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Review Article

Emerging Trends in the Delivery of Resveratrol by Nanostructures: Applications of Nanotechnology in Life Sciences

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Resveratrol (RES) is a stilbene group of natural polyphenolic compounds in trees, peanuts, and grapes. RES is revealed with anticancer, antioxidant, anti-inflammatory, and cardioprotective effects. Though it is proven with prominent therapeutic activity, low aqueous solubility, poor bioavailability, and short half-life had hindered its use to exploit the potential. Also, the first-pass metabolism and undergoing enterohepatic recirculation are obscure in the minds of researchers for their in vitro studies. Many approaches have been investigated and shown promising results in manipulating their physicochemical properties to break this barrier. Nanocarriers are one of them to reduce the first-pass metabolism and to overcome other hurdles. This article reviews and highlights such encapsulation technologies. Nanoencapsulated RES improves in vitro antioxidant effect, and this review also highlights the new strategies and the concept behind how resveratrol can be handled and implemented with better therapeutic efficacy.

1. Introduction

Many molecules had been derived from natural sources and had shown a prominent presence in the medical field. They either act directly or are modified as congeners for the synthetic molecules. The stilbenes are one of those plant-derived molecules that belong to the nonflavonoid class of polyphenols [1]. Chemically, they are 1,2-diarylethenes having two aromatic rings connected by the -C=C- bond. Due to the presence of a styrene double bond, they have two configurations: planar trans or cis [2]. They are the phytoalexins that are used by plants against the foreign invasion of pathogens. They are produced by plants under stress conditions and are synthesized via the phenylpropanoid pathway [3]. In plants, they occur either in methoxylated or oligomeric form. Various stilbenes are reported in nature, such as resveratrol (RES), piceatannol, and 3,5,4-trihydroxystilbene. Resveratrol has been isolated from more than 70 plant

species and is distributed widely in genera and plant families. Its presence in red wine and grapes is reported to lower the incidences of coronary heart diseases [4]. Its presence in grapes is widely influenced by the environmental growing conditions of the plant. In low concentrations, other molecules are also found in grapes, such as astringin and isorhapontin [5].

To boost the bioavailability and cellular uptake of RES, many approaches have been tried and implemented, such as using prodrug- and nanotechnology-based approaches. The nanocarriers have complex structure ranging from the lipoidal layer to inner hydrophilic layers entrapping the RES to deliver it at the target site. Different encapsulating approaches have different pros and cons and affect the properties on a different scale. Hence, there is a need to design and conceptualize such a nanocarrier system that can enhance the life of molecules without compromising their biological and physical properties. This review emphasizes novel techniques and concepts for managing and implementing resveratrol for improved therapeutic efficacy.

2. Pharmacological Actions of Resveratrol

2.1. Pharmacological Effect of Resveratrol on Immunity. The initial study based on the immunomodulatory effect of RES showed that it inhibited the proliferation of spleen cells induced by the ConA and interleukin-2 (IL-2). It acts more prominently on the production of IL-2 and IFN-γ and TNFα/IL-12 by lymphocytes and macrophages, respectively [6]. RES is directly or indirectly responsible for developing and regulating innate and adaptive immunity [7]. RES acts on the immunologic system in a dose-dependent manner. At low doses, it stimulates the immune system for the immunological response, while at the higher dose, immunosuppression is observed [8]. Another study found that it upregulated the immune response and decreased immunocyte apoptosis in chickens, and improvement in their growth was observed [9]. RES also decreased the respiratory syncytial virus's activity and inhibited the Toll/IL-1 receptor [10]. RES stopped the replication of enterovirus and negatively affected the virus-induced elevated IL-6 and TNF-α secretion [11]. In the case of mice, RES improved the spleen lymphocytes proliferation, and enhanced activity of peritoneal macrophages along with the increased number of CD4 + cells was observed [12]. Intravenous administration of RES causes a decrease in inflammation induced by the ischemia and oxidants generated by HX/XO but not the leukotriene B4 [13].

2.2. Pharmacological Effect of Resveratrol on Cancer. Initially, Jang et al. [14] found that RES can inhibit carcinogenesis in mouse skin cancer models; later, many researchers evaluated and evidenced this effect. Later, RES showed their inhibitory effect on cancerous cells such as ovary, stomach, intestinal, prostate, colon, liver, pancreas, brain, and thyroid cancer. RES acted on suppression of free radical formation induced by 12-O-tetradecanoylphorbol-13-acetate in HL-60 leukemic cells [15]. RES shows their scavenging action on the OH and superoxide produced by cells, and it also acts on the lipid peroxidation going on within cell membranes and protects against the DNA damage resulting from ROS generation [16]. RES had shown the antimutagenic effect on inhibiting mutagenicity of N-methyl-N-nitro-N-nitrosoguanidine in the *S. typhimurium* strain TA100 [17]. Recent studies had shown that RES acts as a multitasking factor and has inhibitory action as anti-inflammatory and anticancer function in colorectal cancer [18, 19]. They also have been reported to inhibit the NF-κB-dependent signaling mechanism [20]. Also, it has been reported that the RES can suppress the invasion and viability of colorectal cells induced by the TNF-α and TNF-β [21]. Another study reported the effect of RES on NF-κB. It has decreased the activation of NF-κB and carcinogenic gene products as well as other signaling factors such as vimentin, slug, and E-cadherin in colorectal cells [22]. The mechanism of action of RES-nanoparticles (NPs) on the tumor site has been illustrated in Figure 1.

2.3. Pharmacological Effect of Resveratrol on Obesity. The main contributing mechanisms for obesity are adipogenesis and lipogenesis. In 3T3-L1 preadipocytes, the RES with 100 μM lessened the mitotic colonial expansion and terminal adipogenic differentiation. The adipogenic downregulation occurs through the downregulation of peroxisome proliferator-activated receptor-gamma, CCAAT/enhancer-binding protein alpha, and adipocyte protein 2 [23]. The concentration of 20 or 40 μM causes suppression of lipid accumulation and expression of PPARγ and aP2 in mouse vascular cells, while the concentration of 10 μM showed no effect [24]. RES enhances the level of lipolysis in 3T3-L1 adipocytes and human SGBS cells and epididymal adipose tissue of mice and enhances ATGL expression [25]. The RES was shown to have the apoptotic effect on 3T3-L1 cells, mouse primary adipocytes, and porcine preadipocytes cells [24, 26–33]. It has been shown that the RES-induced apoptosis is routed via AMPKα1 and upregulation of SIRT1 expression [33]. Figure 2 represents the pharmacological action of trans-resveratrol in obesity treatment.

