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Review

ADVANCING RESVERATROL DELIVERY: PROTEIN-POLYSACCHARIDE COMPLEXES AS INNOVATIVE NANOCARRIERS

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ABSTRACT

Resveratrol (RES) has garnered significant attention in the medical field because of its remarkable physiological benefits, including anticancer, antioxidant, anti-inflammatory, neuroprotective, cardioprotective, and antidiabetic properties. However, its development and application are hindered by poor water solubility, inconsistent and low oral bioavailability, and instability in chemical and biochemical environments. A novel biopolymer structure, the protein-polysaccharide (PRO-POL)-based delivery system, offers advantages, such as minimal toxicity, biocompatibility, biodegradability, and controlled release. Numerous studies have explored PRO-POL-based delivery systems to enhance RES bioavailability. This review examines the interactions between various proteins (e.g., gliadin, whey protein, soybean protein isolate, pea protein, and zein) and polysaccharides (chitosan, sodium alginate, and pectin) and their impact on size, surface charge, encapsulation efficiency, and release characteristics. This study highlights how PRO-POL-based delivery systems improve RES bioavailability. Additionally, it provides an overview of PRO-POL complexes incorporating RES, serving as a reference for the development and implementation of PRO-POL delivery systems.

KEYWORDS: Protein-polysaccharides, nanoparticles, bioavailability, RES.

1. Introduction

Resveratrol (RES) is a naturally occurring polyphenolic phytoalexin synthesized by various plant species in response to biotic and abiotic stresses, such as physical damage, ultraviolet (UV) irradiation, and fungal infections [1]. It is primarily found in grapes, red wine, blueberry, mulberry, cranberry, and peanut. Recognized for its extensive therapeutic potential, RES exhibits potent antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and chemopreventive properties. Additionally, it has been shown to mitigate obesity and diabetes while promoting longevity [2]. Despite its promising bioactivity, the clinical application of RES remains challenging owing to its limited aqueous solubility, chemical instability, and poor oral bioavailability [3-5].

The chemical formula of RES (Fig. 1) is $C_{14}H_{12}O_3$, composed of two benzene rings linked by a trans-ethylene (CH=CH) bridge. It contains three hydroxyl (-OH) groups, two positioned at the 3 and 5 locations on one ring (meta-configuration) and one at the 4′ position on the other ring (para-configuration), which classifies it as a phenolic compound. These hydroxyl groups primarily confer the antioxidant properties. The central trans-alkene structure provides molecular rigidity and a planar shape, whereas the aromatic rings support π-π stacking and hydrophobic interactions, all of which enhance its biological function and compatibility with drug delivery systems [6,7].

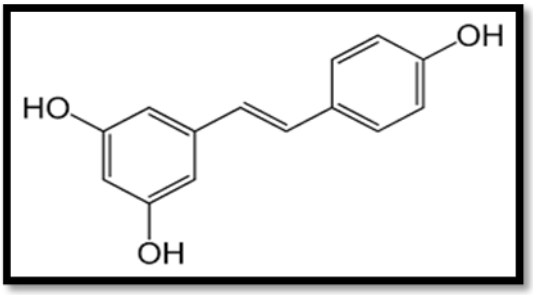

Fig. 1. Structure of resveratrol.

RES is rapidly metabolized in the gastrointestinal tract primarily through glucuronidation and sulfate conjugation by enterocytes, leading to minimal systemic availability.

Consequently, although in vitro studies have demonstrated significant bioactivity, their in vivo efficacy remains limited [8]. The solubility of RES is particularly low in both aqueous and lipid phases, with reported solubilities of 0.023 mg/mL in water and 0.18 mg/mL in coconut oil [9, 10]. Walle et al. examined the metabolism and absorption of ^{14}C-labeled RES in human subjects and found that although dietary intake resulted in approximately 70% absorption, only trace amounts of unmetabolized RES (<5 ng/mL) were detected in plasma, with the majority of the administered dose excreted via urine [11, 12]. Kuhnle et al. further confirmed that RES is primarily converted into its glucuronide derivative (~99%), which is pharmacologically inactive and rapidly eliminated from the body [13]. This extensive first-pass metabolism, along with its lipophilicity and chemical instability, significantly impairs its therapeutic potential [14].

To overcome these limitations, significant research efforts have been directed towards the development of novel delivery systems aimed at enhancing the bioavailability of RES. Among these, protein-polysaccharide (PRO-POL)-based nanoparticles (NPs) have emerged as a promising approach (Fig. 2). Food and pharmaceutical industries have increasingly explored the potential of proteins and polysaccharides as natural carriers for bioactive compounds because of their biocompatibility, biodegradability, and non-toxicity [15]. Proteins derived from both plant and animal sources offer excellent functional properties, such as emulsification, gelation, and stabilization, making them suitable carriers for hydrophobic molecules. Similarly, polysaccharides provide structural stability, mucoadhesive properties, and protection against enzymatic degradation, thereby improving the retention and release profiles of encapsulated bioactives [16, 17].

Although protein- and polysaccharide-based delivery systems have demonstrated improved solubility and stability for hydrophobic compounds, their individual limitations necessitate the development of hybrid PRO-POL systems. The combination of proteins and polysaccharides can occur through covalent and non-covalent interactions, including electrostatic interactions, hydrogen bonding, and hydrophobic associations, resulting in enhanced encapsulation efficiency and the controlled release of bioactives [18, 19]. Furthermore, polysaccharides provide hydrophilic functionalities that improve tissue adhesion and prolong circulation time, making them ideal candidates for nano/microparticle formulation [16]. Recent studies have demonstrated that PRO-POL nanoparticles formed via electrostatic complexation significantly improve the aqueous solubility and biological activity of hydrophobic nutraceuticals, including RES [14]. The interactions between proteins and polysaccharides can be classified as covalent or non-covalent [20]. Non-covalent interactions include attractive and repulsive forces, which influence the formation and stability of polyelectrolyte complexes in solution. These interactions are affected by intrinsic factors, such as pH, ionic strength, charge density, and molecular conformation, as well as extrinsic factors, such as temperature and processing conditions. On the other hand, covalent interactions provide stronger and more permanent linkages, ensuring greater structural integrity and sustained release of bioactives [21, 22]. The choice of interaction type significantly affects the physicochemical properties of the resultant nanocomplexes, including the particle size, surface charge, encapsulation efficiency, and drug release kinetics.

Although numerous studies have investigated the application of PRO-POL nanoparticles for RES delivery, comprehensive summaries discussing the mechanisms governing their enhanced bioavailability are limited. This review aims to provide a detailed examination of PRO-POL-based RES delivery systems, focusing on the interactions between various proteins and polysaccharides, their effects on nanoparticle characteristics, and their potential to overcome the bioavailability challenges of RES. In addition, we highlight recent advancements in PRO-POL-based approaches and discuss their implications for future research and commercial applications. By consolidating the existing knowledge, this review seeks to serve as a foundational reference for the continued development and optimization of PRO-POL NPs as effective delivery vehicles for RES.

