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REVIEW ARTICLE

Resveratrol in Cancer Therapy: From Stimulation of Genomic Stability to Adjuvant Cancer Therapy: A Comprehensive Review

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Abstract: Cancer therapy through anticancer drugs and radiotherapy is associated with several side effects as well as tumor resistance to therapy. The genotoxic effects of chemotherapy and radiotherapy may lead to genomic instability and increased risk of second cancers. Furthermore, some responses in the tumor may induce the exhaustion of antitumor immunity and increase the resistance of cancer cells to therapy. Administration of low-toxicity adjuvants to protect normal tissues and improve therapy efficacy is an intriguing strategy. Several studies have focused on natural-derived agents for improving the antitumor efficiency of radiotherapy, chemotherapy, and novel anticancer drugs such as immunotherapy and targeted cancer therapy. Resveratrol is a naturally occurring substance with intriguing antioxidant, cardioprotective, anti-diabetes, and antitumor properties. Resveratrol has been demonstrated to modulate tumor resistance and mitigate normal tissue toxicity following exposure to various drugs and ionizing radiation. Compelling data suggest that resveratrol may be an appealing adjuvant in combination with various anticancer modalities. Although the natural form of resveratrol has some limitations, such as low absorption in the intestine and low bioavailability, several experiments have demonstrated that using certain carriers, such as nanoparticles, can increase the therapeutic efficacy of resveratrol in preclinical studies. This review highlights various effects of resveratrol that may be useful for cancer therapy. Consequently, we describe how resveratrol can protect normal tissue from genomic instability. In addition, the various mechanisms by which resveratrol exerts its antitumor effects are addressed. Moreover, the outcomes of combination therapy with resveratrol and other anticancer agents are reviewed.

Keywords: Resveratrol, Genomic instability, Cancer, Radiotherapy, Chemotherapy.

1. INTRODUCTION

Cancer is a complex disease that can be triggered by genetic damage within cells. Due to exposure to clastogenic agents, such as radiation, normal cells typically undergo various mutations, including deletions, point mutations, and conversion [1]. These mutations are associated with various types of malignancies, such as gastrointestinal system cancers, non-small cell lung carcinoma (NSCLC), hepatocellular carcinoma, and breast cancer, among others [2, 3]. Anticancer treatment modalities, such as chemotherapy and radiotherapy, are associated with an increased risk of carcinogenesis and recurrence of cancer years after the treatment course [4]. A high incidence of cancer among radiotherapy patients and survivors of the Chornobyl, Hiroshima, and Nagasaki nuclear disasters confirms the potent carcinogenic effect of ionizing radiation [5]. Similar results have been observed for chemotherapy drugs, such as doxorubicin, cisplatin, mitomycin C, and other alkylating agents [6-8]. By inducing reactive oxygen species (ROS) production, DNA cross-linking, and inhibiting DNA repair pathways, these

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drugs may induce DNA damage and damage to other organelles [9].

Resistance to anticancer agents can be induced by mutations and abnormal changes in the metabolism and function of malignant cells. The majority of cancer cells contain mutated tumor suppressor genes. Furthermore, tumors provide some conditions that protect malignant cells from oxidative stress, hypoxia, and immune system attacks. Activating antitumor immunity and tumor suppressor genes and inducing oxidative stress and cell death in cancer are appealing strategies for circumventing tumor resistance. Using adjuvants to protect normal cells and enhance the efficacy of anticancer treatment can mitigate the side effects on normal tissues and sensitize tumors to anticancer drugs or radiotherapy. Certain antioxidants, such as vitamins, have reduced oxidative stress and normal tissue injury. However, there are some concerns regarding its protective effects against cancerous cells [10].

Resveratrol is a natural antioxidant, anti-inflammatory, and anti-fibrosis agent that has been demonstrated to protect normal tissue and act as a tumor sensitizer [11]. It can enhance DNA repair mechanisms and antioxidant defenses in normal tissues; however, it may exacerbate oxidative stress and antitumor immunity in tumors [12, 13]. Resveratrol also possesses some advantageous properties. It can improve endothelial function by modulation of reduction/oxidation responses and attenuating inflammatory responses [14]. The antioxidant effect of resveratrol can prevent apoptosis in endothelial cells [15]. These resveratrol properties can protect against cardiovascular diseases. The production of ROS by pro-oxidant enzymes may contribute to endothelial damage and the progression of cardiovascular diseases. A high glucose level, such as in diabetic patients, can stimulate the production of ROS by NADPH oxidase and lead to the development of pathological conditions such as fibrosis.

Treatment with resveratrol decreases NADPH-oxidase-induced ROS production and endothelial-to-mesenchymal transition (EndMT), thereby protecting against fibrosis [16]. Animal studies have confirmed the cardioprotective effects of resveratrol. According to reports, resveratrol can prevent atherosclerosis, ischemic heart disease, myocardial infarction, and heart failure [17]. Furthermore, resveratrol may protect against diabetic cardiomyopathy through protection against chronic oxidative stress and cell death [18].

Resveratrol has also been demonstrated to prevent metabolic diseases. Resveratrol has been reported to reduce the risk of certain metabolic diseases, including obesity and diabetes [19]. Several clinical trial studies evaluated the efficiency and safety of resveratrol for patients with type 2 diabetes. Clinical trials indicate that resveratrol may improve insulin sensitivity and lower fasting glucose levels. Additionally, resveratrol has been shown to reduce oxidative stress markers in type 2 diabetes patients [20]. Preclinical and clinical trial studies have shown that administering some natural products, such as resveratrol, can lower the lipoprotein (a) level, potentially lowering the risk of cardiovascular disorders [21].

The results of preclinical and clinical trial studies indicate that antioxidant and immunomodulatory effects of resveratrol can protect healthy cells and tissues, reduce the risk of certain diseases, and alleviate the side effects of some diseases, including diabetes and COVID-19 [22-25]. These properties of resveratrol may also be beneficial in cancer treatment. This review aims to review resveratrol's dual role in preventing carcinogenesis in normal tissues and boosting anticancer therapy.

2. STRUCTURE AND GENERAL FUNCTION OF RESVERATROL

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenol found in some herbal food such as grapes. This phenolic compound can help protect herbs from microorganisms, fungi, and bacteria. Due to its potent antioxidant properties, resveratrol is considered a valuable polyphenol [26]. (Fig. **1A**). Although resveratrol cannot directly scavenge free radicals, it can remove ROS and nitric oxide (NO) by stimulating intrinsic antioxidant defense enzymes and peptides [27]. The first beneficial effects of resveratrol were reported in 1982. According to one study, resveratrol may effectively protect against cardiac injury [28]. Several years later, resveratrol's antitumor properties were evidenced. In 1997, an experiment demonstrated that resveratrol protected mice's skin from tumorigenesis. Additionally, resveratrol has been demonstrated to prevent mutations and preneoplastic lesions. These results suggested that resveratrol may inhibit the growth of tumors in cells exposed to carcinogens [29].

The antioxidant and anti-mutagen effects of resveratrol make it an effective compound in preventing human diseases [30]. However, additional research has demonstrated that resveratrol can inhibit tumor growth. As a result of this effect, resveratrol was considered a potential adjuvant in cancer therapy. Anticancer agents, such as alkylating agents and radiotherapy, are highly toxic to normal cells and tissues [31]. On the other hand, tumor cells can resist these anticancer therapies due to mutations, upregulation of survival-related genes, and immune system exhaustion [32]. Resveratrol exhibits a dual role in treating tumors and normal tissues. It has been proposed to protect normal tissues from the toxic effects of ionizing radiation and chemotherapy medications [11]. Furthermore, it may modulate the immune system and induce multiple types of cell death in malignant cells [33].