3. Nanotechnology-Based Approach for Delivery of Resveratrol

3.1. Liposomes. Resveratrol is a multitargeted antioxidative and anti-inflammatory natural polyphenol. When taken orally, the RES gets absorbed and rapidly metabolized and is well tolerated as confirmed by long-term toxicity results [34]. Getting metabolized in the intestine and hepatic metabolism is the main hurdle in the bioavailability with a half-life of 8–14 minutes [35]. RES is photosensitive; the trans-RES gets converted to cis-RES on exposure to 1 hour of light [36]. Thus, there is a strong need to enclose it in a liposomal preparation. It has also been reported for its activity against sexually transmitted pathogens. To compensate for these drawbacks, Jøraholmen et al. prepared liposomal vesicles of chitosan and resveratrol. The liposomes were able to encapsulate about 75% of the drug, which was quite close to what was required for therapeutic action [37].

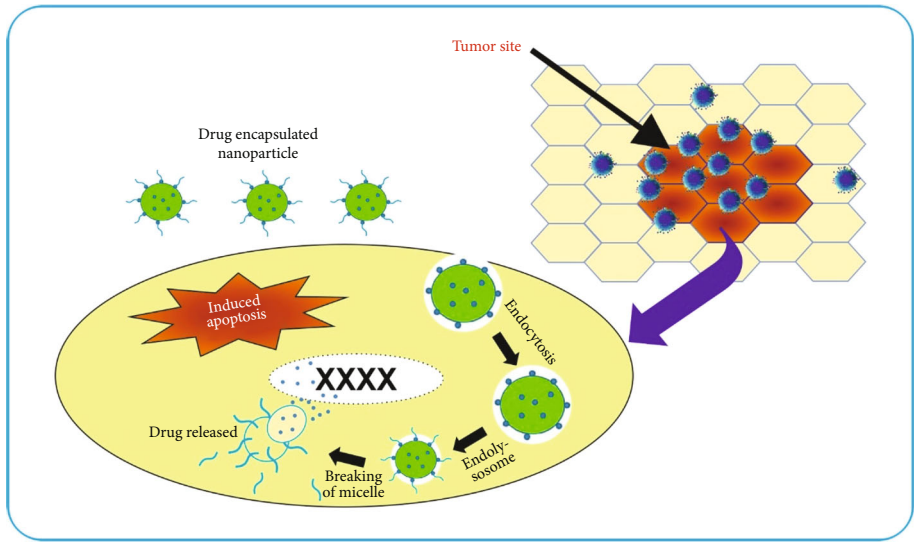

Figure 1: The schematic representation of the mechanism of action of RES-nanoparticle on the tumor site.

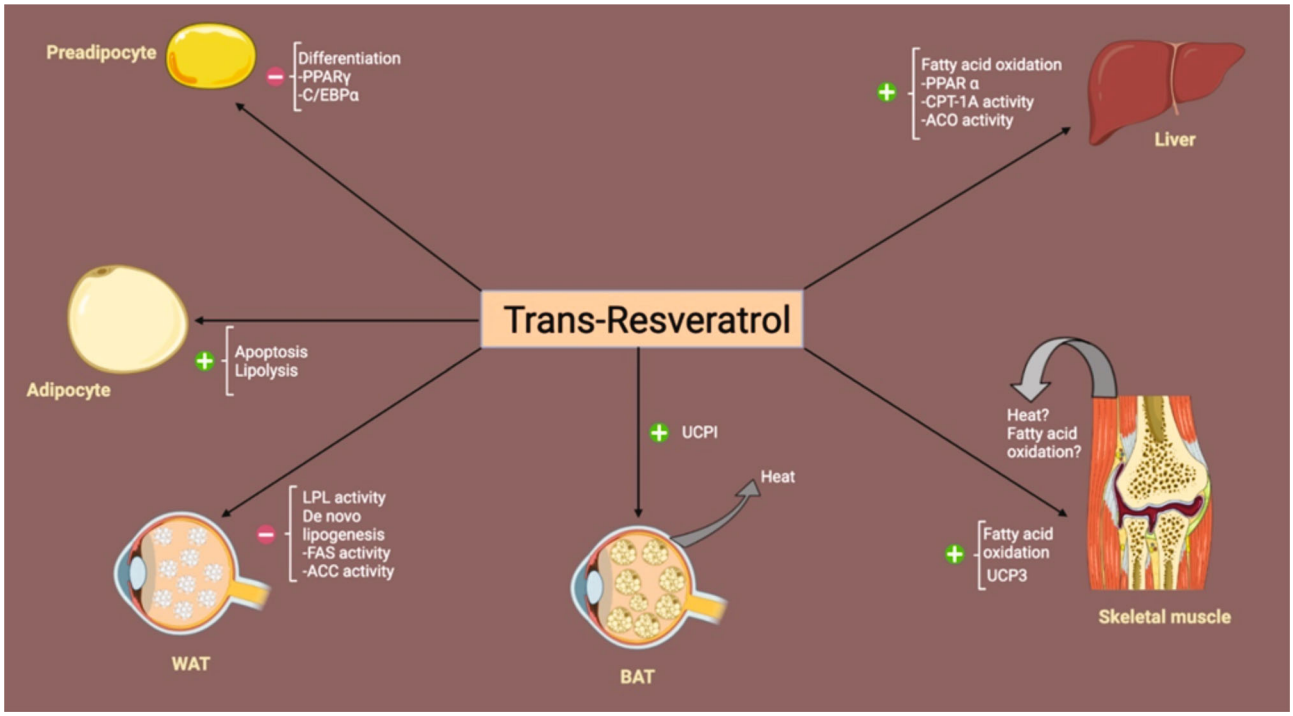

Figure 2: The schematic representation of pharmacological action of trans-resveratrol in obesity treatment.

