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Review Article

Enhancing Resveratrol Delivery: A Nanotechnological Approach

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Abstract

Background: Resveratrol (RES), a natural polyphenol, has gained significant attention for its health benefits, making it one of the most extensively researched compounds of its kind. Its potential was first highlighted in the early 1990s through the French paradox study, which spurred widespread interest and scientific inquiry. **Objective:** This review aims to delve into the diverse health benefits of resveratrol, its routes of administration, and the critical role of nanotechnology in enhancing its therapeutic potential through advanced drug delivery systems. **Conclusions:** Despite its promise, resveratrol's practical application is challenged by its poor water solubility and limited stability, which hinder its commercial success. These limitations can be addressed by encapsulating resveratrol in multifunctional delivery systems, such as micro- and nanoparticles. Such encapsulation significantly improves water solubility, stability, and bioavailability, offering a pathway to more effective and commercially viable formulations, and paving the way for broader therapeutic applications and widespread consumer accessibility.

Keywords: Resveratrol, Polyphenol, Nanotechnology, Drug delivery systems, Encapsulation

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Introduction

Resveratrol ("3,5,4'-trans-trihydroxystilbene") is a stilbene-derived polyphenolic phytoalexin.[1] Grape skin and seeds are the primary sources of this natural dietary plant compound. It is also present in a variety of other plant-based foods, such as peanuts, fruit, and tea, in addition to beverages.[2]

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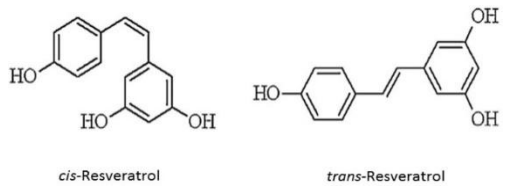

Figure 1: Resveratrol chemical structure (cis and trans forms).[2]

More than 70 plant species produce RES. in response to infection, stress, injury, fungal or bacterial infections, and UV-irradiation. This compound functions as a phytoalexin, a type of antimicrobial agent that assists plants in combating pathogens including bacteria and fungi, thereby facilitating their survival in challenging environments. RES synthase catalyzes this molecule synthesis in plants, a procedure that is analogous to flavonoids, within the phenylpropanoid pathway.[3]

Challenges related to different routes of administration

The transmission of RESs via a variety of routes presents numerous obstacles. Despite its minimal solubility in an aqueous medium and nearly non-existent bioavailability profile, RES isn't suitable to be utilized alone topically or orally. This is the point at which innovative drug delivery systems (DDS) are indispensable. While it is an ideal anti-inflammatory, chemoprotective, and anti-oxidant agent, issues arise as a result of its poor photostability, limited skin penetration, bioavailability and insolubility. [4]

The oral administration of RES offers notable benefits, including convenience and potential health advantages such as cardiovascular protection, antioxidant properties, and support for weight management. However, it also faces significant challenges, particularly due to rapid elimination and metabolism it has low bioavailability, which limits the amount that can exert therapeutic effects. Additionally, the efficacy of RES can vary among individuals based on factors like diet and gut microbiota, complicating dosing recommendations. High doses may lead to adverse effects such as gastrointestinal (GIT) disturbances and interactions with certain medications. Moreover, the formulation of RES supplements can impact their effectiveness, as many products may not contain sufficient levels of the active form (trans-RES). Therefore, while oral RES supplementation presents a promising avenue for health benefits, addressing these challenges is crucial for optimizing its therapeutic potential.[5]

Oral route

As previously mentioned, RES has a variety of effects; however, it is accompanied by challenging issues such as limited solubility (0.05 mg/mL in water) and metabolism. The RES lipophilic characteristics, which has a Log P/Ko/w of 3.10, results in its rapid absorption into the portal vessels at nearly 75%. Conversely, the liver aggressively metabolizes it via phase 2 metabolism and the sulphated, methylated, and glucuronide complexes formation. Sulphate complexes with phenolic groups are responsible for a rate-limiting phase in the

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RES bioavailability. In order to facilitate metabolism, certain of these compounds return to the gastrointestinal tract (GIT). It is interesting to realize that RES enhances its own metabolism.[6]

