of the cardioprotective nature of red wine [12]. As a result, new clinical health research on the benefits of resveratrol has been initiated. In subsequent research, resveratrol was shown to be beneficial to a wide range of disease conditions including cardiovascular diseases, cancer, ischemic disorders, and neurodegenerative disorders [13-17] (Figure 1). Additionally, resveratrol slows down the ageing process in diverse organisms from bacteria to vertebrates by increasing their stress resistance and life span [18-22]

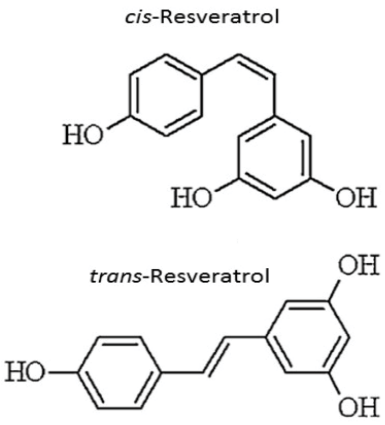

Fig. 1. Structure of Resveratrol (Cis and Trans)

In addition to being a free radical scavenger and antioxidant, resveratrol is also well-known and extensively studied. It modulates intracellular signal transmission pathways and has therapeutic effects such as promoting cell survival, decreasing apoptosis and increasing angiogenesis [23,24]. Resveratrol has been shown to have anti-cancer properties in several scientific studies [25-27]. Research on resveratrol as a chemopreventive agent has increased over time as a result of its remarkable therapeutic potential [28]. Resveratrol may be useful in treating various types of cancer, including prostate cancer, according to scientific studies [29,30], fibrosarcoma [31,32], skin cancer [33-35], lung cancer [36,37], gastric and colorectal cancer [38], leukemia [39,40], breast cancer [41-43], hepatoma [44,45], neuroblastoma [46] and pancreatic cancer [21,22,47]. However, clinical studies in humans did not correlate well with pre-clinical findings. Resveratrol is lipophilic in nature, and its half-life is short, so it may be due to pharmacokinetic issues. This review summarizes the major antioxidative, cardioprotective, and anticancer properties of resveratrol and the related pathways, along with promising therapeutic approaches.

Polyphenolic compounds and cancers

Polyphenols belong to a heterogeneous class of compounds, found in plant sources, with a great variety of effects. They are potent antioxidant agents, interfering with the oxidative antioxidative potential of the cell, or acting as free radical scavengers [48]. Polyphenols are absorbed from the upper gastrointestinal tract [49], after wine ingestion. They are distributed in the body, showing an increased affinity for the heart, liver, and kidney, but chronic ingestion is necessary to obtain bio-effective concentrations. Grapes and wine contain a great number of polyphenols, ranging from 12.6 mmol/L-22.4 mmol/L. Wine polyphenols include phenolic acids (p-coumaric, cinnamic, caffeic, gentisic, ferulic, and vanillic acid), trihydroxy-stilbenes (resveratrol and polydatin), and flavonoids (catechin, epicatechin, and quercetin). Polymeric aggregation gives rise, in turn, to the viniferins (potent antifungal agents) and procyanidins (strong antioxidants that also inhibit platelet aggregation). Polyphenols, among other compounds, including vitamins, pigments, flavonoids, etc., possess antimutagenic properties, as well as blood glucose decreasing activity. The antioxidant effect of red wine and its major polyphenols have been demonstrated in many systems, from *in vitro* studies (human low-density lipoprotein, liposomes, macrophages, cultured cells) to investigations in normal human subjects, although their effects remain controversial. Several of these compounds (notably catechin, quercetin, and resveratrol) promote nitric oxide production by vascular endothelium, inhibit the synthesis of thromboxane in platelets and leukotriene in neutrophils, modulate the synthesis and secretion of lipoproteins in whole animal and human cell lines, arrest tumour growth and inhibit carcinogenesis in different experimental models [50].

Polyphenolic compounds and iron

Polyphenolic compounds can show higher antioxidant activity in the presence of iron. Antioxidant activity refers to both the ability of polyphenol compounds to prevent damage from Reactive Oxygen Species (ROS) (such as through radical scavenging) or to prevent the generation of these species (by binding iron) [51,52]. Many mechanisms have been proposed for polyphenol prevention of oxidative stress and ROS/RNS generation both *in vitro* and *in vivo*. Radical scavenging by polyphenols is the most widely published mechanism for their antioxidant activity, with over hundreds of papers since 1995 alone [53]. Hydroxyl radical, the most reactive ROS knew, abstracts a hydrogen atom from biological substrates at diffusion-limited rates [54]. When H_2O_2 is also present as a result of oxidative stress, redox-active metal ions such as Fe^{2+} or Cu^{+} that are localized or bound to the DNA react with H_2O_2 to form highly reactive -OH in immediate proximity to DNA. Hydroxyl radical then abstracts the 40-hydrogen atom from the deoxyribose sugar backbone, leaving a DNA radical adduct that rearranges, ultimately cleaving the phosphodiester backbone and resulting in strand scission [55]. Alternatively, -OH may damage the nucleotide bases themselves, resulting in oxidized base products such as 8-oxo-guanine and fragmented or ring-opened derivatives [56]. DNA damage of both types (strand breakage or base damage) can ultimately result in genetic mutations, cancer, or cell death. Both Imlay, et al. and Mello-Filho, et al. have determined that iron-mediated oxidative DNA damage by -OH is the primary cause of cell death under oxidative stress conditions for both prokaryotes, and eukaryotes (including humans). Iron-mediated DNA damage is primarily thought to originate from solvated iron that is not bound to proteins (such as haemoglobin, transferrin, or ferritin in eukaryotes, or the ferritin-like DPR protein and Ferric Uptake Regulatory (FUR) protein of prokaryotes), which would otherwise prevent the iron from participating in the Fenton reaction [51].