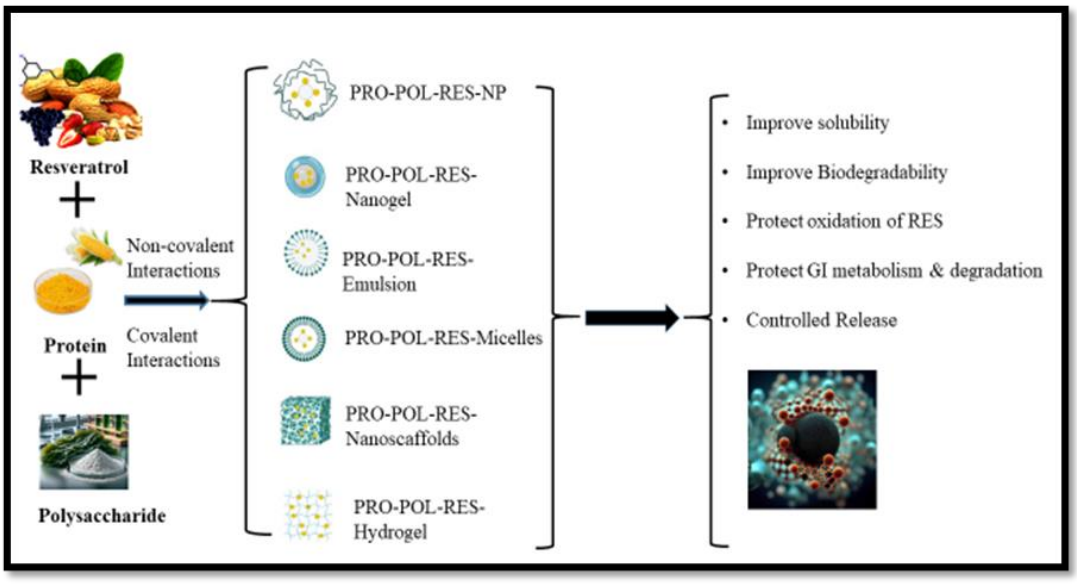

Fig. 2. PRO-POL-based delivery systems for RES delivery.

2. Methodology of Literature Selection

A thorough literature search was performed using various databases, including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. This process involved the thoughtful use of pertinent keywords and Boolean operators to achieve a balance between wide-ranging and targeted article retrievals. The primary search terms encompassed "protein-polysaccharide complexes," "Nanocarriers for Resveratrol," and "resveratrol." The inclusion criteria were original research articles, reviews, and book chapters that had been peer-reviewed and published in English within the last 15 years, allowing for exceptions in foundational works. These studies specifically explored the formulation, characterization, and application of protein-polysaccharide complexes as nanocarriers, as well as studies concerning the encapsulation, stability, release kinetics, and enhancement of resveratrol bioavailability. We excluded studies that did not involve protein-polysaccharide systems, focused on non-polysaccharide nanocarriers, and lacked experimental or theoretical data on resveratrol delivery. Additionally, we did not consider publications in non-English languages, unpublished theses, or conference abstracts. Initially, 2,187 records were identified from five major databases: PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. Following the removal of 812 duplicate entries, we left 1,375 unique records to screen. Through the title and abstract screening process, we excluded 1,023 records and aimed to retrieve 352 full-text articles. Of these, 22 could not be accessed because of accessibility challenges, resulting in 330 articles available for full-text evaluation. After evaluating eligibility, 214 articles were set aside 95 owing to irrelevant subject matter, 62 for not being based on protein-polysaccharides, 22 for being in languages other than English, and 35 for not providing relevant experimental or theoretical data on resveratrol. Finally, 116 studies fulfilled all the necessary criteria and were included in the final review. The last search across all databases was conducted in June 2024.

3. Reasons for Low Bioavailability of RES

Recent research has indicated that the low bioavailability of RES can be attributed to its poor stability, limited solubility, inefficient absorption, and rapid metabolism [23].

3.1. Stability and solubility

The biological activities of RES and its analogs are significantly influenced by their structural determinants, including (i) stereoisomerism, (ii) intramolecular hydrogen bonding, (iii) the number and position of hydroxyl groups, and (iv) the presence of double bonds [24]. Multiple studies have investigated the role of hydroxyl groups in modulating the physicochemical properties of RES, demonstrating that cytoprotective, antioxidant, radical-scavenging, and antiproliferative effects are substantially influenced by the presence of a 4′-hydroxy group [25-29]. However, because of its higher acidity compared to other meta-hydroxyl groups, the stability of the para-4-hydroxy group in RES is relatively low [30].

Furthermore, Cao et al. [31] indicated that the abstraction of the 4-H proton is energetically more favorable than that of the 3-H and 5-H protons. The resonance stabilization of the 4-radical was also more pronounced than that of the 5-radical, rendering the 4-hydroxyl group of RES more reactive. This reactivity is crucial for its biological function, particularly as an antioxidant. The protonation state of RES is another critical factor affecting its bioactivity, as its efficacy significantly diminishes at pH levels that exceed its pKa values. However, inconsistencies remain in the reported pKa values of RES.

The pH of the surrounding medium influences the aggregation behavior of RES. Above a certain threshold concentration, RES tends to aggregate, with this concentration being lower under acidic conditions (12.5 μM at pH 5.5) than under basic conditions (37 μM at pH 10.5) [32]. Moreover, RES exhibits poor aqueous solubility (approximately 30 mg/L [23], which further limits its bioavailability.

3.2. Absorption

Despite its poor aqueous solubility, RES exhibits a relatively high intestinal absorption. Studies employing the human intestinal Caco-2 cell monolayer model, widely recognized for simulating human intestinal absorption, indicate that RES undergoes substantial oral absorption [33]. The primary mechanism of RES transport across intestinal epithelial cells appears to be passive transepithelial diffusion, which occurs independent of directionality [34]. Active transport may also contribute, although it is primarily associated with RES metabolites rather than the parent compound [35,36].

However, absorption of RES is complicated by its extensive metabolism. In Caco-2 cell models, RES transport has been observed to be nonlinear over time, likely due to concurrent metabolic transformations [4]. Approximately 77% of ingested RES is absorbed in the intestine [37]; however, its systemic availability remains low owing to extensive metabolism. Once absorbed, free RES is largely bound to plasma proteins, such as albumin and lipoproteins. These macromolecular complexes function as reservoirs that facilitate the gradual release of RES, allowing for cellular uptake via receptor-mediated interactions with albumin and lipoprotein receptors [38].

3.3. Metabolism

Following oral ingestion, RES undergoes rapid metabolism in both the aglycone and glycosidic forms. Detectable levels of RES and its metabolites appear in plasma and urine within 30 to 60 minutes post-consumption [39]. However, the proportion of free RES in circulation is exceedingly low, often accounting for less than 2% of the total administered dose. Instead, RES is primarily found in conjugated forms, such as glucuronide and sulfate derivatives [11,12,40].

A noteworthy observation was the emergence of a secondary plasma peak approximately six hours after ingestion, suggesting enterohepatic recirculation of RES conjugates following intestinal hydrolysis and reabsorption. While presystemic metabolism significantly affects oral RES bioavailability, intravenous administration also results in extensive systemic metabolism. The excretion profile of RES indicates that 54–98% of the administered dose is recovered in the urine and feces. Urinary analysis identified two glucuronide conjugates and one sulfate conjugate as predominant metabolites. Additionally, hydrogenation of the aliphatic double bond in RES has

been reported, with the resulting reduced metabolite excreted in both glucuronide and sulfate conjugate forms [39].