3. LIMITATIONS AND CHALLENGES FOR THE CLINICAL TRANSLATION OF RESVERATROL

Due to the intriguing properties of resveratrol, several studies have been conducted to investigate resveratrol's potentially beneficial effects through clinical trials. Multiple clinical trials examined the toxicity and possible antitumor effects of resveratrol in cancer patients. While some studies reported benefits, others reported that resveratrol might cause toxicity or have no significant effect on tumor inhibition [12]. Thus, it appears there are limitations to the clinical translation of resveratrol. As a result, some of the limitations

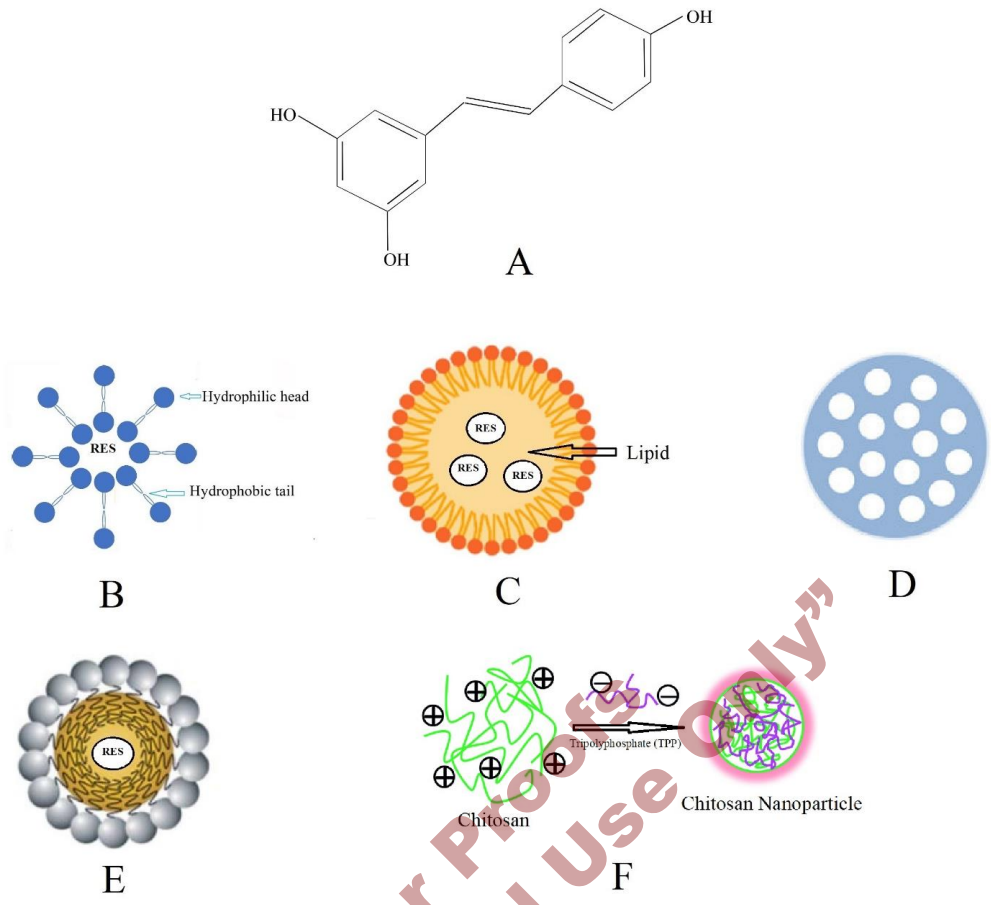

Fig. (1). The chemical structure of resveratrol and the structure of some carriers for its delivery. (**A)**: Chemical structure of resveratrol; (**B)**: Liposome comprising lipid bilayers and an aqueous space. Resveratrol can be located within an aqueous space; (**C)**: Polymeric nanolipid exhibits a core-shell structure. Resveratrol can be loaded within a polymeric core covered by a lipid shell; (**D)**: Mesoporous silica nanoparticles contain cores that can be used to encapsulate drugs such as resveratrol; (**E)**: Micelles consist of hydrophobic and hydrophilic tails. Micelles enclose drugs such as resveratrol and increase absorption and circulation time; (**F**): Chitosan nanoparticles include biocompatible natural polysaccharides that can increase the accumulation of resveratrol within malignant cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of resveratrol must be addressed. To this end, safe resveratrol concentrations must be established for both healthy individuals and those suffering from various types of cancer. Thus, it is necessary to elucidate the safety of resveratrol in patients with various types and grades of tumors. Drug distribution varies between tissues. For instance, oral administration of resveratrol has been reported to accumulate higher concentrations in the liver and skin, while lower concentrations are observed in the muscles and adipose tissue [34, 35].

On the other hand, different resveratrol structures have distinct absorption and distribution properties, which must be considered [36]. It has been reported that gastrointestinal system malignancies may receive a higher resveratrol concentration than other types of malignancies following oral administration of resveratrol [37]. Thus, gastrointestinal tumors may require lower doses of resveratrol to be administered orally. Additionally, this minimizes the risk of resveratrol toxicity in patients with these tumors.

Another significant limitation of resveratrol is its insufficient absorption and bioavailability. Numerous studies have been conducted to increase the bioavailability and abruption of herbal-derived drugs, such as resveratrol. Chemical tags and nanocarriers are two of the most frequently used methods for resolving resveratrol-related issues [38]. Resveratrol can be encapsulated by nanocarriers, facilitating its absorption and cell penetration [39]. Various types of nanocarriers may be advantageous for this purpose. Liposomes, micelles, nanolipids, and nanogels are examples of encapsulated resveratrol particles that can be used to increase their bioavailability. Other carriers, such as biodegradable fibers, biodegradable lipids, mesoporous silica nanoparticles, zinc-pectinate microparticles, and galenic soluble formulations, have been proposed to increase resveratrol's efficacy [40]. Fig. (**1**) illustrates the structure of several resveratrol carriers (Fig. **1**).

To date, no research has been conducted to determine the safety and antitumor activity of resveratrol nanoformulations in cancer patients. For the clinical translation of resveratrol, it is necessary to investigate the safety and bioavailability of the best carrier formulations and resveratrol structures. Although some clinical trials have been conducted to determine the safety of resveratrol, most studies have only determined

its safety in healthy individuals. Nonetheless, new formulations should be evaluated in patients with various types of tumors. Given that resveratrol has a variable distribution in different tissues, it is natural that different types and grades of tumors exhibit variable absorption. Tumor stiffness is a significant barrier to drug delivery, limiting the penetration of antitumor drugs into tumors. The use of nanocarriers may aid in the delivery of drugs, such as resveratrol, into tumors [41, 42].

Toxicity of resveratrol for normal cells and tissues is another significant barrier to its clinical translation. Although most studies have suggested that resveratrol has antioxidant properties, other experiments have confirmed its toxicity. Resveratrol appears to induce oxidative stress in several cell-type-dependent concentrations [43]. Resveratrol may induce mitochondrial impairment and ROS production, leading to oxidative stress, DNA damage, and cell death [44]. Treatment with resveratrol (2, 8, and 20 mg kg) has demonstrated considerable toxicity in mice's spermatogenesis system.

Intriguingly, the outcomes showed that resveratrol reduces the number of sperms. In addition, the results suggested that resveratrol could inhibit the activity of superoxide dismutase (SOD), catalase, and glutathione (GSH) [45]. Another study confirmed that resveratrol (50 mg/kg) could induce apoptosis in the testis [46].

Conversely, other studies have demonstrated that resveratrol protects spermatogenesis against the toxic effects of chemotherapy drugs (1 mg/kg for 4 weeks) and ionizing radiation (100 mg/kg for 3 days) [47, 48]. These findings suggest that although resveratrol may cause oxidative damage in certain organs, it can mitigate the toxicity of chemotherapy and radiotherapy. It has been suggested that low concentrations of resveratrol can prevent the development of cancer in normal cells. However, greater concentrations may be toxic to cancer cells [49]. The toxicity of resveratrol should be investigated for various normal tissues. Furthermore, differences in resveratrol dosages and duration of treatment should be considered.

4. MECHANISM OF GENOMIC STABILITY BY RESVERATROL

As previously stated, normal cells exposed to ionizing radiation or anticancer drugs can induce ROS generation, DNA damage, cell death, and genomic instability. While cell toxicity in normal tissues can have both acute and delayed effects, carcinogenesis is a major concern, especially in chemotherapy and radiotherapy [50]. Protecting normal tissues from genomic instability may help reduce the risk of cancer recurrence in cancer therapy patients [51]. Antioxidants or an antioxidant-rich diet may be beneficial in alleviating oxidative stress and normal tissue toxicity. However, concerns have been raised regarding the potential for tumor protection and diminished anticancer therapy efficacy. Thus, the adjuvant's effect on both normal and tumor tissues must be considered. The dual effects of resveratrol make it an intriguing adjuvant for cancer therapy. It protects normal tissues in numerous ways. This section describes how resveratrol protects against anticancer agents that induce genomic instability.

4.1. Boosting DNA Repair Mechanisms in Normal Cells

DNA damage underlies genomic instability [52]. Damage to DNA can result in DNA breaks, which can either induce cell cycle arrest and DNA repair or cell death [53]. Apoptosis is a critical regulator of genomic instability. However, some mutations may result in mutated cells evading apoptosis, resulting in survival and proliferation. The proliferation of mutated cells can lead to additional mutations, advancing mutated cells toward carcinogenesis [54]. Resveratrol has been shown to boost DNA repair following exposure of normal cells to genotoxic agents [55]. An experiment demonstrated that pre-and post-irradiation treatment with resveratrol enhanced DNA repair and decreased DNA damage in human lymphocytes. Resveratrol exerted the greatest effect when cells were treated immediately or one hour after irradiation [56]. The precise mechanisms by which resveratrol enhances DNA repair following exposure of normal cells to ionizing radiation or highly toxic chemotherapy agents require further elucidation.