In vitro scavenging results confirmed that RES is as potent as vitamins C and E. The in vitro cell line results showed more robust antioxidant and anti-inflammatory activities than pure RES solution. Bonechi et al. [38] prepared liposomes based on saturated phosphatidylcholine (DPPC) and cholesterol (CHOL), and RES was encapsulated in it. The zeta potential values indicated that liposomes had a small negative surface charge in the case of DPPC/CHOL. The net polar head charge of zwitterionic phospholipids is zero. It was reported earlier that in an external electric field, the PC components behave to have slightly negative aggregates [39]. This may be further accounted for because of the preferential absorption of HO- ions from outside the aqueous environment. However, as RES was added, there was no change in surface charge on liposomes. Park et al. prepared chitosan-coated liposomes for transdermal delivery of RES. As the coating with chitosan was increased, particles with larger particle sizes were formed. A similar case was observed for zeta potential results. The presence of a coating on liposomes increased the stability of liposomes and

reduced the aggregation. The transdermal delivery of RES was based on the presence of a positive charge on liposomes, and they interact more strongly with the skin surface and help delay the skin aging process [40].

Bojana et al. [41] prepared liposomes of RES using various techniques and evaluated them against various process parameters. It was found that the process of the thin-film method and proliposomes showed the highest entrapment efficiency; further, the particle size was reduced via extrusion and the sonication technique. However, the extruding process encapsulated and retained more of RES in comparison to the sonication process. Kristl et al. [42] prepared liposomes of RES via the ultrasonication technique and evaluated the effect of cellular stress on liposomes. It was found that liposomes were ingested by cells and altered the intracellular fate. The RES liposomal treatment altered the mitochondrial activity and radiation-induced stress and showed a dose-dependent effect. A higher amount of RES caused a cytotoxic effect and lowered the activity of dehydrogenase. At low concentration, RES inhibited cell proliferation by cell cycle arrest in the G1/S phase. Moreover, the presence of the liposomal membrane prevents the conversion of trans-form to cis-form. The presence of phospholipids prevents the erupt release of RES into the cytosol and controls the cytotoxicity. Similarly, another group of researchers prepared liposomes of RES and evaluated them for the viability of HEK293 cells and their photoprotection properties after UV-B irradiation [43].

At the concentration of 100 μM, the viability of the cell decreased and developed apoptotic features, while at a 10-fold decrease in dose, cell proliferation was observed. The liposomes were able to decrease the cytotoxicity at higher concentrations and increased capability to stimulate the proliferation of cells and the ability to survive under stress conditions. Cadena et al. formulated liposomal preparation entrapping quercetin and RES for subcutaneous administration [44]. The presence of stearylamine provides a positive character to the phospholipid bilayers of liposomes and decreases about 10% of encapsulation efficiency for quercetin. Quercetin is a planar molecule and can easily intercalate into the bilayer structure of phospholipid molecule [45].

However, the presence of stearylamine did not bother the RES encapsulation. All the liposomes had particle sizes less than 100 nm and were thus suitable for subcutaneous administration. The bigger particles were not able to get transported and get settled at the administered site. The smaller liposomal vesicles get transported through aqueous channels and in the interstitial channels and reach the lymphatic system. Caddeo et al. [46] studied the development of PEG-modified liposomes entrapping RES prepared by using the direct sonication technique. The aging of vesicles was determined by using Turbiscan technology, and it was found that the backscattering profile showed the presence of instability phenomenon related to vehicle aggregation and migration forming compact white sediment at the bottom of the test cuvette in the case of RES liposomes. However, the compact can be easily redispersed with gentle shaking, while in the case of PEG-RES, liposomes showed better stability as no compact was found. The literature survey of various liposomal formulations studied so far for resveratrol is demonstrated in Table 1.

3.2. Niosomes. Niosomes (Figure 3) are one of the best-rated carrier systems for natural complex molecules. They are obtained on hydration and contain microscopic lamellar structures formed upon combining the nonionic surfactant of alkyl polyglycerol ethers and cholesterol [67]. The two major components involved in the formation of niosomes are lipid components such as cholesterol or L-α-soya phosphatidylcholine and nonionic surfactants [68]. The nonionic surfactants mainly employed include spans and tweens [69–92]. The presence of surfactants forms the bilayer vesicle in aqueous media depending on its amphiphilic nature and requires some sort of energy for the whole process of creating the structure. Structurally, the entire moiety exists as a bilayer, and the hydrophobic parts orient themselves away from the aqueous front while hydrophilic heads get oriented to remain in contact with aqueous media. Pando and coworkers prepared niosome vesicles of RES by entrapping in the Span 80 and 60-cholesterol system via mechanical agitation and sonication [87]. The niosomes of Span 80 showed low entrapment efficiency, while niosomes of Span 60 and cholesterol had better entrapment efficiency but showed less monodispersity in size distribution. Moreover, the release was more sustained in the case of the Span 60 formulation. Another group of researchers prepared niosomes based on RES for topical administration using Gelot 64 surfactant, oleic acid, and linoleic acid as penetration enhancers [93]. The niosomes were designed using the thin-film hydration method and ethanol injection method. The niosomes prepared via the ethanol injection method were smaller than those prepared via the thin-film hydration method. The ex vivo results showed that niosomes prepared via the ethanol injection technique were more effective in penetration to the epidermis and dermis [93].

Researchers prepared niosomes for the anti-inflammatory action of RES. They prepared RES-loaded niosomal hydrogel using the thin-film and ether injection method using Span 80 as the surfactant. The gel was prepared by using Carbopol 934. It was found that the formulation enhanced the biological half-life and reduced the $T_{\max}$ of drug in both skin layers. Its anti-inflammatory activity was compared with that of diclofenac gel in the carrageenan-induced paw edema model. The gel reduced the edema and showed therapeutic action for a longer interval of time [94].

Similarly, another group of researchers prepared niosomal hydrogel based on kappa-carrageenan and gelatin entrapping the RES inside niosomes made of Tween 80 and Span 80 [95]. The presence of niosomes did not alter the hydrogenation properties of biopolymer, and hydrogel showed diffusion-based release. Alteration in the ratio of carrageenan and gelatin leads to variation in the release profile of RES. Also, the formulation prevented photoisomerization from trans to cis-RES isomer. Researchers encapsulated the proteosomes using maltodextrin, lactose, and pullulan as the wall material using the thin-film hydration method [96]. The niosomes made of maltodextrin were smooth and

Table 1: The literature survey of various liposomal formulations reported for resveratrol.