4. Protein-Polysaccharide Hybrid Systems and Nanocarriers for Enhanced RES Delivery

Numerous strategies have been proposed to reduce the photosensitivity and improve the stability, bioavailability, and solubility of polyphenols including RES. Among these, the development of vesicular systems, such as liposomes, niosomes, transfersomes, and ethosomes, has demonstrated efficacy in improving RES encapsulation and protection from degradation. Additionally, various nanocarrier-based formulations, including nanoparticles, micelles, nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), nanosuspensions, and nanocapsules, have been investigated to enhance their bioavailability and controlled release. Furthermore, size reduction to the micro/nano level through the formulation of microparticles and nanoparticles, along with complexation strategies using cyclodextrins, has exhibited potential in increasing RES solubility and stability [41-45].

In recent years, proteins have been investigated as promising carriers for RES because of their biocompatibility, biodegradability, and capacity to improve bioavailability. Proteins serve as versatile biomaterials in food and biomedical applications owing to their functional properties, including emulsification, foaming, and gelation. Recent studies have highlighted that naturally occurring animal proteins, plant proteins, and protein hydrolysates can function as effective carriers of RES. Both plant- and animal-derived proteins offer advantages, such as biosafety, structural versatility, and widespread availability. However, plant proteins have garnered significant attention over animal proteins because of their non-allergenic nature and broad acceptability, particularly in populations with dietary restrictions based on religious beliefs or vegetarian preferences. In addition, plant proteins offer a sustainable and nutritionally complete alternative for the delivery of bioactive compounds. The primary mechanism governing the formation of RES-protein complexes is hydrophobic interaction [15]. Notably, legume proteins, which are rich in hydrophobic amino acids at the substrate interface, exhibit stronger hydrophobicity than animal proteins [46]. This characteristic enhances their potential as structural components of bioactive delivery systems.

Despite these benefits, protein-based complexes exhibit limitations, including sensitivity to pH variations, temperature fluctuations, salt ions, and enzymatic degradation by proteases. These challenges can result in flocculation near the isoelectric point, reducing the encapsulation efficiency and long-term stability of RES formulations. To address these limitations, studies have demonstrated that proteins can combine with polysaccharides to form hybrid carrier systems [47,48].

Polysaccharides are biopolymers composed of monosaccharide units linked via glycosidic bonds, which further enhance the functionality of such delivery systems owing to their biocompatibility and biodegradability. Polysaccharides can be classified into three main types: anionic (e.g., sodium alginate, hyaluronic acid, pectin), cationic (e.g., chitosan, chitin), and neutral (e.g., dextran, cellulose, starch) [49,50]. Upon degradation, polysaccharides yield sugar chains of varying molecular weights featuring numerous reactive groups (-OH, -NH_2, and-COOH) that can undergo chemical or biological modifications to form a diverse range of polysaccharide derivatives [51]. A key attribute of natural polysaccharides is their bioadhesiveness, which enables them to adhere to biological surfaces, thereby prolonging drug retention and systemic circulation [49]. When combined with proteins, polysaccharides contribute to the formation of encapsulating carriers that protect and stabilize RES through covalent, hydrogen, or electrostatic bonding (Fig. 2).

Interactions between proteins and polysaccharides can occur via covalent or non-covalent mechanisms. Non-covalent interactions, such as hydrophobic, electrostatic, and hydrogen bonding, play a crucial role in complex formation [16]. In particular, electrostatic interactions arise between charged or partially charged biopolymers, in which ionizable functional groups in proteins and polysaccharides interact under specific pH conditions. Proteins exhibit a net positive charge at pH values below their isoelectric point owing to high amino group protonation and low carboxyl group dissociation, enabling them to bind with negatively charged polysaccharides. Conversely, at pH levels above their isoelectric points, proteins acquire a negative charge, facilitating interactions with cationic polysaccharides.

Additionally, hydrogen bonding occurs through directional, short-range interactions between hydrogen atoms and highly electronegative atoms, further stabilizing protein-polysaccharide complexes. Covalent bonds between proteins and polysaccharides can be formed through chemical, physical, or enzymatic processes. A notable example is the Maillard reaction, in which proteins and polysaccharides undergo controlled glycation under specific conditions (pH, relative humidity, temperature, and reaction duration) leading to the formation of PRO-POL complexes with enhanced functional properties.

The solubility and stability of RES were significantly enhanced using PRO-POL-based carriers. This approach also reduces susceptibility to gastrointestinal metabolism and degradation, thereby promoting improved intestinal absorption and systemic bioavailability. Additionally, PRO-POL-RES complexes have demonstrated targeted delivery potential, enabling site-specific release in specific cells or organs. Consequently, the encapsulation of RES within protein-polysaccharide matrices has emerged as a promising strategy to overcome its physicochemical limitations.

4.1. Gliadin-Polysaccharide-Based Carriers

Gliadin, a naturally occurring protein in wheat, constitutes a fundamental component of gluten. Its unique structure, characterized by both hydrophilic and hydrophobic regions, renders it particularly intriguing for researchers and formulators. This dual nature facilitates its self-assembly into nanoparticles, making it an excellent candidate for encapsulating compounds with poor water solubility, such as RES. Gliadins have several practical advantages beyond their structural versatility. They are biodegradable, biocompatible, and readily available from plant sources, rendering them a cost-effective and sustainable option for the development of drug and nutraceutical delivery systems. Their capacity to

adhere to mucosal surfaces further enhances their potential to improve residence time and absorption of encapsulated bioactive compounds within the gastrointestinal tract. As research advances, gliadin continues to emerge as a valuable, food-grade carrier for augmenting the delivery and efficacy of sensitive compounds [52-54]. Multiple studies have explored various ways to harness the structural and functional characteristics of gliadin to enhance the delivery of RES. Below is a study-wise synthesis of the most notable advancements in this field.

Joye et al. used a molecular approach to investigate how RES binds to gliadin in comparison with another cereal protein, zein. Through fluorescence quenching techniques, they discovered that, although both proteins form complexes with RES, gliadin interactions are mainly driven by hydrophobic forces, and interestingly, the binding strength increases with temperature. This is in contrast to zein, whose binding appears to be more reliant on hydrogen bonding. These findings offer valuable insights into how gliadin-RES complexes behave under different conditions, and suggest that heat-stable formulations might benefit from gliadin as a carrier [55].

Davidov-Pardo et al. developed gliadin nanoparticles using a technique called liquid antisolvent precipitation, and compared them with their zein-based counterparts. Their results showed that gliadin particles had a mean diameter of approximately 260 nm and moderate encapsulation efficiency (~53%), which could be significantly improved when coated with hydrophilic biopolymers, such as pectin. Although zein-based systems outperformed gliadin in terms of encapsulation efficiency, gliadin demonstrated good potential for forming stable, dispersible nanoparticles. This study provides essential groundwork for the fabrication and optimization of gliadin-based nanocarriers for RES [56]. In the second part of their investigation, Joye et al. focused on the performance of these particles under stress conditions, such as changes in temperature, pH, and ionic strength. They reported that coating gliadin nanoparticles with pectin improved their resistance to UV degradation and heat. However, uncoated or poorly stabilized particles are prone to aggregation, especially in environments with a high salt content or near the isoelectric point. These observations highlight the need for strategic surface modifications to enhance the functional robustness of gliadin systems [57].