4.2. Suppression of Pro-oxidant Mediators

In addition to the direct production of ROS, anticancer agents may also induce the production of free radicals by cells. This effect of anticancer agents is known as ROS-induced ROS phenomenon [57]. DNA damage may induce the generation of oxidized DNA. This molecule is detectable by inflammatory cells and stimulates the activity of pro-oxidant enzymes [58]. Cell death through apoptosis, senescence, and necrosis also stimulate proinflammatory cytokine production. The release of some cytokines such as IL-1, IL-6, IL-18, IL-33, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β can trigger the expression of pro-oxidant enzymes such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), nicotinamide adenine dinucleotide phosphate (NADPH) oxidases including NADPH oxidase (NOX)1, NOX2, and NOX4, and dual oxidases (Duoxs) including Duox1 and Duox2 [59]. These ROS and nitric oxide (NO) generators are crucial mechanisms of DNA damage and genomic instability following radiotherapy and chemotherapy. The release of the cytokines mentioned above may also activate pro-oxidants in adjacent cells and tissues. This is referred to as the bystander effect. The bystander effect is critical for DNA damage, genomic instability, and cancer incidence following radiotherapy [60].

Resveratrol may protect normal cells from oxidative stress caused by endogenous ROS and NO generation. As stated previously, resveratrol improves DNA repair and reduces the oxidation of molecules and macromolecules, including DNA. Protecting DNA from damage has been shown to reduce inflammation and redox responses [61]. Radiation has been shown to induce apoptosis and senescence in bone marrow cells, resulting in the release of TGF-β and upregulation of TβR1. This pathway also can induce ROS generation *via* stimulating NOX1, NOX2, and NOX4

in bone marrow cells [62, 63]. Inhibiting TGF-β and NADPH oxidases, including NOX2 and NOX4, can decrease genomic instability markers, such as 8-hydroxy-2′-deoxyguanosine (8-OH-dG) and unstable DNA damage such as micronuclei in the progeny of hematopoietic stem cells (HSCs) [64]. Resveratrol may be beneficial in targeting the TGF-β/TβR1/NOX2 and NOX4 pathways. Inhibiting this pathway in bone marrow cells may help prevent genomic instability following HSC exposure to genotoxic agents such as ionizing radiation and high-toxicity chemotherapy drugs.

A study investigated the effect of resveratrol treatment on the long-term effects of ionizing radiation on HSCs; it revealed that resveratrol could help prevent continuous ROS generation by inhibiting NOX4. In this study, mice received resveratrol (20 mg/kg) from 7 days prior to 30 days after whole-body irradiation with a lethal dose of ionizing radiation. The results indicated that although ionizing radiation-induced NOX4 stimulates senescence in HSCs, resveratrol can blunt the expression of senescence markers. Micronuclei reduction in peripheral lymphocytes confirmed that resveratrol protects bone marrow cells from oxidative stress induced by NOX4. Furthermore, treatment with resveratrol could improve survival by 40% [65].

Resveratrol also may protect against chemotherapy-induced redox responses. Certain chemotherapy drugs, including doxorubicin, cisplatin, and cyclophosphamide, can generate ROS by disrupting mitochondrial function and activating pro-oxidant enzymes [66]. A study showed that treating human lymphocytes with different chemotherapy drugs, such as doxorubicin and bleomycin, induces intracellular ROS generation. However, co-treatment with resveratrol suppressed ROS generation [67]. Another study demonstrated that resveratrol significantly reduces oxidative stress and inflammation by inhibiting the inflammation/redox pathways. In this study, rats received resveratrol at a dose of 10 mg/kg for three weeks before receiving cisplatin at 7 mg/kg. Experimental evaluation showed that resveratrol alleviated oxidative stress *via* suppressing inflammatory mediators and cytokines, including the nuclear factor of kappa B (NF-κB), IL-1β, IL-6, TNF-α, and reduced the activity of pro-oxidant enzymes COX-2, and iNOS in the ovary and uterus. Treatment with resveratrol also decreased the level of malondialdehyde (MDA), an indicator of oxidative damage [68].

4.3. Stimulation of the Antioxidant Defense System in Normal Cells/Tissues

Stimulating the antioxidant defense system, including antioxidant enzymes and peptides, is a key protective mechanism of resveratrol against toxic agents [69]. The antioxidant defense system includes enzymes and peptides such as catalase, SOD, GSH, glutathione peroxidase (GPx), and glutathione reductase (GR). These peptides and enzymes scavenge free radicals in both mitochondria and cytoplasm [70]. Resveratrol has been shown to exert a modulatory effect on antioxidant defenses in response to radiation and chemotherapy-induced oxidative stress [71]. Treatment with resveratrol can induce the activity of GPx, SOD, and catalase and reduces the level of MDA in normal tissues following exposure to cisplatin [68]. A significant increase in the level of GSH and the activity of SOD can alleviate nephrotoxicity caused by cisplatin [72].

Another study demonstrated resveratrol's protective effect against doxorubicin-induced oxidative stress. This research determined that resveratrol induces ROS scavenging in the heart by stimulating SOD and regulating calcium ion concentrations [73, 74]. It has been hypothesized that resveratrol stimulates these antioxidant peptides and enzymes by modulating forkhead box O-3 (FoxO3), nuclear factor erythroid factor 2-related factor 2 (Nrf2), and sirtuin 1 (SIRT1) pathways [75-79].

Similarly, resveratrol has been shown to improve antioxidant defenses against oxidative damage caused by ionizing radiation. Ionizing radiation directly damages cells, primarily through water radiolysis and ROS generation. Heavy production of ROS by ionizing radiation can suppress the activity of antioxidant enzymes for an extended period after irradiation. Resveratrol may be beneficial in reversing the inhibition of antioxidant defenses following ionizing radiation exposure of normal cells/tissues. An experiment confirmed that pretreatment with 5 and 10 mg/kg for 30 consecutive days could induce the activity of SOD and catalase and reduce the level of MDA in rat lymphocytes after radiation exposure [80]. Another study by Zhang *et al*. showed that resveratrol could protect high radiosensitive intestinal crypts *via* inducing SOD2 and upregulation of SIRT1 [81]. The activation of antioxidant enzymes, such as SOD and GPx, has been shown to protect bone marrow cells from the genotoxic effects of ionizing radiation [82]. Additional experiments are required to elucidate the precise mechanisms and mechanisms of protection against the toxic effects of ionizing radiation and various types of chemotherapy agents in different tissues (Fig. **2**).

5. ANTITUMOR PROPERTIES OF RESVERATROL

To date, numerous herbal-derived agents have demonstrated antitumor activity. Resveratrol is one of the most potent and well-known herbal anticancer agents. For the first time, resveratrol was shown to inhibit tumorigenesis in mice skin in a 1998 study. This study suggested that resveratrol can inhibit oxidative damage and the expression of cancer-associated genes, such as c-fos and TGF-β1 [83]. Afterward, numerous studies were conducted to assess resveratrol's potential antitumor effects on various types of cancer.

Additionally, several studies have attempted to explain how resveratrol targets tumors [84-86]. This section summarizes the current knowledge regarding the mechanisms by which resveratrol exerts its antitumor effects. Moreover, we discuss recent studies demonstrating promising results when resveratrol is combined with other anticancer therapies.