Resveratrol and the Endoplasmic Reticulum (ER) stress

The Endoplasmic Reticulum (ER) is, in the core, the transportation structure of the eukaryotic cell, and has numerous other significant functions such as protein folding. It is a sort of organelle made up of two subunits-Rough Endoplasmic Reticulum (RER), and Smooth Endoplasmic Reticulum (SER). The endoplasmic reticulum forms an interconnected network of flattened, membrane-enclosed sacs identified as cisternae (in the RER), and tubular structures in the SER [57,58]. The membranes of the ER are continuous with the outer nuclear membrane. Modification and synthesis of proteins, translation and post-transcriptional fabrication occur within this organelle.

ER integrity is essential to maintaining cellular health. ER environments may be influenced by stimuli from various origins, generating nutritional deficiencies and compromising pathological status as a result. It can be physiological or biochemical stimuli leading to moderate to severe abnormalities including glycosylation changes, calcium depletion, oxidative stress and DNA damage [59,60]. The ER is affected by these alternations, resulting in a severe pathological stress condition known as ER stress or ER oxidative stress. An abnormal protein accumulation in the ER coexists with this pathological stress. ER stress following ROS production underlies the protective effects of resveratrol in primary skeletal myotubes in humans [61]. Researchers discovered that resveratrol protects the endoplasmic reticulum in terms of endoplasmic reticulum morphology restoration and downregulation of marker protein (C/EBP) [61].

In a mouse oxidative stress model and diabetic nephropathy, resveratrol displayed defensive activity apparent from numerous parameters including Urinary Albumin Excretion (UAE) data, biomarkers of oxidative stress (mitochondrial 8-hydroxy-2'-deoxyguanosine and nitrotyrosine expression) along with activity of manganese-superoxide dismutase (Mn-SOD). In terms of reducing UAE and attenuating associated renal pathological changes, resveratrol has been shown to be beneficial. Normalization of Mn-SOD function and stabilization of glucose and lipid metabolism were observed in the study [62]. Researchers found that resveratrol protected against oxidative stress due to diabetes-induced ER stress. A unique environment that allows protein synthesis and protein-oxidizing folding are provided by the Endoplasmic Reticulum. Additionally, Reactive Oxygen Species (ROS) production is tightly regulated by protein folding events in the ER. Unfolded Protein Response (UPR) is a stress response mechanism that occurs at the cellular level. After proteins were accumulated in the ER, this response was activated. UPR is activated by oxidative stress as an adaptive mechanism [63,64]. Interruptions in the protein folding mechanism cause ER stress, which tends to produce ROS, thereby causing oxidative damage [64].

In addition, numerous studies have confirmed resveratrol's powerful antioxidant properties [65-67]. Studies on HTR-8/SVneo cell lines following hypoxic treatment have demonstrated that resveratrol inhibits the generation of reactive oxygen species and p53-dependent apoptosis induced by interleukin-1b [68]. Various *in vitro* and *in vivo* tests, including superoxide dismutase assays, malondialdehyde assays, and flow cytometric analyses, corroborate the statement [68]. A rat model of Optic Nerve Transaction (ONT) demonstrated that resveratrol had neuroprotective properties *via* Sirtuin 1 pathway. Cultured retinal ganglion cells (RGC-5) were tested for neuroprotective effect by using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Results showed resveratrol had a sirtuin 1 pathway-dependent neuroprotective effect [69].

Pro-inflammatory agents like arachidonic acid and iron can increase ROS production in mitochondria and cause oxidative stress. Treatment with resveratrol can reverse this mitochondrial stress and impairment Resveratrol is proven to be able to protect mitochondria from effects caused by arachidonic acid combined with iron. Researchers found that resveratrol could reduce glutathione depletion, apoptosis and ROS production of cells induced by arachidonic acid/iron in a study involving HepG2 cell lines. The AMPK (AMP-activated protein kinase) pathway has been hypothesized as contributing to the protective effects of resveratrol.

Resveratrol induced apoptosis in colon cancer cells (HT29 cells) by possibly triggering stress-induced ER responses. Resveratrol has been proposed to affect several ER stress markers, including CHOP (C/EBP homologous protein) and GRP78 (glucose-related protein 78) splicing and phosphorylation of eIF-2α.

Resveratrol as a cardioprotective agent

Researchers have found that resveratrol protects against ischemic and reperfusion injuries, atherosclerosis, hypertension and heart failure. In addition to its cardioprotective effects, resveratrol produces an adaptive response through a preconditioning-like mechanism. As a preconditioning factor, resveratrol shows an adaptive stress response through the expression of cardioprotective genes and proteins, such as heat shock and antioxidant proteins [16]. There have been correlations between these effects of resveratrol and the modulation of the mTOR-Rictor survival pathways [70]. In animal models, resveratrol showed inhibition of LDL oxidation, suppression of platelet aggregation, and reduction of ischemia-reperfusion induced myocardial injury, which in turn indicated potential cardiovascular safety [17,71,72]. Resveratrol also demonstrated anti-inflammatory activity that may be related to NO (Nitric Oxide) production. A rat model of Myocardial Ischemia and Reperfusion (MI/R) also demonstrated that resveratrol has cardioprotective effects by inhibiting the Toll-like receptor 4 (TLR4)/NF-B signal pathway. Stroke is another very common cardiovascular disease that is responsible for a large number of deaths throughout the world. The predominant pathophysiological modality associated with stroke seems to be oxidative stress [73,74]. As a natural antioxidant, resveratrol exhibits potent anti-inflammatory and cardioprotective effects. Resveratrol may help alleviate oxidative stress by aggravating the production of nitric oxide and inhibiting inflammation through the production of nitric oxide [75]. Contrary to popular belief, it has been shown that red wine consumption is associated with a low prevalence of Coronary Heart Disease (CHD) among French individuals [12,76-78]. Studies have shown that red wine contains resveratrol, which is responsible for its cardioprotective effects [79]. Additionally, resveratrol has been shown to exert cardioprotective properties through a variety of mechanisms [77,78]. Significant levels of oxidative stress neutralizing protein markers were observed in myocardial ischemia in association with significant expressions of critical protein markers [80]. Resveratrol also showed protective effects against cardiotoxicity induced by doxorubicin, another potent anti-cancer agent [81]. According to electron microscope examinations, resveratrol restored mitochondrial structure in these cases [81]. Preclinical results recommended mitigation of cardiac toxicity made by doxorubicin in terms of lipid peroxidation in the left ventricle as well as tumour necrosis factor-alpha levels and serum creatine kinase levels [21,82-84].