Qiu et al. explored how chemical modifications of gliadin can be harnessed to improve RES delivery. They focused on the deamidated and glycosylated forms of gliadin and found that these versions formed stable colloidal complexes with resveratrol. Glycosylation enhances the solubility and light stability of RES. These complexes also demonstrated better performance during simulated gastrointestinal digestion and showed promise in reducing lipid oxidation when incorporated into emulsions. Their work highlighted how even small molecular tweaks to gliadin can significantly increase its effectiveness as a carrier [58].

Wu et al. introduced a multilayered strategy by combining gliadin with gum arabic and chitosan hydrochloride to create more robust nanoparticles. This approach helped overcome common limitations, such as poor redispersibility and instability at low pH. The resulting nanoparticles maintained their structure over a pH range of 3–7 and demonstrated a high encapsulation efficiency (~68%). Additionally, they offered improved antioxidant performance and controlled release of RES under simulated digestive conditions. This study demonstrated that layering and electrostatic interactions can be strategically employed to stabilize gliadin-based carriers [59].

Teng et al. presented a more advanced and multifunctional design using gliadin nanoparticles modified with hyaluronic acid (HA) and sophorolipid (SPL). These biodegradable, naturally derived materials not only increase particle stability and encapsulation efficiency but also significantly enhance the gastrointestinal release of RES. Molecular studies have shown that multiple interactions, such as hydrogen bonding, van der Waals forces, and π-alkyl stacking, are responsible for the strong binding of RES to modified gliadin. This formulation stands out by offering sustained release, improved bioavailability, and high compatibility with biological systems, making it a strong candidate for oral delivery [60].

Each of these studies adds a critical piece to the puzzle of how gliadin can be optimized for effective resveratrol delivery. From understanding the fundamental binding mechanisms to advancing smart surface modifications, the literature shows clear progress towards making gliadin-based nanocarriers more functional, stable, and bioavailable. However, some limitations remain, such as slightly lower encapsulation efficiency compared to zein, and the versatility of gliadin, especially when paired with other biopolymers or surfactants, positions it as a powerful and adaptable material for future nutraceutical and pharmaceutical formulations.

4.2. Soy Protein-Polysaccharide-Based Carriers

Protein–polysaccharide conjugates and complexes have been synthesized using various protein sources, including soy protein isolates, whey proteins, egg white proteins, and polysaccharides, such as chitin, pectin, and soy hull hemicelluloses. These conjugates exhibit key functional properties, including enhanced solubility, thermal stability, emulsification, stabilization, and improved rheological and structural characteristics [61].

Among plant proteins, soy proteins function primarily as amino acid storage reservoirs, with their monomers linked via amide bonds to form polypeptide chains [62, 63]. Soy proteins have been investigated as biodegradable alternatives to synthetic plastics. Owing to their biodegradability, availability, and high strength, soy protein isolates (SPI) are preferred over other soybean-derived products in composite formulations [62,63]. Their amphiphilic structure enables them to interact effectively with hydrophobic bioactives, such as RES. SPI not only offers a biocompatible and biodegradable platform, but also aligns with the current demands for green, food-grade delivery systems [64].

Pujara et al. developed SPI-based nanoparticles via a simple rotary evaporation method, encapsulating RES into stable nanocomplexes. These particles were approximately 100 nm in size and displayed a more than two-fold increase in the solubility of RES. Notably, encapsulated RES maintained its biological activity and showed improved dissolution behavior, suggesting enhanced clinical utility [65].

To overcome the challenge of protein-based nanoparticle instability under harsh conditions (e.g., pH and salt), Zhang et al. designed alginate-shelled SPI nanoparticles (RSAN). The alginate coating imparted superior colloidal and chemical stability, resisting aggregation over a wide pH range and high ionic strength. The encapsulation efficiency was over 91%, and UV-induced RES degradation was significantly reduced compared to that of the uncoated systems. These results indicate that surface functionalization with polysaccharides, such as alginate, can dramatically improve the delivery performance [66].

Fang et al. introduced a physical treatment strategy combining ultrasonication with pH shifting to structurally modify the SPI. This approach yielded nanoparticles with smaller sizes and enhanced surface hydrophobicity, leading to a remarkable encapsulation efficiency of 91.4%. The modified SPI exhibited improved binding with sodium alginate and formed more stable complexes, underscoring the potential of pretreatment techniques for optimizing protein-based carriers [67].

Taking the design a step further, Li et al. used a Maillard reaction to conjugate SPI with polyguluronate (PG), forming SPI-PG nanoparticles. This conjugation improved RES encapsulation and dramatically enhanced its antioxidant activity and bioavailability both in vitro and in vivo. In a mouse model of colitis, SPI-PG-RES significantly alleviated the symptoms, highlighting its therapeutic relevance. The grafted polysaccharide not only improved particle stability but also acted as a functional component, contributing to its biological efficacy [68].

Zhong et al. explored a protein engineering approach using dithiothreitol (DTT) to reassemble soy lipophilic protein (LP), thereby improving its solubility and structural flexibility. When stabilized with hydroxypropyl methylcellulose (HPMC), the resulting LP-RES nanoparticles exhibited improved temperature and pH resilience. The dual-layered structure also allowed for controlled release during digestion, enhancing RES bioavailability and antioxidant effects. This study highlights the value of redox-mediated structural reassembly in protein-based nanoformulations [69].

Cui et al. presented an advanced SPI-glycyrrhizin (DG) system for RES delivery. The SPI-DG nanocomplex was fabricated via a green, ultrasonic-assisted, pH-driven method, eliminating the need for organic solvents. It achieved exceptional encapsulation efficiency (97.6%) and a particle size below 70 nm. Notably, this system formed a pH-responsive hydrogel that enabled targeted intestinal release of RES. In vivo, the formulation boosted RES bioavailability more than fivefold and demonstrated liver-protective effects in a drug-induced injury model. This multifunctional system showed the synergy of SPI with bioactive polysaccharides such as glycyrrhizin for next-generation nutraceutical delivery [70].

Together, these studies highlight the versatility of soy proteins as nanocarriers. Whether through surface engineering, chemical modification, or physical restructuring to enhance the solubility, stability, and targeted delivery of RES. Although challenges such as scalability and uniformity remain, SPI continues to prove its merit as a sustainable, food-safe option in the evolving landscape of nanonutraceuticals.

4.3. Whey Protein (Wp) - Polysaccharide-Based Carriers

Whey proteins including bovine serum albumin (BSA), ß-lactoglobulin (ß-LG), and α-lactalbumin (α-LA), are widely valued for their excellent nutritional profile, functional properties, and biodegradability [71]. Their amphiphilic nature and structural flexibility allow them to interact with polyphenols, such as RES, through non-covalent mechanisms to form stable complexes and nanoparticles. Recent studies have explored how these interactions improve the solubility, stability, antioxidant activity, and targeted delivery potential of RES.