6. BOOSTING ANTITUMOR IMMUNITY

The tumor microenvironment (TME) includes various cells and secretions that affect the response of the tumor to radiotherapy, chemotherapy, immunotherapy, and targeted cancer therapy drugs [87, 88]. Cells and secretions within

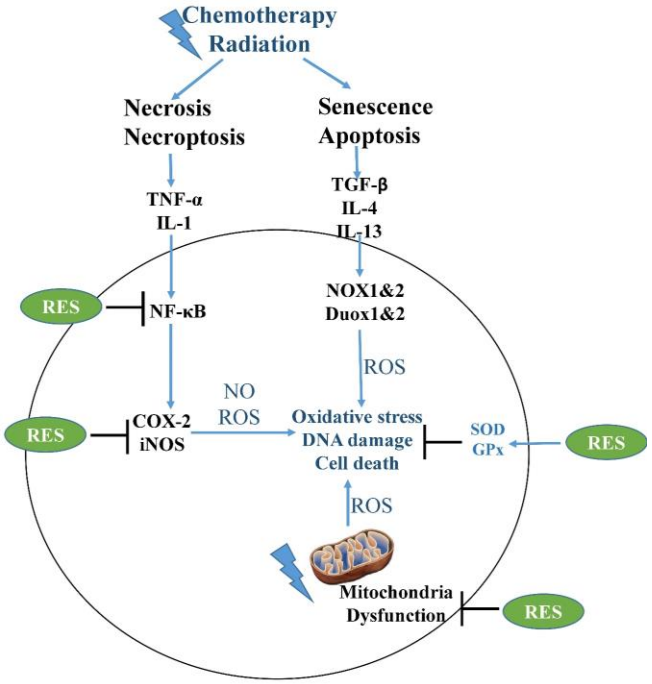

Fig. (2). Schematic diagram of the protective mechanisms of resveratrol against radiation/chemotherapy-induced normal tissue toxicity. It can reduce oxidative stress and DNA damage, thus reducing cell death, inflammatory responses, and the release of cytokines. The inhibition of proinflammatory and pro-fibrosis cytokines such as IL-1, IL-4, IL-13, TNF-α, and TGF-β may reduce the expression and activity of pro-oxidant enzymes such as NOX2, NOX4, iNOS, and COX-2. Furthermore, resveratrol can suppress the continuous production of superoxide by mitochondria. Resveratrol also can modulate redox reactions through the stimulation of antioxidant enzymes. These modulatory effects can attenuate oxidative stress, DNA damage, and genomic instability, which may reduce the probability of cancer incidence. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

TME affect angiogenesis, metastasis, the metabolism of cancer cells, and antitumor immunity function. The most significant cells within TME are lymphocytes, natural killer (NK) cells, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), and macrophages, including M1 and M2 cells. CD4+ and CD8+ T lymphocytes, NK cells, and M1 macrophages can release inflammatory cytokines and antitumor molecules among these cells. Nonetheless, other cells can inhibit the function of these antitumor immune cells [89]. The most significant secretions of antitumor immune cells are TNF-α, interferon (IFN)-γ, and specific molecules such as Granzyme B and perforin that can induce cancer cell lysis. Immunosuppressive cells, on the other hand, release immunosuppressive molecules such as TGF-β, IL-10, IL-4, and IL-13, as well as immune checkpoint molecules, including programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4), which inhibit the proliferation and activity of antitumor cells [90].

TME suppression is an intriguing strategy for combating tumor resistance to therapy. By inhibiting immunosuppressive cells and secretions, antitumor immunity can be boosted, resulting in the death of cancer cells [91]. Resveratrol can modulate immune system function within TME in favor of antitumor immunity. Research has proposed that resveratrol induces the release of IFN-γ by antitumor cells. An increase in the release of IFN-γ following treatment with resveratrol can stimulate the reprogramming of immunosuppressive M2 macrophages to antitumor M1 macrophages [92]. It is self-evident that a decrease in the number of M2 macrophages following resveratrol administration can reduce the release of immunosuppressive cytokines such as TGF-β, IL-10, IL-4, and IL-13.

Furthermore, resveratrol can inhibit the release of IL-1 and IL-6 by macrophages. Since these cytokines are involved in tumor invasion and metastasis, resveratrol may inhibit tumor invasion by modulating macrophages [93]. Additionally, resveratrol has been shown to inhibit the infiltration and proliferation of other immunosuppressive cells, such as Tregs and MDSCs. Resveratrol treatment of mice with Lewis lung carcinoma reprograms MDSCs to myeloid cells, resulting in the activation and proliferation of CD8+ T cells [94]. Another study assessed the effect of resveratrol and its nanoformulation as N,O-carboxymethyl chitosan resveratrol nanoparticles (CMCS-Res nanoparticles) on the frequency of MDSCs in colon tumor-bearing mice. The results indicated that free resveratrol reduces the percentage of MDSCs from 20% to 15.88%. However, CMCS-Res nanoparticles have the potential to reduce MDSCs to 1%. Additionally, treatment with CMCS-Res nanoparticles may be more effective than treatment with free resveratrol in inhibiting the growth of tumors. The results indicated that treatment with CMCS-Res nanoparticles improves the antitumor activity of oxaliplatin. Although free resveratrol cannot significantly reduce the number of MDSCs, the authors concluded that resveratrol nanoformulation is a potent inhibitor of MDSCs in colon tumors [95].

Resveratrol inhibits Foxo3 expression and Treg proliferation, resulting in an increase in the release of antitumor cytokines through CD8+ T lymphocytes [96]. CD4+CD25+ FoxP3+ Tregs are the predominant type found in tumors. Several additional studies have confirmed that resveratrol treatment can decrease the number of CD4+CD25+FoxP3+ Tregs in breast and melanoma tumor models [97, 98]. Resveratrol treatment of mice with hepatocellular carcinoma tumors inhibited the proliferation and recruitment of CD8 + CD122 + Tregs, another subfamily of immunosuppressive Tregs [99]. Resveratrol has been shown to inhibit positive cross-talk between malignant cells and macrophages by suppressing macrophage inhibitory cytokine 1 expression (MIC-1) [100]. Additionally, resveratrol promotes macrophage reprogramming to M1 macrophages, increasing the release of Th1 cytokines and suppressing the release of immunosuppressive and tumor-promoting cytokines [101].

The activation of antitumor cells and attenuation of immunosuppressive cells enhance the production and concentration of anticancer molecules within TME. The exhaustion of antitumor immunity, such as the inhibition of CD8+ T lymphocytes and NK cells, is associated with the accumula-

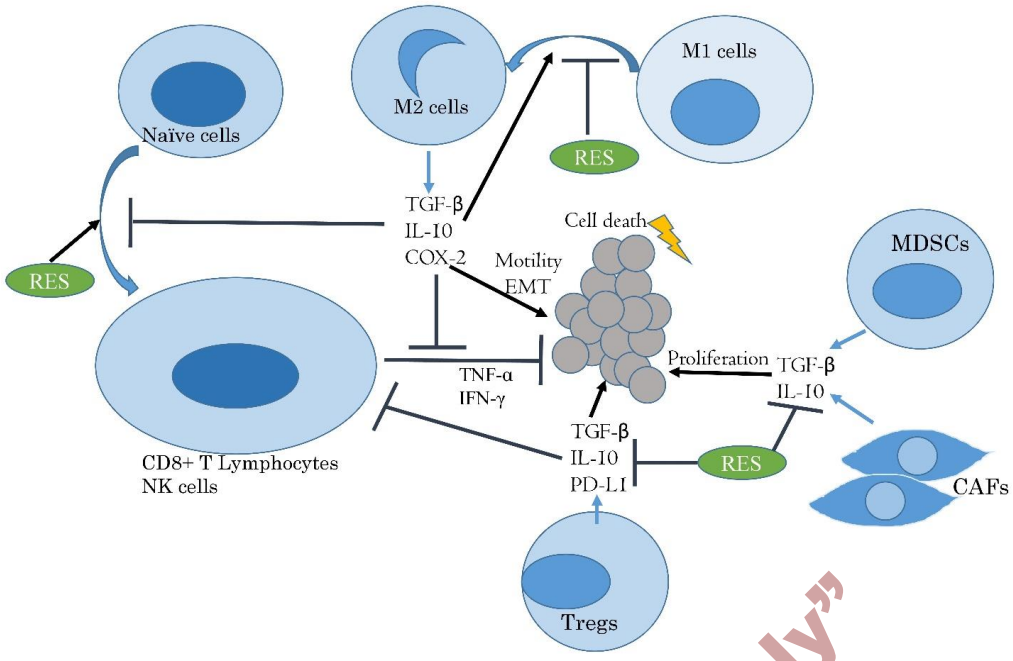

Fig. (3). Mechanisms of immune system stimulation against cancer by resveratrol. Exposure of cancer cells to anticancer drugs and radiation stimulates cell death. Immune cells can release immunosuppressive cytokines in response to apoptosis. Resveratrol can suppress the release of immunosuppressive cytokines by CAFs, Tregs, and M2 macrophages. On the other hand, it can stimulate the release of TNF-α and IFN-γ, which trigger the proliferation of NK cells and CD8+ T lymphocytes. Resveratrol also blunts the positive cross-talk between CAFs, MDSCs, Tregs, and M2 macrophages. These changes can improve the release of antitumor molecules by NK cells and CD8+ T lymphocytes, leading to tumor suppression. Furthermore, inhibition of immunosuppressive cytokines by resveratrol may reduce EMT, motility, invasion, and resistance of cancer cells to antitumor immunity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tion of protumor, pro-angiogenesis, and metastasis-related molecules. Boosting antitumor immunity through resveratrol can reduce these molecules' expression and enhance the concentration of tumor-suppressive molecules such as Granzyme B, perforin, TNF-α, IFN-γ, TNF-related apoptosis-inducing ligand (TRAIL), and Fas ligand (FasL). These molecules have the ability to induce cell death in cancer cells. Furthermore, increased release of inflammatory cytokines, including TNF-α and IFN-γ, can boost the proliferation of CD4+ T cells to CD8+ T lymphocytes. Moreover, it has been demonstrated that resveratrol can stimulate NK cell proliferation by inducing the release of IL-12 [102] (Fig. **3**).

