Review

Resveratrol Nanoparticles: A Promising Therapeutic Advancement over Native Resveratrol

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Abstract: The importance of fruit-derived resveratrol (RES) in the treatment of various diseases has been discussed in various research publications. Those research findings have indicated the ability of the molecule as therapeutic in the context of in vitro and in vivo conditions. Mostly, the application of RES in in vivo conditions, encapsulation processes have been carried out using various nanoparticles that are made of biocompatible biomaterials, which are easily digested or metabolized, and RES is absorbed effectively. These biomaterials are non-toxic and are safe to be used as components in the biotherapeutics. They are made from naturally available by-products of food materials like zein or corn or components of the physiological system as with lipids. The versatility of the RES nanoparticles in their different materials, working range sizes, specificity in their targeting in various human diseases, and the mechanisms associated with them are discussed in this review.

Keywords: resveratrol; nanoparticles; biomedical activities

1. Introduction

The most commonly and abundantly available polyphenol that is most useful to the human is resveratrol (RES) for their uses in pharmaceuticals and nutraceuticals [1]. It is most abundant in grapes, peanuts, and other foods that are consumed in some daily human diet [2]. RES is chemically known to have both cis and the trans-forms with the trans-form being the most stable of them and also functionally active [3,4]. The health-promoting activities of the trans-form have been widely studied as anti-oxidants [5,6] in reducing the lipid peroxidation [7], lowering of blood pressure, and anti-inflammatory activities. However, their use has been limited for a long time since they were considered to be unstable and heat-labile and due to shorter and faster metabolism and thereby...
elimination [5]. Several researchers have attempted to increase the residence time of RES and to prolong its activity by encapsulating it in biopolymers, lipids, and the use of surfactants to increase the absorption [8,9]. They include beta-cyclodextrin and tween-20, lipids, and chitosan, and also some proteins as biopolymers [10]. They are known to improve the bioavailability of RES by protecting them against unfavourable conditions such as heat, oxidative enzymes, and other metabolic interference. The encapsulated material helps the molecule to get released slowly and hence increase the residence time for its action in the plasma and better bioactivity of the molecule.

The properties of RES that make it challenging to use in medicine because of the following features.

1. It has a very less aqueous solubility of 0.03 mg/mL [2].

2. When exposed to light, oxygen, temperature, and oxidative enzymes, they are sensitive and degrades quickly [11].

3. Despite getting isomerized into cis-RES, the activity of the molecule gets reduced from its original trans-RES [12,13] and hence could not be advantageous in using under various environmental and physiological conditions.

4. The importance of RES in its usage in medicines gets reduced with its rapid metabolism [14], and hence they are eliminated from physiology, and in turn, the effectiveness of the molecule is not ‘captured’.

5. Also, the phenolic groups of the molecule get conjugated to the sulfates by the intestinal enterocytes, and due to glucuronidation, the molecule is not metabolized systematically to absorb the nutritional and therapeutic value from it.

6. In the intestines, the gut microbiota hydrogenates the aliphatic trans double bonds of RES and the other metabolites such as RES-3-O-sulfate, RES-3-O-glucuronide, and dihydro-RES conjugates generated after oral administration of RES make the molecule biologically less available [11,15].

To deliver RES for its safe use at various organs of the body specifically to have the desired effects by exploiting the beneficial properties of RES, various methods of encapsulation of RES in different biomaterials have been employed. The decision to use the various biomaterials has been with the chemistry of the materials and also the existing data that is available for their use in nanoparticle preparation. We have attempted to project the versatility of RES in the treatment of various diseases by pooling the different results published by the researchers on them. The following would give elaborate information on the RES usage in various diseases and their possible mechanism that it employs in the treatment (Table 1).

Table 1. A promising therapeutic advancement of various resveratrol nanoparticles.

| Properties          | Size of the Particles and Encapsulation Efficiency of RES | Action of RES on the Target                | Cellular Effect                      | Disease                  |
|---------------------|----------------------------------------------------------|--------------------------------------------|--------------------------------------|--------------------------|
| Chitosan            | 160.58 and 206.52 μm, 94.59%                              | Hippocampal region, MDA-MB cell line       | Neuroprotective, anticancer           | Alzheimer’s, colon cancer, diabetes |
| Zinc-Pectinate      | 950 μm, 94%                                               | Direct effect by pectinase for digestion in the colon | Colon-specific                       | Gastric complications    |
| Casein              | 200 nm                                                   | Thromboxane A2                            | Cardioprotective as anti-vasoconstrictor | Cardiac failure          |
| Polysorbate 80-coated poly(lactide) | 250 nm                                   | Reducing the lipid peroxidation and TH loss in the MPTP-treatment | Antioxidant and the neuroprotective properties | Parkinson’s              |
| Material                                                  | Diameter | Effect                                                                 | Disease/Condition                                                                 |
|-----------------------------------------------------------|----------|------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Zein                                                      | 300 nm   | Reduction in the pro-inflammatory mediators                           | Anti-inflammatory                                                                 |
| Transferrin (Tf)-modified polyethylene glycol-poly lactic acid (PEG-PLA) | 239.57 ± 2.53 nm | Toxic effects on glioma cells with tumor                              | In vitro cell cytotoxicity, anti-tumor activity, and cellular uptake              |
| Gelucire 50/13 lipid matrix/HPβCD matrix                  | 329.9 ± 1.9 nm, 72.2 ± 1.5% | ROS or free radicals in the lenses                                    | Improvement in countering the oxidative stress by improving the SOD activity      |
| Poly (lactic-co-glycolic) acid (PLGA) poly-(caprolactone)-poly(ethylene glycol) (PCL–PEG) nanoparticles | 200 nm (approx.) | Cochlear cells                                                        | Countering the generation of ROS due to cisplatin                                |
| Silk fibroin                                              | 250 nm (approx.) | Epithelium of the mouth                                                | Decreasing the levels of IL-1beta and IL-6                                      |
| Polymeric micelles with polycaprolactone (PCL)-polyethyleneglycol (PEG) | 83.47 ± 0.44 nm | Crossing the blood-brain barrier                                       | ROS generated by the amyloid-beta peptide, caspase-3 reduction                   |
| Oat protein-shellac complex nanoparticles                | 323 nm, 60–90% | Anti-oxidant mechanism                                                 | Scavenging hydroxyl radicals                                                     |
| Gold nanoparticles                                        | 10 nm    | Reducing the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and NF-KP phosphorylation | IL-1beta, IL-6, and TNF-alpha, Vascular Cell Adhesion Molecule 1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1) and Monocyte Chemoattractant Protein-1 (MCP-1) |
| Mesoporous Carbon nanoparticles                           | 187 nm   | Caspase 3 activation, scavenging ROS in PC3 cells                      | Cytotoxic effect, anti-oxidative                                                 |
| Poly(ethylene oxide–poly(propylene oxide) PEO-PPO block copolymers | 10–100 nm | Reduction in TNF-alpha                                               | Anti-inflammation, tissue swelling and synovial inflammation                     |
| Solid lipids                                              | 248 nm   | Snap23, Stx4, and Vamp2 have increased                                 | Improved insulin resistance                                                      |
| Cellulose acetate butyrate (CAB), and carboxymethylcellulose wafer | 87–92% | Necrosis of the tissue                                                | Increase in collagen                                                            |
|                                                           |          |                                                                        | Wound dressing and healing                                                       |
2. Neuroprotective Effects of Resveratrol against β-amyloid (Aβ) Administration in Rats are Improved by Lipid-Core Nanocapsules

The efficacy of RES was evaluated in Wistar rats with RES being loaded into lipid-core nanocapsules [16] after inducing Alzheimer’s disease with the intracerebroventricular injection of the pathogenic peptide Aβ1-42 [17]. This causes memory loss due to synaptic dysfunction. The induction of RES-nanocapsules has protected the brain function by increasing the intracerebral concentration of RES in rats that increases the stability of the molecule and prevents synaptic impairment. The memory dysfunction was improved with the RES-nanocapsule treatment, and the animals were able to improve their recognition indices that indicate the neuroprotective effects of RES on the hippocampal regions of the Alzheimer-induced rats. The presence of synaptophysin at the synapse is crucial to the memory [18] and object recognition tasks and is altered or reduced in Alzheimer-treated animals. RES was able to restore the levels of this major synaptic vesicle protein at the synapse back to normal levels and reduced the synaptotoxicity exerted by the pathogenic peptide, Aβ1-42 [19]. The improvement in the brain function offered by RES is due to the increased bio-distribution of RES through the lipid-core nanocapsules, but such results should not send the message that lipid nanocapsules could be found in the brain crossing the blood-brain barrier (BBB), as specific experimental results have not been performed.