Composition	Particle size	Liposomes Preparation method	Notes	References
DOPE, DOTAP, and DPPC	ND	Homogenization and ultrasonication	Demonstrated the cellular uptake of fluorescent RES liposomes via cerebromicrovascular endothelial cells and decreased production of ROS and inhibited apoptosis	[47]
Cholesterol and human holo-transferrin, egg phosphatidylcholine, DOPE cholesteryl hemisuccinate, and 1,2-dipalmitoyl-sn-glycerol-3-phosphoethanolamine-N-(lissaminerhodamine B sulfonyl)	<200 nm	Film hydration method	The transferrin-loaded liposomes showed internalization in U-87MG cells. Induced apoptosis followed by activation of caspase-3/7 in glioblastoma cells	[48]
DSPE-PEG-2000	200–250 nm	Film hydration method	The thermal analysis showed that the presence of RES gets itself localized near the glycerol backbone and 5-fluorouracil gets localized near the phosphate moiety of liposomal, and release kinetics of both were altered. Liposomal preparation improved the cytotoxicity in comparison to free drug	[49]
(3ß-[N-(N9,N9-Dimethylaminoethane)-carbamoyl]cholesterol, cholesterol, DPPC	110–360 nm	Film hydration method	RES interacted with the bilayer and is more deeply inserted in cationic liposomes than zwitterionic liposomes. No effect on the viability of fibroblast NIH-3T3 cells, and U373-MG was observed	[38]
Phosphatidylcholine, DSPE-mPEG2000	25 nm–102 nm	Thin hydration method	RES and paclitaxel were encapsulated in liposomes and found improvement in efficacy on drug-sensitive MCF-7 and drug-resistant MCF-7 cell line	[50]
Cholesterol and soy PC	110 nm	Film dispersion method	Encapsulated RES using liposomes and nanocarriers. Liposomal preparation showed more physical and chemical stability. An increase in cellular concentration was observed in 3T3-L1 cells	[51]
DSPC, DPPE, DPPA, glycerol	1000 nm	Supercritical method	The liposomal formulation was influential in the treatment of acute blunt injury of gastrocnemius muscles in rats	[52]
Ethanol and lipoid S 100	100 and 200 nm	Film hydration method	Prepared liposomes-in-hydrogel encapsulating RES. Formulation enhanced the antichlamydial effect of RES	[53]
Soy phospholipid mixture	200–260 nm	Ultrasonication	The liposomes prepared using curcumin, resveratrol and epicatechin gallate showed induction of p53 and acetyl p53 and activation of caspase-3. The liposomes showed suppression of CD133 and SOX2 glioblastoma cells, which are known for tumor recurrence	[54]
DOPE, DOTAP	ND	Film hydration method	RES was entrapped in fusogenic liposomes that can easily target cerebromicrovascular endothelial cells and age-related oxidative stress	[55]
4-Carboxybutyl triphenylphosphonium bromide-polyethylene glycol-distearoylphosphatidylethanolamine; dequalinium-polyethylene glycol-distearoylphosphatidylethanolamine; DSPE-PEG2000-COOH	100 nm	Film hydration method	Liposomal preparation enhanced the mitochondrial targeting and anticancer activity of RES. The TPP-based liposomes showed better efficacy on B16F10 cells in terms of ROS generation	[56]
Soy lecithin, Tween 80, and cholesterol	122–140 nm	Film hydration method	It was found that the pectin-coated liposomes were more stable at pH, ionic strength, and temperature. The coating also prevented leakage of RES	[57]

Table 1: Continued.

Composition	Particle size	Liposomes Preparation method	Notes	References
DSPC, cholesterol, DHDP	150–190 nm	Film hydration method	Prepared liposomes encapsulating RES and EGCG. Functionalization with leptin increased permeation in the blood-brain barrier and helped in rescuing dopaminergic neurons	[58]
Phospholipon 100H, cholesterol dicetylphosphate	146–195 nm	Film hydration method	Liposomal RES leads to reduction in the number of epileptic signals in the penicillin-induced model	[59]
Phospholipon 90 NG	412 nm	Proliposomal method	RES encapsulated inside the coating of sodium alginate, alginate-sucrose, and alginate-chitosan microbead insider microspheres for sustained release	[60]
3ß-[N-(N′, N′-dimethylaminoethane)-carbamoyl] cholesterol hydrochloride, cholesterol, and sodium deoxycholate	105–157 nm	Film hydration method	Prepared liposomal formulation entrapping psoralen and RES for treatment of vitiligo	[61]
Soy phosphatidylcholine, Tween 80	64–176 nm	Film hydration method	The presence of a high amount of ethanol in liposomes leads to fluidity in bilayers and helps in the accommodation of RES in the lipid layer	[62]
Lipoid S75	80 nm	Ultrasonication	Topical administration of quercetin and RES-loaded liposomes led to a significant reduction in edema and leukocyte infiltration	[63]
l-a-Phosphatidylcholine, chitosan	280–550 nm	Film hydration method	Liposomal preparation was effective in reducing the skin aging process	[40]
Phospholipon 90G, cholesterol	300 nm	Film hydration method	Encapsulation of RES and 5-FU leads to an increase in skin permeation and treatment of nonmelanoma cancer cells	[64]
Dihexadecyl phosphate, Phospholipon 90H, cholesterol	103–138 nm	Film hydration method	Enhancement in antioxidant effect in comparison to free RES	[65]
LIPOID S 100, DSPE-PEG-2000, and cholesterol	121–250 nm	Film hydration method	Enhanced passive brain targeting for glioma and plasma half-life	[66]
Phospholipon90G, soybean phosphatidylcholine, cholesterol, dicetyl phosphate	70–100 nm	Ultrasonication	Liposomes prevented the cytotoxicity of resveratrol at high concentrations and increased its ability to survive against the stress conditions caused by UVB light	[43]
Lipoid S 100	200 nm	Film hydration method	Liposomal preparation showed more robust antioxidant and anti-inflammatory action	[37]