Resveratrol's role as cancer therapeutics

Researchers have recently focused attention on natural product compounds for their potent effects against inflammation-driven diseases, including cancer. Preclinical, clinical and epidemiological studies have shown that dietary consumption of polyphenols, found in high amounts in cereals, pulses, vegetables, and fruits, may prevent the evolution of a range of diseases, including cancer [60,85]. The development of cancer begins when normal cells acquire genetic mutations that cause the cells to grow, colonize, and metastasize to other organs such as the liver, lungs, colon, and brain. Potential anti-cancer agents that regulate these oncogenic processes may ultimately find their way into clinical trials [60, 85, 86].

Natural stilbene and non-flavonoid polyphenol resveratrol is an anti-oxidant, anti-inflammatory, cardioprotective, and anti-cancer phytoestrogen [19,84]. As a result of resveratrol's ability to reverse drug resistance in cancer cells, it has been reported that, when combined with ordinary drugs, it can increase cancer cells' susceptibility to standard chemotherapy [87]. The most common cause of cancer mortality among women worldwide is breast cancer; therefore, a strategy to defeat this disease should be an extremely important issue for medicine. Multidrug Resistance (MDR) was one of the biggest challenges in this regard. As part of an overall strategy for defeating breast cancer, resveratrol, a well-known phytoestrogen, may be helpful. In cancer therapy, which is particularly relevant for hormone-dependent cancers, resveratrol plays both agonist and antagonist roles for estrogen receptors [88, 89]. There has been some evidence that resveratrol reverses multidrug resistance *in vitro*. Despite this, poor bioavailability of resveratrol has been suggested as a potential limiting factor in resveratrol treatment and cancer outcome. It is encouraging that resveratrol's bioavailability is improved by combining it with certain selected compounds [90].

There are a number of anti-ageing health benefits of Resveratrol, including improving metabolism, preventing cancer, and cardioprotection [84,86]. *In vitro* studies have focused mainly on resveratrol's actions on cancer cell pathways and outcomes. Nonetheless, few studies have investigated resveratrol treatment and cancer outcomes *in vivo*, possibly because of its low bioavailability when taken orally. Resveratrol has shown positive effects in cell culture, but research on rodents and humans has been inconsistent. According to Carter, et al. *in vivo* effects of resveratrol treatment on cancer cells included cancer of the breast, colon, liver, pancreas and prostate [46]. According to studies conducted using resveratrol at various dosage levels, routes of administration, tumour models, species and other factors, resveratrol supplementation has shown positive, neutral, as well as negative effects. In specific cancer types, different studies measure cancer endpoints using different strains, age and sex of animals, resveratrol supplementation timing and method, and resveratrol dose. Collectively, these findings suggest there are a number of factors to consider before using resveratrol to prevent or treat cancer in humans [46]. Over the past 25 years, extensive research has identified the molecular mechanisms that spur hormone-dependent cancers such as breast cancer and prostate cancer, elucidating the interaction between genomic and non-genomic steroid receptor mechanisms. Collectively, these mechanisms contribute to the resistance to endocrine therapy and the progression of cancer. Using multi-target inhibitors, together with endocrine therapies, suggests a treatment for resistant disease based on bidirectional molecular crosstalk between the growth factor receptors and steroid receptors. In the review by [91], the authors address the novel understanding of Resveratrol (3,5,4'-trihydroxystilbene) (RSV), a phytoalexin found in grapes and acting on a variety of targets. Resveratrol was shown to affect steroid receptor signalling and may be used in the treatment of hormone-dependent cancer. In order to improve the rate of complete and durable clinical responses in patients, it will be important to understand the molecular mechanisms by which the bioactive compound influences cancer cell behaviour by interfering with steroid receptor function [91].

Plant-derived active compounds that show potential for preventing cancer development have recently garnered increasing interest. Literature has demonstrated that resveratrol, commonly found in grapes, tomatoes, and red wine, is the most promising candidate. The benefits it offers to the human body can be observed in both prevention and therapy. There is a link between resveratrol's anti-carcinogenic effects and its ability to neutralize reactive oxygen species and to modulate cellular processes such as apoptosis and both cancer cell proliferation and differentiation. Research has identified resveratrol as a bioactive compound derived from natural sources with anti-cancer properties, and because of its wide array of biological activities, may be useful in the prevention of cancer. Such preventative anti-cancer properties have been demonstrated in numerous *in vitro* and animal studies. As support for conventional cancer treatment using chemotherapy and radiotherapy, resveratrol was shown to have beneficial effects [92]. In addition to its anti-glycation, anti-oxidative stress, anti-inflammatory, anti-cancer, and anti-ageing properties, resveratrol also fights inflammation. It is believed that resveratrol may play a role in the prevention of many diseases, such as diabetes and its complications, as it is generally well tolerated. The Bio-availability and solubility of this compound were both low [86]. In a number of cancer types, resveratrol has shown tumour-suppressive effects. The role of resveratrol in regulating the tumour microenvironment remains unclear. According to recent research, resveratrol can enhance its tumour-suppressive effect by modulating the signal pathways in cellular components (fibroblasts, macrophages, and T cells). Moreover, studies have shown that resveratrol suppresses malignant phenotypes of cancer cells acquired in response to the tumour microenvironment, such as hypoxia, oxidative stress and inflammation. Hans, et al. presented a review of the effects of resveratrol on cancer cells in tumour stress environments as well as the interactions between cancer cells and non-cancer cells [60].