The progress of Alzheimer’s disease was monitored by evaluating the pro-inflammatory cytokines produced by the reactive astrocytes and microglial upon Alzheimer’s induction by Aβ1-42. RES-nanocapsules could decrease the cytokine release and ROS formation and astrocyte and microglial activation. The activation of stress-activated protein JNK was evaluated with the increase in pro-inflammatory cytokines and the treatment with RES thereafter. The effect of RES was directly observed on the c-Jun N-terminal kinase (JNK), as RES could decrease the release of the inflammatory cytokines and also break the subsequent events of microglial activation and astrocytes, thereby preventing JNK from being activated, and thus preventing the neural dysfunction. The amyloid β peptide (Aβ1–42) toxicity caused due to the phosphorylation of β-catenin and in-turn the glycogen synthase kinase 3 beta (GSK-3β) was inhibited by both the free RES and the RES-nanocapsules indicating that the RES effect in reducing the toxicity caused due to the pathogenic peptide and nanocapsules is effective in improvement of the memory and the neuronal deficits in Alzheimer’s disease.

3. RES Encapsulation in Casein Nanoparticles against Cardiac Failure Applications

Resveratrol (RES) is a potent anti-vasoconstrictor, acting against the prostaglandin, thromboxane A2 [20]. It inhibits the production of thromboxane A2 by acting against cyclooxygenase-1 (COX1) and thereby preventing the vasoconstriction [21] of blood vessels and helps in preventing cardiac failure and maintaining the normal blood pressure and physiological functioning. Hence, RES is known to be a vasodilator [22]. It is also known to be enhancing the bioactivity of nitric oxide and exerting its inhibitory effect on platelet aggregating factors like COX1 and NF-KB [11]. Its inhibitory activity on COX2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB), and protein kinase c (PKC) can be correlated with its cancer-preventive and chemotherapeutic activity. It also acts against the formation of new blood vessels in the case of tumor-induced cells and can be known as an antiangiogenic agent with its activity against neovascularization [23,24].

3.1. Casein Nanoparticles for Oral Delivery of RES

Casein is a milk protein and is found abundantly in milk, which can be used for preparing nanodelivery of RES due to its ability to be converted into nanoparticles. They have a high affinity for RES, and under mild conditions, they can be prepared as nanoparticles along with RES through the hydrophilic and hydrophobic interactions [25,26].

Casein nanoparticles, when loaded with RES, obtained a polyhedron in shape with a size of 200 nm loading around 31 μg/mg of casein nanoparticle. The delivery of RES into the physiological system is dependent neither on the pH nor on any of the external factors governing the niche. It
follows zero-order kinetic that when water is in the milieu, it enters into the casein nanoparticle and dissolves the structure to release the molecules or lets it diffuse from the nanoparticles [27]. Hence, the delivery of RES in casein nanoparticles is comprehensive and is not affected by any external factors.

Conventional methods of RES administration orally along with PEG400 with water did not release the molecule, and it was not available in large amounts in the plasma with a meager 2.6% after 30 min of oral administration and saturated in a short span of 4 h. Enzymes such as UDP-glucuronosyltransferase and sulfotransferases localized in the liver [28] and small intestine [14] converts the molecules into glucuronides and other sulfates derivatives. The casein-based nanoparticle delivery of RES has an edge over the conventional methods with the prolonged plasma levels of the molecules even after 8 h of post administration and could find the traces even after 24 h of post-delivery. The delivery of RES through casein nanoparticles termed the self-nanoemulsifying drug delivery systems (SNEDDS) is about 10 times more than that of oral administration of the same molecule without casein [29].

3.2. Pharmacokinetic Superiority of Casein Nanoparticle Delivery of RES

The pharmacokinetic parameters of RES with casein nanoparticles delivered into the physiological system was studied with the parameters such as the half-life of the molecule in plasma (t1/2), clearance (Cl) and the distribution volume (Vd). It was observed that obtaining these parameters for casein-based delivery is simple and is as efficient as delivery through intravenous administration. Radiolabeled casein nanoparticles, when administered in rats, remained in the gastrointestinal tract of the animal, and the nanoparticles were not absorbed by the parts such as the liver, spleen, lungs, or kidneys of the animals. It reinstates that the nanoparticles are not, but only the RES molecule is absorbed. Luminogen red labeled fluorescent casein particles crossed the mucus and were observed to be present on the surface of the epithelium, and hence the RES molecule was released on the surface of the organ [30]. The subsequent release of RES was made possible by the enzymatic digestion of casein particles and eliminating them with the RES absorbed by the enterocytes. Furthermore, the molecule was metabolized in rats to RES-O-3-glucuronide [31] and was quantified in the plasma. This casein-based nanoparticle-RES delivery has exempted the molecule to undergo pre-systemic metabolism by bypassing it towards the intestinal lymphatic transport, and such methods would be useful for delivery lipophilic compounds into the systemic circulation [32].

4. Polysorbate 80-Coated Poly(lactide) Nanoparticles Loaded with RES Offers Neuroprotection in Parkinson’s Disease

The antioxidant [16,33,34] and neuroprotective properties [16,35,36] of RES have been used in the treatment of Parkinson’s disease (PD). In many experimental models, it has been shown to improve mitochondrial function. In the case of treatment of Parkinson’s disease, the transport of drugs across the BBB is a challenge, and it has to be overcome with a suitable coating on the delivery vehicle.

Polysorbate 80 (PS80) is a hydrophilic surfactant and is capable of modifying the surface of the particles and can easily cross the BBB. Apolipoprotein E has been surface-modified with PS80 and used for the delivery of RES [37]. They can cross the barrier and bind to their receptors on the brain capillary endothelial cells in the luminal membranes. RES is released into the brain after endocytosis of the particles in the brain and maybe transported across the endothelium [38]. In an experimental model with rats, the administration of pro-neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rats caused Parkinson’s disease [39]. Rodents which were treated intra-nasally with MPTP have had olfactory, cognitive, and motor problems due to oxidative stress and mitochondrial dysfunction [40–42]. These animals were then treated with PS80-coated polylactide nanoparticles that improved the brain targeting and the concentration of the drug in the brain [43,44]. The mean sizes of the particles that were prepared with RES load were 250 nm in diameter, and with negative zeta potential, these particles have high physical stability. RES diffuses out of the particles by eroding the
outer layers of the particles and diffusing out the drug. Established laws of drug release and pharmacokinetics (Fick's law and Higuchi model) were followed in the delivery of RES [45].

After the treatment of PD mice with free RES, there was no significant change in the MPTP-infused PD mice towards improving the olfactory and motor functions. However, those that were treated with RES-loaded particles of PLA-PS80, significant improvement in the olfactory discrimination and social recognition of the animals have been observed. Another important marker tested for oxidative stress through lipid peroxidation, and dopamine synthesis is the tyrosine hydroxylase (TH), which is involved in dopamine synthesis. MPTP has significantly reduced the TH expression, which is characteristic of the molecule in PD. RES loaded-PS80 coated PLA particles have significantly reduced the lipid peroxidation and TH loss in the MPTP-treatment, which is an accretum of the already improved emotional and behavioural changes of the animals. Free RES was ineffective in reducing the effects of MPTP on the animals, as it is not easily available in the brain tissues. These nanoparticles that were used in this model have crossed the BBB, improved the bioavailability of RES in the brain, and hence the improvement [44,46]. The apolipoproteins are adsorbed on to the surface of the nanoparticles and are endocytosed by the brain endothelial cells [37,47]. The coating of PS80 has prevented the reversal or efflux of the loaded-nanoparticles out of the brain through P-gp pump [48]. The combined coating of PS80 and the selection of the nano-delivery vehicles has concentrated RES in the brain tissues and give neuroprotection [47].

5. Zein-Based Nanoparticles Improve the Oral Bioavailability of RES and Its Anti-Inflammatory Effects in a Mouse Model of Endotoxic Shock

Another natural protein that has been used in the preparation of nanoparticles and the delivery of RES is zein, which is a naturally occurring abundant protein of corn [49] and is a mixture of smaller peptides of alpha, beta, gamma and delta zein [50]. Zein is an amphiphilic protein and is insoluble in water due to its hydrophobic amino acid composition of leucine, proline, and alanine which can be exploited to prepare nanoparticles that are hydrophobic and can be controlled in the release of RES makes it a suitable solid particle in the preparation of nanoparticle for molecule delivery [51]. Zein is biodegradable and can accommodate various types of molecules that do not interfere in the encapsulation or their delivery [52]. Though these characteristics make it a suitable material for the preparation of nanoparticles, Juan et al. have observed that the non-polar amino acids have made the dispersion of zein nanoparticles, with the subjected molecule for delivery, in the physiological system challenging and have suggested the use of phosphate, citrate, and chloride to make the nanoparticle more soluble (the effects of divalent cations in the presence of phosphate, citrate and chloride on the aggregation of soy protein isolate) and available although they have used lysine in their nanoparticle preparation. This has enabled them to make the nanoparticle of zein with RES more available as suspension with simple dispersion techniques with water [52].