Malaiya et al. developed chitosan-decorated BSA nanoparticles for the intranasal delivery of RES in a rat model of Alzheimer's disease. The nanoparticles showed a uniform size, good colloidal stability, and biphasic release behavior. In vivo studies demonstrated that this nose-to-brain formulation significantly improved memory and cognitive function in aged rats compared with free RES. The chitosan coating enhanced mucoadhesion, making the system suitable for bypassing the blood–brain barrier via the nasal route [72].

Cheng et al. investigated the binding characteristics of both trans- and cis-resveratrol to three major whey proteins: BSA, ß-lactoglobulin, and α-lactalbumin. Spectroscopic and docking studies revealed that all three proteins formed stable complexes with RES, with ß-lactoglobulin exhibiting the highest binding affinity. The interaction is mainly governed by hydrogen bonding and hydrophobic forces, offering insights into the structural compatibility and stabilization of RES within whey protein matrices [73].

Fu et al. prepared glycated BSA–resveratrol nanocomplexes and studied the impact of the degree of glycation on structural stability and antioxidant function. They found that a higher extent of glycation significantly improved RES encapsulation, oxidative stability, and long-term storage resistance. The glycation process reduced the flexibility of the protein, creating a more rigid and protective microenvironment for RES. These complexes also maintain their integrity during in vitro gastrointestinal digestion [74].

Fan et al. constructed a Pickering emulsion system using α-lactalbumin–chitosan nanoparticles encapsulating RES and curcumin. The resulting high-internal-phase emulsions demonstrated physical stability, resistance to coalescence, and strong protection of the encapsulated actives during digestion. This dual-delivery system shows promise for co-encapsulating lipophilic compounds in functional emulsified formulations [75].

Ma et al. studied nanocarriers based on polysaccharides from *Lentinus edodes* (LEP) and bovine serum albumin (BSA) and their photoprotection against UV radiation. LEP-BSA NCs were created through electrostatic recombination followed by heat treatment, demonstrating stability over an extended storage period. The NCs protected the RES structure from UV light exposure [76].

4.4. Pea Protein / Pea Protein Isolate – Polysaccharide Based Carriers

Pea protein (PP) primarily comprises two storage protein types: globulin and albumin, which are further

classified into legumin and vicilin [77]. Owing to its surface activity and structure-forming properties, PP is a promising candidate for the development of encapsulation and delivery systems [78].

Fan et al. fabricated pea protein isolate (PPI) nanoparticles using a calcium-induced cross-linking method to encapsulate RES. The nanoparticles formed through salt-bridge formation, hydrophobic interactions, and hydrogen bonding exhibited an encapsulation efficiency of 74% and maintained particle stability under stress conditions. Compared with soy protein-based nanocomplexes, PPI nanoparticles demonstrated superior physicochemical stability and antioxidant activity, suggesting their effectiveness as food-grade nanocarriers for RES [79].

In a separate study, Guo et al. developed ternary complexes using PPI, high-methoxyl pectin (HMP), and food-grade surfactants, such as rhamnolipid, tea saponin, and ethyl lauroyl arginate. The resulting complexes significantly delayed the photo- and thermal degradation of RES and enhanced its stability during in vitro digestion. The incorporation of surfactants provided additional hydrophobic sites and improved the structural integrity, enabling the controlled release of RES and highlighting the synergistic benefits of multicomponent complexation [80].

Expanding on this approach, Guo et al. designed ternary nanocomplexes for the co-delivery of curcumin and RES using a similar PPI-HMP-rhamnolipid system. These complexes achieved encapsulation efficiencies above 93% for both compounds, and showed controlled release during intestinal digestion. Intermolecular forces, such as hydrogen bonding, hydrophobic interactions, and electrostatic attraction, play crucial roles in complex formation, ensuring high bioactive retention under simulated physiological conditions [81].

From a structural and mechanistic perspective, Zhang et al. demonstrated through spectroscopic and molecular docking analyses that RES binds primarily through hydrophobic interactions with PPI, especially with the 11S protein fraction. The encapsulated RES transitioned from a crystalline to an amorphous state, thereby enhancing its chemical stability and antioxidant potential. Molecular docking further confirmed favorable binding energies, supporting the strong compatibility between RES and PPI [82].

Yan et al. developed Pickering emulsions stabilized by PPI-alginate microgels. These emulsions formed robust interfacial layers around the oil droplets and significantly improved the thermal and photostabilities of the encapsulated RES. PPI microgels and their conjugates effectively resisted environmental stresses, such as heating and freeze-thaw cycles, opening new possibilities for stable and scalable RES delivery systems in emulsified food products [83].

4.5. Zein-Polysaccharide Based Carriers

Zein is a naturally occurring, biodegradable, and biocompatible protein derived from corn [84]. It is a hydrophobic protein that is soluble in ethanol but insoluble in water because of its high content of nonpolar amino acids [85]. Zein is an amphiphilic molecule that contains both lipophilic and hydrophilic domains. However, more than half of these amino acids, primarily leucine, proline, and alanine, are hydrophobic. Zein exhibits high solubility in aqueous ethanol (>70%) but remains insoluble in pure water. Owing to its unique properties, zein is extensively utilized in the food, pharmaceutical, and biotechnology industries for the formulation of spherical colloidal nanoparticles [86-88].

Huang et al. developed zein/pectin core–shell nanoparticles via antisolvent precipitation, achieving ~78% encapsulation efficiency and excellent colloidal stability. RES-loaded nanoparticles showed superior antioxidant activity and improved antiproliferative effects on hepatocarcinoma cells compared with free RES, highlighting their dual potential in food and pharmaceutical applications [1].

Khan et al. further stabilized zein nanoparticles using an alginate-chitosan bilayer coating. This layered system exhibited enhanced photostability and controlled release characteristics. Post-digestion studies have shown that the bioaccessibility of RES increased to 81%, confirming the synergistic effect of polysaccharide coatings in improving gastrointestinal resilience and delivery efficiency [2].

In one study, zein nanoparticles were developed and characterized as carriers of RES by coating them with CHI. Employing the liquid-liquid dispersion method, spherical nanoparticles with a mean diameter of 295 nm and low polydispersity index were successfully synthesized. CHI coating enhanced the encapsulation efficiency to 51%, while the zeta potential increased to +29 mV. Moreover, RES remained in an amorphous state within the nanoparticles during encapsulation. In simulated gastrointestinal fluids, the CHI coating improved the protection of nanoparticles against premature RES release. An in vitro release study demonstrated the biphasic and extended-release profile of RES. The antioxidant activity of RES-loaded CHI-coated zein nanoparticles was attributed to the synergistic effects of RES and amino acids present in the zein structure. Additionally, the mucoadhesive properties of CHI played a crucial role in mucin adsorption onto the nanoparticle surface, further supporting its potential for oral delivery applications. These findings demonstrate the potential of CHI-coated zein nanoparticles as effective carriers for RES, offering enhanced stability, bioavailability, and controlled release [89].

Hu et al. examined zein/pectin nanoparticles for their behavior under simulated digestion. Notably, the encapsulated RES retained its antioxidant potential post-digestion and exhibited significantly higher bioaccessibility than the unencapsulated RES. These findings reinforce the role of electrostatic deposition and polysaccharide pairing in enhancing the digestive stability [90].