Resveratrol has been well recognized for its ability to influence all 3 major phases of carcinogenesis (initiation, promotion, and progression). Resveratrol's potential for chemoprevention and treatment are highlighted here with a particular focus on skin and colorectal cancers. The most prevalent cancer type in the

United States is skin cancer, while Colorectal Cancer (CRC) is the third most common cause of cancer-related death worldwide. Every year, billions of dollars are spent on skin and CRC cancers, making developing a strategy to stop the spread of cancer an immediate necessity. Resveratrol's low bioavailability and robust accumulation in the colon might make the colon the ideal target for injection; also, the skin could be a suitable target by topical application [93, 94]. The effectiveness of resveratrol in cancer prevention has been well documented by quite a few studies in the past few years. DMBA and 12-O-tetradecanoylphorbol-13-acetate (TPA) have been shown to cause skin cancer in CD-1 mice, where 7-12-dimethylbenz[a]anthracene (DMBA) causes skin cancer [94].

The beneficial effects of resveratrol can be attributed to a number of mechanisms, such as its ability to defeat and suppress cancer growth, support cancer cell death through autophagy and apoptosis, in addition to inhibiting angiogenesis and metastasis. It has been shown that resveratrol inhibits cancer progression by targeting numerous molecules, particles, and pathways involved in cancer growth. Although its ability to act therapeutically in humans remains doubtful and dubious due to its insufficient oral bioavailability. Researchers have taken advantage of this rationale to develop new derivatives and combinations with upgraded properties, with emphasis on enhancing their defensive and therapeutic effects [94]. There is evidence that resveratrol induces apoptosis in colon carcinoma cells (HT29 cells), possibly through ER stress mechanisms. Resveratrol has been proposed to affect several ER stress markers, including CHOP (C/EBP homologous protein) and GRP78 (glucose-related protein 78) splicing and phosphorylation of eIF-2α.

Antiproliferative and pro-differentiation activity/cell proliferation and apoptosis

Gap Junction Communication (GJC) controls differentiation, proliferation, and apoptosis, which constitute the three main controls of cell growth. A GJC is an intercellular channel that helps exchange information, nutrients, and waste products. An intercellular gap junction is made up of six connexin proteins from each adjacent cell for a total of 12 connexin proteins [94]. The expression of connexins varies by cell type and developmental stage in mammals. The most widely expressed connexin is connexin 43 (Cx43), which is induced by carotenoids and stilbenoid [96]. There are therefore clear indications that GJC is a marker for cancer development. Gap-junctional communication is enhanced when Connexin 43 levels are increased. Increased levels of Connexin 43 are some of the mechanisms by which Resveratrol can enhance communication across gap junctions in 10T1/2 cells [95] (Table 1).

Resveratrol is supposed to inhibit all the possible stages of cancer invasion through its antiproliferative activity [94,96]. Resveratrol was first shown to inhibit cell growth, and research indicates it is a stronger inhibitor than beta-carotene [97]. In several cell lines, including prostate cancer, breast cancer, lung cancer, human colon cancer cells, oral cavity cancer cells, as well as normal prostrate epithelial cells, this growth inhibition was observed. In addition to cyclins, CDKs, and CDK inhibitors, Cyclin-Dependent Kinases (CDKs) are involved in cell cycle control. Cyclin D specifically regulates the transition from G0 to early G1, while Cyclin E controls the transition from late G1 to S phase [94,97,98]. The P21 and P27 CDK inhibitors bind

Tab. 1. A few key studies indicating the implications of Resveratrol in cancer

Findings	Topic	Reference
Much of the work on resveratrol and cancer comes from in vitro studies looking at resveratrol actions on cancer cells and pathways.	Resveratrol and cancer: focus on in vivo evidence	(Carter, et al.) [46]
This review summarises the available published literature dealing with the effects of resveratrol on multidrug resistance in cancer.	Resveratrol as MDR reversion molecule in breast cancer	(Alamolhodaei, et al.) [90]
This article presents the characteristics of resveratrol as a bioactive compound derived from natural sources exhibiting anti-cancer properties.	The occurrence of resveratrol in foodstuffs and its potential for supporting cancer prevention and treatment	(Dybkowska, et al.) [92]
This review explores the full potential of resveratrol in breast cancer prevention and treatment with current limitations, challenges and future directions of research.	Resveratrol for breast cancer prevention and therapy: Preclinical evidence and molecular mechanisms	(Sinha, et al.) [94]
Resveratrol's role in reducing different human cancers, including breast, cervical, uterine, blood, kidney, liver, eye, bladder, thyroid, esophageal, prostate, brain, lung, skin, gastric, colon, head and neck, bone, ovarian, and cervical, has been reviewed	Resveratrol as an anti-cancer agent	(Rauf, et al.) [97]
Resveratrol has the potential for cancer prevention and the possibility of use in therapy, the following must be taken into account: data from epidemiology, clinical protocol (case and control), preclinical studies (lab animals), use of established cell lines as models of cancer cells, test tube assays (enzymes activities), and requirements of nanotechnologies in order to discover new drugs to fight cancer.	The Potential Use of Resveratrol for Cancer Prevention.	(Vervandier-Fasseur and Latruffe) [98]
Resveratrol shows potent anti-tumour therapeutic properties in various tumours.	Resveratrol eliminates cancer stem cells of osteosarcoma by STAT3 pathway inhibition	(Peng and Jiang) [102]
The use of nanotechnology-based carriers in the delivery of plant-derived anticancer agents, such as RSV, has already demonstrated to surpass the poor water solubility, instability and reduced bioavailability associated with phytochemicals, improving their therapeutic activity, thus prompting pharmaceutical developments.	Targeting Cancer Via Resveratrol-Loaded Nanoparticles Administration	(Santos, et al.) [110]

and inhibit the cyclin E/CDK2 complex, preventing cell cycle progression during the G1 phase. A reduction of G1-S cell cycle progression, a decrease in cyclin D1 expression, and equilibrium of p27 expression in the cyclin E-CDK composite was observed when Resveratrol inhibited growth in MCF-7 breast cancer cells.