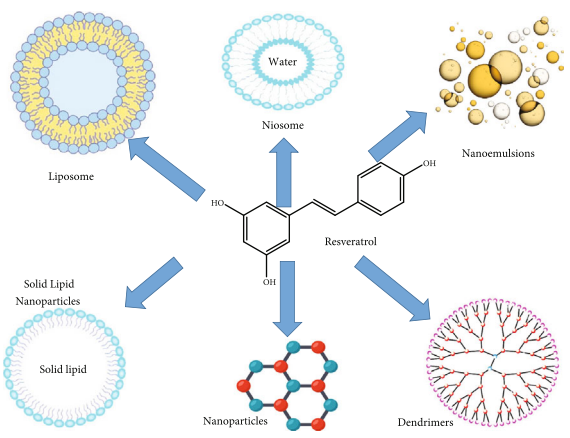

Figure 3: The various nano-encapsulation-based technologies applicable for resveratrol.

spherically walled while lactose and pullulan were with flaky with sharp edges. The encapsulation resulted in enhancement in bioavailability. Schlichet et al. [97] prepared niosomal RES formulation for application in the food industry. The niosomes were prepared using Polysorbate 20 and Span 60 via the slurry method. The process of hydration and sonication resulted in the formation of homogenous lipid nanoparticles with high entrapment value. A biocompatibility test was conducted on the intestinal cells, and the minimum sign of toxicity was observed, indicating their potential use via the oral route [97].

3.3. Dendrimers. Dendrimers (Figure 3) can be defined as water-soluble, highly branched polymers consisting of three main constituent parts: three-dimensional core, branching unit, and functional groups attached as an outer surface [98]. There are two methods for the synthesis of dendrimers as convergent and divergent methods [99]. The outer

dendrons are prepared by the convergent method and then attached to the 3-dimensional central core, while the divergent method starts with core molecules followed by branching units towards the outer surface group in the stepwise manner [100]. Researchers prepared dendrimers made of glucans extracted from the endosperms of sugary-1 maize, and later, RES was entrapped in it using high-speed dispersion treatment. The characterization results showed that the dendrimers could anchor and capture RES due to the presence of hydrogen linkage. The cell line studies showed that it could increase the bioactivity and bioavailability of RES [101].

Chanphai and Riahi worked together to develop the encapsulation process of polyphenols for enhancement in solubility and bioavailability [102]. They encapsulated the RES, genistein, and curcumin using folic acid-based PAMAM-G3 and G4 nanoparticles. The polyphenol binding occurs through hydrophilic, hydrophobic, and H-bonded forces resulting in more stable complexes. As the size increased, the loading capacity also increases proportionately. Pentek et al. [103] developed dendrimers of RES for topical drug delivery systems. It was found that the dendrimers can protect the RES from a harsh acidic environment and their release also. RES is a weaker acid having a hydroxyl group, and it shall remain under basic conditions as an ionized drug, while the PAMAM dendrimers have a basic amine structure and shall remain ionized at acidic pH. As such, pure RES has no solubility while 1% dendrimer complex has low solubility. This increase in solubility can be accounted for due to the presence of dendrimers causing molecular entrapment of RES, while at neutral pH, both dendrimer and RES remain partially ionized. Thus, the dendrimer RES complex is beneficial and can be added to any stage of drug formulation. Mekonnen et al. prepared in situ sodium deoxycholate-based hydrogel loaded with doxorubicin and RES at pH of the tumor microenvironment. The G4.5-doxorubicin was entrapped inside the RES-loaded sodium deoxycholate hydrogel. On HeLa, MDA-MB-231, and HaCaT cells, the cytotoxicity was evaluated, and negligible effects were observed. The RES showed release of around 70% followed by doxorubicin (54%) evaluated at pH 6.5 in 7 days. Single dose of the complex was able to suppress the tumor growth during the 28-day treatment [104].

3.4. Nanoparticles. Kim et al. [105] prepared NPs of RES based on a temperature-controlled antisolvent precipitation mechanism using hydroxypropyl methylcellulose as a stabilizer. It was found that the mean particle size decreased as the precipitation temperature decreased. This may be attributed to a greater nucleation rate and a slower growth rate. When the nanoparticles are mixed with aqueous medium, they create a reconstituted solution, and SEM images indicate some particle aggregation. However, the FTIR studies evidenced no change in the molecular structure during the precipitation process. Solid lipid nanoparticles (SLNPs) are composed of solid lipids and surfactants generally used in parenteral applications. They are new-generation submicron-sized lipid emulsions in which liquid oil has been substituted with lipid layers. They have a wide range of properties such as smaller size, large surface area, and high drug loading, improving pharmaceuticals' properties. Teskac et al. [106] found that about 40% of the drug is entrapped inside the lipid shell and released initially with burst while others are entrapped inside the central core and are released in a sustained manner. The cellular uptake of RES-loaded SLNPs and improvement in cellular fate were also studied. It was observed that the SLNPs with a size of less than 180 nm pass easily through the keratinocyte's membranes, causing negligible alterations in the cell morphology or cellular cycle.

Researchers prepared the SLNPs of RES using the hot homogenization technique and using Polysorbate 60 as the surfactant [107]. The presence of Polysorbate 60 helps in increasing the stability and avoids the formation of aggregates. The SLNPs were spherical and uniform with smooth surfaces and showed an encapsulation efficiency of 70%. The physical characteristics such as particle size (150–250 nm), zeta potential (−30 mV), and PI (0.2) all indicated the physical stability and homogeneity of particles. The presence of RES in lipid nanoparticles led to no change in melting point; however, a disorder in the crystal structure decreases the melting enthalpy and refractive index of nanoparticles and promises more controlled release. Pandita et al. [108] formulated SLNPs of RES using poloxamer 188 and stearic acid. The stearic acid-coated SLNs were prepared using the solvent diffusion solvent evaporation method. The SLNPs showed particles of size less than 140 nm and zeta potential near 35 mV. The encapsulation efficiency was quite high close to 89 with prolonged release near 120 hours. The formulation showed an 8-fold improvement in oral bioavailability compared to a drug suspension. Rigon et al. [109] prepared SLNPs for the transdermal delivery of trans-RES.