By pushing the boundaries of functional layering, Wei et al. designed ternary composite nanoparticles using zein, propylene glycol alginate (PGA), and rhamnolipid. These particles demonstrated exceptional physicochemical stability and resistance to gastric conditions. Notably, RES remained in an amorphous state, which enhanced its solubility and absorption. Spectroscopy confirmed that hydrogen bonding and hydrophobic interactions were the dominant stabilizing forces [91].

The stabilizing effect of divalent ions was explored by Wei et al., who found that calcium ions could modulate the structure and digestion fate of zein-PGA-tea

saponin ternary complexes. A Ca^{2+} concentration of 2–4 mM yielded optimal particle stability and sustained release of RES, with higher levels triggering aggregation [92].

Liu et al. developed fucoidan-coated zein nanoparticles with impressive encapsulation efficiency (~95%) and a mean particle size around 121 nm. These particles provide strong pH and storage stability, UV protection, and controlled release under digestive conditions. The electrostatic and steric stabilizing effects of fucoidan are crucial for preventing aggregation, establishing a promising marine-polysaccharide pairing for zein-based carriers [93].

In a novel approach using ultrasound-assisted coacervation, Liu et al. enhanced the encapsulation efficiency of RES in zein–gum arabic systems from 26% to over 74%. Ultrasound significantly reduced particle size and increased surface charge, forming compact nanoparticles stabilized by hydrogen bonding and electrostatic interactions [94].

In addition to typical colloidal systems, Zhang et al. embedded zein (and gliadin)-based nanoparticles into starch gels to create nanoparticle-filled delivery matrices. These systems increase mechanical strength, improve RES protection from heat and UV, and reduced release in the gastric phase, achieving higher bioaccessibility in the intestine (82–93%) [95].

By combining zein with various natural polysaccharides, surfactants, or ions, researchers have developed highly stable and functional RES delivery systems. These formulations enhance antioxidant activity, prolong release, and improve bioavailability, making them promising candidates for functional foods, supplements, and oral drug delivery.

Table 1 outlines different protein–polysaccharide (PRO-POL) formulations developed for RES encapsulation, detailing the materials used, encapsulation techniques, and the main physicochemical characteristics. These findings emphasize enhanced RES stability, improved bioavailability, antioxidant potential, and sustained release, indicating their suitability for use in the food, pharmaceutical, and nutraceutical fields.

Table 1. Different PRO-POL formulations for RES delivery.

Materials for encapsulation	Encapsulation method	PRO-POL complexes characterization	Application effect/ bioactivity outcomes of PRO-POL-RES complexes	Ref.
Zein-pectin	Strong electrostatic repulsion	Size: 235 nm Zeta potential: - 33.0 mV PDI: 0.24	EE: 77.9%. Good water-soluble redispersibility. Increased antioxidant activity in vitro. Greater activity against proliferation.	[1,96]
ALA-CHI	Electrostatic interactions	Mass ratios of 5:1 Size: 211.0 nm Zeta potential: 13.23 mV	Improved antioxidant activity EE: 58.86% Improved bioaccessibility and thermal stability in vitro.	[14]
Gliadin-pectin	Electrostatic deposition	Mass ratios of 5:1 Size: 500–650 nm Zeta potential: −50 to −60 mV	EE: 90%. Promising encapsulation systems to enrich functional foods with resveratrol	[56]
Gliadin - gum arabic - chitosan	Hydrogen bond, electrostatic interaction and hydrophobic interaction	Mass ratios of 1:2:1 Size: 301.1 ± 13.2 nm Zeta potential: 33.6 ± 2.1 mV PDI: 0.267 ± 0.010	EE: 68.2 ± 3.1% Improved chemical stability, dissolution and antioxidant activity	[59]
Gliadin - hyaluronic acid (HA), and sophorolipid	Hydrogen bond, electrostatic interaction and hydrophobic interaction	Gliadin to HA ratio of 4:1 (w/w). Gliadin to SPL of 2:1. Size: 482.5 ± 3.54 nm Zeta potential: 35.5 ± 0.52 PDI: 0.335 ± 0.027	EE: 90.7 ± 1.7 %, Bioavailability of GHS/RNPs reached a peak of 83.1 ± 3.7 % after the termination of the digestion phase	[60]
Alginate - soy protein isolate	Electrostatic interaction	Mass ratios of 1:0.8 Size: 204.5 ± 12.1 nm Zeta potential: - 36.4 ± 1.2 mV PDI: < 0.4	EE: 91.9 ± 3.3 %. Improved pH-dependent solubility. Enhanced both colloidal stability and more efficient chemical protection to the encapsulated resveratrol	[66]
SPI-PG	Hydrophobic interactions, hydrogen bonding, and van der Waals interactions	Mass ratios of 1:40 Size: 200–300 nm Zeta potential: - 45.83 mV PDI: 0.255	EE: 86.66 ± 1.22 % Enhanced the RES-containing nanoparticles' pH stability, storage stability, ionic stability and digestive stability. It is well absorbed in the intestine and has a high bioavailability. Increased action of antioxidants.	[68]

Materials for encapsulation	Encapsulation method	PRO-POL complexes characterization	Application effect/ bioactivity outcomes of PRO-POL-RES complexes	Ref.
Zein-Chitosan	Electrostatic interaction	Mass ratios of 1:2.4 Size: 295± 38 nm Zeta potential: + 29.7 ± 1.2 mV PDI: 0.20 ± 0.04	EE: 51 ± 2% Improved stability. Enhancement of mucin adsorption onto the surface of nanoparticles. Increased action of antioxidants.	[89]
Avidin-chitosan	Ligand linking	Size: 319 nm PDI: 0.16	EE: 66.4 ± 1.8% Potent drug delivery vector specially targeting to hepatic carcinoma	[97]
Lecithin- Alginate & carboxy methyl chitosan	Electrostatic repulsive force	Mass ratios of 40:3:0.5. Size: 12.171 ± 0.960 µm. Zeta potential: -30.86 ± 1.37 mV.	Improve bioaccessibility and stability. EE: 92.78 ± 0.82 %. Prevents release in a gastric simulation setting. Encourages prolonged release in an artificial gut environment & Increases RES's bioavailability during in vitro digestion simulation.	[98]
PPI-HMP-Rha	Electrostatic repulsive force	Mass ratios of 100:50:100. Size: 515 nm. Zeta potential: -18 to -20 mV.	Improvement of the PPI-Cur-HMP-Res-Rha complexes' physical stability. EE: 93.59% Improved their water solubility and reinforced their stability in both UV and heat conditions. Able to postpone their release in a gastrointestinal simulator.	[99]
Zein-PGA-TS	Hydrogen bonds, hydrophobic effects and electrostatic interactions	Mass ratios of 5:2.5:1. Size: 281.9 and 309.7 nm. Zeta potential: - 20.17 ± 0.50 to -28.80 ± 0.24 mV.	EE: 58.43% to 85.58%. The small intestine offers the best sustained release. Enhanced RES's chemical stability and transport efficiency. Enhancement of RES's intestine absorption, stability, and solubility.	[100]
Zein-rhamnolipid	Electrostatic repulsive force	Mass ratios of 1:0.2 Size: < 200 nm Zeta potential: more negative charge on the nanoparticles	Preserved antioxidant activity. EE: 85% Enhanced chemical stability, bioaccessibility, and water-dispersibility. Prevent the agglomeration of the protein nanoparticles.	[101]
OVA-PHP	Electrostatic repulsive force	Mass ratios of 1:1 Size: 256.83 ± 2.78 nm Zeta potential: - 21.3 ± 1.23 mV PDI: 0.4123 ± 0.043	EE: 95.38% Boost RES's absorption and stability.	[102]
MCP-zein	Electrostatic cross-linking	Mass ratios of 1:40 Size: 174.03 ± 3.14 nm Zeta potential: −34.2 ± 1.15 mV PDI: < 0.2	EE: 92.93 ± 4.51% RES's solubility and in vivo bioactivity should be improved.	[103]
Gliadin-HA-sophorolipid	Hydrogen bonds, π-alkyl interactions, electrostatic forces, and van der Waals attractions	Mass ratios of 4:1:2 Size: 482.5 ± 3.54 nm Zeta potential: - 28.8 ± 0.34 mV PDI: 0.335 ± 0.027	EE: 90.7 ± 1.7 %. Superior stability and sustained Res retention, facilitated the controlled release of Res, enhancing its bioavailability	[60]
Zein-Succinylated Hyaluronic Acid	Hydrophobic interaction and hydrogen bonding	Mass ratios of ~2:1 Size: 150–200 nm Zeta potential: −29 to −20 mV PDI: 0.1	EE: 54.26- 68.60%. Improved water dispersibility, stronger antioxidant and anticancer activities	[104]