Additionally, resveratrol suppressed tumour invasion, angiogenesis, and cell proliferation in the lungs of nude mice inoculated with K562 cell lines [99]. Apoptosis is another important inhibitory action of Resveratrol. In studies, water-soluble Resveratrol was found to suppress the growth of LNCaP prostate cancer cell line, while 5 mM Resveratrol was found to block G2/M and arrest cell division, suggesting high concentrations of Resveratrol can disrupt DNA [100, 101] (Figure 2).

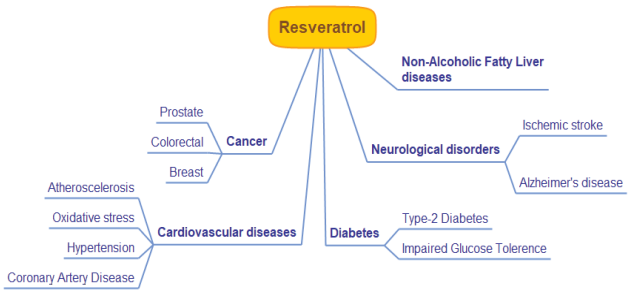

Fig. 2. Clinical benefits and overall therapeutic effect of Resveratrol

In-vitro anticancer study of Resveratrol

Jiang, et al. [102] evaluated the enhanced anticancer effects of Res (resveratrol) on PA (paclitaxel) in HepG2 human liver cancer cells. The MTT (thiazolyl blue tetrazolium bromide, 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide), flow cytometry, qPCR (real-time quantitative polymerase chain reaction) and western blot assay were used for cells growth inhibitory effects, cells apoptosis (DNA content of sub-G1), mRNA and protein expressions, respectively. Using the results of the study as the basis for their conclusion, it was concluded that Res could increase the therapeutic effects of PA in HepG2 cells, that Res would have value as a sensitizer [102].

Kong, et al. [103] examined the effects of both Resveratrol (Res) and Paclitaxel (PA) on Non-Small Cell Lung Cancer (NSCLC) cell line A549. Res at 10 μg/ml did not affect human fetal lung fibroblast MRC-5 cells nor did it affect A549 cancer cells, while PA at 5 or 10 μg/ml did not affect MRC-5 normal cells. A549 cells treated with PA-L (5 μg/ml) and PA-H (10 μg/ml) produced growth inhibition, which was further enhanced by Res. Following Res (5 μg/ml)+PA-H (10 μg/ml) treatment, A549 cells showed the greatest proportion of apoptotic cells as compared to other treatments, and both PA concentrations increased after additional Res treatment. Res+PA could reduce the mRNA and protein expressions of COX-2, and Res+PA could reduce the COX-2 related genes of VEGF, MMP-1, MMP-2, MMP-9, NF-κB, Bcl-2, Bcl-xL, procollagen I, collagen I, collagen III and CTGF, TNF-α, IL-1β, iNOS and raise the TIMP-1, TIMP-2, TIMP-3, IκB-α, p53, p21, caspase-3, caspase-8, caspase-9, Bax genes compared to the control cells and the PA treated cells. According to these results, Res may be a better sensitizing agent for PA than PA itself, therefore Res might be useful as a sensitizing agent for PA [103].

Yousef, et al. [104] report that cancer cells are characterized by uncontrolled cell division and resistance to apoptosis. Cell proliferation and apoptosis are directly regulated by signalling molecules mutated in cancer cells, and alteration of these molecules can lead to both of these features. Resveratrol (RSV), a naturally occurring plant polyphenol, has been proven to have biological effects that counteract different diseases. Its health benefits include cardioprotection, neuroprotection, immunomodulation, and anti-cancer activity. The ability of RSV to inhibit cancer cell proliferation, induce cell cycle arrest, and induce apoptosis may be due to its ability to modulate the signaling molecules involved in these processes [104].

Humaniecki and Horbaczu [105] demonstrated that Resveratrol inhibits cancer cells *in vitro* and has hypothetical chemopreventive effects *in vivo* [105]. A range of genes is affected, resulting in epigenetic reprogramming and pleiotropic effects. Consequently, functional genomic studies could be performed on them. The study also considered technological advancements (which also impacted the effectiveness of the study). Apoptosis, cell cycle, and proliferation are linked to differentially expressed genes in response to resveratrol treatment. It is unclear whether resveratrol targets these primary and specific pathways [105].

Kumar, et al. [106] evaluated the effects of Grape Powder Extract (GPE) on cell viability, proliferation, and metastatic capability. Prominently, the study discovered the likely novel mechanism of GPE through Metastasis-Associated Protein 1 (MTA1) downregulation in prostate cancer, since the earlier studies elected resveratrol (Res)- and pterostilbene (Pter)-induced MTA1-mediated anticancer activities in prostate cancer. The study found that GPE inhibited the cell viability and growth of prostate cancer cells only at high 100 μg/mL concentrations. However, at low 1.5 μg/mL¯15 μg/mL concentrations, GPE suggestively reduced the colony formation and wound healing abilities of both DU145 and PC3M cells. The conclusion srein forced sustained the interest in GPE as a chemopreventive and anti-cancer agent against prostate cancer but also highlighted the exclusive and precise properties of stilbenes on MTA1-mediated anticancer effects on prostate cancer [106].

Zhang, et al. [107] synthesized a novel anticancer drug, nano-gold loaded with resveratrol (Res-GNPs), which were categorized using UV-Prove, zetasizer and transmission electron microscope. MTT assay, flow cytometry, TUNEL, immunohistochemistry and western blot analysis were accomplished to discover the antitumour activity of Res-GNPs in liver cancer cells and tumour xenografts. Res-GNPs exhibited a sturdier consequence on inhibiting cell proliferation and indorsing apoptosis in Hepg2 cells than that of free Res. Res-GNPs induced apoptosis in Hepg2 cells by down-regulating pro-caspase-9, pro-caspase-3, PI3K and Akt and upregulating caspase-8 and bax. In xenograft studies, Res-GNPs remarkably repressed tumour growth encouraged tumour apoptosis and reduced the expression of Vascular Endothelial Growth Factor (VEGF) in tumour tissue. Additionally, HE staining exhibited that no observable toxicity was found in the heart, liver, kidney and spleen. The

datum confirmed that Res-GNPs possess a better antitumour effect than Res *in vitro* and *in vivo*, which may be due to gold nanoparticles carrying more resveratrol into cells and locating in mitochondria. These results suggested that Res-GNPs possess a significantly better anti-cancer effect than Res alone *in vitro* and *in vivo*, which may be helpful for the clinical therapy of liver cancer [107].

