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Review article

Nano Resveratrol and Its Anticancer Activity

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Abstract

Cancer is one of the leading causes of death in the world, and there are various treatments for cancer. Although most of them cause adverse side effects, plant-based phytochemicals are studied for their anticancer properties to overcome these limitations. Among these, resveratrol has shown a prominent anticancer activity against different types of cancers such as ovarian, colorectal, breast, and liver cancers. Despite its pharmacological activities, resveratrol possesses some physiological and pharmacokinetic limitations including low bioavailability and poor solubility, and several other factors, and these limit the usage of resveratrol as an anticancer agent. These limitations of resveratrol can be rectified with the help of nanotechnology whereby resveratrol is nanoformulated with various types of nanoparticles including polymers, liposomes, dendrimers, and metals, which have different nanostructures such as spears, rods, and nanoflowers. Some of these have shown promising effects against the proliferation and migration of various types of cancer when used at low drug concentrations. Scientists have also observed the synergistic effects of nanoformulated resveratrol with other components. In this review, we discuss nano resveratrol and its anticancer activity against various types of cancer.

1. Introduction

Cancer is the leading cause of death worldwide; around ten million people died in 2020 and 19.3 million new cases were reported [1]. Cancer is caused by various environmental factors that cause alteration in numerous biological processes, leading to DNA alteration and protein cross-linking and thus cancer cell formation [2, 3]. Multiple types of cancer treatment are carried out depending upon the type and stage of the disease, and included are chemotherapy, radiotherapy, immunotherapy, hormone therapy, and bone marrow transplantation. Bioactive natural components that are present in various fruits and vegetables were used in traditional medicine for decades due to their different

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therapeutic effects. In the 1940s, scientists first identified resveratrol (3,4-,5-trihydroxy-*trans*-stilbene) (Res) in white squash extract, and since that time onwards, it has been identified in various plants, such as grapes, Mexican bamboo, peanuts, raspberries, and so on. It is a type of phytoalexin, a naturally found phenol that various plants form due to injury response or pathogenic attacks by fungi or bacteria. Res plays a significant role in the protection of plants during stress-induced conditions. Res can be extracted from different parts of the plant such as fruit, seed, root, leaf, stem and flower, and is obtained from 34 families, including 100 species. When stress is induced, plants usually trigger the biosynthesis of Res [4]. Res is a phenol that has gained a lot of attention because of its potential therapeutic activities, such as antioxidant, anticancer, cardioprotective, anti-aging, anti-osteoporosis, anti-diabetic, anti-atherosclerosis, and anti-inflammatory properties [5, 6]. However, the clinical significance of Res has never been firmly established due to its low pharmacodynamics/ pharmacokinetics properties such as low aqueous solubility, poor bioavailability, rapid clearance from the systemic circulation, and chemical instability [7, 8]. To rectify these disadvantages, Res was nanoformulated, and its anticancer activity was studied (Figure 1). Nanotechnology is a field of science that deals with particles of smaller sizes ranging from 0.1-1000 nm. It is an emerging field of science that has applications in various areas such as dairy industries, diagnosis and so on [9-11]. Nanoparticles also have promising applications in medical fields, notably in environmental sustainability, biosensing, imaging, theranostics, and cancer, where various agents are used to stabilize the active agent and improve its bioavailability [12-15]. Scientists have nanoformulated various phytochemicals including kaempferol, curcumin, and Res, with various nanoparticles such as liposomes, micelles, metal nanoparticles, solid lipid nanoparticles, protein nanoparticles, and so on [16-20]. In this mini-review, we will be discussing nanoformulated Res and its recent studies of its applications in cancer treatments.

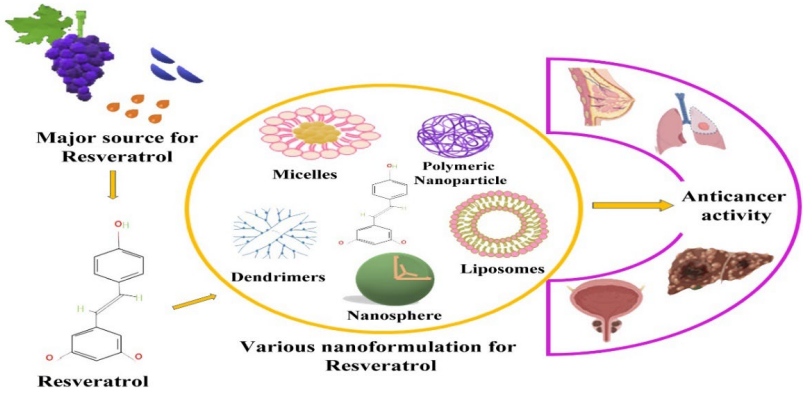

Figure 1. Nanoformulated resveratrol and its recent studies in different types of cancer

2. Anticancer Activity of Nanoformulated Resveratrol Against Different Types of Cancer

2.1 Breast cancer

Breast cancer is one of the cancer types that affect women and the second leading cancer which causes death, and around 2.5 million women are diagnosed with this cancer every year [21, 22]. Various nanoformulations with different drugs are studied for their anti-breast cancer activity [23].

