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From Stability to Functionality: Bridging the Evidence Gap in Food-Grade Liposomal Systems

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Food-grade liposomal systems have emerged as promising carriers for protecting and delivering bioactive compounds in food and nutraceutical applications. However, current research often emphasizes formulation-level outcomes, such as encapsulation efficiency, physicochemical stability, and controlled release, without sufficiently demonstrating their biological relevance. This opinion argues that improved retention should not be considered an endpoint, but rather an intermediate step toward meaningful functionality. Future research should therefore establish clearer links between liposomal performance, bio accessibility, absorption, systemic exposure, and biological effects under realistic food, gastrointestinal, and physiological conditions.

Keywords: Food-grade liposomes; Bioactive delivery; Bio accessibility; Biological functionality; Functional foods.

Introduction

Food-grade liposomal systems have emerged as versatile carriers for sensitive bioactive compounds because their phospholipid bilayers can accommodate both hydrophilic and lipophilic molecules while remaining compatible with food and nutraceutical formulations (Ajeeshkumar et al., 2021; Chai and Park, 2024) [1]. This structural flexibility is particularly valuable for compounds whose application is limited by poor stability, low retention, or unfavorable interactions with the surrounding food matrix; moreover, the composition, size, lamellarity, and surface characteristics of liposomes can be adjusted to influence membrane permeability, protection, and release behavior (Chai and Park, 2024) [2] thereby extending their potential beyond simple encapsulation

toward the preservation of sensitive ingredients during processing, storage, and gastrointestinal transit. The technological benefits reported so far are meaningful, especially when compared with the behavior of free bioactive compounds under stressful conditions. Liposomes can reduce exposure to light, oxygen, moisture, and temperature fluctuations, while their membrane structure may also provide slower or more controlled release profiles and help preserve the chemical integrity of encapsulated compounds (Ajeeshkumar et al., 2021; Liu et al., 2020) [3]. In the case of hydroxytyrosol (HT), a phenolic compound naturally present in olives, olive oil, and olive-derived by-products and associated with the EFSA-recognized protection of low-density lipoproteins against oxidative damage, liposomal incorporation has been linked

to improved stability, slower release, and enhanced DPPH radical-scavenging activity compared with the free compound (Yuan et al., 2017), thereby suggesting that encapsulation can protect HT while preserving its antioxidant functionality. Similarly, polymer-coated liposomes containing HT and curcumin have shown reduced premature release during simulated gastrointestinal digestion, indicating that surface modification may further regulate vesicle behavior under changing digestive conditions (De Leo et al., 2023) [4].

Taken together, these findings establish a credible technological promise for food-grade liposomes, as they can protect bioactive compounds, improve formulation flexibility, and modulate release behavior under selected experimental conditions. However, this progress should be interpreted primarily as evidence of improved formulation performance rather than as definitive proof of enhanced biological functionality; in other words, the field has successfully demonstrated that liposomes can retain and protect bioactive compounds, yet the more demanding and scientifically relevant question concerns what happens after that protection has been achieved. The progress achieved at the formulation level is important, yet it can also encourage an overly narrow definition of success. Higher encapsulation efficiency, improved storage stability, smaller particle size, or slower release all describe how a carrier behaves, although none of these measurements alone establishes that the encapsulated compound will become more available to the body or produce a stronger biological response (De Leonardis et al., 2020; Liu et al., 2020) [5]. This distinction is particularly important because a liposome may retain a bioactive efficiently while delaying its release; therefore, the central question is not simply how much of the compound remains encapsulated, but whether the formulation delivers an appropriate amount at the appropriate stage of digestion.

Simulated gastrointestinal studies provide valuable information regarding liposomal integrity, compound release, and apparent bio accessibility; nevertheless, these outcomes should be interpreted as intermediate evidence rather than as direct proof of enhanced absorption or systemic exposure (De Leo et al., 2023; Rudzińska et al., 2024) [6]. Once ingested, liposomes encounter changing pH conditions, digestive enzymes, bile salts, ionic environments, and mechanical stresses that can alter vesicle size, membrane organization, and release behavior, while the surrounding food matrix may further influence the metabolic fate of the encapsulated compound (Liu et al., 2020) [7]. Moreover, evidence obtained from food-derived phenolic compounds indicates that pharmacokinetic behavior can be strongly influenced by the matrix in which they are consumed, meaning that results generated in simplified aqueous digestion models cannot be automatically extrapolated to complete foods or nutraceutical products (Alemán-Jiménez et al., 2021) [8].