Uvez, et al. [108] evaluated the Anti-proliferative, anti-angiogenic and apoptotic effects of resveratrol on various cancer cells. The cytotoxic effect of resveratrol (1.56 μM-100 μM), doxorubicin (0.01 μM-0.92 μM) and their combination was analyzed in the Human Umbilical Vein Endothelial Cells (HUVECs) by ATP assay. *In vitro* angiogenesis was evaluated using tube formation assay in HUVECs. *In vivo* anti-angiogenic activity was assessed in a chick Chorioallantoic Membrane (CAM) model using fertilized chicken eggs. All test groups were compared to thalidomide as a positive control, three concentrations of resveratrol (10, 5, 2.5 μg/pellet) and a 2 μg/pellet concentration of doxorubicin was examined. All data were evaluated statistically. Resveratrol and doxorubicin alone displayed inhibitory effects on angiogenesis and cell viability at higher doses. However, the combination of resveratrol and doxorubicin exhibited a significant dose-dependent inhibition of CAM angiogenesis *in vivo* as well as proliferation and tube formation in HUVECs compared to the positive control (±) thalidomide. The results suggested that resveratrol in combination with doxorubicin is a novel strategy in the prevention and treatment of angiogenesis [108].

In-vivo anticancer study of Resveratrol

Huminiecki and Horbańczuk [105] studied the anti-cancer effects of Resveratrol *in vitro*, and hypothetical chemopreventive effects *in vivo*. Effects are pleiotropic, mediated by changes in expression of many genes and epigenetic reprogramming. Thus, they are well suited for functional genomic studies. We carried out a systematic review of such studies (reflecting also on technological progress). Differentially expressed genes commonly linked to resveratrol treatment were linked to cell cycle, proliferation, and apoptosis. However, it was unclear if these were primary and specific targets of resveratrol. The study concluded by discussing areas where additional functional genomic studies were desirable, including experiments that better model in vivo effects of dietary intake [105].

Chatterjee, et al. [109] explored the *in vitro* anticancer activity and *in vivo* anti-tumour potential of these two structurally similar compounds (resveratrol and pterostilbene) on HPV oncogene E6 and E7 positive murine TC1 cells. *In vitro* analysis confirmed the cytotoxic potential of both resveratrol and pterostilbene compounds with each having a low IC50 value and each showing the ability to downregulate viral oncogene E6. Further *in vivo* studies on TC1 tumours developing in mice indicated that treatment with either resveratrol or pterostilbene can significantly inhibit tumour development, with both compounds capable of downregulating E6 and VEGF tumour protein levels. Interestingly, the decrease in tumour size in pterostilbene was associated with tumour cell apoptosis, as indicated by upregulation of activated caspase-3 whereas in resveratrol-treated mice it was accompanied by the arrest of the cell cycle, as indicated by downregulation of PCNA. Thus, resveratrol and pterostilbene can serve as potential antineoplastic agents against HPV E6+ tumours and may suppress tumour growth via two different mechanisms [109].

Santos, et al. [110] systematically investigated Resveratrol (RSV) which was a polyphenol endowed with potential therapeutic effects in chronic diseases, particularly in cancer, the second leading cause of death worldwide in the twenty-first century. The advent of nanotechnology application in the field of drug delivery allows overcoming the constraints associated with the conventional anticancer treatments, in particular chemotherapy, reducing its adverse side effects, off-target risks and surpassing cancer multidrug chemoresistance. Moreover, the use of nanotechnology-based carriers in the delivery of plant-derived anticancer agents, such as RSV, has already been demonstrated to surpass the poor water solubility, instability and reduced bioavailability associated with phytochemicals, improving their therapeutic activity, thus prompting pharmaceutical developments. This study highlighted the *in vivo* anticancer potential of RSV achieved by nanotherapeutic approaches. First, RSV physicochemical, stability and pharmacokinetic features were described. Thereupon, the chemotherapeutic and chemopreventive properties of RSV were underlined, emphasizing the RSV numerous cancer molecular targets. Lastly, a comprehensive analysis of the RSV-loaded nanoparticles (RSV-NPs) developed and administered in different *in vivo* cancer models to date was presented. Nanoparticles (NPs) had shown to improve RSV solubility, stability, pharmacokinetics and biodistribution in cancer tissues, enhancing markedly its *in vivo* anticancer activity. RSV-NPs were, thus, considered a potential nanomedicine-based strategy to fight cancer; however, further studies were still necessary to allow RSV-NP clinical translation [110].

Karabekir and Özgörgülü [111] aimed to investigate the chemopreventive effect of different doses of RSV against Hepatocellular Carcinoma (HCC) induced by Diethylnitrosamine (DEN) in rats. The rats were randomly divided into six groups of seven rats each (n=42). The control group (group 1) was injected with saline, group 2 with dimethyl sulfoxide (DMSO), group 3 with DEN, group 4 with DEN and 50 mg/kg of RSV (DEN+RSV 50), group 5 with DEN and 75 mg/kg of RSV (DEN+RSV 75), and group 6 with DEN and 100 mg/kg of RSV (DEN+RSV 100). Pro-apoptotic Bax/anti-apoptotic Bcl-2 and tumour suppressor p53 markers were analyzed by immunostaining. Superoxide dismutase, glutathione, and malondialdehyde concentrations were not statistically significant in DEN+RSV 100 group but were closest to the concentrations in the control group. Liver function tests showed that enzyme activity (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transferase) increased in DEN+RSV 50 and DEN+RSV 100 groups compared with the control group but decreased in DEN+RSV 50 and DEN+RSV 100 groups compared with DEN group. Bax/Bcl-2 and p53 analysis showed a statistically significant increase in apoptotic cells in DEN+RSV 100 group. A 100 mg/kg dose of RSV may be a promising treatment for HCC [111].