The SLNPs consisted of stearic acid, poloxamer 407 and soy phosphatidylcholine, and RES. The SLNPs have an average diameter of less than 200 nm, while the addition of phosphatidylcholine in RES-loaded SLNPs increased the PI; in the case of RES-free SLNPs, PI was decreased. About 45% of RES showed penetration through the skin in 24 hours and showed better activity than kojic acid by inhibiting the tyrosinase. Researchers found that dietary long-chain omega-3-polyunsaturated fatty acid and docosahexaenoic acid (DHA) can enhance the antineoplastic activity against the colon cancer cells, with RES-SLNs [110]. Encapsulating the DHA in RES-SLNPs could attenuate the irritation and inflammation caused by environmental factors as studied on HaCaT and NCTC 2544 cells. The SLNs were able to show the cytotoxic effect on SDS and could inhibit the TNF-α-induced production of inflammatory markers. Moreover, it reduced the rise of ROS levels formed in the presence of hydrogen peroxide. Thermosensitive PNIPAAM-PEG copolymeric nanoparticles, encapsulating the RES, were prepared by formulators [111]. The RES was encapsulated in a hydrophobic core, and it increased the therapeutic bioavailability of RES. It showed better in vitro anticancer activity against the B16 cell lines. It reduced TPA-induced skin edema and oxidative stress response and showed significant reduction in tumor incidence, and tumor burden was observed in mice [112].

Imran et al. [113] developed a dual drug-loaded nanostructured lipid carrier gel of quercetin and RES for enhancement in disposition in dermal and epidermal layers' carrier consisting of lipid binary mixture and Cremophor RH40 as the surfactant and having a particle size of 191 nm with encapsulation efficiency close to 90% for both drugs. The dermatological results indicated an increase in $C_{skinmax}$ for 8 hours in skin treated with the lipid carrier compared to conventional gel. Moreover, the confocal microscopic evaluation showed that disposition in the lipid carrier was 3-fold higher than that in the conventional gel. The IC_{50} of the lipoid carrier and the conventional gels were around 86.50 μM and 123.64 μM on the human epidermoid carcinoma cell line, as evaluated by the MTT assay. Formulation of poly (d,l-lactide-*co*-glycolide) PLGA-based cationic chitosan and anionic alginate-based NPs was performed using the nanoprecipitation method for RES encapsulation. The particles with the size range of 135–580 nm were observed, and encapsulation efficiency was increased from 8% of uncoated to 23% and 32% for alginate- and chitosan-coated NPs. It was also observed that the higher the polyelectrolyte concentration, the more effective the controlled release pattern was observed. Nassir et al. [114] formulated the PLGA-based NPs of RES for their cytotoxic and apoptotic cell death against the prostate cancer cell line. The preparation of NPs was done using the solvent displacement method. The NPs exhibited decreased cell viability with 50% and 90% inhibitory concentrations of 15.6 and 41.1 μM. The results further reported cell arrest at the G1-S transition phase, externalization of phosphatidylserine DNA nicking, and ROS generation in cell lines. Sanna et al. [115] developed polymeric NPs encapsulating the RES for prostate cancer treatment. The NPs consisted of a biocompatible blend of poly (epsilon-caprolactone) and poly (d,l-lactic-co-glycolic acid)-poly(ethylene glycol) conjugate prepared by the nanoprecipitation method. Encapsulation efficiency was around 74–98%, with an average diameter of 150 nm. The NPs showed release at pH 6.5 and 7.4, which is also valid for acidic tumor microenvironment and physiological conditions, and it released 55% of RES for 7 hours. In acid gastric media, about 55% of RES was released for 2 hours followed by the total release which was observed at 5 hours at pH 7.4.

Formulators developed sericin protein-based nanoparticles loaded with resveratrol via a solventless precipitation technique [116]. The presence of pluronic surfactants helps in the formation of spherical-shaped, monodisperse NPs with a mean size of 200–400 nm. The NPs were nontoxic to normal skin fibroblasts. The process showed encapsulation efficiency of 71–75% for RES. The NPs showed strong inhibitory action on colorectal adenocarcinoma cells but proved noncytotoxic to skin fibroblasts. The NPs showed sustained release for 72 hours and enhanced drug solubility. Thipe et al. [117] developed gold NPs using the green synthesis method conjugated with the RES. The RES reduced Au^{3+} to Au^0 for the novel synthesis of NPs at room temperature. The NPs were further encapsulated in gum arabic and increase the stability of AuNPs. The higher RES corona on NPs showed enhanced anticancer effects, and after 24 hours, optimum cellular intake was observed.

Researchers encapsulated the RES in gelatin NPs and studied their anticancer activity on NCI-H460 lung cancer cells. The SEM results indicated the development of spherical-shaped particles, while DLS results showed the formation of the particle with an average diameter of 294 nm. The presence of glutaraldehyde through Schiff-base reaction and hydrogen bonding acted as the agonist for successful encapsulation (93.6%) of RES. The cellular uptake of NPs was quite rapid compared to free RES and showed antiproliferative action on NCI-H460 cells [118]. The literature survey of various NP-based studies performed for resveratrol is given in Table 2.

3.5. Nanoemulsion. Nanoemulsions of RES were prepared and evaluated by various researchers. Pangeni et al. [142] prepared nanoemulsion of RES using vitamin E and sefsol as the oil phase while using Tween 80 and Transcutol P as the surfactant via the spontaneous emulsification process and high-pressure homogenization later. The nanoemulsions thus prepared showed an average globule size of 102 nm with PDI 0.158. The nanosuspensions showed an average release rate of near 88% in 24 h. Histopathology results showed a decrease in degenerative changes in the RES nanosuspension-administered group. Another group of researchers developed oil-in-water food-grade nanoemulsions via the high-pressure homogenization method. The nanosuspensions based on soy lecithin/sugar esters and Tween 20/glycerol monooleate were more stable physically and chemically during accelerated aging and gastrointestinal digestion. It was found that formulation was absorbed through the intestinal wall, as evidenced by chemical and cellular antioxidant activities comparable to encapsulated RES dissolved in DMSO [143].