The amount of drug that is unchanged and enters the systemic circulation is considerably lower. On the other hand, most of drugs develop complexes with lipoprotein and albumin, that promote temperature-mediated diffusion and passive diffusion. Nevertheless, the drug distribution and transportation to the various compartments for cellular uptake are primarily facilitated by the drug's combination with albumin complexes after administering 25 mg, Kumar et al. reported that doses administrated orally results in approximately 70% absorption, a maximal plasma level of 491 ± 90 ng/mL, and a half-life of 9.2 ± 0.6 h. In the urine utilizing liquid chromatography-mass spectrometry majority of the concentrations are detected. Epithelial cells readily absorb RES. Consequently, the concentration of medications in these cells is elevated. [4]. In conclusion, the compound exhibited a robust binding to human plasma proteins at 37°C, with a 98 percent binding rate.[7]

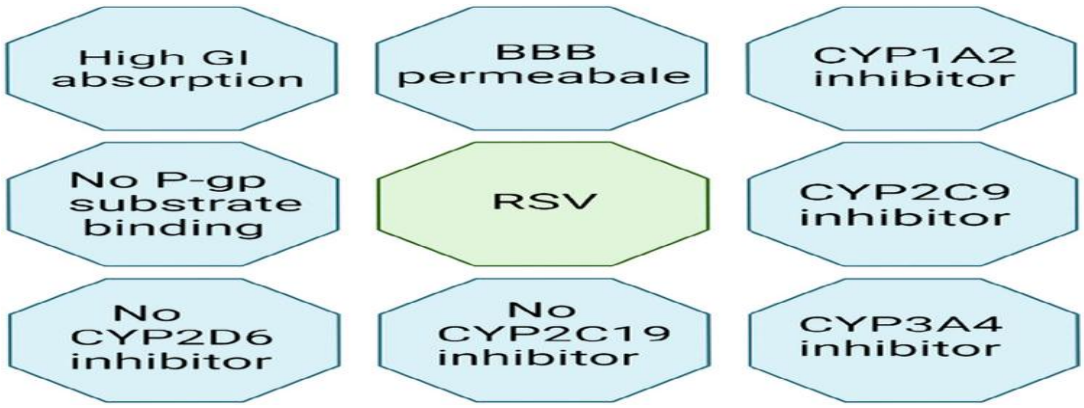

Figure 2: RES pharmacokinetic properties. CYP1A2: cytochrome P450 1A2; P-gp: P-glycoprotein; CYP2C9: cytochrome P450 2C9; CYP2D6: cytochrome P450 2D6; CYP3A4: cytochrome P450 3A4.[4]

Topical route

A topical therapy that is particularly effective necessitates a high degree of evident permeability throughout the skin, while simultaneously exhibiting minimal skin irritation. The RES topical application is restricted due to its weak skin retention and minimal permeability. This leads to a decreased required concentration of the active pharmaceutical ingredient (API) for achieving therapeutic efficiency, allowing a smaller drug quantity to effectively reach the target site. RES is unable to permeate the stratum corneum (SC) due to its large partition coefficient and molecular weight exceeding 500 Da. Additionally, RES is linked to moderate erythema and allergic reactions that results in inadequate patient compliance. Therefore, the primary causes of RES's inadequate therapeutic effectiveness

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are its ineffective delivery and unwanted skin interactions.[8]

The RES nanoliposomes significantly increased the RES transdermal penetration and retention in addition to enhancing cellular absorption. In contrast to free RES, RES nanoliposomes significantly boosted the skin-care effects by increasing collagen synthesis and antioxidant capacity, while simultaneously decreasing the secretion of matrix metalloproteinases, melanin synthesis and tyrosine activity. The RES nanoliposomes' anti-wrinkle and skin-brightening effect was demonstrated in human clinical trials. This is particularly noteworthy. for enhancing the RES anti-aging and skin-brightening properties, as indicated by three levels of systematic studies RES nanoliposomes were found to be a promising transdermal drug delivery system (TDDS) .[9]

Resveratrol Stability

Natural compounds have proven useful for instructing us on the chemical functionality that is consistent with the biological microenvironments aqueous milieu. A stilbene that is extensively researched in this regard is RES. Nevertheless, it was imperative to investigate the molecule's safety, bioavailability, and stability prior to assessing its therapeutic potential.[10]