In the preparation of solid nanoparticles with zein for the delivery of RES, the mean size of particles that were obtained in the preparation was 300 nm and could obtain zero zeta potential for them to precipitate as solid for the stable preparation. RES was encapsulated in these solid nanoparticles with a maximum of 80 ug of the molecule in a milligram of the encapsulation material that is on par with their other solid counterparts [8,53,54]. The resultant RES–zein nanoparticles were resistant to pH changes and followed the Fickian diffusion model [45] for the release of RES with the degradation of zein by Peppas-Sahlin model [45]. The maximum availability of RES from zein was constant for 8 h reaching the zero-order kinetics, and it was approx. 19-fold higher bioavailability than that for the same with PEG400: water solution. The plasma of animals when tested for the presence of RES-O-3-glucuronide, the main metabolite of RES, the time of residence in the plasma and the concentration was higher and could be explained due to higher stability of the zein nanoparticle which is protected from degradation and has the ability to attach to the gut mucosa due to its adhesive properties.

The anti-inflammatory activity of the zein nanoparticles encapsulated with RES is higher when tested in mice inoculated with lipopolysaccharides (LPS) of gram-negative bacteria. LPS from these bacteria would activate the innate immune system of the animals similar to that of the multiple organ
failure in humans [55,56]. They activate pro-inflammatory mediators such as TNF-alpha, NO, and prostaglandin E2 that get released [57] and affect the infiltration of various immune cells to cause inflammation. The resultant symptoms would be chills, tachycardia, and slowness in the movement of the animals due to reduced coordination of the various organs in exerting their influence on human activity. Mice showing such symptoms when treated with RES-loaded zein nanoparticles showed a greater presence of RES in their plasma and helped absorb the endotoxic shock induced by the LPS by the reduction in the pro-inflammatory mediators. Such effects may be observed when RES is treated daily for a week in the ‘guided’ delivery of zein.

6. Colonic-Specific Delivery of RES Using Pectin-Based Delivery Vehicles

The prevalence of colon-specific diseases is gaining importance, and hence so is their treatment. Colon-specific delivery is primarily based on food additives, and anionic polysaccharide pectin is important for its safe-to-use characteristics [58]. The use of zinc as the divalent cation in the preparation of multi-particulate delivery beads has been already studied [59,60]. The oral delayed-release system based on Zn-pectinate gel (ZPG) microparticles are used as an alternative carrier to calcium pectinate beads for colonic drug delivery. In vitro evaluation and modification of pectinate gel beads containing trimethyl chitosan as a multi-particulate system for delivery of water-soluble macromolecules to colon [61,62]. Colon-specific drug delivery: Influence of solution reticulation properties upon pectin beads performance. Colonic drug delivery: influence of cross-linking agent on pectin beads properties and role of the shell capsule type [63].

These preparations with pectin have been tested under in vitro conditions where they were sturdy against degradation in the upper GI tract and get enzymatically digested in the colon due to the digestive enzyme pectinase of the colonic bacteria [64–66]. Das and his colleagues have already prepared and tested the amidated low-methoxy pectin-based beads, encapsulated with RES, which were cross-linked with calcium. The performance of the beads under in vitro conditions was fine with a good release of the drug in simulated intestinal fluid, but the retention was high under in vivo conditions, and the release of the colon-specific RES was delayed [67,68]. The zinc-pectinate formulation prepared by Das et al. has improved properties compared to the Ca-Pectinate beads [69]. The release of RES under the controlled condition of simulated intestinal and gastric media was below the performance of the beads in terms of drug release when they were tested separately. However, when in vivo conditions were simulated and tested, the same beads’ rapid release of RES was observed. However, the ability of the beads to prevent drug release in the upper GI was not attributed to zinc and pectin alone but to the added glutaraldehyde in the formulation, which acts as a hardening agent in the pectin preparation [59,70]. With this preparation, the drug release profile specifically at the colon was tested in vivo and is explained by preparing various formulations that are with RES with glutaraldehyde, unmodified microparticles, and oral administration of RES.

6.1. Formulation

The preparation of pectin beads that are used for drug delivery of RES was performed with zinc acetate, which developed into zinc-pectinate microbeads. However, the absence of zinc acetate and even in the presence of glutaraldehyde did not develop into microbeads for drug delivery. The interactions between the zinc cations and the carboxyl group of pectins have developed into a cross-linking matrix for the formation of microparticles [59,70].

6.2. Shape and Size

The size of the formulated zinc-pectinate particles was 950 μm in diameter on an average, and it is dependent on the glutaraldehyde concentration, cross-linking time, pectin-to-RES ratio, and the pH of the cross-linking solution.

6.3. Weight of the Microbeads
The weight of the particles is influenced by drying and also the concentration of the cross-linking solution pH. The reduction of the pH of the cross-linking solution has produced a reduced weight of the beads. The concentration of the glutaraldehyde in the cross-linking solution is inversely proportional to the weight of the beads formed. Increasing the concentration of glutaraldehyde combined with the cross-linking time at a low pH produced lighter and compact microbeads. These particles, when prepared with a higher RES but lower pectin, would produce heavier beads due to less pectin availability.

### 6.4. Encapsulation Efficiency

RES can be easily encapsulated at an efficiency of 94% in pectin due to its poor aqueous solubility and the characteristics of pectin in transforming itself into a gel at lower concentrations. The efficiency improved at a low pH of the cross-linking solution but fared badly when glutaraldehyde concentration increased and cross-linking time increased. Although the dissolution of RES has increased with increasing pH of the cross-linking solution and increasing glutaraldehyde concentration, the increased availability of RES decreased the efficiency of encapsulation, but at the same increased in marginal solubility at low pectin: RES ratio. The following factors are responsible for the release of RES from the microparticles and are discussed below.

### 6.5. Effect of pH of the Cross-Linking Solution

The influence of the pH of the cross-linking solution on the drug release from zinc-pectinate beads is similar to the drug release profile observed for the same. The drug retention effect is more pronounced when the pH of the cross-linking solution is 1.5 and is completely reversed when the pH is 6. This is due to the closer association of the pectin chains formed due to enhanced ionic and hydrophobic and hydrophilic interactions that occur at low pH. Defined crystalline or 3D network is formed at low pH, making it difficult for the drug particles of RES to come out of the bead structure. Moreover, swelling and erosion of microbeads would happen at high pH, which is favourable for drug release and would occur with the assistance of pectinase enzyme that its effect is prominent in simulated gastric fluid.

### 6.6. Glutaraldehyde Concentration

The concentration of glutaraldehyde can be maintained at a max of 0.5% of the solution for a sufficiently stronger matrix for encapsulation. This would allow the penetration of the aqueous solution into the beads and release the RES. Higher concentrations of glutaraldehyde, such as 1%, would be harder for the penetration of the solution as the pores are tightly formed in the beads [59,70].

### 6.7. Effect of Cross-Linking Time of the Zinc-Pectinate Beads

The zinc-pectinate beads that were cross-linked for a shorter time did not retain the RES for a longer time, and rapid release occurred at the upper GI, which is undesirable. This release would make RES get metabolized into undesirable intermediate (discussed earlier), and the effect of the drug is not achieved at the colonic sites. Cross-linking time when increased to 2 h and till 24 h would make it more retainable in that the drug is not released prematurely in the upper GI rather than in the colon.

### 6.8. Pectin to RES Ratio

A greater pectin-to-RES ratio is to be maintained for the release of RES, specifically into the colon. However, RES concentration must be high for greater encapsulation of the drug into the beads. 3:1 pectin: RES is better for greater availability for matrix formation and RES encapsulation so as not to release it in the initial GI tract. The fact that lower pectin favours more RES encapsulation is overshadowed by the fact that swelling is dominated by higher pectin, which does not let the erosion occur at the upper GI, which is necessary for preventing the early release of RES in the upper GI. A 3:1 ratio is sufficient and necessary for the release of RES only specifically in the colon.
6.9. **Swelling and Erosion of the Matrix**

The release of RES from the zinc-pectinate matrix follows the same principle as with the Ca-pectinate microbeads. The pH of the cross-linking solution did influence the swelling-erosion ratio (SER), with the highest being observed at a pH of 6 and the least at pH 1.5 due to the stronger matrix formation at this pH.

6.10. **Cross-Linking Time**

The time taken to cross-link the matrix for RES encapsulation affects the release of the molecule with higher the cross-linking time lower is the release of the molecule and vice versa due to the stronger association that was necessary for closer matrix formation.