The same caution applies to chemical antioxidant assays, including DPPH and ABTS, which measure radical-scavenging capacity under controlled experimental conditions but do not reproduce absorption, metabolism, tissue distribution, or interactions with cellular targets. Although encapsulation may preserve the chemical antioxidant activity of a bioactive compound, this does not necessarily imply that its antimicrobial,

anti-inflammatory, or broader biological effects will improve, particularly because these outcomes may depend on distinct metabolites, cellular pathways, and exposure levels (Yuan et al., 2017; De Leonardis et al., 2020) [9]. Accordingly, the field should more carefully distinguish between the preservation of chemical activity and the demonstration of improved biological efficacy, since the latter requires evidence from cell-based models, pharmacokinetic studies, animal experiments, and ultimately well-designed human investigations. From this perspective, the formulation-level improvements commonly reported should be regarded as encouraging indicators rather than definitive outcomes, because they still do not answer the central question: do more stable liposomes actually deliver better biological performance? The transition from a promising liposomal formulation to a useful food product requires more than demonstrating stability in water or simplified buffer systems. Real foods contain proteins, minerals, salts, carbohydrates, lipids, and surfactants capable of interacting with the phospholipid bilayer, while processing conditions such as heating, homogenization, pH fluctuations, and variations in ionic strength may promote aggregation, leakage, or structural disruption (Ajeeshkumar et al., 2021; Chai and Park, 2024). Consequently, food-grade liposomes should be evaluated within representative food matrices rather than solely as isolated vesicular systems, since formulations that perform well during laboratory characterization may behave quite differently when incorporated into beverages, dairy products, emulsions, powders, or other structured foods.

This issue is closely connected to digestion and manufacturing, as simulated gastrointestinal models can help identify changes in vesicle integrity and release behavior while also providing preliminary information about bio accessibility; however, these approaches should ideally be complemented with standardized assessments of intestinal uptake and pharmacokinetics, otherwise it remains difficult to determine whether a formulation offers a meaningful advantage beyond improved retention (Liu et al., 2020; Rudzińska et al., 2024). At the same time, laboratory methods such as thin-film hydration often require solvent removal, hydration, extrusion, and size-reduction steps that can complicate scale-up and increase process variability, whereas microfluidic and micro fluidization approaches offer greater process control while still facing challenges related to throughput, equipment requirements, energy consumption, and reproducibility (Ajeeshkumar et al., 2021; Rocas et al., 2020). Consequently, the formulation that performs best at laboratory scale may not necessarily be the most practical option for industrial production.

Finally, real-world functionality must encompass economic, regulatory, safety, sensory, and consumer-related considerations. Although the use of food-grade ingredients may facilitate product development, additional coatings, specialized equipment, or more complex manufacturing strategies can increase production costs while simultaneously raising new regulatory concerns, particularly when nanoscale systems are intended for routine food consumption (Chai and Park, 2024; Eugster and Luciani, 2025). For this reason, future studies should compare liposomal systems directly with free bioactives and conventional formulations across processing, storage, digestion, and biological evaluation, while also determining

whether the added complexity results in a reproducible and measurable benefit. Ultimately, a food-grade liposome should not be considered a successful product merely because it achieves high encapsulation efficiency or stability; rather, it should remain functional within the food matrix, withstand relevant processing conditions, behave predictably during digestion, and provide a clear advantage over the non-encapsulated compound.

The next stage of food-grade liposomal research should move beyond formulation optimization as an isolated objective and, instead, adopt an evidence framework that directly connects carrier properties with biological outcomes. Standardized reporting of particle size, polydispersity, membrane composition, encapsulation efficiency, loading capacity, storage stability, release behavior, and bioaccessibility would certainly make comparisons more reliable; however, these measurements should be integrated with studies of intestinal uptake, pharmacokinetics, metabolism, and biological response under progressively more realistic conditions (De Leonardis et al., 2020; Xu et al., 2025). In parallel, formulations should be tested in representative food matrices and evaluated for reproducibility, sensory acceptability, cost, safety, and scalability, because a technically sophisticated system offers limited practical value if it cannot be produced consistently or incorporated into a real product (Chai and Park, 2024; Eugster and Luciani, 2025).

In my view, the central challenge is no longer whether food-grade liposomes can encapsulate bioactive compounds, since this capability has already been demonstrated across a wide range of formulations; rather, the key question is whether they can provide a meaningful and reproducible advantage after processing, digestion, absorption, and metabolism. The field should therefore place less emphasis on maximizing encapsulation efficiency and more emphasis on establishing clear links between formulation design and measurable functionality through direct comparisons with free compounds and conventional delivery systems. Ultimately, the future of food-grade liposomal systems depends less on achieving higher retention values and more on demonstrating meaningful functionality under realistic food, gastrointestinal, and physiological conditions, because encapsulation is a formulation achievement, whereas functionality is a biological claim that still requires convincing evidence.

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Conflict of interest

No conflict of interest.

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