In addition to its biological activity, the RES trans isomer is stable. It can be converted to the cis isomer in the conditions of light, temperature, and pH. A contributing factor to the increased the cis configuration instability is the two center-chain hydrogen atoms on the same side. A second explanation is that the molecule undergoes deprotonation in basic conditions, which then follows by a procedure of self-degradation or polymerization and oxidation.[11]

Consequently, the cis form is only stable in the absence of light and at neutral pH. Conversely, the trans isomer remains stable in the presence of acidic pH, at room or body temperature, and with limited exposure to light or oxygen. After the thermal characterization of trans-RES, it has been shown that RES remains stable for approximately 30 minutes at 70 °C. However, the molecule degrades swiftly at higher temperatures.[12]

The study results indicated that the process of dimerization and photoisomerization of stilbenes has been initiated over time as a consequence of their exposure to sunlight and UV radiation. Robinson et al. conducted an experiment that examined numerous attributes of RES. Initially, RES exhibited the highest solubility in alcohol (87.98 mg/mL) and PEG-400 (373.85 mg/mL), and the lowest in water (0.05 mg/mL). Additionally, it has been demonstrated that the polyphenol remains stable for a period of up to 193 hours in acidic to neutral conditions.[7]

Poor skin penetration and transdermal delivery barriers

Because of the SC barrier, which restricts its anti-aging and skin-brightening effects RES is difficult to be transdermal absorbed. In addition, there is a scarcity of systematic research on the RES efficacy on human skin, particularly in clinical trials and three-dimensional skin models. RES was encapsulated into nanoliposomes utilizing

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the high-pressure homogenization technique to resolve the limited transdermal delivery issue, resulting in a successful TDDS. The efficiency of the system in terms of anti-aging and skin-brightening was systematically assessed utilizing human skin, cell line models, and a three-dimensional skin model.[13]

Overview of nanotechnology and its role in drug delivery

Nanotechnology has been increasingly employed by researchers to encapsulate RES to improve tissue-specific or targeted delivery. Encapsulation is a practice in which the active molecule, RES, is enclosed within a matrix known as the "shell" or the "wall." The water dispersibility of RES is enhanced by encapsulation, allowing for its incorporation into a variety of food items. In addition, it enhances its chemical stability, that shields it from environmental factors like oxygen and ultraviolet radiation. Additionally, encapsulation can facilitate the RES absorption by enterocytes, increase its solubility in GIT fluids, and reduce its metabolism prior to absorption, thereby increasing its bioavailability. A wide range of DDS are available for the RES encapsulation, including liposomes, niosomes, nanoemulsions (NE) , nanoparticles (NPs), and dendrimers.[14]

Nanocarriers: Types and properties (e.g., liposomes, nanoparticles, dendrimers, micelles)

Nanocarriers have been recognized as a promising DDS that offers a variety of benefits over traditional passive delivery. These benefits include elevated drug loading, a larger surface area, higher solubility, active ingredients controlled release , reduced skin irritancy, improved stability, protection from degradation, , and enhanced penetration of actives into the skin.[15]

There are numerous cosmetic applications for lipid nanocarrier products that already exist on the marketplace. The second generation of lipid nanoparticles nanostructured lipid carriers (NLCs) are highly drug-loaded and resistant to leaking. Topical usage has been explored for lipid-based nanosystems, involving solid lipid nanoparticles (SLN), nanoemulsions (NE), and NLC. NLC are composites of solid and liquid lipids, whereas SLN are comprised of lipids that are solid at room temperature. The absence of organic solvents, the established scale-up processes availability, the ability to manufacture concentrated lipid suspensions, and the physiological lipids inclusion in the composition are among the SLN and NLC advantages. A variety of active compounds, including vitamin E, retinoic acid, and vitamin A , have been evaluated for SLN- and NLC-based systems topical application.[16]

A comprehensive review of nanoformulations containing RES has been released lately with a particular emphasis on the RES potential as a cancer treatment. In this regard, because of the enhanced permeability and retention (EPR) effect, that enables these molecules to build up selectively in cancer tissues, as suggested nano-sized formula are also beneficial in cancer treatment.[17]

RES-loaded SLN have been utilized for cutaneous application, and the cellular uptake, transport, and internalization in keratinocytes

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have been investigated. The SLN-encapsulated drug demonstrated superior stability, intracellular delivery, and solubility in comparison to RES in solution, as the particles were able to cross the cell membrane in as minimum as 15 minutes. RES protected from photo degradation, its absorption in porcine ear skin was improved, and its anti-lipoperoxidation activity was enhanced by SLN, which demonstrated its potential as a delivery system.[18,19]