Wang *et al*. [24] did a study on the anti-cancer activity of both free Res and solid lipid nanoformulated Res (Res-SLNs) on breast cancer cell lines (MDA-MB-231). In this research, they identified that the *in vitro* cytotoxicity of Res and Res-SLNs inhibited the growth of cells in a dose and time-dependent manner. The IC_{50} value of Res was 72.06±7.85 µg/ml, and for Res-SLNs the value was 40.82±3.92 µg/ml. The results indicated that Res-SLNs had a higher cell cytotoxicity effect in comparison to free Res. The percentage of apoptotic cells present in three groups, namely, control, Res, and Res-SLNs was 5.72%, 19.2%, and 25.6%, respectively, which showed that Res-SLNs had more potential for apoptosis induction. Res-SLNs have also been shown to inhibit cell proliferation at the G_0/G_1 phase, and the percentage of cells arrested in this phase was 25.5±1.38% for Res-SLNs, and for free Res, it was 19.2±0.68%. Bcl-2 and cyclin D1 were also inhibited in MDA-MB-231 after the treatment with Res-SLNs. This study proved that Res-SLNs have the ability to inhibit the growth of MDA-MB-231 at a higher rate when compared to free Res [24]. A group of scientists did another study to improve the targeting ability of Res on breast cancer cells. It was done by encapsulation of Res in Pluronic F127 block copolymer with the help of Vitamin E-TPGS, which was an emulsifier. Another similar nanoencapsulation was also done with coumarin-6, a fluorescent dye used for monitoring drug release at the tumor site, and the treatment capacity of the coumarin-6 loaded nanocomposite. In this study, they used coumarin-6 to identify the amount of drug uptake by the cells after treatment. They used three types of cell lines which were MDA-MB-231 and MCF-7 (invasive breast carcinoma cell line) and MCF-10A (non-malignant immortalized breast cells). The maximum mean of fluorescence intensity (Y_0) released by coumarin-6 in each type of cell line and time constant (τ) after treatment were found to be 27,300 (a.u) and 11 min for MDA-MB-231, 9,618 (a.u) and 46 min for MCF-7 and, 8,748 (a.u) and 140 min for MCF-10A, respectively. This observation indicated that the nanoformulation targeted the invasive cells where the fluorescent intensity was higher than free Res. They observed the cell viability of MCF-7, MDA-MB-231, MCF-10A after treatment with nano-Res in MCF-10A normal cells, which did not show any effect after treatment, whereas the MDA-MB-231 cell viability decreased by up to 39.8%, 14.0%, 7.1%, and in MCF-7 cells, where the viability was reduced by up to 58.7%, 37.9%, 20.7% post 24 h, 48 h, 72 h treatment with nano-Res (2.5 µg/ml), respectively. This study showed that the nano-Res could inhibit the growth of breast cancer cell lines and that nano-Res did not have any effect on normal cells [25]. Gadag *et al*. [26] developed a nanostructured lipid carrier loaded with Res (Res-NLCs) that was administered via a microneedle for localized delivery of the drug for breast cancer therapy. The *in vitro* studies were done in the MDA-MB-231 breast cancer cell line, and the cytotoxicity of Res-NLCs and Res resulted in the IC_{50} of 27.50±3.43 µg/ml and 33.93±7.34 µg/ml, respectively. The results showed that the Res-NLCs had less cytotoxicity compared to free Res and the cells treated with placebo NLCs did not show any effect on cells taken as control. They also observed that Res-NLCs could inhibit cell migration which was observed up to 24 h after treatment. The activities of Res, Res-NLCs-1 (administered orally), and Res-NLCs-2 (microneedle) were observed in female Sprague Dawley rats for tissue and plasma distribution of the drug. The peak plasma concentration (Cmax) was 1251.02±93.34 ng/ml at 0.25±0.07 h for Res-NLCs-1, whereas in Res-NLCs-2, the Cmax was 343.75±31.89 ng/ml at 2 h. Twenty-four hours post-administration, and the drug concentration of Res in plasma was hardly detected in the case of Res-NLCs-1. In contrast, in Res-NLCs-2 the amount of Res was found to be of reasonable quantity [26]. Scientists have also studied the synergistic effect of Tamoxifen (Tam) and Res; Tam is a well-known chemotherapeutic agent for breast cancer treatment. They loaded Tam in a solid self-nano emulsifying drug delivery system (s-SNEDDS) along with Res (Tam-Res-s-SNEDDS), and a nanosuspension was also prepared using the conventional method with Tam and Res (Tam-Res-suspension). These nanoformulations were tested for their stability, *in vitro* anticancer activity, and bioavailability of the plasma of healthy Wistar rats. The study's outcome showed that the optimal size of the droplet of Tam-Res- s-SNEDDS was 200 nm, and the percentage of drug release was found to be 85% after 750 min for the Tam-Res-s-SNEDDS, which was significantly higher when compared to Tam-Res-