6.11. **Morphology of the Zinc-Pectinate Beads and the Encapsulated RES Inside**

The only difference in pectinate beads is that zinc cation is substituted for calcium, and hence there was no difference is observed in the morphology of the beads when compared with the beads of calcium pectinate. The hydrophobic nature of RES has made the molecule to settle on the surface of the beads, which gave a rugged structure. The presence of glutaraldehyde has a different topology to the beads than those without it. Characteristic peaks of RES for C=O stretching, C-C olefinic, and C-C aromatic double-bond were observed for zinc-pectinate-RES loaded beads. They are uniformly dispersed within it.

6.12. **Pharmacokinetics of Zinc-Pectinate with RES**

The study of the release of RES loaded in zinc-pectinate particles with 0.5% glutaraldehyde, 2 h cross-linking time was compared with beads without glutaraldehyde and oral administration of RES. As expected, RES concentration was highest in oral administration, and subsequently, the beads prepared without glutaraldehyde released RES in plasma after 2 h, and then the glutaraldehyde + beads released RES into the plasma after approximately 4 h. The specific delivery of RES was evaluated on the basis of the fact that the particles would reach the colon only after 5 h of administration [64], and that only those beads that were prepared with glutaraldehyde could achieve this in comparison to those beads which were prepared without glutaraldehyde. This explains the fact that glutaraldehyde would make the matrix sturdier and hence does not permit the premature release of the particle by protecting them from upper gastrointestinal (GI) metabolism and only through the pectinase action in the colon. Thus, the RES delivery to the GI and colon is high in this case [71–73]. In vivo release of RES would be effective with zinc-pectinate microbeads.

7. Dermal Application of RES-Loaded Nanoparticles

Solid lipids were prepared as lipid nanoparticles, which are first-generation lipid nanoparticle carriers for drug delivery and were seen as an alternative to already-existing lipids such as emulsions, liposomes, and as other polymers. The lipid component was replaced by solid lipids, which were advantageous as they remained as solids during preparation, as well as after administration into the body [74]. When solid lipids and oils are blended to produce second-generation lipid nanoparticle technology, they are known as nanostructured lipid carriers (NLC) [75]. These lipid nanoparticles have been used for dermatological applications, in which these lipids are considered generally to be safe. They have a controlled release profile on the skin, and their small size ensures good absorption on the stratum corneum, and they are non-irritants for the skin and eyes and have low toxicity for the normal human keratinocytes [76]. Furthermore, lipid nanoparticles have the enhanced chemical stability of those compounds that are encapsulated and have enhanced sensitivity towards light, oxidation, and hydrolysis [77–81].

Solid lipid nanoparticles (SLNs) and NLCs are primarily prepared with encapsulated RES, and studies have been performed to evaluate the amount of ROS that has been produced in fibroblasts treated with SLNs and NLCs, while at the same time evaluating the cytotoxicity and antioxidant effects in those cells and evaluated the amount of RES accumulated in the skin.
7.1. SLN Particle Size and its Physical Properties

SLN particles prepared with RES have larger nanoparticles, and this is due to the amount of RES that is used in the formation, and the polydispersity index is high due to the decreased ratio between the lipid that is used in the preparation to the amount of RES used for encapsulation. The zeta potential of the SLN preparation with RES increased from −23 mV to −15.3 mV, and encapsulation efficiency of 96% was obtained. Miglyoil was added to the formulations to obtain NLC, and the particle size decreased with an increasing percentage of Miglyoil. At 45% Miglyoil, the NLC particle size was found to be the highest. When replacing the solid lipids with liquid lipids, the tendency to return to solid was higher with higher numbers of fatty acid triglycerides present in them. Miglyoil helps to distribute the energy required by the solidified fatty acids to remain in liquid form by distributing the energy required for the change equally. Emulsification with oil helps in reducing the melting point of the preparation due to the presence of higher unsaturated fatty acids in the oil, and the result would be better emulsification of the NLC droplets [82]. On the basis of DSC studies, the C 888 lipid, used for the solid particles’ preparation, was crystalline and had a characteristic peak at its melting point. The use of oil in the NLC preparations reduced the melting point of the same particles slightly with the decrease in concentration [83]. In both the solid and the liquid preparation, RES lost peaks due to the higher solubility of the molecules in them.

The colloidal sizes of the RES-loaded SLNs and NLCs were determined by TEM. The particles that were unloaded were round and spherical and became amorphous in shape with the loading of the RES due to the settlement of molecules on the surface of the solid lipid matrix. This is due to the difference in the melting points of the lipid used for encapsulation and the RES molecule. In the loading of RES into SLNs, the presence of RES in the outer matrix of the particle is explained by the drug-enriched shell model, and according to it, the solid lipid core that is formed is devoid of RES due to the early reaching of the re-crystallization temperature of the lipids [79,84] than RES, and hence it is pushed out to the exterior. However, in the case of NLCs, the loading of RES is enhanced, and even when the matrix cools, it remains amorphous [79] and has greater loading capacity than the SLNs [85].

7.2. Effect of RES-Loaded Particles on Cell Viability—Cell Culture Studies

The concentration of RES used in the preparation of SLNs and NLCs was tested on cell viability. At increasing concentrations of RES (250 μM–500 μM), the cell toxicity was high, and more cell death was observed. The optimal concentration of RES was 50 μM, at which the cells were more viable. The type of particles—SLNs or NLCs—did not affect the cell cytotoxicity.

Fluorescence intensity, which is directly proportional to the amount of ROS production, in cells that were treated with H₂O₂ was measured. It was observed that the fluorescence intensity decreased on the treatment of the cells with RES. However, the effect was more pronounced when the cells were treated with RES-loaded SLNs or NLCs. This is because the stability of the molecule was greater when they were encapsulated in colloids [86–88], rather than being administered orally. Among the solid and liquid lipid encapsulations, NLCs were found to have reduced the fluorescence intensity and is primarily due to the higher encapsulation efficiency of the NLCs due to their greater accommodation of the molecules within them rather than driving out of RES to the outer matrix in case of SLNs.

The reduced fluorescence intensity of the NLC-loaded with RES is explained by the morphological features of the particle, such as reduced size, lower zeta potential, and lesser anionic charge. Hence, they are not repelled by the cells, and in turn, they are endocytosed [89,90], and hence the effect on the fibroblasts is higher in terms of reducing the ROS produced within the cells than the preparation with enhanced size, which was repelled easily and not taken inside the cells.

Ex vivo diffusion studies have pointed out that the encapsulation of RES into SLNs and NLCs has improved the delivery of RES rather than get extracted from the lipid particles. However, the delivery of RES, which is loaded into NLCs, has deeper penetration into the dermis of the skin with smaller particle sizes and correspondingly reduced electrical charge of repulsion when compared to the solid lipid particle-encapsulated RES that was accumulated on the epidermis.
When evaluating using RES for therapeutic applications, the biocompatibility, stability, and intestinal permeability of the SLNs and NLCs that are loaded with RES were evaluated using Caco-2 cell monolayers, which are intestinal models for membrane barriers. They were grown on permeable filter transwell devices, and the efficiency of drug delivery systems on drug permeation with the Caco-2 cell monolayers form microvilli, growth with differentiation after 21 days, along with tight junctions, enzymes, and transport systems [91,92]. Simulated testing on SLNs and NLCs was carried out under conditions of physiological fluids that mimic gastrointestinal conditions with media such as Fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF). Apart from these media, Hanks’ balanced salt solution (HBSS) was used as the control medium. Bile salts and lecithin, which are natural surfactants, made it as if the micelles were in gastrointestinal fluids, with the media mimicking fasted and fed digestive conditions [93,94]. NLCs improved absorption of RES, whereas the SLNs did not affect it. Moreover, the effect was better when intake was during meals, as the secretion of intestinal juices, which also increase the intestinal permeability, was improved. These carriers are proven to enhance the permeation of the particles across the epithelial cell layers, and the particles retained the nanostructures during the process.

8. RES-Loaded Transferrin (Tf)-Modified Polyethylene Glycol-Poly Lactic Acid (PEG-PLA) Nanoparticles (Tf-PEG-PLA-RSV) in the Targeted Therapy against Glioma

Glioblastoma is a malignant tumor affecting the adult brain for which treatments include radiotherapy, surgery, and chemotherapy [95]. The side effects and the median survival time for these patients have led researchers to look for RES-based therapies for targeted delivery against glioblastoma as RES has neuroprotective effects by inhibiting proliferation and inducing apoptosis of glioma [96,97]. In the reported study, RES was loaded into polyethylene glycol-PLA copolymer nanoparticles, which have been used for many years as drug carriers [98–100]. Although PEG and PLA materials have been regarded to be safe for their usage in the delivery of drugs, loading RES into them would not pose a problem for their development as nano-delivery vehicles [101], but the presence of blood-brain barrier which restricts the translocation of these materials would prevent its usage in therapy for glioblastoma [102]. However, the presence of transferrin (Tf) receptors on the brain capillaries have been exploited [103,104] in the targeted delivery on the glioma [104,105]. Another variation tried was the use of poly epsilon-caprolactone (mPEG-PCL) as nano-delivery vehicles.