Kuo, et al. [112] investigated whether mEHT can increase the anti-cancer efficacy of nanosized curcumin and resveratrol in *in vitro* and *in vivo* models. The *in vitro* study included cell proliferation assay, cell cycle, and apoptosis analysis. Serum concentration was analyzed for the absorption of curcumin and resveratrol in SD rat model. The *in vivo* CT26/BALB/c animal tumour model was used for validating the safety, tumour growth curve, and immune cell infiltration within tumour tissues after combined mEHT/curcumin/resveratrol treatment. The results indicated co-treatment of mEHT with nano-curcumin and resveratrol significantly induced cell cycle arrest and apoptosis of CT26 cells. The serum concentrations of curcumin and resveratrol were significantly elevated when mEHT was applied. The combination also inhibited the growth of CT26 colon cancer by inducing apoptosis and HSP70 expression of tumour cells while recruiting CD3+ T-cells and F4/80+ macrophages. The results of this study had suggested that this natural, non-toxic compound can be an effective anti-tumour strategy for clinical cancer therapy. mEHT can enable cellular uptake of potential anti-tumour materials and create a favorable tumour microenvironment for an immunological chain reaction that improves the success of combined treatments of curcumin and resveratrol [112].

In-vitro cardioprotective study of Resveratrol

Hernandez-Cascales [113] studied the antiarrhythmic effects of resveratrol that has recently been shown to inhibit Phosphodiesterase (PDE) enzyme activity. Thus, it was possible that resveratrol increased the inotropic effect of sympathomimetic agents, as PDE inhibitors do but, unlike other PDE inhibitors, its effect may not be accompanied by proarrhythmia due to its antiarrhythmic action. This work was aimed to test this hypothesis. This is an "*in vitro*" concentration-response relationship study. The effects of noradrenaline, tyramine and isoproterenol, alone or in combination with either resveratrol or with the typical PDE inhibitor 3-isobutylmethylxantine (IBMX), were studied in electrically driven strips of right ventricle or in the spontaneously beating free wall of the right ventricle of rat heart in order to investigate inotropic or proarrhythmic effects respectively. Also, the effects of resveratrol or IBMX on the sinoatrial node rate were examined in the isolated right atria of the rat heart. Resveratrol (10 μM and 100 μM) produced a leftward shift in the concentration-response curves for the contractile effects of noradrenaline, tyramine or isoproterenol and reduces the -log EC (50) values of these three agents. IBMX produces similar effects. The spontaneous ventricular beating rate was increased by all three compounds, an effect that was further enhanced by the addition of IBMX. In contrast, resveratrol (100 μM) abolished the effects of these sympathomimetic agents on the ventricular rate. Resveratrol (1 μM-100 μM) had no effect on the sinoatrial node rate, while IBMX produce a concentration dependent sinoatrial tachycardia. Taken together, the finding, indicated that resveratrol, like the PDE inhibitor IBMX enhances the contractile effects of sympathomimetic agents but, in contrast to IBMX, it did not enhance their proarrhythmic effect or produce sinoatrial tachycardia. This was most probably consequence of the antiarrhythmic effect of resveratrol which protect against the proarrhythmic effects resulting from PDE inhibition [113].

Kulashekar, et al. [114] indicated thatfindings from numerous preclinical experiments and clinical trials in humans suggested that resveratrol may play an important role in managing or preventing a variety of diseases. Some of the health benefits included cardioprotective effects; chemopreventive properties; metabolic changes, such as improved glycemic control; protection from diabetic consequences; and synergistic therapeutic effects when administered with other treatment modalities. Resveratrol was safe and reasonably well tolerated in humans, with mild to moderate gastrointestinal side effects. This study provided a summary of recent preclinical experiments and clinical trials pertaining to the effects of resveratrol on cardiovascular disease, obesity, diabetes, Alzheimer disease, and cancer. It also identified suggested mechanisms by which resveratrol functions and presented issues surrounding resveratrol concentrations in vitro vs plasma levels reported in vivo [114].

Liberale, et al. [115] indicated that epidemiological and mechanistic evidence of a J-shaped relationship between red wine intake and CV risk further supported the "French paradox". Specific components of red wine both *in vitro* and in animal models were discovered. Polyphenols and especially resveratrol largely contribute to CV prevention mainly through antioxidant properties. They exert beneficial effects on endothelial dysfunction and hypertension, dyslipidemia, metabolic diseases, thus reducing the risk of adverse CV events such as myocardial infarction ischemic stroke and heart failure. Of interest, recent studies pointed out the role of ethanol itself as a potential cardioprotective agent, but clear epidemiological evidence is still missing. The aim of this narrative review was to update current knowledge on the intracellular mechanism underlying the cardioprotective effects of polyphenols and ethanol. Furthermore, the study summarized the results of epidemiological studies, emphasizing their methodological criticisms and the need for randomized clinical trials able to clarify the potential role of red wine consumption in reducing CV risk. Caution in avowing underestimation of the global burden of alcohol-related diseases was particularly used [115].

Tan, et al. [116] aimed to investigate the cardioprotective effects and underlying mechanisms of polydatin on myocardial injury induced by hyperglycemia. Diabetes in rats was made by high-fat diet combined with multiple low doses of streptozotocin, and then treated with polydatin (100 $mg \cdot kg^{-1} \cdot day^{-1}$, by gavage) for 8 weeks. Cardiac function was examined by echocardiography. Myocardial tissue and blood samples were collected for histology, protein and metabolic characteristics analysis. In cultured H9c2 cells with 30 mM of glucose, the direct effects of polydatin on myocyte injury were also observed. In diabetic rats, polydatin administration significantly improved myocardial dysfunction and attenuated histological abnormalities, as evidenced by elevating left ventricular shortening fraction and ejection fraction, as well as reducing cardiac hypertrophy and interstitial fibrosis. In cultured H9c2 cells, pretreatment of polydatin dose-dependently inhibited high glucose-induced cardiomyocyte

injury. Further observation evidenced that polydatin suppressed the increase in the reactive oxygen species levels, NADPH oxidase activity and inflammatory cytokines production induced by hyperglycemia *in vivo* and *in vitro*. Polydatin also prevented the increase expression of NOX_4, NOX_2 and NF-κB in the high glucose-stimulated H9c2 cells and diabetic hearts. The results demonstrated that the cardioprotective effect of polydatin against hyperglycemia-induced myocardial injury was mediated by inhibition of NADPH oxidase and NF-κB activity. The findings may provide a novel understanding the mechanisms of the polydatin to be a potential treatment of diabetic cardiomyopathy [116].