suspension. In the cytotoxicity studies on MCF-7 cells treated with Tam-Res-s-SNEDDS and Tam-Res-suspension, the IC_{50} values were found to be 4.311 µg/mL and 3.224 µg/mL for Tam-Res-s-SNEDDS and Tam-Res-suspension, respectively. The oral bioavailability of Tam-Res-s-SNEDDS and Tam-Res-suspension was studied in healthy Wistar rats and the maximum concentrations (C_{max}) of Tam and Res increased up to 4.16- and 3.64-fold in Tam-Res-s-SNEDDS when compared to the suspension. These observations confirmed that s-SNEDDS could be used as an efficient nanoformulation to improve the bioavailability of the Tam and Res in combination [27]. To improve the drug's targeted delivery and increase the bioavailability of Res in cancer sites, Antoniraj *et al*. [28] created a redox-responsive Res-loaded nanocarrier (Res-NC) with stearic acid-disulfide-methoxy poly (SA-SS-mPEG). The amount of Res released in the presence of glutathione was at two different pH, 5.0 and 7.4, and the percentages of drug release were found to be 89.23±1.03% and 79.83±1.15% in 6 h, respectively; whereas the free Res release was 47.22 ± 1.18% and 59.67 ± 0.78% at 18 h, respectively. They confirmed the biocompatibility of Res-NC using hemolytic assay, and it was found to be safe up to a concentration of 200 µg/mL. The anticancer activity of Res was also improved when it was used on the breast cancer cell line MDA-MB-231; the percentage of cell viability was found to decrease by 10% at a higher concentration of 50 µg/mL of Res-NC, whereas in free Res the percentage of cell viability was 50 % when compared to control. In this study, it was observed that the redox responsive Res loaded nanocarrier had the ability to inhibit the growth of the cancer cells and also improved the availability of Res at the targeted site [28]. Various other nanoformulations of Res have been shown to inhibit breast cancer and are listed in Table 1. There are numerous studies on the anticancer activity of nanoformulated Res with different types of nanoparticles such as lipids, gold, silver and polymers. They have been found to decrease the growth of breast cancer cell lines and animals bearing breast cancer.

Table 1. Various resveratrol nanoformulations and their anticancer activity

S.no	Nanoparticle	Model used	Observation	Reference
1.	Phospholipid coated with reduced graphene oxide nano assembly	MCF-7 breast cancer cell line and male athymic *Balb/c* mice	The nanoformulation of Res with this component has shown to deliver the drug at a specific site, and controlled drug release was also observed. It also inhibited the growth of tumours in an animal model.	[29]
2.	Shell-crosslinked zein nanocapsules	MCF-7 and 4T1 breast cancer cell line and female Sprague Dawley rats	The combination of Res and exemestane (Exm) was shown to enhance the cytotoxicity against the MCF-7 and 4T1 breast cancer cells, and it also reduced the tumor volume in an *in vivo* study up to 2.4-fold compared to the free drug.	[30]
3.	Oxidized mesoporous carbon nanoparticles (oMCNs)	Triple-negative breast cancer (TNBC) cells	oMCNs-Res promoted cellular cytotoxicity and apoptosis mediated via caspase-3 cleavage and PARP protein.	[31]
4.	Bilayer-enveloped casein micelles	MCF-7 cells and female *Balb/c* mice	Cytotoxicity studies confirmed the superiority of multi-reservoir nanocarriers against MCF-7 breast cancer cells. The *in vivo* antitumor efficacy was revealed by the reduction of the tumor volume and growth biomarkers.	[32]

Table 1. Various resveratrol nanoformulations and their anticancer activity (continued)

S.no	Nanoparticle	Model used	Observation	Reference
5.	α-tocopherol self-nanoemulsifying drug delivery system (SNEDDS) loaded with Res and coenzyme Q10 (, α-TOH-RES-CoQ10-SNEDDS)	Caco-2 cells and female Sprague Dawley rats	The cellular uptake of coumarin-6 loaded in SNEDDS was higher compared to free coumarin-6 in Caco-2 cells, and the size of the tumor was reduced up to 3.64 folds after treatment with α-TOH-RES-CoQ10-SNEDDS compared to control.	[33]
6.	BSA and Chitosan (CS) polymer nanoparticle	MCF-7 and HUVEC cell lines	The cellular uptake of Res nanoformulation (Res-BSA/CS) was 1.5 times higher than Res loaded in CS (Res-CS). The cytotoxicity was 3 times higher than free Res in MTT assay.	[34]
7.	solid lipid (stearic acid) and liquid lipid (oleic acid) Nanostructure lipid carriers (NLCs) and folic acid modified NLCs	MCF-7 and A549 cell lines and female Wistar rats	The Res encapsulated NLCs (Res-NLCs) were modified with folic acid (Res-FA-NLCs) to improve their specificity. There was increased cytotoxicity in MFC-7 cells for Res-FA-NLCs compared to Res- NLCs. There was a 9-fold increase in tumor growth inhibition in female Wistar rats post Res-FA-NLCs treatment compared to Res-NLCs.	[35]
8.	Gold nanoparticles	MDAMB-231 (breast cancer), PANC-1 (pancreatic cancer), and PC-3 (prostate cancer) cell lines	Res corona around the AuNP was increased (3x Res-AuNP and 1x Res-AuNP). 3X Res-AuNP showed high anticancer activity compared to 1x Res-AuNP.	[36]
9.	peptide-cationic lipid (CDO14) liposome	Hela (Cervical cancer) and MCF-7 cell lines	The Res liposome nanoformulation (Res-lipo) was tagged with p53 gene (Res-lipo-p53), and its transfection efficiency, cell cytotoxicity, and induction of apoptosis were higher in cells treated with Res-lip-p53 when compared to Res-lipo.	[37]
10.	peptide and sucrose liposome (PSL)	MCF-7 and male *Balb/c* nude mice bearing tumor	Res PSL nanoformulation was shown to inhibit cancer growth in both in *vitro* and *in vivo* study in low doses compared to free Res. It also promoted apoptosis via inhibiting p53 upregulation, downregulation of Bcl-2, and upregulation of Bax proteins.	[38]