The anti-tumor effects of Tf-PEG-PLA-RES and mPEG-PCL in vitro and in vivo were elucidated to substantiate the use of these nanoparticles in the targeted therapy against glioblastoma. The results of this research have clearly shown that the effects observed positively in the therapy against glioblastoma are due to the loaded RES and have nothing to do with the nanoparticles fabricated using PLA-PEG or mPEG-PCL, as already evidenced, improving the bioavailability of RES and reducing the toxicity of the delivery vehicles [106]. The RES-loaded particles were packed intact, with the particle size being smaller than the free RES. The varying pH in the physiological system from 4.0 to 7.0 did not affect the release of the molecule [107] from the encapsulation or the Tf-modification incorporated in the fabrication of the nanoparticles. Overexpression of Tf receptors on the glioma cells enabled the use of Tf on the surface of the loaded-nanoparticles for targeted delivery and for crossing the blood-brain barrier. Treatment of C6 and U87 glioma cells in vitro with nanoparticles alone did not cause any cytotoxicity, whereas the RES-loaded particles had the highest cytotoxicity without affecting the normal cells. Similarly, the effect of nanoparticles without any Tf coating but RES loading produced reduced therapeutic effects as the effect of RES is specific, and only when coated with Tf could they pass through the brain barrier to exert toxic effects only on the brain glioma cells with the tumor. This effect gave protection to rats and enhanced their survival. Hence Tf-coated PEF-PLA-RES nanoparticles have the highest in vitro cell cytotoxicity, anti-tumor activity, and cellular uptake and are potential candidates for targeted therapy for glioblastoma.

9. RES-Loaded Nanoparticles in the Treatment of Cataract
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Cataract is an important disease that causes blindness worldwide. ROS play an important role in the pathogenesis of cataract formation. RES has been known to reduce the oxidative stress and hence would be effective against the cataract formation [108]. It scavenges 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical and superoxide radical and effective in reducing the superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx). To effectively target the ocular sites, polymer-lipid nanoparticles are prepared and are used as nano-delivery vehicles for RES [109].

Using Gelucire 50/13 as the lipid matrix, and 2-Hydroxypropyl-beta-cyclodextrin (HPβCD) as the complexing agent, RES-loaded nanoparticles were prepared and also included curcumin and dibenzoylmethane within them [109]. The overall miscibility of all the polyphenols was good in the Gelucire/HPβCD matrix, with the thermostable particles having RES (discussed here for its importance) in the amorphous state. The RES-loaded nanoparticles were 329.9 ± 1.9 nm in particle size, with a polydispersity index of <0.3 indicating the particles were uniform in distribution without aggregation. RES loading was achieved with an entrapment efficiency of 72.2 ± 1.5%. The release of RES followed the usual pattern of initial burst and then stabilized release from the particles and is due to the release of those adsorbed molecules on the surface of the particles. These RES-loaded nanoparticles are stable for 50 days and can be used without any change in the activity of RES.

The anti-oxidant potential of RES that is loaded into the nanoparticles was evaluated by using 1,1-Diphenyl-2-picryl-hydrazyl (DPPH) and ferric-reducing/antioxidant power (FRAP) assays, which give an estimate of the scavenging capacity of the RES on the free radicals that are generated in cataract [109]. The percentage of scavenging for RES-nanoparticles was close to 80%. These RES-nanoparticles were tested on the cataract formation in bovine lenses and observed that the opacity decreased in the treated lenses when compared to the lenses that were treated with free RES or with nanoparticles without RES. Similarly, the effect of pure RES on the cataract characteristics of percentage transmittance, glutathione (GSH) content, and superoxide dismutase (SOD) activity was poor and did not improve them, whereas when the RES-loaded nanoparticles have significantly improved the SOD activity. Hence, only on encapsulation is RES able to rescue bovine lenses from degradation. The resultant effect would not be in favour of RES in countering the oxidative stress in cataract formation as the nanoparticles cannot be considered to be exclusively on RES activity but also with curcumin [110] and dibenzoylmethane (DBM) and hence there is no validity to the claim that RES alone could help counteract the effect of H2O2-induced oxidative stress in the formation of cataract. However, this does not negate the fact that improvements were observed with the anti-oxidant activity of RES in comparison to the free RES, and this is a first step towards treating the ROS generated in the wake of H2O2 activity, which plays a prime role in cataract treatment.

10. RES-Loaded Poly (lactic-co-glycolic) acid (PLGA) Poly-(caprolactone)-poly(ethylene glycol) (PCL–PEG) Nanoparticles in Cochlear Cells

Cisplatin is a major chemotherapeutic agent in the treatment of various types of tumors [111]. The ototoxicity [112] of the cisplatin treatment includes ear pain, hearing loss, and deafness. This is due to the apoptosis that is triggered in the cochlear cells, which is associated with the generation of reactive oxygen species (ROS) [113,114]. Several anti-oxidant agents to counter the ROS have been tested but not approved by the FDA for countering the hearing loss due to cisplatin treatment. Since RES has been known to have cancer prevention property [5], it has been used in the treatment by encapsulation in nanoparticles.

Nanoparticles prepared with biodegradable Poly (lactic-co-glycolic) acid (PLGA) are prepared, as they are safe for encapsulating RES and have good drug control release kinetics. To stabilize the nanoparticles, poly-(caprolactone)-poly(ethylene glycol) (PCL–PEG) di-block was used, which is amphiphilic and improves the RES loading. In the preparation of RES-loaded nanoparticles, the solvent-diffusion method is used. The concentration of PLGA has increased the viscosity of the organic phase and increase the size of the nanoparticles that are prepared, resulting in increased diameters of the particles. PLGA also influences the zeta potential of the particles, in which it tends to decrease the RES-loaded particles, but the addition of PCL-PEG has a neutralization effect. Hence, the zeta potential values are shifted towards neutral values, and hence the PLGA carboxylic groups...
are protected by the outer PCL-PEG molecules at physiological pH. The encapsulation efficiency of these particles for RES loading is more than 100%. This is due to the increased hydrophobicity of the PCL-PEG in the core [115] of the particles and the good RES to polymer ratio [116]. Greater encapsulation efficiency may have a burst effect, but this was not observed with these loaded nanoparticles. Considering the burst effect for this model, the release studies have shown that the RES release would not be compromised under conditions other than the cytoplasm of the cochlear cells. This model is highly favourable as the burst effect is low and the release of RES from the nanoparticles at physiological fluids before the cochlear cells’ uptake.

10.1. Cryoprotection and Storage

RES-loaded particles cannot be stored with lyophilization as the particles get unstable during the preparation, with the crystalline structure getting collapsed. Hence various cryoprotectants such as mannitol, lactose, sucrose, and trehalose for protecting the nanoparticle [117] were tested. Trehalose was concentration-dependent, and it builds up ice crystals to give physical stability to the particle [118], and hence can be used for cryoprotection.

10.2. Evaluation of the Toxicity of the Nanoparticles

The toxicity of the nanoparticles prepared was evaluated in in vitro studies using primary cochlear and mouse fibroblast cells. It was found that they are concentration-dependent, and the nanoparticles are toxic at a concentration higher than 785 μg/mL [119]. The unloaded nanoparticles were themselves toxic to the HEI-OC1 cells at concentrations greater than 800 μg/mL, but not to SVK-1 cells.

This is because these two cells have different origins. HEI-OC1 cells are immortalized cells derived from the murine corti [120] and are used to test the otoxicity of the drugs, and SVK-1 cells are from murine stria vascularis [121]. The nanoparticles are toxic to the organ of the corti cells, as these cells require specific environmental conditions for them to hearing process and that the nanoparticles concentrations tilt the osmotic balance to make it more stressful to the cells. This makes the conditions toxic to the cells and hence exhibits a decrease in the cell viability to the nanoparticles. However, the morphology of the SVK-1 cells is like that of epithelial cells, and hence they are more resistant to the osmotic modulation due to the nanoparticle concentrations.

Both these cells do not exhibit any toxic effects due to RES concentration below 50 μM but decreased their cell viability at higher RES concentrations due to the direct effect of RES on the mitochondria functions. Overall, the RES-loaded PCL-PEG-PLGA nanoparticles are suitable for delivery into the cytoplasm of cochlear cells for improving the hearing that is lost during treatment with cisplatin.