5. Comparative Analysis of PRO-POL Nanoparticles for RES Delivery

A comparative evaluation of various PRO-POL nanoparticles developed for RES encapsulation revealed distinct differences in their molecular interactions, structural behavior, formulation efficiency, and biological performance (Table 2).

Gliadin-based systems, as studied by Joye et al. and Davidov-Pardo et al., showed that RES binding is predominantly driven by hydrophobic interactions, with the binding strength increasing with temperature, which may favor thermally stable formulations. However, native gliadin nanoparticles typically display moderate encapsulation efficiency (~53%) and are prone to aggregation under acidic and high-ionic-strength conditions. These limitations were partially overcome by incorporating surface coatings, such as pectin or chitosan hydrochloride, or through chemical modifications, such as glycosylation, which enhance colloidal stability, light protection, and digestive resilience. In contrast, soy protein isolate (SPI) nanoparticles consistently achieve superior encapsulation efficiencies, often exceeding 90%, especially when structurally optimized through ultrasonic treatment, Maillard conjugation with polysaccharides (e.g., polyguluronate), or formulation into pH-responsive hydrogels with glycyrrhizin. These SPI-based systems not only effectively stabilize RES but also demonstrate in vivo biological benefits, including improved antioxidant activity, hepatoprotection, and anti-colitic effects. Whey proteins, such as BSA, ß-lactoglobulin, and α-lactalbumin formed stable complexes with RES via a combination of hydrogen bonding and hydrophobic forces, with ß-lactoglobulin exhibiting the strongest affinity. Glycated BSA nanoparticles showed improved storage stability and digestive resistance, while BSA-chitosan carriers enabled the nasal delivery of RES with neuroprotective effects, making them uniquely suited for targeting the central nervous system.

PPI has emerged as another promising carrier, particularly when formulated into ternary nanocomplexes with high methoxyl pectin and surfactants, such as rhamnolipid or tea saponin. These formulations showed a high encapsulation efficiency, strong digestive stability, and synergistic antioxidant and anti-inflammatory effects. Additionally, PPI-based Pickering emulsions provide robust interfacial stabilization for the dual delivery of RES and curcumin, illustrating the versatility of the platform.

Among all the systems, zein-based nanoparticles stand out for their structural robustness and formulation flexibility. Zein's hydrophobic character allowed it to self-assemble into stable nanoparticles, which were further enhanced by polysaccharide coatings (e.g., fucoidan, gum arabic), surfactants, or functional biopolymers like *Athyrium multidentatum* polysaccharide. Several zein formulations have demonstrated encapsulation efficiencies above 90%, excellent photothermal stability, and effective RES release modulation during gastrointestinal transit. Techniques such as calcium ion induction and ultrasound processing further refine particle morphology and enhance stability. Additionally, embedding zein nanoparticles into starch gels or designing core–shell structures significantly improves mechanical integrity, gastric protection, and intestinal bioaccessibility.

In summary, while each protein-based system brings unique advantages to the table – gliadin for thermoresponsive interactions, SPI and PPI for structural tunability and bioactivity, whey proteins for mucosal and CNS-targeted delivery, and zein for multi-layered robustness – the most effective RES carriers are those that combine molecular compatibility with strategic surface engineering. The synergy among protein type, modification method, and delivery design plays a pivotal role in determining the overall functionality, bioavailability, and therapeutic potential of PRO-POL nanoparticles for resveratrol. Future developments should prioritize not only encapsulation efficiency and stability but also the scalability and bioperformance of these systems under physiologically relevant conditions.

Table 2. A comparative evaluation of the various PRO-POL nanoparticles developed for RES encapsulation.

Protein Type	Binding Mechanism	Encapsulation Efficiency	Stability	Bioaccessibility	Highlights
Gliadin	Hydrophobic (↑temp.)	Moderate (↑with coating)	Requires coating	Moderate to good	Good for heat-stable delivery
SPI	Hydrophobic, H-bonds	High (>90%)	Excellent (↑with glycosylation)	Very high (pH-responsive)	In vivo validated, green fabrication
Whey (BSA, ß-LG)	H-bonds + hydrophobic	Good (↑with glycation)	Moderate (↑with chitosan)	Improved in dual-delivery systems	Nose-to-brain, antioxidant, storage stability
PPI	Hydrophobic, electrostatic	High (>90% in ternary)	Good (↑with surfactants)	Controlled release, high bioaccessibility	Effective for co-delivery; stable Pickering emulsions
Zein	Hydrogen bonding, hydrophobic	High (>95% with coating)	Very stable (coated)	Excellent with polysaccharide layers	Versatile; tunable with Ca^{2+}, ultrasound, or gels

6. Application Of RES-Loaded PRO-POL Complexes

RES possesses a range of pharmacological properties, including antitumor [105,106], antioxidant [107], anti-inflammatory [108], neuroprotective [109], cardioprotective [110] and antidiabetic effects [111]. However, its limited bioavailability restricts its therapeutic potential. Encapsulating RES within PRO-POL complexes has been demonstrated to enhance bioavailability and improve anticancer and antioxidant properties. Fig. 3 summarizes the pharmacological activity of RES.