2.2 Prostate cancer

The occurrence of prostate cancer has been increasing worldwide in recent years. It is the fifth leading cause of mortality in men throughout the globe and the second most common cancer detected in major populations in the United States. A total of 1,414,259 new cases were reported in 2020; among them, the deaths were 375,304 in the United States [39]. Nassir *et al*. [40] formulated a polymeric nanoparticle encapsulated with Res (Res-PLGA) that inhibited the growth of prostate cancer cell line (LNCaP) with IC_{50} and IC_{90} values of 15.6±1.49 mM and 41.1±2.19 mM for Res-PLGA, respectively, which were much lower than the free drug. The IC_{50} and IC_{90} values for free Res were 29.7 mM and 77.2 mM, respectively, which were two-fold higher than Res-PLGA. The cellular cytotoxicity was also found to increase in the case of Res-PLGA treated against LNCaP. They also observed that the Res-PLGA induced apoptosis, and the percent of apoptotic cells were 65.60±3.25% for Res-PLGA, whereas in the case of Res it was 39.79±1.33%. The apoptotic factors such as caspase -3 and ROS generation were also shown to be elevated in the sample treated with Res-PLGA. This study concluded that the Res-PLGA could act as a superior anticancer agent against LNCaP [40]. Another group of scientists developed two types of modified mesoporous silica nanoparticles (MSNs) loaded with Res, namely- phosphonate modified MSNs (Res-PO3-MSN) and amine-modified MSNs (Res-NH2-MSN). Their drug release ability was studied at two different pHs (7.4 and 5.5), and the amount of drug released at pH 7.4 was 100% in both the free drug and Res-NH2-MSN, whereas Res-PO3-MSN showed a controlled drug release which reached 65% after 24 h. At the low pH of 5.5, Res-NH2-MSN showed 40% drug release, and Res-PO3-MSN showed 60% release after 24 h. *In vitro* studies were done in the prostate cancer cell line PC3, where the IC_{50} value was 14.86 µM for free Res at 72 h, whereas for Res-PO3-MSN, the IC_{50} value was 7.15 µM after 72 h treatment, which was a two-fold reduction in IC_{50} value compared to free Res. They also studied the synergistic effect of Docatexal (Doc) with Res-PO3-MSN in hypoxia-induced Doc-resistant PC3 cells. The viability was shown to be decreased at lower doses of Doc (0.1-10 nM) with 10 µM of Res. On the other hand, free Res and Res-PO3-MSN did not significantly affect hypoxia-induced Doc-resistant PC3 cells [41]. Nanoformulation of Res with polymeric and mesoporous silica nanoparticles was shown to inhibit the growth of prostate cancer cell lines LNCaP and PC3. Polymeric nanoformulation of Res resulted in induction of apoptosis in LNCaP, and furthermore, silica-based nanoparticles combined with Res were used against drug-resistant pancreatic cell line PC3 [40, 41].

2.3 Lung cancer

Lung cancer is the leading cause of global cancer incidence and mortality, accounting for an estimated 2 million diagnoses and 1.8 million deaths. Neoplasms of the lungs are the second most common cancer diagnosis in men and women. Men are twice as likely to be diagnosed with lung cancer, which largely reflects differences in tobacco consumption. Tobacco smoking is the greatest preventable cause of death worldwide, accounting for up to 90% of lung cancer cases, and continued consumption is projected to increase global cancer incidence, particularly in developing nations such as China, Russia, and India [42]. Karthikeyan *et al*. [43] studied the anticancer efficacy of Res in gelatin nanoparticles (GNPs) in NCI-H460 lung cancer cells. The *in vitro* drug release of Res-GNP at various pH such as 1.4, 7.4 and 10.5 at 12 h was found to be 28.1%, 40.6% and 32.5%, respectively, and after 24 h the drug release reached up to 63.7%, 80.2% and 69.9%, respectively. *In vitro* cytotoxicity test was performed by MTT assay for Res and Res-GNP at different concentrations, such as 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 µg/ml in NCI-H460 lung cancer cells. The IC_{50} was found to be 10 µg/ml for Res alone, and for Res-GNPs, it was five µg/ml. Thus, Res-GNPs showed significant cytotoxicity compared to Res, and the percentage of apoptotic cells seemed to be higher in Res-GNP (98%) compared to free Res (42%). They also observed a reduction