7. BOOSTING DNA DAMAGE IN CANCER CELLS

Although low doses of resveratrol can enhance DNA repair capacity in normal cells, multiple studies have demonstrated that treatment with resveratrol may induce DNA damage in different cancer cells [103, 104]. This differential effect of resveratrol may be due to the difference in metabolism and oxidative phosphorylation between cancer and normal cells. While resveratrol has been shown to increase the number of mitochondria in both normal and malignant cells, activating the antioxidant defense in normal cells can scavenge free radicals [105]. Furthermore, resveratrol may effectively stimulate damaged DNA repair, suppressing cell death in normal cells [106]. It has been reported that the treatment of cancer cells with resveratrol enhances oxidative phosphorylation in mitochondria, leading to the overproduction of ROS during cellular respiration. ROS generation can induce mitochondrial dysfunction in cancer cells, leading to chronic ROS generation and oxidative stress [107].

Another significant distinction between cancer and normal cells is the expression and activity of DNA repair enzymes and tumor suppressor genes. Resveratrol treatment has been shown to stimulate p53 activity by inducing SIRT1 [108]. A study found that activating SIRT1 following resveratrol treatment in mice increased DNA repair and decreased cell death in the intestine [81]. In contrast to normal cells, activation of p53 is a vital process for malignant cell suppression. Mutations in tumor suppressor genes, such as p53 or p21 render cancer cells resistant to apoptosis and other forms of cell death. Activating these proteins in malignant cells induces apoptosis and senescence [11, 109].

Additional research has revealed that resveratrol inhibits the activity of DNA repair enzymes in malignant cells. According to one study, resveratrol treatment of MCF-7 breast cancer cells suppressed the expression of the homologous recombination (HR) pathway *via* downregulation of the MRN complex proteins (including MRE11-NBS1-RAD50) [110]. Another study demonstrated that resveratrol's downregulation of RAD51 is critical for the sensitization of MCF-7 cancer cells to cisplatin [111]. Resveratrol has been shown to inhibit RAD51 in Hela cancer (ovarian) stem cells, leading to the sensitization of these cells to apoptosis [112]. Resveratrol also improves the chemotherapy sensitivity of

lung cancer cells *via* downregulation of X-ray Repair Cross-Complement Group 1 (XRCC1) [113].

It has been reported that inhibiting NF-κB plays a critical role in resveratrol's ability to inhibit DNA repair pathways. Cancer cells express NF-κB at a higher level than normal cells. Suppression of NF-κB can render cancer cells more susceptible to apoptosis without causing significant toxicity to normal cells. Thus, inhibiting NF-κB may impair cancer cell DNA repair capacity without impeding DNA repair in normal cells [114]. A study confirmed that resveratrol suppresses NF-κB in glioblastoma cancer cells by downregulating O(6)-methylguanine-DNA-methyltransferase (MGMT), a key protein involved in DNA repair and drug resistance in glioblastoma cells [115].

8. STIMULATION OF CANCER CELL DEATH PATHWAYS

As previously stated, resveratrol may improve cancer cell redox responses and DNA damage. DNA damage plays a critical role in cell death regulation. While resveratrol's induction of DNA damage is critical for initiating cell death pathways, emerging evidence indicates that resveratrol can modulate multiple cell death pathways in cancer [33]. The regulation of molecule secretion within TMEs is critical for initiating cell death pathways. Cancer cells may upregulate the expression of survival-related genes in response to death signals, thereby suppressing apoptosis or other types of cell death. Apoptosis is the most well-known type of cell death in cancer therapy that can occur following DNA damage and an increase in the release of death signals such as TNF-α, IFN-γ, FasL, and TRAIL. Apoptosis and cellular senescence cannot be induced without p53. Nevertheless, mitotic catastrophes can occur in the absence of p53. Severe oxidative stress-induced damage to critical organelles and macromolecules may result in autophagic cell death, necrosis, and necroptosis [116].

Resveratrol can regulate intercellular and intracellular mediators within TME and cancer cells. Activating NK cells and CD8+ T lymphocytes can improve the release of ROS, TNF-α, IFN-γ, FasL, and TRAIL [117, 118]. An increase in ROS release can enhance DNA damage and oxidative stress in the tumor. On the other hand, the release of TNF-α, IFN-γ, FasL, and TRAIL stimulates apoptosis by inducing the expression of caspases 8 and 9 in cancer cells. ROS generation and mitochondrial dysfunction following resveratrol treatment can also induce ROS-induced ROS release in cancer cells, which may result in the mitochondrial apoptotic pathway [119]. Apoptosis incidence depends on the expression and activity of several proapoptotic genes and mediators, including Bax, p53, and the phosphatase and tensin homolog (PTEN) [120].

Certain cancer cell mutations promote multidrug resistance by inhibiting these apoptotic mediators. The majority of cancer cells contain a mutated form of p53. In this state, p53 is inactive and unable to initiate apoptosis, preventing malignant cells from evading apoptosis [121]. Furthermore, the upregulation of some oncogenes can suppress the expression and activity of PTEN. Downregulation of PTEN leads to overexpression of phosphoinositide 3-kinase (PI3K)/Akt pathway, which causes upregulation of B-cell lymphoma 2 (Bcl-2) and downregulation of Bax [122]. Resveratrol has been shown to reverse the suppressed expression of tumor suppressor genes, including p53 and PTEN. Resveratrol activates p53 *via* Sirt1 and mono-methylation of p53 at lysine 372 [123, 124]. Resveratrol can also reactivate PTEN in cancer cells *via* the modulation of epigenetics modulators. Upregulation of miR-17 and miR-21 plays a key role in inhibiting PTEN in malignant cells. The inhibition of these miRNAs by resveratrol can upregulate the expression of PTEN, leading to the downregulation of anti-apoptosis genes such as PI3K, Akt, and Bcl-2 [125, 126].

Senescence can also be induced by stimulating redox responses and tumor suppressor genes. This type of cell death can occur due to DNA damage, chromosome shortening, activation of p53 and PTEN, or specific changes in the metabolism of cells [127, 128]. Activation of p53 may stimulate the activity of p21, leading to cell cycle arrest. Resveratrol has been shown to stimulate p53/p21 and redox responses such as ROS production by NADPH oxidases [129]. Treatment with resveratrol may induce mitotic catastrophe in cancer cells. According to some reports, the induction of mitotic catastrophe may occur in cells with higher resistance to apoptosis following resveratrol treatment [130]. Severe damage to cells during oxidative stress may cause necrosis or necroptosis. The overproduction of antitumor cytokines, including TNF-α, IFN-γ, and death signals such as FasL and TRAIL, plays a crucial role in the necroptosis of cancer cells [131, 132]. As resveratrol can boost antitumor immunity and release these molecules, it may stimulate necroptosis in malignant cells [33]. However, additional research is required to elucidate this issue (Fig. **4**).

Modulating cell death and tumor-promoting genes in cancer cells can improve antitumor immunity and inhibit angiogenesis and metastasis [133]. Resveratrol enhances the toxicity of death signals in cancer cells by modulating oncogenes and survival-related genes. Certain oncogenes, such as C-Myc, promote resistance to antitumor agents. A study found that resveratrol could induce apoptosis and cell cycle arrest in human medulloblastoma cells by suppressing C-Myc [134]. Inhibiting C-Myc expression in breast cancer cells can improve cancer cell lysis and induction of apoptosis in response to NK cell-released molecules [135].

Resveratrol has been shown to suppress tumor growth, invasion, and metastasis by inhibiting C-Myc and inducing apoptosis [136, 137]. These experiments indicated that resveratrol's activation of PTEN and suppression of PI3K strongly correlate with its inhibitory effect on C-Myc. Additionally, it has been demonstrated that novel forms of resveratrol, such as resveratrol nanoemulsions and resveratrol-loaded gold nanoparticles, induce cell cycle arrest and cell death in pancreatic cancer cells. These effects are associated with increased expression of cell cycle arrest markers such as cyclin A and B, cyclin-dependent kinase (CDK) 1 and 2, and increased p53 and p21 expression.