11. Silk Fibroin Nanoparticles Encapsulated with RES Can Fight Periodontitis

Periodontal disease is associated with both inflammatory and non-inflammatory conditions of diabetes and coronary heart disease [122]. Significant increases in the levels of expression of IL-1β, IL-6, or transforming growth factor (TGF-β) have been observed in this disease [123]. IL-6 is a pro-inflammatory mediator and is responsible for the induction of acute-phase protein—C-reactive protein and for the proliferation and differentiation of B-cells and monocytes, respectively, and in the formation of osteoclasts [124,125]. Since the implication of IL-6 in the regulation of bone metabolism [126], this cytokine is found to be involved in the progression of many diseases. TGF-beta is an important cytokine with pleiotropic effects responsible for the production of IL-1 and IL-6 and in the suppression of humoral response and wound healing and tissue regeneration. Chronic oral diseases like gingivitis, periodontitis, and periimplantitis have observed significant levels of TGF-beta involvement studied in them. The fact that RES could be used as a protective agent in periodontitis by reducing the blood glucose levels has been the key reason for encapsulating it in silk fibroin for effective delivery in case of periodontitis [127].
The properties of wound healing and the ability to carry the drug within it have made silk fibroin an attractive molecule for drug delivery. Furthermore, it can stimulate glucose transport in adipocytes and can tackle the proinflammatory IL-1β and IL-6. The composition of natural materials in silk fibroin have made it non-toxic and biocompatible [128], and thus it can be easily assimilated into the body [129].

When these RES-loaded silk fibroin nanoparticles are administered into animals which have induced-periodontitis, the levels of IL-1β and IL-6 are decreased significantly. IL-1β has been implicated in the inflammation caused due to bone remodeling and also IL-6. The reduction in the levels of both these pro-inflammatory cytokines due to the RES-silk fibroin particles are the indices for the recovery from periodontitis [130,131]. These decreased levels were not obtained with silk fibroin nanoparticles only and are due to the anti-inflammatory activity exhibited by RES that has been encapsulated. Greater increases in the epithelium due to increased migration on inflammation have been controlled with RES-silk fibroin, and the epithelium appears normal in animals treated with RES—silk fibroin nanoparticles. Other physiological features such as collagen compaction [132,133] due to inflammatory cytokines and angiogenesis due to periodontitis [134] have been effectively reduced by this treatment in animals.

12. Protection of Cells from Oxidative Stress by RES-Loaded Polymeric Micelles

An important disease that is primarily caused due to beta-amyloid peptide-induced oxidative stress is Alzheimer’s disease, which is most common among the elderly. RES has been known to be effective in containing the oxidative stress due to its antioxidant property [135–137] and is a probable candidate to be used in the therapy of this disease. In vitro studies [135–137] have given a clear picture of its therapeutic use in human umbilical vein endothelial cells (HUVECs), SHSY5Y neuroblastoma cells in protecting them against the oxidative stress induced by amyloid beta-peptide [135]. However, existing pieces of evidence in using RES against fighting oxidative stress in in vitro and in vivo studies do not give plausible results in extrapolating these towards their usage in therapeutic applications. This is because the concentration of RES used in in vitro studies is different from that used in rat models, and the pharmacokinetics and pharmacodynamics used in in vivo studies have been different [115].

A long-term treatment involved in Alzheimer’s disease cannot be taken as a model for resveratrol testing without understanding the toxicity of the molecule in the physiological system, but only with cell-culture-based results. Furthermore, available evidence has proved that the availability of RES in humans is affected [138] by the rapid metabolization of the molecules into glucuronic and sulfate metabolites [139], making oral intake unsuitable for the treatment. Hence biodelivery devices using polymeric micelles with polycaprolactone (PCL)-polyethylene glycol (PEG) are shown to be suitable for the delivery of RES in neurodegenerative medicine [138]. They are self-assembling and have a hydrophobic core for encapsulating the drug and hydrophilic exterior for protection [140]. Using these fabricated nanoparticles, the effect of RES in acting against the ROS and assessing the caspase-3 activity, the cell viability, and hence the improvements in the disease were evaluated.

In the evaluation of RES-loaded nanoparticles, since Alzheimer’s treatment is long-term, the administration of RES has not rescued the cells even at a concentration of 10 μM against a 10 μM concentration of the amyloid peptide. However, no toxicity was observed in PC12 cells at a concentration of 50 μM. Since RES has pro-oxidant and anti-oxidant properties, and it causes apoptosis of the cells at high concentrations, RES cannot be used as preventive care against Alzheimer’s without researching the cytotoxicity extensively in in vivo conditions. The concept of killing cancer cells may not be applicable in Alzheimer’s as it requires rescuing the cells from cell death. As the target of RES for Alzheimer’s disease is in the brain, crossing the blood-brain barrier would be a challenge and has been considered for treatment in neurodegenerative diseases. In the case of RES-loaded PCL-PEG nanoparticles, polymeric micelles are prepared with RES being hydrophobic can be accommodated in the hydrophobic core with the hydrophilic PEG in the exterior, giving protection to RES and easy dissolution in the solvent for RES release.
When these RES-loaded nanoparticles were pretreated with PC12 cells, which were then treated with amyloid-beta peptide at 10uM concentration, the long-term treatment affects the cells in rescuing them from cell death and is has reversed its effect of free usage of RES without nanoparticle encapsulation. This encapsulation prevented the accumulation of lipophilic RES in the cell membrane [23,141] and took the endosome–lysosome pathway [142,143] to become endocytosed and slowly released from the core of the nanoparticles. The phenolic groups of RES then scavenge the ROS generated by the amyloid-beta peptide and attenuate the oxidative stress [143,144], rescuing the cells from cytotoxicity followed by a reduction in caspase-3 and enhancing the cell viability [145]. This is advantageous than the free RES, which is highly toxic to the cells and cannot be used for therapy in Alzheimer’s disease treatment.

Another model with Resveratrol-Oat protein-shellac complex [Oat protein-shellac nanoparticles as a delivery vehicle for resveratrol to improve bioavailability in vitro and in vivo] was used as a delivery vehicle for RES delivery to fight against oxidative stress. These particles were spherical, and the OP-shellac structure was better in encapsulation of RES with size 323 nm and zeta potential of -35 mV for limited diffusion into the aqueous medium. The encapsulation efficiency of the nanoparticles without shellac was 60% and increased to 90% with shellac coating. The release of the RES from the nanoparticles was following a diffusion-controlled mechanism, and at a pH of 7.4, the release was sustained, and the absorption at the small intestine for RES was complete.

Nanoparticle delivery that was loaded with RES were transported across the small intestine and absorbed by the Caco-2 cells, which are having tight junctions at monolayers and are similar to the human intestinal cells. The uptake of the nanoparticles was higher when the particle sizes were bigger, and the particles were taken up by energy-dependent endocytosis. Experiments performed with Chang liver cells for determining the effect of these loaded nanoparticles on the liver response, H2O2-treated cells exhibited higher oxidative stress, whereas the cells, when treated with RES-nanoparticles, have the functionality to scavenge the hydroxyl radicals that are generated in the decomposition of H2O2. Similarly, the GSH content of the cells has increased, which is a clear indicator of the anti-oxidant mechanism that is activated in the RES-loaded-nanoparticle-treated cells.

In vivo studies indicated an increase in the bioavailability of the RES-nanoparticles as the carboxyl groups on the surface of the nanoparticles are helpful in the intake by the cells and aids in internalization. These small-sized particles were then easily transported from the intestine to the circulation. Upon CCl4 treatment for hepatotoxicity, the treatment with RES-nanoparticles reduced the generation of ROS and increased the activities of CAT and GSH enzymes to prevent the hepatotoxicity. The reduction in the accumulation of fat in the hepatic lesion also indicates the RES-mediated protective effect against oxidative stress.

13. Effect of RES and Gold Nanoparticles on Diabetic Retinopathy

Diabetic retinopathy is one of the most frequent complications arising due to hyperglycemia in diabetic patients [146]. It often leads to edema in the retina, blood-retinal barrier breakdown, and finally, loss of vision [147]. An increase in oxidative stress and generation of reactive oxygen species along with the subsequent changes in the amount of glycation end products due to oxidative reactions, peroxidation of protein, lipids, and DNA are mostly implicated in the pathogenesis of this disease [146]. They active the NF-KB transcription factor in increasing the proinflammatory cytokines to complicate the situation [148].