of mitochondrial membrane potential in Res-GNP, and they further observed enhanced tail length percentage in Res-GNPs treatment on NCI-H460 cell line. Pharmacokinetics observation in mice showed that the level of Res in serum was twice in Res-GNPs when compared to the free Res treated group. This study indicates that GNPs nanoformulation of Res had effective anticancer activity against NCI-H460 lung cancer cells and improved the availability of Res in male *Swiss albino mice* [43]. Song *et al*. [44] studied epidermal growth factor (EGF) conjugated lipid polymer hybrid nanoparticles (LPNs) that were fabricated to deliver docetaxel (DTX) and Res, which was one of the promising strategies for non-small cell lung cancer cell line (NSCLC). *In vitro* cytotoxicity assay was performed in NCIH2135 cells and HCC827 cells in which a significant tumor cell inhibition took place in EGF DTX/Res LPNs than DTX/Res LPNs. The IC_{50} DTX/Res LPNs were <1, and the Fa values were between 0.2-0.8, indicating synergistic effects. In *in vivo* study of lung tumor-bearing, *Balb/c* nude mice after treatment, the mice treated with EGF DTX/Res LPNs showed maximum size reduction compared to other treatments. This observation indicates that the EGF DTX/Res LPNs have the ability to inhibit the growth of lung cancer in both *in vitro* and *in vivo* models [44]. Aldawsari *et al*. [45] studied chitosan (CS)-coated PLGA nanoparticles of Res against the H1299 lung carcinoma cell line. CS coating enhanced the Res-loaded PLGA nanoparticles in comparison to free Res. In free Res, the IC_{50} was found to be 57.31±2.3 µg/ml, and in Res-PLGA NPs, it was 49.51±1.06 µg/ml, whereas CS coated Res-PLGA NPs showed an IC_{50} value of 34.99±1.51 µg/ml. Res and CS coated Res-PLGA NPs were shown to induce apoptosis in H1299 cells, and the percentages of apoptotic cells were found to be 56.65% and 83.65% in Res, and CS coated Res-PLGA NPs, respectively. They also observed an increase in Bax level and downregulation of Bcl-2. Thus, enhanced cytotoxicity and induction of apoptosis were more prominent in CS-coated Res-PLGA NPs compared to free Res [45]. To improve Res's solubility and anticancer effect, Kamel *et al*. [46] used nanoformulated Res with self-assembling lectin-based nanocarriers doped with chitosan (LP5). The size of the nanoparticles was 59 nm, and they were spherical in shape. The nanoformulation and free Res were tested for their anticancer activity in lung cancer cell line A549, and the IC_{50} values were found to be 1.708 µg/ml and 2.200 µg/ml for LP5 and free Res, respectively. LP5 induced apoptosis in 73.1% of cells, and drug uptake was increased up to 40000 folds after 24h treatment. This study indicated that the nanoformulation of Res with lectin-based nanocarrier increased its availability, stability, anticancer activity and induction of apoptosis in lung cancer cell line [46]. These recent studies on nanoformulation of Res with different NPs and nanoformulation methods have improved its targeting ability and its availability at tumor sites in a lung cancer models.

2.4 Colorectal cancer

Colorectal cancer is rated to be the second most common cancer that causes death worldwide and the third in cancers that cause malignancy. In the year 2020, new cases of colorectal cancer were found to be 1.9 million, and total deaths were 0.9 million globally. The global new case prediction for colorectal cancer predicted is about 3.2 million new cases by year 2040. Even though the treatment for colorectal cancer have generally been good, the increase in the number of cases in the younger generation due to constant changes in food habits has increased the global burden for colorectal cancer [47]. Feng *et al.* [48] studied the anticancer activity of Res loaded in lipid core nanocapsules. The nanoencapsulated Res was prepared by precipitation method, and the average size of the nanoformulation was 159 nm, and the drug release percentage was 70% after 48 h. The anticancer activities of the nanoformulated Res and free Res were studied against colorectal cancer cell line HT29, and the IC_{50} value of free Res was 50 µg/ml, whereas for free Res it was 40 µg/ml. The cytotoxicity study showed that nanoformulated Res inhibited the growth of HT29 cells based on a dose and time-dependent manner. They also observed that the percentage of cells undergoing