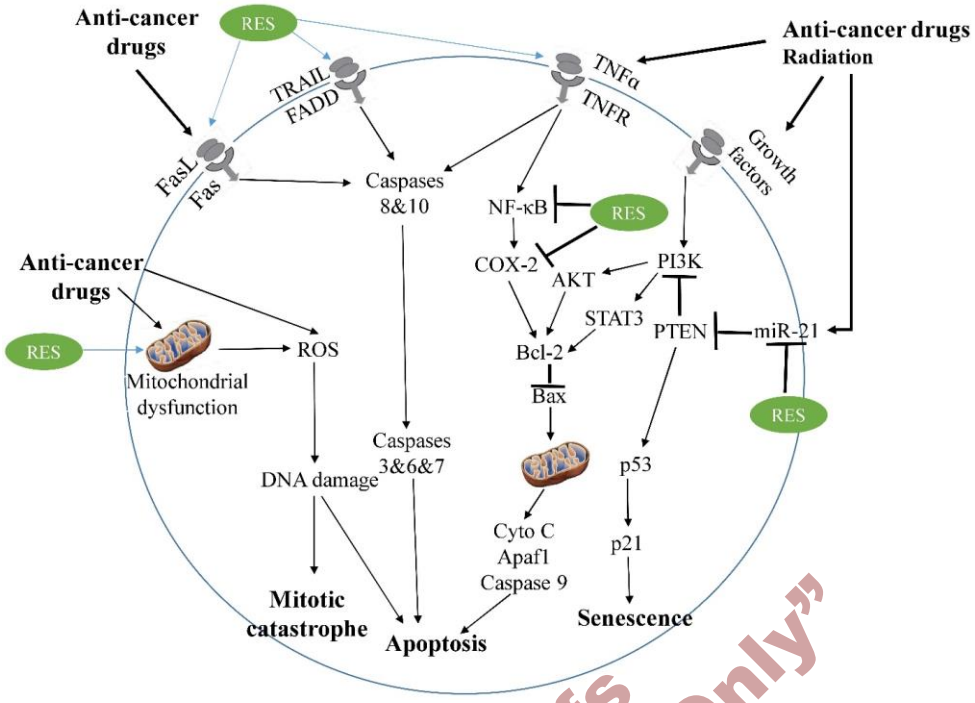

Fig. (4). Mechanisms of cell death amplification through resveratrol. Resveratrol induces the release of death molecules, such as FasL, TRAIL, and TNF-α. It also reduces the release of some growth factors, such as TGF-β. Increased release of death signals leads to the activity of initiator caspases such as caspases 8 and 10. These enzymes induce apoptosis *via* both extrinsic and mitochondrial pathways. Resveratrol can stimulate ROS generation by mitochondria, leading to DNA damage and cell death. DNA damage can also trigger the expression of p53 and Bax, leading to apoptosis. Activation of p53 can trigger both apoptosis and senescence signaling pathways. Resveratrol can suppress several survival-related proteins, such as PI3K, STAT3, miR-21, and NF-κB. An increase in the activity of tumor suppressor genes, stimulation of redox responses, and the inhibition of survival-related proteins lead to cell death through various pathways, such as mitotic catastrophe, apoptosis, and senescence, among others. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

9. ANTI-ANGIOGENESIS ACTIVITY OF RESVERATROL

Hypoxia and angiogenesis are the key regulators of tumor resistance to different therapy modalities. Hypoxia-inducible factor (HIF) family proteins are responsible for initiating biological signaling pathways at low oxygen concentrations. These proteins can be degraded when exposed to oxygen. However, inhibition of prolyl hydroxylase domain (PHD) proteins stabilizes HIF proteins under hypoxia conditions [138]. HIF-1α is the most significant subfamily of HIF proteins. It can induce angiogenesis by modulating the expression of several pro-angiogenesis mediators, including vascular endothelial growth factor (VEGF) and angiopoietins (including Ang-1 and Ang-2). HIF-1α also can stimulate the release of several angiogenesis-related factors such as stromal cell-derived factor-1 (SDF-1), platelet-derived growth factor (PDGF), and matrix metalloproteinases (MMPs), including MMP-2 and MMP-9. These factors can trigger the proliferation of endothelial cells and the formation of new vessels and microvessels.

Resveratrol has been shown to suppress several pro-angiogenesis mediators, thus inhibiting tumor growth. Resveratrol can inhibit HIF-1α directly. According to one study, the inhibition of HIF-1 in Panc-1 and Mia Paca-2 cells (pancreatic cancer cells) was associated with the suppression of VEGF and SDF-1. These factors mediate the invasion of prostate cancer cells. Thus, resveratrol's inhibition of HIF-1 and its downstream genes, such as VEGF and SDF-1, may inhibit prostate cancer cells' invasive properties [139].

The inhibition of the HIF-1/VEGF axis by resveratrol has also been revealed in an *in vivo* study. In one experiment, mice bearing MCF-7 and MDA-MB-231 breast tumors were treated with resveratrol (20 mg/kg), and the expression of HIF-1/VEGF was subsequently examined. The results indicated that resveratrol inhibited HIF-1/VEGF, suppressing microvessel markers and tumor growth [140]. Another angiogenesis pathway that resveratrol can target is fibroblast growth factor 2 (FGF2). FGF2 is a subfamily of FGF that can induce VEGF in endothelial cells [141]. Resveratrol administration to mice with fibrosarcoma inhibits angiogenesis by impeding the proliferation of endothelial cells mediated by FGF receptors [142]. Resveratrol has been suggested to induce apoptosis in endothelial cells by downregulating antiapoptotic genes such as c-IAP1, c-IAP2, and XIAP [143].

Another key mechanism of angiogenesis suppression through resveratrol is inhibiting tumor-promoting cells. The reprogramming of macrophages to M1 macrophages and the inhibition of the release of some cytokines such as IL-1 and IL-6 can reduce the expression and phosphorylation of pro-

angiogenesis mediators such as signal transducers and activators of transcription 3 (STAT3) and VEGF [144]. Resveratrol can suppress other pro-angiogenesis cells, such as Th17/Tregs and CAFs [145]. Furthermore, it can attenuate the release of some cytokines, such as TGF-β [146], which promote angiogenesis and tumor growth [147]. However, additional research is required to explicate the complete and precise mechanisms by which resveratrol inhibits angiogenesis *via* modulation of the tumor immune microenvironment.

In addition to the modulation of cytokines and other secretions, resveratrol can suppress angiogenesis through the modulation of the expression of several genes and proteins in cancer cells. The induction of apoptosis partly mediates resveratrol's ability to inhibit angiogenesis. Resveratrol impedes endothelial cell tube formation and angiogenesis progression *in vitro* [148]. Resveratrol has been shown to stimulate apoptosis in vascular endothelial cells by inhibiting VEGF and several other pro-angiogenesis genes, such as thrombospondin-1 (TSP1). Resveratrol exerts this effect by activating p53 and suppressing HIF-1 [149].

Several experimental studies evaluated the anti-angiogenesis properties of nano-formed resveratrol. As previously stated, nanoforms of resveratrol may be more effective at penetrating tumor and cancer cells than the bulk form of resveratrol. The experiment examined the effect of nanogold loaded with resveratrol on the expression of angiogenesis genes in hepatocellular carcinoma cells *in vitro* and *in vivo*. This experiment established that treatment with nanogold loaded with resveratrol results in increased resveratrol concentrations within cancer cells. Nano-gold loaded with resveratrol has been shown to significantly suppress tumor growth by inhibiting VEGF in the tumor. Moreover, additional examinations revealed no evidence of toxicity to critical organs [150].

10. RESVERATROL AS AN ADJUVANT IN CANCER THERAPY

As resveratrol can modulate multiple tumor properties, such as multidrug resistance, antitumor immunity, angiogenesis, cell death pathways, and redox metabolism, it may improve the therapeutic efficacy of anticancer treatment modalities. This section summarizes the findings of experimental studies examining resveratrol's potential as a sensitizer for anticancer agents.

11. RESVERATROL COMBINED WITH RADIOTHERAPY

Ionizing radiation kills cancer cells by inducing the generation of free radicals and direct interactions with DNA and other macromolecules. While ionizing radiation can cause significant damage to cancer cells, these cells may contain mechanisms that increase their resistance to radiotherapy. For example, the upregulation of immune checkpoints can exhaust antitumor immunity. In addition, radiation-induced mutations in the tumor may promote angiogenesis, metastasis, and downregulation of cell death signaling pathways. Resveratrol has been demonstrated to sensitize cancer cells to ionizing radiation by modulating multiple pathways and mediators. As resveratrol can boost antitumor immunity, it may prevent the exhaustion of NK cells and CD8+ T lymphocytes following radiotherapy [151].