Resveratrol, with its anti-oxidative properties and which acts as an anti-inflammatory agent, has been encapsulated in gold nanoparticles (AuNP) [149] and tested for its efficacy [148] in reducing the effects of diabetic retinopathy. The prepared nanoparticles were 10 nm in size and had a crystalline structure. The blood glucose levels in the STZ-diabetic rats treated with RES-AuNP decreased and the HbA1C values also decreased after treatment when compared to the untreated rats. The obvious observation is that when the diabetes-induced rats were evaluated for their retinal vascular permeability after treatment with RES-AuNPs, the permeability got reduced, and the blood vessels remained normal. Also, the thickness of the retina of the normal group animals was sizably thick, and the retineae became thinner on treatment with RES-AuNPs [149].
On examination of the gene expression for the pro-angiogenic factors of the retina, the protein, as well as the expression of mRNA of vascular endothelial growth factor, decreased in the AuNP-treated rats when compared to the untreated diabetic rats although the expression of pigment epithelium-derived factor remained the same among the rats of both the groups. Inflammatory cytokines that are increased as a part of the oxidative stress in the diabetes-induced animals had higher levels of expression of IL-1beta, IL-6, and TNF-alpha. The trend was reversed in rats that were treated with AuNPs when compared to the ones that are un-treated. Subsequently, the levels of Vascular Cell Adhesion Molecule 1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1) and Monocyte Chemoattractant Protein-1 (MCP-1) also increased due to diabetes-induced changes and the conditions returned to normal after treatment with AuNPs. The increase in inflammatory cytokines and chemokines occurs through the phosphorylation of the extracellular signal-regulated kinase (ERK) 1/2 and NF-KP phosphorylation, and it appeared to be higher in the diabetes-induced groups which were reduced significantly using AuNP when compared to the normal group [149].

14. Mesoporous Carbon Nanoparticles and RES in the Treatment of Triple-Negative Breast Cancer

A highly aggressive and metastatic breast cancer, triple-negative breast cancer (TNBC), due to absence of progesterone receptor (PR), estrogen receptor (ER) or human epidermal growth factor receptor-2 (HER2) on their cells, is difficult to treat, as present treatments with anthracyclines are not specific and can affect both the cancerous and normal cells [150]. This would increase the drug resistance, and a less toxic and viable alternative was searched and prepared with RES in place of the existing drug for TNBC.

The nanoparticles were prepared with mesoporous carbon nanoparticles (MCNs) that have a carbonaceous network that has higher absorption capacity and drug loading within them when compared to the silica nanoparticles [151]. These MCNs are superior in accommodating the drugs in the amorphous state and have greater solubility of the drug, but the hydrophobicity of MCNs makes it unsuitable to use it without modifications. The oxidized-modified MCNs (oMCNs) are used to load RES, which displayed high loading and bio-compatibility [152].

The surface area of the oMCNs loaded with RES has decreased, indicating RES encapsulation, with the particle size remained the same as 187 nm on average. The morphology of the oMCNs-RES was spherical with the pores aided in the dispersion in water to increase the hydrodynamic radii. About 25% of RES was loaded into the nanoparticles, and it was loaded in the amorphous form inside [151].

The intake of RES-oMCNs was tested with MDA-MB-231 cells and it was observed that 24 h after treatment, the delivery capacity increased to observe the fluorescence of the RES-loaded nanoparticle around the nuclei. No toxicity was observed for the oMCNs and hence it would be a better nano-delivery vehicle for drug delivery. It was also noted that the RES solubility and release from oMCNs after loading increased when compared to the free RES which can be attributed to the encapsulation where it follows the Ostwald-Freundlich equation, in which the size of the nanoparticle was less but the surface increased and due to which there is a significant interaction area between the medium in which RES was dissolved and RES and hence there is an increase in its solubility. The free energy of RES was high as it was packed inside the oMCNs in the amorphous state has also contributed to the large solubility of RES in the medium.

The MDA-MB-231 cells that were treated with RES-oMCNs have exhibited cytotoxic effects due to RES in a concentration-dependent manner, and the results for proteins expressed during apoptosis by Annexin V/PI staining and Western blot reiterated this. It was also shown that the apoptosis of the cells occurs through the cleavage of PAPR and caspase-3 activation [153]. The oMCNs loaded with RES were taken up by the cells through endocytosis mechanism instead of the passive diffusion process that occurs in free RES, and hence this method of RES encapsulation ensures greater availability to the cells and specific in toxicity to increase the delivery.

15. Solid Lipid Nanoparticles Loaded with RES in the Treatment of Colon Cancer Cells by Targeted Delivery
In the treatment of colon cancer, solid lipid nanoparticles were used and were loaded with multiple drugs for the synergistic action of the drugs at the point of concern and to avoid resistance from the cells to a single drug [79,154]. To target colon cancer, RES, ferulic acid (FER) and stearic acid were encapsulated together. Ferulic acid can inhibit colon cancer cells and stearic acid for conjugation with folic acid [155]. To increase the biocompatibility and the mucoadhesive properties of the SLNs, the particles were coated with chitosan and used. Since cancer cells overexpress folic acid receptors, coating the nanoparticles with its ligand, folic acid would increase the chances of availability, the specific target of cancer cells and conjugating properties. Hence, chitosan-coated-RES-FER-loaded SLNs along with stearic acid that has a surface ‘decorated’ [156] with folic acid were prepared.

The RES-FER-SLNs were prepared by the solvent evaporation method and coated with chitosan by hot homogenization method and further added folic acid to chitosan and the prepared nanoparticles were spherical in morphology in uniform. The final coated and loaded particles have 174 ± 5 nm diameter with a polydispersity index of 0.166, indicating the uniformity of the particles. The zeta potential of C-RSV-FER-FA-SLNs was −25.9 mV indicating no aggregation of the particles [157]. X-ray diffraction and FTIR results suggest that RES and FER are dispersed evenly within the solid lipids and are stable inside the encapsulation.

When the HT-29 cancer cells and the normal 3T3 cells were treated with C-RSV-FER-FA-SLN particles, folic acid-containing these nanoparticles would bind greatly to the HT-29 cells, which have over-expressed receptors for folic acid [158]. The normal cells did not have any interaction with the fabricated and drug-loaded nanoparticles, and hence the effect is observed as cytotoxic to the cancerous cells leaving behind the normal cells intact. These nanoparticles are specific and have an anti-cancer and a cytotoxic property exerted by RES. Apoptosis is accompanied by a decrease in the mitochondrial membrane potential [159] and integrity of the HT-29 cells and a reduction in the expression of cyclins and cyclin-dependent kinases: cyclin D1 and E, CDK4, and CDK2 and Bcl-2 proteins and upregulation of pro-apoptotic proteins such as Bax. The expression of cytochrome C indicates that apoptosis occurs through the mitochondria-dependent cellular apoptosis and activating caspases [160]. Furthermore, C-RSV-FER-FA-SLNs have arrested the cellsregarding being in the G0/G1 phase of the cell cycle [156,160] and did not allow the cells to replicate characteristic of the RES property in using as an anti-cancer agent. Hence C-RSV-FER-FA-SLN can be used as an anti-cancer agent in the treatment of colon cancer.

16. RES-Loaded Mesoporous Silica Nanoparticles for Prostate Cancer Therapy

The importance of prostate cancer has interested researchers looking for a possible therapy that has the advantages of acting against the resistance that plagues existing therapies [161,162]. The resistance to chemotherapeutics exerted by cancerous cells is due to the presence of hypoxia that helps the cells to metastasize and become resistant to therapy. The hypoxia-inducible factor is the transcription factor that is implicated in the transcription of various proteins that are known to resist the chemotherapeutics and survive under hypoxic conditions [163]. Docetaxel (Doc) has been used in the treatment of prostate cancer, but the cells acquire resistance due to usage and cannot be considered viable [164]. Hence, the idea to supplement the therapy using RES has been underway as RES is known for its anti-inflammatory, anti-oxidant, and anti-apoptotic properties [165]. RES is proven to act against the prostate cancer cell lines of LNCaP and PC3 [166].

In the development of a nano-delivery vehicle for RES, mesoporous silica nanoparticles (MSNs) has been advocated for its silanol functional groups on its surface for modification of the surface [167,168], improved pore size, and particle size, and is used in for encapsulation of hydrophilic and hydrophobic molecules. The fabricated nanoparticles of MSNs have positively charged surface amine groups and negatively charged phosphonate groups and are loaded with RES to effectively act against those cancer cells that are found resistant to Doc in PC3 cells.

The surface of the MSNs was modified with functional groups such as phosphonate and amines using silane chemistry and observed that the modifications did not affect the size, shape, and morphology of the MSNs. The sizes of the MSNs thus prepared were uniform with approx. The diameter of 72 nm after modifications [168]. The zeta potential of the RES-loaded and functional
group modified MSNs were in the range of -42.8 and -11.2 mV, indicating the non-aggregation in preparation.