In contrast to the encapsulation of a single polyphenol, skin penetration experiments demonstrated that the RES delivery into deeper skin layers increased significantly during co-delivery. The curcumin interaction with the lipid bilayers of the SC allowed the lesser lipophilic RES to penetrate the skin barrier and cross the epidermis and dermis, as observed by the authors.[20]

Entrapment efficiency values of the formulas that included the solitary antioxidant were negatively impacted by the RES and curcumin co-encapsulation in niosomal systems. The in vitro percutaneous penetration of antioxidants was found to be modulated and improved relative to the comparable free solutions utilized as controls. Furthermore, the antioxidant combinations' synergic antioxidant action lead to an increased capacity to decrease free radicals. Consequently, these liposomal formulas demonstrated a possibility of the antioxidant molecules transdermal delivery and may be beneficial in the cosmeceutical sector. [21]

Numerous nanocarrier technologies have been created to improve the distribution and effectiveness of resveratrol (RES) and other bioactive chemicals. Nanoemulsion-encapsulated thermosensitive hydrogels containing RES-infused coconut oil exhibited cytotoxicity against breast cancer cells, with an in vitro release profile indicating 80% release within 6 hours. Glycosylated liposomes exhibited significant antibacterial efficacy against Gram-positive bacteria, including Methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, at concentrations 10-60 times below the lowest inhibitory concentration, contingent upon the biofilm species. Resveratrol-encapsulated liposomes demonstrated potential in oncological treatment by reducing the expression of cancer-associated fibroblast (CAF) markers such as α-SMA and IL-6, which are essential for cancer cell proliferation and metastasis. In both 2D and 3D co-culture settings, cancer-associated fibroblasts (CAFs) enhanced the invasive and drug-resistant properties of colorectal cancer (CRC) cells; however, this impact was diminished by RES treatment. Polymeric micelles containing both doxorubicin (DXR) and RES enhanced DXR cytotoxicity in lymphoma cells while mitigating its cardiotoxicity, with DXR release rates surpassing those of RES in a pH-dependent fashion. Polymeric micelles co-delivering RES with quercetin or curcumin substantially alleviated Adriamycin-induced cardiotoxicity, resulting in a decrease in ovarian tumor growth. Amphiphilic maltodextrin-based micelles, dual-targeted with lactobionic acid and folate, co-loaded with RES and sulfasalazine, demonstrated increased cytotoxicity, enhanced internalization into HepG-2 liver cancer cells, and decreased liver/body weight ratios, while also inhibiting angiogenesis and augmenting antitumor efficacy against hepatocellular carcinoma. Solid lipid nanoparticles (SLNs)

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encapsulating D-α-Tocopheryl polyethylene glycol 1000 succinate and RES enhanced bioavailability provided protection against oxidation and hydrolysis, and shown superior efficacy compared to free RES in triggering apoptosis in breast cancer models. Gold nanoparticles (NPs) encapsulated with RES reduced the growth of human hepatoma HepG2 cells by upregulating Bax and caspase-8, while downregulating PI3K, pro-caspase-9, pro-caspase-3, and Akt, so efficiently inducing apoptosis. Furthermore, chitosan-coated PEG-NPs improved bioavailability and diminished colon tumor progression in xenograft and orthotopic implantation mice relative to unbound RES. Poly(lactic-co-glycolic acid) nanoparticles coupled with lactoferrin, a natural iron-binding glycoprotein, facilitated internalization into human brain microvascular endothelial cells, hence enhancing blood-brain barrier penetration and brain accumulation, in contrast to unconjugated RES nanoparticles or free RES. Finally, nanostructured lipid carriers (NLCs) formulated with lecithin and RES exhibited intrinsic antioxidant and anticancer characteristics while preserving stability at room temperature and 4°C for a duration of up to 12 months. [14]

Advantages of nanotechnology in enhancing drug bioavailability, stability, and controlled release

Trans-RES's stability is enhanced by nanoencapsulation, which shields it from deterioration caused by light exposure. Detoni CB et al. conducted a comparison of the photostability of various trans-RES integrated NPs, such as nanospheres, liposomes, SLNs, and polymeric lipid-core nano capsules. Trans-RES's photostability was enhanced by all of the NPs that were tested, and liposomes maintained trans-RES concentrations for the longest duration. [22]