On the other hand, resveratrol can reduce resistance to ionizing radiation by modulating several cell death pathways. The inhibition of STAT3 and NF-κB in cancer cells following treatment with resveratrol reduces the expression of anti-apoptosis genes such as Bcl-2, thus enhancing mitochondrial apoptosis following exposure to ionizing radiation [152, 153]. Due to the release of proinflammatory cytokines and upregulation of Akt, exposure of cancer cells to anticancer drugs and radiotherapy improves the expression and activity of STAT3 and NF-κB [154].

Induction of PTEN and Sirt1 also contributes to radiation-resistant apoptosis in cancer cells. Exposure of tumors to radiation can stimulate the release of some growth factors, such as epidermal growth factor receptor (EGFR) and TGF-β, which induce the activity and expression of PI3K/Akt proteins. Thus, inhibiting this pathway may be promising for decreasing cancer cells' resistance to radiotherapy. Resveratrol treatment of breast and prostate cancer cells has shown that it can increase their radiosensitivity by inhibiting the PI3K pathway [155, 156]. Another mechanism by which resveratrol acts as a radiosensitizer is the activation of p53. As previously stated, most cancers exhibit low p53 expression and activity levels. Low p53 activity has been linked to resistance to ionizing radiation. An experiment demonstrated that low p53 and p21 activity plays a crucial role in PC-3 prostate cancer cells' resistance to apoptosis and senescence after exposure to ionizing radiation. However, when cancer cells were treated with resveratrol, activating p53 and p21 promoted apoptosis and senescence [156].

12. RESVERATROL COMBINED WITH CHEMOTHERAPY

Multiple chemotherapeutic drugs act on cancer cells *via* distinct mechanisms. However, most conventional chemotherapy agents, including cisplatin, doxorubicin, 5-fluorouracil (5-FU), and bleomycin, can induce apoptosis in cancer cells by impairing DNA repair and increasing ROS generation. Cancer cells can induce several mechanisms following chemotherapy treatment that increase their resistance to apoptosis. To this end, cancer cells may undergo several mutations and changes, such as epithelial-mesenchymal transition (EMT) and upregulation of some anti-apoptosis genes, such as PI3K and STAT3. Additionally, tumors may develop tolerogenic responses to deplete antitumor immunity [157].

Resveratrol may act synergistically with certain chemotherapy drugs. Certain evidence suggests that resveratrol may induce cell cycle arrest when combined with chemotherapy drugs, inhibiting cancer cell proliferation. Two independent studies have shown that resveratrol decreases the proliferation of H22 cells (murine hepatic carcinoma cells), TE-1, and A431 (skin cancer cells) in combination with 5-FU *via* inducing S-phase arrest [158, 159].

Komina *et al*. conducted an experiment to examine the synergic effect of resveratrol on cell cycle arrest in human leukemia HL-60 cells following treatment with a combination of resveratrol and roscovitine (a CDK inhibitor). The results indicated that pretreatment with resveratrol and roscovitine decreased the frequency of cells in the S and G2/M phases while significantly increasing the number of arrested cells in the G1 phase (up to 80%). Additionally, the results indicated a synergic increase in the incidence of apoptosis [160]. Resveratrol has been shown to play a critical role in cell cycle arrest and apoptosis by modulating miR-122-5p. MiR-122-5p functions as an oncosuppressor in various cancers, including breast cancer [161]. Upregulation of miR-122-5p by resveratrol leads to the inhibition of CDKs such as CDK2, CDK4, and CDK6, causing cell cycle arrest. Moreover, it can inhibit Bcl-2, thereby inducing apoptosis in malignant cells [162].

It appears that activation and phosphorylation of p53 are critical for apoptosis and cell cycle arrest. It has been reported that phosphorylating p53 at Serin-20 following resveratrol treatment of MCF-7 cells reduces cisplatin resistance by inducing apoptosis and increasing the Bax/Bcl-2 ratio [163]. Resveratrol activates several kinases, including AMP-activated protein kinase (AMPK), which results in the phosphorylation and activation of p53. Resveratrol-induced AMPK activation may also sensitize HT-29 colon cancer cells to etoposide [164].

Additionally, the upregulation of certain oncogenes and antiapoptotic mediators such as PI3K and NF-κB increases cancer resistance to chemotherapy. Anti-apoptosis mediators can inhibit EMT and sensitize cancer cells to chemotherapy. The study investigated the chemosensitization effect of resveratrol on Adriamycin-resistant MCF-7 and MDA-MB-231 cells. Cancer cells were treated with both doxorubicin and resveratrol. Results showed that resveratrol could ameliorate EMT by inhibiting NF-κB and activating Sirt1. This pathway's inhibition also increased apoptosis induction in cancer cells [165]. Another study showed that the inhibition of the PI3K pathway is involved in the chemosensitization of MCF-7 breast cancer cells. Results indicated that reducing PI3K/Akt expression following treatment with resveratrol enhances apoptosis and reduces resistance to doxorubicin [166].

Chemotherapy may stimulate cancer cells' stemness and induce cancer stem cells' survival (CSCs). Several limited studies have been conducted to determine the effect of resveratrol in combination with chemotherapy on CSC survival and resistance. A study evaluated the effect of resveratrol and gemcitabine on pancreatic cancers, including MiaPaCa-2 and Panc-1, *in vitro* and *in vivo*. The results indicated that treatment with gemcitabine alone was associated with increased expression of cancer stemness markers, including SRY-Box transcription factor 2 (SOX2), octamer-binding transcription factor 4 (Oct4), and Nanog. Furthermore, gemcitabine induced the expression of sterol regulatory element-binding protein 1 (SREBP1), a key regulator of cancer stemness. Results showed that CSCs highly resist apoptosis following treatment with gemcitabine. However, inhibition of SREBP1 reduced the stemness of cancer cells and increased apoptosis following the administration of gemcitabine.

Intriguingly, resveratrol reversed the increased expression of SREBP1 following gemcitabine treatment, resulting in increased apoptosis and a significant decrease in cancer cell viability [167]. Another study showed that resveratrol sensitized CD133+ LoVo (human colon cancer) cells to 5-FU. These cells were resistant to 5-FU compared to other differentiated cancer cells. However, resveratrol could induce the expression of Bax in CSCs, leading to the stimulation and enhancement of apoptosis [168].

Resveratrol may enhance the antitumor effects of chemotherapy drugs by inhibiting angiogenesis when combined with chemotherapy. A synergic anti-angiogenesis effect of resveratrol and doxorubicin was demonstrated in an experiment. The study established the inhibitory effect of resveratrol at various concentrations and doxorubicin on the formation of new vessels and endothelial cell proliferation. Results also showed resveratrol's dose-dependent and synergic effect on suppressing angiogenesis [169]. The synergic anti-angiogenesis effect of resveratrol combined with gemcitabine and 5-FU has been demonstrated. These combinations reveal that resveratrol enhances chemotherapy drug-induced angiogenesis suppression by inhibiting COX-2, VEGF, and microvessel density [170, 171].

13. RESVERATROL COMBINED WITH TARGETED CANCER THERAPY

Some molecules within the tumor can attenuate tumor growth by inhibiting angiogenesis or proliferation of malignant cells. Herceptin is a well-known antitumor drug that has been shown to suppress the proliferation of HER2+ breast cancer cells. Receptor tyrosine kinase inhibitors (RTKIs) are intriguing drugs that can suppress tumor growth by inhibiting several signal transduction pathways involved in cancer cell growth. The inhibition of tyrosine kinases by RTKIs can facilitate apoptosis *via* the downregulation of anti-apoptosis genes such as PI3K and Akt [172]. Downregulation of EGFR and its downstream can reduce the expression of Bcl-2. Although ROS generation is not a key antitumor mechanism for RTKIs, some drugs, such as gefitinib, may stimulate ROS generation [173]. Since resveratrol can increase ROS production and modulate several other antitumor mechanisms, the combination of resveratrol and RTKIs may increase the efficacy of anticancer therapy.

A study showed a synergic effect of resveratrol and gefitinib on NSCLC cells. Gefitinib can suppress proliferation and cancer cells and induce apoptosis by inhibiting EGFR. The results indicated that gefitinib could induce apoptosis in cancer cells. However, when cells were treated with both resveratrol and gefitinib, cancer cells underwent different types of cell death. Resveratrol improved the induction of apoptosis by inducing the activity of p53. Furthermore, this combination amplified G2/M arrest and senescence in cancer cells [174]. Another study showed a synergic effect of erlotinib (EGFR inhibitor) on NSCLC, including A549, H460, H1975, and PC-9 cells. The results revealed that resveratrol

enhanced erlotinib's antitumor effect by inducing ROS and activating proapoptotic mediators such as p53 and PUMA.