Nanoemulsion gel of RES has been reported in the literature [144]. The main aim behind nanoemulsion gel preparation was to enhance the permeability and antioxidant activity against UV-induced skin damage. Confocal microscopic studies confirmed the deep penetration of RES from nanoemulsion gel. Analytical techniques further also proved that nanoemulsion gel enhanced stratum corneum lipids' fluidization and disrupted the lipid bilayer, thus enhancing the skin permeation. Pardo et al. prepared the nanoemulsion of RES using the spontaneous emulsification method [145]. The nanoemulsion consisted of grapeseed oil and orange oil as the oil phase and Tween 80 as the surfactant. The emulsification process resulted in the formation of small droplets with $d \approx 100$ nm. About 120 μg/ml of RES was dissolved in the oil phase and resulted in the retention of RES near 88% in nanoemulsion compared to 50% as dissolved in DMSO. The formulation thus increased the stability and lifetime of RES against UV degradation. RES has also been assessed for its countereffect in neuroinflammation and plays a vital role in treating postoperative cognitive disorder [146]. The emulsion based on RES was deployed in evaluating the oral and brain bioavailability. It was found that

Table 2: Nanoparticle-based systems reported for resveratrol.

Type of nanoparticulate systems	Drug/s	Disease targeted	References
Chitosan-coated NPs	Resveratrol	Lung cancer	[119]
Alginate NPs	Curcumin and resveratrol	Prostate cancer	[120]
Gelatin-coated NPs	Resveratrol	Lung cancer	[121]
Mesoporous silica NPs	Resveratrol	Melanoma	[122]
Solid lipid NPs	Resveratrol	Contact dermatitis	[123]
Oxidized mesoporous carbon NPs	Resveratrol	Triple negative breast cancer	[124]
Super paramagnetic iron oxide NPs	Resveratrol	Glioma	[125]
Solid lipid NPs	Curcumin and resveratrol	Colorectal cancer	[126]
Solid-lipid microparticulate	Resveratrol	Melanoma	[127]
Lipid-core nanocapsules	Curcumin and resveratrol	Human skin disease	[128]
Galactosylated NPs	Resveratrol	Anti-inflammatory	[129]
PEG-PLGA NPs	Resveratrol	Liver cancer	[130]
Hyaluronic acid-functionalized chitosan nanoparticles	Curcumin and resveratrol	Diabetic wound	[131]
Poly (D,L-lactide-co-glycolide)-D-α-tocopheryl polyethylene glycol 1000 succinate blend NPs	Resveratrol	Glioma	[132]
Silk fibrin-coated NPs	Resveratrol	Inflammatory bowel disease	[133]
Mesoporous silica nanoparticles (MSNPs)	Anti-miR21 and resveratrol	Gastric carcinoma	[134]
Hepatic-targeted oxidized starch-lysozyme (OSL) nanocarriers	Resveratrol	Nonalcoholic fatty liver disease	[135]
Ethanol extract of Angelica gigas Nakai- (AGN Ex-) based NPs	Resveratrol	Ovarian cancer	[136]
Glyceryl behenate or polyoxyethylene 40 stearate-based lipid carriers	Resveratrol	Hyperpigmentation and melanogenesis	[137]
Chitosan-coated SLNs	Resveratrol (RSV) and ferulic acid	Colon cancer	[138]
Technetium-99 m labeled gold NPs	Resveratrol	Colon cancer	[139]
Polyethylene glycol-polylactic acid (PEG–PLA; M.W. 5000-5000) polymer NPs	Resveratrol	Colon cancer	[140]
Solid lipid NPs	Omega-3 PUFA and resveratrol	Colon cancer	[141]

emulsion-based RES attenuated the surgery-induced cognitive impairment and hippocampal neuroinflammation. Ex vivo results confirmed that the preemptive RES regimen reduced the hippocampal microglial immune reactivity to lipopolysaccharide. The oregano essential oil and RES-loaded pectin edible coatings had shown promising results in preserving fresh pork [147].

The packaging showed good stability at 4°C for 15 days. The packaging prolonged the shelf life of pork by minimizing the pH and color change. Moreover, it also retarded lipid and protein oxidation, preserving the tenderness of the meat and controlling microbial growth. Labrasol has been proven to inhibit the glucuronidation of RES. The nanoemulsions of Lab-N and F68-N (poloxamer 188) were prepared and evaluated. The Lab-N showed an inferior drug release profile but showed dose-dependent transport of RES in comparison to F68-N by decreasing the amount of permeated metabolite, RES-3- glucuronide. The Lab-N formulation exhibited a rise in plasma concentration and RES bioavailability and decrease in those with F68-N [148]. Formulation of nanoemulsions of RES has been reported in Table 3.

3.6. Silica-Based Nanoparticles. Chaudhary et al. [153] formulated RES-loaded mesoporous silicon nanoparticles (MSNPs), for the antiproliferative activity and sensitization of docetaxel in hypoxia-induced drug resistance in prostate cancer. At pH 7.4, the loaded NH2-MSNs showed burst release which get plateaued after 90% release after 12 hours, while phosphate-liganded MSN showed slower release of 50% value but affected the antiproliferative activity in greater context. Juère and coworkers developed tablet formulation of RES using MCM-48-type mesoporous nanoparticles and succinylated beta-lactoglobulin as a protein excipient [154]. Due to protein coating, the resveratrol was not eluted in gastric media; rather, release occurred in intestinal media.

3.7. Metallic Organic Framework (MOF). Qiu et al. [155] prepared a metal-organic framework coupled with chitosan as nanocapsules. The nanocapsules have a hydrophobic core and hydrophilic shell prepared using electrostatic deposition of cationic chitosan on the anionic cyclodextrin MOF core [155]. The chitosan coating increased the encapsulation efficiency of resveratrol and provided the antioxidant activity, along with photostability to nanocapsules.

Table 3: The literature survey of nanoemulsions studied for the RES.