In comparison to the free trans-RES solution, the trans-RES concentrations in the epidermis and dermis increased more significantly when the free or nano encapsulated trans-RES was applied to the porcine tissues subsequent to UVA radiation. In accordance with these discoveries, the trans-RES photostability was significantly improved by PLGA NPs when subjected to UVA for two hours. [23]

The RES aqueous solubility is extremely low (3 mg/100 mL). RES exhibits in organic solvents a higher solubility, including ethanol and dimethyl sulfoxide (DMSO), with solubility values of up to 50 mg/mL and 16 mg/mL, respectively. RES can be incorporated or encapsulated in the NPs lipid compartment, particularly SLNs and NLCs, which leads to an increase in aqueous solubility. The hydrophobic interior of lipid nanocarriers has effectively encapsulated RES. As a result, the aqueous solubility of RES was enhanced by over 100 times (unpublished data). RES aqueous solubility has also been enhanced by other NPs, such as SLNs, NLCs, and liposomes. The characteristics of the nano-formulations used to encapsulate RES, as well as the proven advancements that have resulted from such encapsulation. [24]

Diverse nanoparticle (NP) systems have been engineered for the delivery of resveratrol (RES), exhibiting a range of properties and uses. Poly(D,L-lactide-co-glycolide) nanoparticles, measuring 135–580 nm, have an encapsulation effectiveness of

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18–24% and a zeta potential of around ±20 mV, demonstrating enhanced stability and prolonged release in vitro, indicating potential for nano-chemoprevention. Lipid-core nanocapsules, nanospheres, liposomes, and nanostructured lipid carriers (NLCs), measuring 170–266 nm with an exceptional encapsulation efficiency of 98–99%, facilitated enhanced resveratrol permeation through porcine skin and improved chemical photostability in an 8-hour automated Franz cell study, suggesting potential applications in skin cancer treatment. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), exhibiting a size range of 110–280 nm, a zeta potential of around −14 mV, and an encapsulation efficiency of 73–91%, diminished reactive oxygen species generation and enhanced RES concentrations in the dermis, rendering them appropriate for dermal applications. In a hepatotoxicity model, Eudragit E100 and polyvinyl alcohol (PVA) nanoparticles, measuring approximately 73.8 nm with an encapsulation efficiency of 99.5%, mitigated oxidative stress and inflammation while enhancing hepatoprotective effects when administered orally to male Wistar rats subjected to carbon tetrachloride, indicating potential for the treatment of chronic liver diseases. Likewise, SLNs and NLCs, measuring 150–250 nm with a ZP of −30 mV and an EE of 70%, exhibited improved stability and prolonged release, hence enhancing oral bioavailability. Lipid-core nanocapsules, measuring around 241 nm with an encapsulation efficiency of 99.9%, enhanced gastrointestinal safety and elevated RES concentrations in the brain, liver, and kidney, positioning them as a potential therapeutic option for Alzheimer's disease. Bovine serum albumin nanoparticles, with an encapsulation efficiency of 34% and a size range of 400–500 nm, elevated RES concentrations in the liver, enhanced the expression of caspase-9 and caspase-3, and diminished tumour size in xenograft ovarian cancer nude mice, indicating potential for ovarian cancer therapy. In human keratinocyte cell lines, solid lipid nanoparticles (SLNs) with a size of around 180 nm and a zeta potential of −38 mV increased cellular uptake and decreased keratinocyte proliferation, indicating possible applications in skin cancer treatment. PCL-PEG polymeric micelles, measuring 100 nm with an encapsulation efficiency (EE) of 89% and a loading capacity (LC) of 20%, enhanced Aβ-induced PC12 cell survival, facilitated sustained release, and diminished reactive oxygen species accumulation, indicating potential in the treatment of Alzheimer's disease. Ultimately, mPEG-PCL-based nanoparticles, exhibiting a size of around 80 nm, a zeta potential of −6.5 mV, an encapsulation efficiency of 91%, and a loading capacity of 19%, improved the cellular uptake of resveratrol, facilitated sustained drug release, and diminished cell survival in rat C6 glioma cells, suggesting their potential for malignant glioma treatment. [25]