In addition, a reduction in anti-apoptosis gene regulation, including survivin and Mcl-1, was observed [175]. A study investigated the antitumor effect of resveratrol and Herceptin in double-negative breast cancer cells, including T47D and MCF-7 cells. The findings suggested that this combination was more toxic to cancer cells than Herceptin alone. Furthermore, this combination caused significant induction of cell cycle arrest at the G2/M phase [176]. Nonetheless, additional research, particularly *in vivo*, is required to determine the synergic effect of resveratrol and RTKI in various tumor models.

14. RESVERATROL AND IMMUNE CHECKPOINTS

Immunotherapy aims to suppress tumor growth by improving the immune system's function. The most promising anticancer immunotherapy drugs are immune checkpoint inhibitors (ICIs). ICIs include antibodies and drugs that inhibit the expression of immune checkpoints such as CTLA4, PD-L1, programmed death 1 (PD-1), T cell immunoreceptor to Ig and ITIM domains (TIGIT), and others [177]. The PD-L1/PD-1 axis is the most well-characterized target for ICIs [178]. ICIs boost antitumor immunity, which leads to the release of antitumor cytokines, including IFN-γ and TNF-α. IFN-γ can stimulate the release of PD-L1 by cancer cells and other immune cells such as Tregs and DCs. Chronic release of IFN-γ is associated with the upregulation of PD-1 by antitumor immune cells, leading to the exhaustion of NK cells and cytotoxic CD8+ T lymphocytes [179]. Thus, inhibiting the PD-L1/PD-1 axis using other adjuvants can prolong antitumor immunity, enhancing therapeutic efficiency [180, 181].

Resveratrol has also been shown to target the PD-L1/PD-1 axis. Verdura *et al*. recently examined the modulatory effect of resveratrol (100 μM) on PD-L1 expression. They observed that resveratrol could inhibit glyco-PD-L1-processing enzymes directly in the JIMT-1 cell line (HER2+ and PD-L1 overexpressed breast cancer cells). The results showed that resveratrol disrupted N-glycan branching, which caused the dimerization of PD-L1. Resveratrol's effect disrupted PD-L1 stability and localization, impairing its engagement with PD-1 in T cells [182]. In contrast to this study, other experiments have shown that treatment with different concentrations of resveratrol causes upregulation of PD-L1 in the breast (following treatment with 5-20 μM), lung, and colorectal cancer cells (1-30 μM) [183, 184]. This aspect of resveratrol's action appears to require further investigation. These findings indicate that lower resveratrol concentrations may induce PD-L1 expression, whereas higher concentrations cause suppression. Additionally, the combination of ICIs and resveratrol should be evaluated independently for each type of tumor.

The PD-L1/PD-1 axis is recognized as a key mechanism of NK cell and CD8+ T lymphocyte exhaustion. In addition to the modulation of PD-L1 in cancer cells, resveratrol has been shown to inhibit the expression of PD-1 by CD4+ and CD8+ T lymphocytes [101]. Both PD-L1 and PD-1 are interesting targets for immunotherapy [185]. Inhibiting both can significantly enhance antitumor immunity [186]. Dual suppression of PD-L1 and PD-1 by resveratrol at appropriate concentrations may be an intriguing mechanism of resveratrol to stimulate the immune system when combined with other anticancer modalities such as immunotherapy and radiotherapy.

15. RESVERATROL COMBINED WITH HYPERTHERMIA

Hyperthermia is an anticancer modality that utilizes temperatures above the physiologically optimal level. Using a temperature range of 40-45 °C can result in the denaturation of enzymes and proteins within cancer cells, inducing various types of cell death [187]. Typically, hyperthermia is recommended in combination with chemotherapy and radiotherapy as an adjuvant therapy modality. However, using additional adjuvants, such as nanoparticles and herbal-derived agents, appears to improve hyperthermia's antitumor efficacy [188, 189]. The study examined how resveratrol could act as a sensitizer when combined with hyperthermia. The results showed that hyperthermia alone could induce necrosis and apoptosis in MCF-7 breast cancer cells. Treatment of MCF-7 cells with resveratrol prior to hyperthermia resulted in a potent 80% inhibition of cell viability. The results also revealed a significant synergic effect of resveratrol on the expression of Bax, caspase-8, caspase-9, and caspase-3. Additionally, cells treated with resveratrol prior to hyperthermia significantly reduced Bcl-2 gene expression. Moreover, the results suggested that when combined with hyperthermia, resveratrol may enhance necrosis and apoptosis [190].

16. CLINICAL IMPLICATIONS

Several epidemiological and clinical studies on the safety and efficacy of resveratrol in healthy individuals and cancer patients have been conducted to date. These studies suggest that resveratrol may be useful for preventing genomic instability and cancer and may be a promising candidate for enhancing the efficacy of anticancer therapy modalities. An epidemiological study investigated the risk of breast cancer among women with or without the dietary intake of resveratrol. This study enrolled 369 women on a resveratrol-containing diet and 602 women as controls. The findings revealed a 50% reduction in the risk of breast cancer in women who consumed grapes containing resveratrol over ten years [191]. This implies that resveratrol may reduce the risk of secondary cancer in patients undergoing radiation or chemotherapy for cancer. However, this issue requires clarification in future clinical trials.

Several limited clinical trials have been conducted to determine resveratrol's safety in cancer patients. A clinical study showed that administration of 5 g resveratrol/day for 14 days was associated with no significant side effects for patients with colorectal cancer [192]. In comparison, another clinical research found nephrotoxicity when resveratrol (5 g/day for three weeks) was administered in combination with chemotherapy to patients with multiple myeloma [193]. Alt-

hough nephrotoxicity due to chemotherapy was observed in this study, additional research is required to determine the safety of resveratrol alone or in combination with other anti-cancer drugs. These two clinical studies suggest that consideration should be given to the toxicity of other chemotherapy drugs that may impair the function of normal tissues when resveratrol is administered. Furthermore, administering resveratrol to patients undergoing radiotherapy, hyperthermia, or drugs with low kidney toxicity, such as ICIs and RTKIs, may be an intriguing approach.

CONCLUSION

According to this review, resveratrol may be used as an adjuvant in various cancer treatment modalities. The dual action of resveratrol on normal and tumor tissues is unique and intriguing. Resveratrol has been shown to reduce oxidative stress, DNA damage, cell death, and the release of several cytokines associated with the progression of chemo/radiotherapy side effects. The main protective mechanisms of resveratrol include the inhibition of pro-oxidant enzymes, stimulation of DNA repair and antioxidant defense enzymes, and suppression of inflammatory mediators. Resveratrol can induce multiple cell death mechanisms in cancer by stimulating several mechanisms. Resveratrol also boosts the immune system, which leads to a reduction in the resistance of tumors to therapy.

The inhibition of M2 macrophages and Tregs can reduce the release of immunosuppressive cytokines such as IL-10, IL-4, IL-13, and TGF-β. The reduction of these cytokines can improve antitumor immunity. These cytokines' inhibition in normal tissues can also ameliorate redox responses and suppress pro-oxidant enzymes. Resveratrol also can activate tumor suppressor genes, including PTEN and p53. These enzymes can induce DNA repair and prevent genomic instability. Activating p53 and PTEN in normal cells can reduce the accumulation of unrepaired DNA, preventing genomic instability. However, activation of tumor suppressor genes in tumors can induce apoptosis and senescence in cancer cells.

Resveratrol can also normalize the metabolism of cells *via* modulating mitochondria. In normal cells, it can prevent mitochondrial dysfunction; malignant cells may increase oxidative phosphorylation and ROS production. Overall, it appears resveratrol possesses intriguing properties for cancer therapy. However, it exhibits limitations in terms of clinical translation. Resveratrol's low bioavailability is a significant issue. The development of nanocarriers may aid in increasing resveratrol's bioavailability. Although preclinical studies have yielded intriguing results, additional clinical trials are necessary to determine the safe and effective doses for cancer patients. Resveratrol may also be absorbed in varying concentrations in tumors. This point should also be clarified in future clinical trials.

LIST OF ABBREVIATION

EndMT = Endothelial-to-mesenchymal transition

GSH = Glutathione

NSCLC = Non-small cell lung carcinoma

ROS = Reactive oxygen species

SOD = Superoxide dismutase

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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