apoptosis was 36% in nanoformulated Res treated cells, which was higher than it was for free Res, which was 15% after 24 h treatments. This study showed that the nanoformulated Res had higher anticancer activity when compared to free Res against colon cancer cell line HT29 [48]. Kuo *et al.* [49] studied the anticancer activity of curcumin and Res nanocomposite in mice colorectal cancer cell line CT26 along with modulated electronic hyperthermia treatment (mEHT). The nanocomposite of curcumin and Res was prepared using physical grinding in the presence of reverse osmosis water and the diameter of formulated nanocomposite was approximately 320 nm. The cancer cell viability was done in CT26 cells in the presence of curcumin, resveratrol, and nanocomposite of curcumin and Res, and the IC_{50} values were found to be 160 µM, 200 µM, and 26.76 µM, respectively. The antiproliferative effect of nanocomposite via cell cycle arrest analysis was also found. The cycle arrest ratio in the G0/G1 phase was 45.3±3.45%, which was significantly lower compared to the control (54.23±0.46%). They also observed the reduction of cyclin D1 and cycle A in CT26 cells after treatment with curcumin and Res nanocomposite. The combined therapy of mEHT with curcumin and Res nanocomposite induced apoptosis in CT26 to a greater extent at 42°C in the mEHT group compared to other temperature-treated groups (30°C, 37°C). They also did *in vivo* analysis of tumor regression in colorectal cancer-induced *Bacl/c* mice, after 14 days of treatment with mEHT and curcumin and Res nanocomposite. A reduction in tumor growth was observed in the treatment group which was significantly higher in comparison to that of the control. This study showed that the mEHT with curcumin and Res nanocomposite had a synergistic effect on CT26 tumor inhibition [49]. The researchers identified that Res coated on lipid core nanocapsules and nanocomposites consisting of curcumin could inhibit the growth of colorectal cancer cell lines. They also found that the nanocomposites could reduce colorectal tumors in mice and inhibit cell growth, thereby inducing apoptosis in the CT26 cell line [48, 49].

2.5 Oral cancer

Oral cancer is most commonly due to a range of infectious agents that can be present in the oral cavity, such as human papillomavirus, *F. Nucleatum*, and so on. Approximately 2% of the human population is affected by oral cancer worldwide [50]. The progression of this cancer is associated with inflammation through various cytokines. Pradhan *et al*. [51] created a polymer-based Res nanoparticle (Res-NPs) using solvent evaporation technique and the size of the spherical shape nanoparticles ranged from 50-100 nm. They studied the anticancer and anti-inflammatory activities of Res and Res-NPs in a cytokine-enriched population of niche cancer cells (CSCs) containing oral cancer cell line H-357 and THP-1 cells. The enrichment of cytokines and macrophages in the cells was done with the help of external stimuli PMA and LPS, which exhibited an increase in cell growth compared to the control and elevation of cytokine markers (TNF-α, IL-6, IL-1β, iNOS, TGF-β, IL-10). Macrophage markers (CD14, CD68, and CD163) were also observed. The cell viability was found to be 110% after treatment with the combination of external stimuli after 96 h of incubation. This CSCs cell viability was found to have decreased up to 25% after treatment with Res-NPs at the concentration of 5 µg/ml, and it also decreased the invasiveness of CSCs cells to 3.6-fold. The level of stemness, and cytokine markers were found to have decreased by more than 8.6-folds after treatment. The anti-angiogenic properties of Res-NPs were also observed in the CAM model, and the formation of the blood vessel was decreased by 3.5-fold at the treatment concentration of 5 µg/ml Res-NPs. There was downregulation of major angiogenic proteins up to 1.4-fold. They also studied the activity of Res-NPs in a mice model, which was implanted with CSCs cells for 25 days, and an increase in tumor volume was observed. Then treatment with Res-NPs showed a significant decrease in tumor growth, and depletion of tumor markers was also found in the tissue sample. This study identified that Res-NPs could inhibit the growth of oral cancer via downregulation of inflammatory cytokines by targeting macrophages associated with tumor growth [51].

2.6 Liver cancer

Liver cancer is also one of the cancers that cause death worldwide, most notably in Asia, but also in the southern and eastern parts of Asia. Over the past 5 years, the overall survival rate was 60%. There have been various therapeutic strategies employed for liver cancer, but the most common treatment was chemotherapy [52]. Most chemotherapeutic agents show various limitations and side effects. Wu *et al.* [53] nanoencapsulated Res in glycyrrhizin acid conjugated with human serum albumin (GLA-HSA-RES-NPs) using high-pressure homogenization emulsification method. The average size of the nanoemulsion particles was 108.1±5.3 nm, and the sustained release of Res 73.8% at 15 h was also observed from the GLA-HSA-RES-NPs. *In vitro* anticancer activity of GLA-HSA-RES-NPs and free Res was observed in HepG2 cells, and the IC_{50} values were found to be 62.5 µg/ml for GLA-HSA-RES-NPs and 96.5 µg/ml for free Res. They also studied the targeted release of drugs at the tumor site *in vivo* mice model (KM mice bearing liver cancer and normal mice). They injected GLA-HAS in RES-NPs at the tail vein, and after 12h post-injection, accumulation of Res in the liver region was observed up to 48 h in both groups of mice, which disappeared after 48 h in healthy mice.