The free RES concentration in the bloodstream is extremely low due to the rapid metabolism of circulating RES. In contrast to free RES, nano-encapsulated RES demonstrated a sustained release pattern. After four hours of incubation at 25°C and 37°C, less than 10% of RES was released from SLNs or NLCs . [26]

Male Wistar rats were administered 5 mg/kg body weight of either free or nano-RES orally daily for 2 weeks by Frozza R et

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al., who encapsulated RES in lipid-core NPs. Nano-RES significantly increased the RES concentrations in rat tissue (liver, kidney, blood brain, and; was not assessed) by over twofold in comparison to unbound RES. Furthermore, the GIT safety of RES-loaded lipid-core NPs was superior to that of unbound RES. [27]

In comparison to free RES and void NPs, nano-RES has the potential to enhance antioxidant capacity and reduce the reactive oxygen species production in cell culture and research animal models. [28] The rats with CCl4-induced hepatotoxicity were orally administered control (no RES), free RES, and nano-RES by Lee CW et al. The researchers discovered that nano-RES doubled the unbound RES positive influence on inhibiting inflammatory cytokine production, reducing hepatocyte mortality, and oxidative stress. [29] Shao J et al. proved that the free RES inhibitory impact on the viability of rat C6-glioma cells doubled by nano-RES in vitro. [30]. For four weeks, Guo et al. utilized free RES, saline, and RES-loaded bovine serum albumin NPs to the implant ovarian tumor-bearing mice through intraperitoneal injection once a week. In terms of body weight, the concentrations of free and nano-RES were 50, 100, and 200 mg/kg. RES concentrations in the ovary have risen by 1.8 times when compared with unbound RES by RES-loaded bovine serum albumin albumin nanoparticles. Free and nano-RES both exhibited a dose-dependent reduction in the weight of ovarian tumors. Free and nano-RES inhibited tumor development at 200 mg/kg body weight at rates of 46% and 62%, respectively. The animal's body weight was not affected by any of the treatments. Furthermore, nano-RES has the potential to improve the preventive effect of RES on Alzheimer's disease. [31]

Conclusions

RES is a multi-potent compound that can be utilized to treat a wide range of diseases, involving cutaneous diseases. However, its characteristics, such as poor stability and low water solubility, may impose limitations that must be surmounted in order to achieve effective therapy. Consequently, any commercially effective formulation necessitates increased water solubility and improved RES stability. By encapsulating RES in multifunctional delivery systems, such as micro- and albumin nanoparticles, it is possible to achieve this enhancement. The appropriate encapsulating substance selection is a critical step in the preparation of micro- and nanocarrier formulations, as it defines the API mechanism and release rate. Particularly in the context of long-term patient therapy, the potential adverse health effects that may result from the utilization of biodegradable polymers are a significant unknown. Consequently, it is evident that the utilization of such carriers is of particular interest. The potential of such nanosystems is demonstrated by the available data on topical formulations with RES-loaded micro- and nanocarriers. Conventional treatments that utilize synthetic antioxidants may be considered clinical equivalents to RES-loaded nanoformulations, but with diminished adverse effects. In contrast to conventional formulations, they enable the reduction of the substance's dosage and the implementation of targeted action. In clinical treatment the natural substances inclusion such as those from the polyphenol group, including RES, is of particular significance in

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order to avoid the escalating issue of antibiotic resistance. Scientists are particularly interested in clinical, drug-resistant variants of microorganisms that pose a health and even life hazard to cases in critical condition. The potential for RES to be utilized as a treatment adjunct is made possible by the extensive documentation of its antimicrobial activity in in vitro research. Furthermore, the encapsulation of the antibiotic into micro- and nanocarriers would enable the antibiotic dosage reduction while preserving the treatment's efficacy.

The pursuit of novel formulations that minimize toxicity while also confirming the active substance targeted delivery to the neoplastic tissue is an additional significant objective of numerous studies. Additionally, these RES formulations may induce a synergistic effect between medications that are administered concurrently, such as orally or in conjunction with RES in the NPs. Some studies results discovered that RES alone demonstrated insufficient action. Nevertheless, systematic analyses of the subject matter are still scarce and inadequate, as they are primarily conducted in vitro. In order to verify the novel nano formulations containing RES efficacy in the skin diseases treatment, additional in vivo studies are required, particularly clinical trials that involve a significant number of patients.

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