The fabricated nanoparticles were thus tested on PC3 cells and proliferation inhibition of the treated cells was observed at a concentration of 20 μM of free RES at the highest, which was dose-dependent. This is a significant inhibition when compared with the similar controls with DMSO treatment, whereas the highest proliferation inhibition was observed for NH2-MSNs at an IC50 of 7.15 μM. Previous studies on the use of RES in synergistic action against cancer cells were tested with PO3-MSN-RES with Doc, as a high concentration of Doc was usually required to significantly inhibit the proliferation of PC3 [169]. It was observed that RES was capable of reducing the concentration of Doc required for the prostate cancer cells to exert its therapeutic action and rescue the normal cells from the Doc-induced toxicity. The conditions tested were hypoxic similar to the tumor microenvironment in prostate cancers, where the expression of MDR has rendered the cancer cells to be resistant to chemotherapeutics [169].

A combination of (0.1–10 nM) Doc of Doc and (10 μM) RES would be effective in exerting toxic reactions in PC3 cells without affecting the normal cells. This is made possible with the increased anti-oxidant potential of RES in scavenging the ROS that is generated under hypoxic conditions [168]. Hence, RES encapsulated in PO3-MSN nanoparticles are a promising tool for providing an alternative to chemotherapy resistant-prostate cancer.

17. RES-Co-Micellar Nanosystems in the Treatment of Arthritis

Inflammation of joints due to the destruction of cartilage and soft tissue results in a diseased condition of arthritis, and it is necessary to find a cure for it [170]. The medicines so far administered have renal, cardiac, and hepatic side effects. Another treatment that included intra-articular corticosteroid administration of indomethacin caused joint dystrophy in rats [171], and the need is rising for a cure that does not have side effects. Hence RES was tried as a therapeutic molecule due to its potency against arthritis as a known anti-inflammatory and anti-oxidant agent [172]. RES has been known to reduce paw swelling and inflammatory cell infiltration into the affected area. To encapsulate RES for its delivery to the inflamed joints, amphiphiles of poly(ethylene oxide)--poly(propylene oxide) PEO-PPO block copolymers that form micelles coated with polyactic acid (PLA) were used [173]. The success obtained when using PLA for IA injection was high, and it had a high loading capacity for delivering RES.

Poloxamer 188 (Pluronic® F-68) and poloxamer 407 (Pluronic® F-127) were employed for preparing mixed micelles. P188, being anti-inflammatory and cytoprotective, serves as both a pharmaceutical and as a therapeutic agent in this preparation. Poloxymethylene hydrophilic chains reduced the use of P188 for encapsulating the hydrophobic RES, but when mixed with P407, which is less hydrophilic, micellization of these copolymers could make these polymers suitable for RES loading. An increased proportion of P188 to P407 gave a better combination for RES encapsulation, as P407 has high molecular weight and cannot entrap a higher amount of drug due to steric hindrance, and hence hindrance of encapsulation efficiency [173]. This proportion also enabled a better in vitro release of the RES from the copolymers due to the faster degradation of the polymers.

In vivo studies in rats tested with PLA-coated-P188+P407-RES on induced arthritis reduced the size of the swelling in arthritic rats after treatment and is significant when compared to the group in which arthritis was induced but which was left untreated. The evaluation of the pro-inflammatory cytokine TNF-α also indicated that the co-micellar system-treated animal group showed an effect of the treatment by decreasing the levels of TNF-α, which is an indicator of reduction of synovial inflammation [171]. This could be due to the synergistic effect exhibited by both P188 and RES on the tissue inflammation [173]. Histopathological information also indicates that this system is more specific with IA administration on the inflamed joints and is a suitable agent for the delivery of RES in the treatment of arthritis.

18. Treatment of Insulin Resistance in Type 2 Diabetes with Resveratrol-Loaded Solid Lipid Nanoparticles
Insulin resistance in Type II diabetes is influenced by SNARE protein complex, which comprises of synaptosomal-associated protein 23 (SNAP-23), syntaxin-4 (STX4), and vesicle-associated membrane protein 2 (VAMP-2) [174]. GLUT2 and 4 are disrupted in the muscles and adipose tissues and hence develop insulin resistance [175]. Reports have suggested that when SNARE proteins are down-regulated, they develop insulin resistance. The use of RES against insulin resistance is very well documented. The administration of RES through intraduodenal decreases the SIRT1 protein of the duodenum [176] and improves insulin resistance. It also reduces the glucose production in the liver in rats. Another research report informs about improving insulin resistance by improving the expression of visfatin and RES feeding has improved the expression of glucose transporter GLUT2 and 4 in rats which are induced with diabetes [177]. Hence, RES was encapsulated in SLNs and tested the following parameters, such as fasting blood sugar (FBS), insulin, and oxidative stress in type II diabetes-induced rats [178].

The SLN-RES nanoparticles that were prepared [178] had an average of 248 nm in size, zeta potential at 16.5 mV, and with a RES entrapment efficiency of 79.9%. These nanoparticles with RES had a sustained release of RES and hence had good bioavailability for RES. The effect of RES-SLN on the glucose content in the blood serum was low, and the hypoglycemic effect was better and significant when compared to the effect observed with free RES. This was attributed to the increased absorption of the encapsulated nanoparticles in the intestines and the presence of RES in the blood circulation for a long time. When the same was administered into the peritoneum, the effect was significantly better in streptozotocin-induced diabetes in rats.

The administration also helped in maintaining the antioxidant status and reduced the expression of lipid peroxidation malondialdehyde [179]. This effect is considered superior to free RES treatment, as the bioavailability of RES-SLN is high for a better effect. The gene expression of Snap23, Stx4, and Vamp2 increased with the RES-SLN treatment than in free RES and improved the insulin resistance [180]. This is due to the better muscle permeability of the RES-SLN in having the elevated expression of these genes and hence the biodistribution of RES in the muscle cells in type II diabetes.

19. Application of Resveratrol-Loaded Nanoparticles on the Wafer for Wound Healing

Wound healing is a complex process involving many stages from inflammation at the site of tissue destruction to infiltration of immune cells to those sites and then healing [181]. Disturbances in those processes are critical to wound healing, and various wound dressing is tried to minimize the infection and enhance healing. To prepare a matrix that has greater drug loading, wafers are used, which are porous in structure and can be prepared by freeze-drying owing to their large surface area [182]. Carboxymethyl cellulose has been used for wound dressing for its biocompatibility with the mucous layer of the skin, low immunogenicity, greater drug loading capacity, swelling capacity, and biodegradability [183]. Using these, wafers were produced and were loaded with resveratrol nanoparticles that can be used to topically treat the wound area on the skin. RES has the wound healing capacity with its anti-oxidant property and can enhance the expression of vascular endothelial growth factor (VEGF) and the activity of endothelial nitric oxide synthase [184].

RES was loaded onto cellulose acetate butyrate (CAB), and the nanoparticles were prepared by a solvent evaporation method, which is a biodegradable and non-toxic material and tested in a wound model in Wistar rats [181]. The optimal formulation includes 20 mg of CAB and achieves an encapsulation efficiency of 87.58%–97.43% with a negative zeta potential value range from –0.66 mV to –5.03 mV, indicating the higher colloidal stability of the fabricated particles. The wafers prepared were smooth on the surface and have a spongy texture for water uptake and for them to adhere to the wound site and can influence the drug response with the desired concentration and desired retention time. Hence the CMC-HPMC copolymer wafers possessed superiority with respect to the parameters of hydration capacity and adhesive ability.

On the application of these RES-nanoparticles-wafers on the wound of Wistar rats, the wound healing process was accelerated when compared with the wafer only and RES-wafer. It was observed that the necrosis and inflammation were present in the wounded areas of the skin and that treatments with RES-wafer have regenerated the appendages [181]. The superiority of the RES-wafer-
nanoparticles was established when the epithelialization and regenerated appendages were reported to be enhanced. Moreover, the necrosis in the tissue was reduced, and the number of inflammatory cells in the RES-wafer-nanoparticle-treated animals was reduced with more intact collagens making it towards the path of recovery [181]. These have the edge over the RES-wafer or just wafer treatment results. Hence, the encapsulation of RES in the form of the wafer for drug delivery on to the wounds with a more pronounced effect is observed for the more adhesiveness that has promoted effective delivery for cell proliferation.

20. Conclusions

The application of nanoparticles (NP) in the healthcare industry is growing rapidly. It has great potential to tackle the obstacles of toxicity and can efficiently target the different organs and cell types. However, the challenge is to ensure that RES is delivered to targeted organs and its desired effect. Hence, understanding the molecular mechanism would help design the NP for drug delivery for specific diseases to deliver the confirmation of the drug. The therapeutic outcome of any of these NP preparations also depends on the mode of internalization of these NP in these cells, preparation of NP with the use of different materials, route of administration and dose of the drug to be delivered after absorption, distribution, metabolism and elimination mechanisms happen in the cells. In the course of writing this review, careful consideration was given to all the discussed parameters for achieving a better NP preparation of natural materials to encapsulate RES against various diseases. Furthermore, this will only materialize in the use of RES-nanoparticles after passing the stringent regulations of the FDA.

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