Mirhadi, et al. [117] reviewed the cardioprotective role of Resveratrol. Resveratrol, trans 3,5,4'-trihydroxystilbene, is a stilbenoid polyphenol with a wide range of properties including antioxidant, neuroprotective, cardioprotective, anti-inflammatory and anticancer activities. It is found in the skins of grape (50 μg/mL-100 μg/mL), red wine, peanuts, bilberries, blueberries and cranberries. The most important effects of resveratrol have been found in cardiovascular disease, with Pulmonary Arterial Hypertension (PAH) being a major severe and progressive component. Many factors are involved in the pathogenesis of PAH, including enzymes, transcription factors, proteins, chemokines, cytokines, hypoxia, oxidative stress and others. Resveratrol treats PAH through its actions on various signaling pathways. These signaling pathways are mainly suppressed SphK1-mediated NF-κB activation, BMP/SMAD signaling pathway, miR-638 and NR4A3/cyclin D1 pathway, SIRT1 pathway, Nrf-2, HIF-1 α expression, MAPK/ERK1 and PI3K/AKT pathways, and RhoA-ROCK signaling pathway. Resveratrol efficiently inhibits the proliferation of pulmonary arterial smooth muscle cells and right ventricular remodeling, which are underlying processes leading to enhanced PAH. While supportive evidence from randomized controlled trials is yet to be available, current *in vitro* and *in vivo* studies seem to be convincing and suggest a therapeutic promise for the use of resveratrol in PAH [117].

In-vivo cardioprotective study of Resveratrol

Song, et al. [118] studied the role of Resveratrol in Diabetic Cardiomyopathy (DCM). DCM is a common cardiovascular complication of diabetes mellitus that is characterized by a diastolic disorder in the early stage and clinical heart failure in the later stage. Presently, DCM is considered one of the major causes of death in diabetic patients. Resveratrol (RSV), a naturally occurring stilbene, is widely reported as a cardioprotective substance in many heart diseases. Thus far, the specific roles of RSV in DCM prevention and treatment have attracted great attention. Here, the study discussed the roles of RSV in DCM by focusing on its downstream targets from both *in vivo* and *in vitro* studies. Among such targets, Sirtuins 1/3 and AMP-activated kinase have been identified as key mediators that induce cardioprotection during hyperglycemia. In addition, many other signalling molecules (e.g., forkhead box-O3a and extracellular regulated protein kinases) were also regulated in the presence of RSV and exerted beneficial effects such as opposing oxidative stress, inflammation, and apoptosis in cardiomyocytes exposed to high-glucose conditions. The beneficial potential of an RSV/stem cell cotherapywas also reviewed as a promising therapeutic strategy for preventing the development of DCM [118].

Tian, et al. [119] aimed to determine the effect of Resveratrol (RSV) on Doxorubicin (DOX) induced cardiotoxicity, and further explored the underlying mechanism in this process. Male Sprague-Dawley (SD) rats were randomly divided into four groups: CON, DOX, RSV, or DOX+RSV group (10 rats in each group). DOX treatment significantly decreased cardiac function and increased the release of serum Lactate Dehydrogenase (LDH) and Creatine Kinase isoenzyme (CK-MB) in rat serum. Increased cell death and apoptosis of cardiomyocytes were also observed in DOX group in comparison with CON group. DOX treatment dramatically down-regulated expression of VEGF-B either *in vivo* or *in vitro*. In contrast, the combination of RSV and DOX markedly attenuated DOX-induced cardiotoxicity with the up-regulation of VEGF-B. Inhibition of VEGF-B by small interfering RNA (siRNA) abolished the protective effects of RSV on DOX-treated cardiomyocytes. Consequently, the findings indicated that RSV attenuates DOX-induced cardiotoxicity through up-regulation of VEGF-B [119].

Probable side effects of resveratrol

The biological effects of Resveratrol, as well as it's *in vitro* and *in vivo* outcomes, appear to be strongly associated with a hormetic effect where Resveratrol low doses usually are associated with beneficial effects while high doses usually have a toxic effect [120]. In this regard, evidence suggests that Resveratrol's hormetic property may be due to its dose-associated biphasic effect on the cellular redox state, which was reported to be antioxidant at low doses and a pro-oxidant at high doses [121-123]. Notwithstanding the substantial number of human and animal studies that support the beneficial and protective properties of Resveratrol, there are not enough clinical studies that report on Resveratrol's harmful effects, which are indeed full of controversy. Moreover, the molecular mechanism of Resveratrol action needs to be better identified. All of these contradictions call for an urgent need to appraise and investigate the adverse outcomes of this compound despite its documented benefits. As per a new finding suggested by Valentovic MA, Resveratrol (RES) is a natural product generated in plants in response to environmental stress and growing conditions. RES has been recognized since 1997 to possess anticancer activity [124].

CONCLUSION

This review indicates that resveratrol may play a significant role in the prevention of not only cardiovascular diseases, but also cancer, diabetes, and inflammation. With its unique antioxidant properties, resveratrol is a highly functional ingredient in various

functional foods. The number of studies in terms of dosage regimens and pharmacokinetic profiles of resveratrol are scant and newer studies should be carried out to profile the same. There is a growing body of scientific literature supporting the potential health benefits of functional ingredients including resveratrol. The mechanism by which resveratrol exert their beneficial effects should, however, be further studied to evaluate and identify the mechanism.

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