On the other hand, in the liver of mice bearing H22 cancer cells, drug accumulation was observed till 72 h post-injection. From this study, it was observed that the GLA-HSA-RES-NPs exhibited enhanced cancer inhibition activity compared to free Res and superior targeting ability for the treatment of liver cancer [53]. Zhang *et al.* [54] used the green syntheses method, loaded Res in gold nanoparticles (Res-GNPs), and the average size of the nanoparticles prepared was 39 nm. They studied the cytotoxic activity of Res-GNPs and free Res against liver cancer cell line HepG2, and the IC_{50} values for Res-GNPs and free Res were 3.84 µg/ml and 24.74 µg/ml, respectively. The percentage of apoptosis induction in HepG2 cells after 24 h treatment of Res-GNPs and free Res was 11.2% and 7.24%, respectively. An *in vivo* tumor growth model (BALC/c nude mice) bearing liver tumor was used, and 57.2% of tumor growth reduction was observed in the Res-GNPs group, whereas in free Res it was 35.5%. This study inferred that the Res-GNPs could inhibit cell proliferation and induce apoptosis in HepG2 cells effectively compared to free Res in both *in vivo* and *in vitro* models [54]. From these studies, scientists have identified that the nanoformulation of Res has a prominent activity in inhibiting the growth of liver cancer in both *in vitro* and *in vivo* models.

2.7 Ovarian cancer

Ovarian cancer is the seventh most cause of death worldwide, and due to this cancer, there has been only a 30% survival rate in the past 5 years [55]. As we previously mentioned, there are no available target-specific drugs for the treatment of ovarian cancer, and there is a need for more studies on target-specific drug delivery of chemotherapeutic agents that can be achieved by nanotechnology. Nam *et al.* [56] formulated a nanocomposite with Res and ethanolic extract of *Angelica gigad Nakai* (AGN) (AGN/Res NPs) using the solvent evaporation method and studied its anticancer activity in ovarian cancer cell SKOV-3. The particle sizes of the AGN-NPs and AGN/Res NPs were 221±15 nm and 224±32 nm, respectively. The drug release percentages after 24 h were found to be 35.44±2.29% and 38.90±10.10% for AGN-NPs and AGN/Res NPs, respectively. The cellular uptake of AGN/Res NPs was found to be 4.85-fold higher compared to AGN-NPs after 1h of treatment. The IC_{50} values of AGN-NPs and AGN/Res NPs on inhibiting the proliferation of SKOV-3 cells were 60.0±3.9 µg/mL and 38.5±2.1 µg/mL, respectively. This study shows that the AGN/Res NPs have superior anticancer activity against ovarian cancer cell lines compared to AGN NPs, free Res [56].

2.8 Skin cancer

From the recent epidemiological data, about 5.4 million cases of skin cancer were detected globally. In the Caucasian population, skin cancer is the most common form of cancer diagnosed. The highest diagnosis of skin cancer was recorded in the year 2018 in Australia, and in that country 300 people out of 1,000,000 people were affected [57]. Arora and Parkash [58] synthesized nano Res loaded in calcium phosphate nanoparticles (Cpa-Res NPs), and the particle size of the Cpa-Res NPs ranged between 15-35 nm and with an average diameter of 20 nm. The cytotoxicity activity of Cpa-Res NPs, free Res, and 5- fluorouracil (5-fu) was studied in B16 melanoma cells (skin cancer) using propidium iodide stain, and from the observations, it was found that Cpa-Res NPs elicited higher cytotoxicity towards B16 cells compared to other groups. DNA condensation was also observed in the cells treated with Cpa-Res NPs, and a DNA ladder was observed in the Cpa-Res NPs, and the 5-FU treated group. This study confirmed that the Cpa-Res NPs can induce apoptosis and have remarkable anticancer activity in the B16 melanoma cell line [58]. The same group of scientists studied the anticancer activity of Cpa-Res NPs and their anti-inflammatory activity on a mouse skin cancer model. The skin cancer was induced in Swiss albino mice with the help of 7, 12-dimethylbenz[a]anthracene (DMBA)-induced/12-Otetradecanoylphorbol-13-acetate (TPA). They divided the animals into 5 groups based on the treatment of drug such as vehicle control (Cpa), TPA treatment, TPA+ Res (Res:10µg/ml), TPA+ Cpa-Res NPs1 (Res: 0.5 µg/ml) and TPA+ Cpa-Res NPs2 (Res: 1µg/ml). They identified that the percentage of inhibition of skin edema in the TPA+ Cpa-Res NPs2 group was 94.34% which was higher than in other groups. In TPA+ Cpa-Res NPs1 and TPA+ Res, the skin edema was 78.3% and 59.4% after 18 weeks of treatment, respectively. They also observed that Cpa-Res NPs could prevent other processes such as ODC activity, and oxidative stress, which might lead to carcinogenesis. From this study, the researchers showed that Cpa-Res NPs could inhibit the development of skin cancer in the *in vivo* model that involved causation by chemical exposure [59]. To increase the stability and effective delivery of Res, Yee *et al*. [60] chemically modified Res by conjugating it with a low-weight co-polymer and nanoformulated it with mPEG-PLA (Conjugated-Res-NPs). Free Res was also nonencapsulated (Free-Res-NPs) to study the effect of chemical modification of Res. The Conjugated-Res-NPs were found to be more stable in the plasma in *in vitro* studies, and the cytotoxicity of Conjugated-Res-NPs had less effect on B16-F10 cancer cells compared to Free-Res-NPs. The *in vivo* studies were done on C5BL/6J mouse model injected with B16-F10 melanoma and the results showed that the metabolism rate of Res in the liver in mice treated with Conjugated-Res-NPs was altered, and the tumor reduction was also most prominent in the Conjugated-Res-NPs treated group [60]. Scientists nanoformulated Res with calcium phosphate, and this nanoformulation inhibited the growth of B16 cells by induction of apoptosis in *in vitro*. This nanoformulation was also found to reduce skin edema. Chemical modification of Res was done with copolymers and its subsequent nanoformulation was shown to increase stability, and also to reduce skin edema in the mice model [58-60].