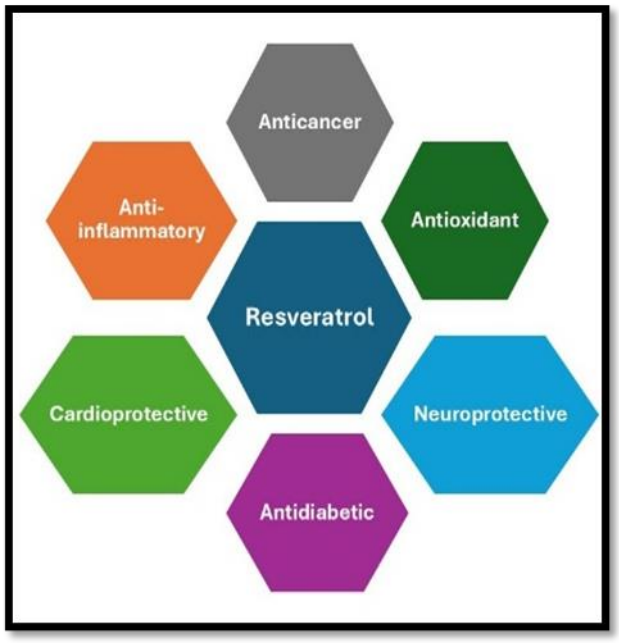

Fig. 3. Pharmacological activity of resveratrol.

PRO-POL complexes loaded with RES have significant scientific value, particularly in cancer therapy, as they facilitate both passive and active targeting of tumor cells [112]. Hepatocarcinoma is the sixth most common cancer globally, and ranks third in terms of cancer-related mortality. Conventional anticancer drugs often have limited efficacy against hepatocarcinoma, with approximately 67% of patients developing rapid resistance to chemotherapy [113]. Previous research has suggested that RES may exert antiproliferative effects on hepatocarcinoma cell lines [97].

Huang et al. investigated the cytotoxic effects of free RES (solubilized in DMSO) and RES encapsulated in biopolymer nanoparticles in human hepatocarcinoma Bel-7402 cells. The MTT assay revealed that both free and encapsulated RES significantly reduced cancer cell viability in a dose-dependent manner. After a 24-hour treatment at 197.2 μM, cell viability was 24.7% for free RES and 19.3% for encapsulated RES. Notably, the empty biopolymer nanoparticles exhibited no cytotoxicity. Encapsulated RES demonstrated significantly higher cytotoxicity than free RES, with IC_{50} values of 17.61 μg/mL (77.2 μM) and 25.57 μg/mL (112.0 μM), respectively ($p < 0.05$). These findings suggest that encapsulated RES may be more effective in inhibiting hepatocarcinoma cell proliferation [97].

The antioxidant activity of RES-loaded nanoparticles was assessed using the DPPH radical scavenging assay, which evaluates the ability of antioxidants to donate hydrogen to O- and N-centered radicals [114]. Unloaded SPI-RES (RSN) nanoparticles and sodium alginate-shelled SPI nanoparticles (RSAN) exhibited moderate DPPH scavenging activity of approximately 14% and 18%, respectively. In contrast, free RES showed a scavenging activity of 64.4 ± 0.7%, whereas RSN and RSAN achieved 74.3 ± 0.7% and 82.3 ± 2.7%, respectively. These results indicated that encapsulation did not diminish the antioxidant effect of RES, as the overall activity was nearly equivalent to the combined activities of free RES and unloaded RSN or RSAN [66]. These findings are consistent with those of previous studies on quercetin encapsulation in soy protein isolate [115].

Penalva et al. developed and evaluated a zein-based RES nanoparticle formulation to investigate its anti-inflammatory activity, oral bioavailability, and therapeutic potential in a mouse endotoxic shock model. Their results indicated that zein nanoparticles provide an effective oral delivery system for RES, prolonging its plasma levels for up to 48 h owing to a combination of nanoparticle matrix erosion and polyphenol diffusion. This encapsulation strategy significantly improves the oral bioavailability of RES by approximately 50% [116]. In a mouse model of lipopolysaccharide (LPS)-induced inflammation, the oral administration of RES-loaded zein nanoparticles effectively suppressed inflammatory responses and mitigated endotoxic shock mediators.

7. Conclusions and Outlook

RES, a polyphenolic compound with notable pharmacological properties, including antioxidant, anti-inflammatory, anticancer, neuroprotective, cardioprotective, and antidiabetic effects, has significant limitations owing to its poor solubility, low bioavailability, and rapid degradation. To address these challenges, PRO-POL nanocarriers have emerged as a promising approach for substantially enhancing the stability, solubility, and controlled release of RES.

Various protein-based nanocarriers, such as WP, PP, SPI, gliadin, and zein, in combination with polysaccharides, such as CHI, pectin, and sodium alginate, have been extensively investigated. These biopolymer-based nanoparticles utilize electrostatic interactions, hydrophobic forces, and hydrogen bonding to encapsulate and protect RES. Studies have demonstrated that such nanoformulations not only improve bioavailability but also extend the release kinetics of RES and enhance its therapeutic effects. For instance, α-lactalbumin-CHI nanoparticles increase the water solubility of RES, whereas zein-based formulations improve mucoadhesion and provide controlled gastrointestinal release. Additionally, ternary complexes incorporating PP, HPM, and surfactants exhibit superior structural stability and photoprotection.

In addition to improving the physicochemical properties, these PRO-POL nanocarriers have demonstrated substantial biological efficacy. RES-loaded nanoparticles exhibited enhanced cytotoxicity against hepatocarcinoma cells, increased antioxidant potential, and superior anti-inflammatory effects in in vivo models. However, translating these findings into practical applications requires further optimization to ensure large-scale production feasibility, long-term stability, and site-specific delivery.

Future research should focus on refining the nanoparticle architecture to optimize mucoadhesion, targeted drug delivery, and prolonged systemic circulation of RES. Integrating PRO-POL nanoformulations with stimuli-responsive materials could enable precise controlled drug release in response to physiological triggers, which may contribute to enhancing the pharmacological potential of RES. Additionally, extensive in vivo studies and clinical trials are essential to validate therapeutic efficacy and ensure regulatory compliance.

In conclusion, PRO-POL-based nanocarriers represent an innovative approach to RES delivery, optimizing its pharmacokinetics and therapeutic benefits. Their successful translation into nutraceuticals, functional foods, and pharmaceutical formulations could significantly advance RES-based interventions and ultimately improve health outcomes and enhance disease management.

Abbreviations

UV-Ultraviolet, ng/ml - Nanograms Per Milliliter, mg/mL - milligrams per millilitre, µM - micrometer, RES/RSV - Resveratrol, PRO-POL - Protein-Polysaccharide, NLC - nanostructured lipid carriers, SLN - solid lipid nanoparticles, SPI - soy protein isolate, HA - Hyaluronic acid, PG - polyguluronate, WP - Whey protein, BSA - bovine serum albumin, BLG - ß-lactoglobulin, ALA - α-lactalbumin, CHI- Chitosan, TEM -transmission electron microscopy, AFM - atomic force microscopy, EE - encapsulation efficiency, XRD - X-ray diffraction, PP - Pea protein, PPI - Pea protein isolate, HMP - high methoxyl pectin, Rha - rhamnolipid, PGA- propylene glycol alginate, TS - tea saponin, LAE - ethyl lauroyl arginate, DMSO - dimethyl sulfoxide, MTT - 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide, DPPH - 2,2-diphenyl-1-picrylhydrazyl, RSN - resveratrol in soy protein isolate-resveratrol complex, RSAN - sodium alginate shelled soy protein isolate nanoparticles for encapsulation of resveratrol, LPS - lipopolysaccharide, STZ - streptozotocin.

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