Components	Technique	Notes	Reference
Coconut oil, Pluronic-P107, Cremophor EL, RES	Ultrasonication process	Formulated nanoemulsion can be used via nasal treatment to target the brain	[149]
Purity gum 2000 (PG) and purity gum ultra (PGU), curcumin, tuna fish oil, resveratrol	Ultraturrax homogenization	Improved oxidative stability of fish oil	[150]
Tween 80/phospholipids, RES, cyclodextrin	Ultrasonication emulsification method	Decreased rate of degradation by UV exposure	[151]
Grape seed oil plus orange oil, Tween 80, and RES	Spontaneous emulsification	Enhanced life against the degradation stimuli	[145]
Soy lecithin Solec IP, glyceryl monooleate, sugar ester P1670, Tween 20, and RES	High-pressure homogenization	Enhance stability and bioavailability	[152]

3.8. Gold Nanoparticles. Park et al. [156] prepared gold-conjugated RES-loaded nanoparticles, using the green nanotechnology approach for their use in breast cancer metastasis. The nanoparticles reduced the 12-O-tetradecanoylphorbol-13-acetate (TPA) and induced enzymatic migration and invasion ability of breast cancer. Moreover, the nanoparticles reduced the TPA-induced nuclear translocation and transcriptional activation of nuclear transcription factor and activator protein-1. Thipe et al. studied the gold NPs coupled with gum arabic for the enhancement of stability of gold NPs which can be used in the treatment of human breast and pancreatic cancers [157]. Similarly, Lee et al. [158] studied the effect of gold nanoparticles, encapsulating the RES for inducing the cell arrest in MCF-7 cell lines.

3.9. Miscellaneous Data. Researchers developed a hyalurosome nanodelivery system based on hyaluronic acid and curcumin loaded with curcumin and RES (CRHs) [159]. The CRHs can easily assemble and develop nanosized spherical shapes with an average diameter of 134 nm. The formulation showed dose-dependent higher radical scavenging action. Using an extrusion process, Gani et al. [160] prepared nanoencapsulated RES-based snacks prepared from horse chestnut, water chestnut, and lotus stem starch particles. The horse chestnut, water chestnut, and starch particles showed low viscosities and elastic behavior that can interfere with the human sensory evaluation. The snacks prepared have higher antioxidant, antidiabetic, and antiobesity properties. In another literature, the same authors reported formulation of nanocapsules of RES for pharmacological action [161]. Salem et al. [162] developed nano-nasal-based emulgel entrapping RES, Carbopol 934, and poloxamer 407 as a gelling agent for brain targeting. The nanoemulsion part consisting of Tween 20, Capryol 90, and Transcutol showed transmittance of 100%. The ex vivo permeation confirmed the release of RES for 12 h. The formulation showed enhancement in skin permeation through the sheep mucosa layer. The C_{max} and AUC of RES after nasal treatment were 2.23 and 8.05 times. Researchers developed spiral dextrin and RES-based crystals for targeting colon-specific drug release [163]. The inclusion complex showed results improving the indigestion ability. As the length of spiral dextrin increased, the thermal stability increased and prevented degradation of RES from gastric acids and pancreatic enzymes. Pujara et al. [164] prepared soy protein isolate nanoparticles (size 100 nm) encapsulating the RES using the rotary evaporation technique. Due to amorphous nature of RES nanoparticles, the solubility and dissolution increased significantly. β-Lactoglobulin-based RES nanospheres were developed for the enhancement in solubility and dissolution of RES. Animal subjects with intestinal bowel disease showed anti-inflammatory activity of nanospheres encapsulated [165].

4. Recent Patents

RES is a prevalent molecule among researchers. Therefore, it has been patented by various researchers for its therapeutic activity. We reported the patent since 2015 that has been reported globally from standard database sites such as www.uspto.gov, www.epo.org, and www.wipo.int.

As per patent WO2017137957A1, Tripathi worked to develop RES nanoparticles coated with tree fat [166]. The nanoparticles were stabilized with unconjugated form stable up to a range of 10000 nmol/liter to 40000 nmol/liter, with a half-life of 3 hours when administered to mammal. Normally, RES is metabolized by the process of sulfonation and glucuronidation, but when NPs were prepared using a reported method, such instances are lowered, and the half-life is increased. Similarly, Tripathi filed another US patent US11033514B2, disclosing synthesis of modified colloidally stable RES nanoparticles covered with jackfruit tree fat coat [167]. These NPs could be administered to mammals suffering from insulin resistance, metabolic syndrome, aging, etc. Wen and Wenbo disclosed patent nanoencapsulation of RES using lecithin [168]. The presence of lecithin enhanced its transdermal penetration and resident time on the skin. Also, the lecithin retarded the rate of release of RES. Wang and Han developed RES-polydopamine core-shell nanomaterial, formed using dimethyl sulfoxide [169]. The polydopamine layer establishes the release of RES only after entering near target tissue and hinders its premature release. In a Chinese patent, CN111920771A, researchers disclose the formulation of resveratrol-based nanoliposomes using soybean phospholipid, cholesterol, and antioxidant using a rotary evaporator. These nanoliposomes can be administered to treat or prevent cardiovascular disorders, tumors, and blood fat reduction [170].

5. Conclusions

There is no doubt that RES is very promising in terms of its therapeutic efficacy. But its erratic pharmacokinetics hinders its path. To circumvent these challenges, a number of researches had been designed and carried out. In the past decade, enormous research had been done taking nanotechnology into the limelight. These nanocarriers have augmented the improvement in solubility, stability, and encapsulation efficiency. Encapsulating the RES into nanocarriers had magnificently overpowered the hurdle of physicochemical characteristics. Though it has shown promising results in preclinical studies, the suitability of RES nanocarriers is still under the scanner for human trials due to incompetent systemic delivery and poor bioavailability. Many people around the globe are consuming RES with doubtful clinical pieces of evidence. Some researchers provided evidence for the role of RES in reducing the progression of the disease and boosting the immune system. But still, despite so many researches, the hunt for an ideal drug delivery system is going on. It seems that a significant amount of progress made in nanotechnology would act as a pathway for further researches to develop strategies. The nanotechnology-based formulations lack scientific evidences from the clinical trial data. Due to genetic variations, the streamline effect of nanoformulations on the populations cannot be derived. Thus, there is a need to rationalize and address this issue before product marketing. Moreover, the reproducibility with techniques with which products are synthesized or produced is lacking. The techniques should be scaled up from a pilot scale to an industrial scale, to reproduce the batch to batch uniformity.

Conflicts of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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