2.9 Pancreatic cancer

Among all the cancer types, pancreatic cancer is found to be the 14th most common cancer and the 7th most common cancer that causes mortality in humans. Due to the increasing number of detections of pancreatic cancer, scientists have predicted that it may rise to the 2nd most occurring cancer in the United States by the year 2030 [61]. Geng *et al.* [62] formulated three different types of nanocomposites with human serum albumin (HSA) and Res, i.e. HSA-RES NPs, HRP–RGD NPs (HAS and Res functionalized with the tumor-targeting molecule, arginine–glycine–aspartate (RGD) via a PEG), and HRP–RGD NPs-RGD blocked. The particle sizes of the nanoformulations ranged

from 113±3.1 nm to 120±2.6 nm, and in HRP–RGD NPs, the drug release percentage was found to be 58.4.2±2.8% after 60 h. The HRP–RGD NPs and free Res biocompatibility were studied using a hemolysis assay. The stability of HRP–RGD NPs was found to be 96.8% after the 4th week, whereas the free Res compatibility decreased gradually from the 1st week to the 4th week from 100% to 12.1%. The cellular uptakes of HSA-RES NPs, HRP–RGD NPs, and HRP–RGD NPs-RGD blocked were 16.2±4.9%, 58.5±3.5%, and 7.1±5.1% in pancreatic cancer cells PANC-1, respectively. The percentages of cell viability were approximately 20%, 40%, and 50% at the concentration of 50 µg/ml for each group of HRP–RGD NPs, HSA-RES NPs, and free Res, respectively. *In vivo* study was done on tumor xenograft model mice (*Balb/c* nude mice) with pancreatic cancer. After treatment with the same concentration of HSA-RES NPs and HRP–RGD NPs, tumor regression was found to be higher in HRP–RGD NPs compared to HSA-RES NPs and control. From this study, the researchers identified that the functionalized nanoformulation of Res with HSA had a higher growth inhibition capacity for pancreatic cancer cells in both *in vivo* and *in vitro* models [62].

3. Conclusions

Resveratrol is a polyphenolic compound, and many researchers have found that it has antioxidant activities. Scientists have nanoformulated Res with different types of nanoparticles using various methods. Various types of nanoparticles were used for nanoformulation of Res including chitosan, lipids alginate, glycosine, calcium phosphate, gold, silver and different types of nanocomposites. When the nanocomposite was synthesized with other anticancer drugs such as curcumin and herbal extract of *Angelica gigad Nakai,* the average particle size of the nanoformulations of Res was found to be in the range of 10- 250 nm. The nano Res has shown a prominent anticancer activity against different types of cancer cell lines and cancer models such as breast, lung, prostate, and pancreatic cancer. The Res and nano-formulated Res were shown to inhibit the growth of different cancer cell lines by induction of apoptosis. For example, nanoformulation with gelatin induced about 98% apoptosis in lung cancer cell line NCI-H460. Further, the reduction of anti-apoptotic BCL-2 reduction was identified, and pro-apoptotic protein Bax upregulation was also observed. Nanoformulation of Res improved various properties of it, including its stability, bioavailability, targeted drug delivery, and minimized toxicity which in turn improvd the drug availability and drug circulation, causing more cancer cell death and tumor reduction in the animal models. There have been few recent studies of various nanoformulations of Res for some cancer types such as pancreatic, skin, and ovarian cancer. The role of nanoformulated Res needs to be explored in other cancer models in the future. Nanostructures are also known to exert toxicity in various cell lines and *in vivo* models. Thus, an important goal of future research will be to design a Res nanoformulation that is non-toxic to animals but can exert superior anti-cancer activities.

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