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Review Article

A Systematic Review of Nano-Encapsulation for Improving the Bioavailability of Dietary Supplements and Nutraceuticals

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Abstract

Nanoencapsulation is a growing technique in the field of nutraceuticals and dietary supplements, offering several advantages over non-encapsulated forms. This systematic review assesses the impact of nanoencapsulation on key factors such as bioavailability, stability, tolerance, and encapsulation efficiency. The selected studies demonstrate that nanoencapsulation enhances the protection and controlled release of bioactive compounds, leading to improved efficacy and therapeutic potential. Furthermore, it increases the bioavailability of nutrients and active ingredients while maintaining their stability under different conditions. The review also highlights the positive effects on product safety and consumer tolerance, making nanoencapsulation a promising strategy for optimizing the formulation of dietary supplements. These findings suggest that nanoencapsulation could play a critical role in advancing the effectiveness of nutraceutical products.

Keywords: Nanoencapsulation, dietary supplements, nutraceuticals, efficacy, bioavailability, stability

INTRODUCTION

In recent years, the growing demand for dietary supplements and nutraceuticals has spurred research into innovative delivery systems to enhance the efficacy, safety, and stability of active ingredients. Nano capsulation, a technology that involves encapsulating bioactive compounds within nanoscale carriers, has emerged as a promising approach to overcome the limitations of traditional formulations. This technique aims to improve the stability of active ingredients, enhance their bioavailability, and minimize potential side effects, thus offering significant benefits in the fields of dietary supplements and nutraceuticals. The present systematic review aims to evaluate the impact of nano capsulation on key parameters, including the efficacy, bioavailability, stability, and tolerance of dietary supplements and nutraceuticals. By synthesizing evidence from high-quality studies, this review seeks to provide a comprehensive overview of the advantages and contributions of nano capsulation technology. Our objective is to highlight how nano capsulation can optimize the therapeutic potential of dietary supplements and nutraceuticals, making them more effective and safer for consumer use.

The findings of this review are expected to contribute valuable insights into the role of nanoencapsulation, enhancing the effectiveness of dietary supplements, potentially informing future research and development in this field.

MATERIALS AND METHODS

Search Strategy

A comprehensive literature search was conducted to identify studies relevant to the nanoencapsulation of dietary supplements and nutraceuticals. The search was performed across multiple electronic databases, including **ScienceDirect, PubMed, Springer, MDPI, Wiley** and **Google Scholar**. These databases were chosen to ensure broad coverage of the literature, spanning various disciplines related to pharmaceutical sciences, food technology, and biomedical research. The search strategy was developed in collaboration

with experts in the field to maximize sensitivity and specificity. The following search terms and Boolean operators were employed: Nanoencapsulation AND Dietary Supplements OR Nutraceuticals; Nanoparticles OR Nanocarriers AND Bioavailability OR Stability; Controlled Release AND Encapsulation Efficiency.

Search queries were tailored to the specific indexing and search capabilities of each database to optimize the retrieval of relevant articles. The literature search was restricted to studies published between January 1, 2019, and July 31, 2024. This time frame was selected to focus on contemporary advancements in nanoencapsulation technologies. Only articles published in English were considered for inclusion in the review to maintain consistency in the analysis and interpretation of data. The search was conducted between June 1, 2024, and August 1, 2024. All search results were imported into Zotero for reference management, where duplicate records were identified and removed.

Inclusion and Exclusion Criteria

This systematic review included only original research articles published between January 1, 2019, and June 31, 2024. Reviews, book chapters, conference abstracts, and other forms of non-primary research were excluded. The included studies were required to report on in vivo experiments and/or clinical trials investigating the effects of nanoencapsulation on dietary supplements and nutraceuticals, as we focused on research with direct implications for clinical or preclinical applications. Articles published exclusively in English were considered, ensuring consistency in data interpretation. We specifically included studies that assessed key outcomes such as bioavailability, clinical efficacy, and stability of the nanoencapsulated compounds. Studies that only conducted in vitro experiments without subsequent in vivo or clinical validation were excluded. Additionally, non-peer-reviewed articles or publications from predatory journals were excluded to maintain the reliability of the included studies.

Study Selection

The study selection process followed the PRISMA guidelines and involved a multi-step approach to ensure the inclusion of relevant and high-quality studies. Initially, duplicate records were identified and removed using Zotero. The remaining studies were then subjected to a two-phase screening process.

In the first phase, the titles and abstracts of all retrieved articles were independently reviewed by two researchers. This phase aimed to exclude studies that clearly did not meet the predefined inclusion criteria, such as reviews, book chapters, and studies focusing solely on in vitro experiments. Any discrepancies between the reviewers were resolved through discussion and, if necessary, by consulting a third reviewer. In the second phase, the full texts of the studies that passed the initial screening were reviewed in detail. This full-text review was conducted to confirm that each study met all inclusion criteria, specifically focusing on the relevance of the nanoencapsulation intervention, study design, and the reported outcomes. Studies that did not meet these criteria were excluded, with the reasons for exclusion documented systematically.

Data Extraction

Data extraction was performed independently by two researchers using a standardized data extraction form designed specifically for this review. The extracted data included essential study characteristics such as the study design, sample size, and population characteristics. Details of the nanoencapsulation interventions were recorded, including the type of nanoparticles, materials used, and the specific dietary supplements or nutraceuticals encapsulated. For each included study, information on the comparator (e.g., non-encapsulated compounds), primary and secondary outcomes (e.g., bioavailability, clinical efficacy, stability), and the study setting were meticulously documented. Additionally, data on follow-up duration, reported conflicts of interest, and any potential biases were extracted. To ensure accuracy, the extracted data were cross-checked by the two researchers. Any inconsistencies were resolved through by revisiting the original study documents. Data management was facilitated using Microsoft Excel, where the extracted data were compiled for subsequent analysis.

Quality Assessment

Although a formal quality assessment tool was not employed, the included studies were evaluated based on several key methodological criteria to ensure the robustness and reliability of the findings. Specifically, attention was given to the randomization quality, with studies reporting adequate randomization methods considered to be of higher quality. The sample size of each study was also carefully reviewed, with studies providing justification for their sample sizes or employing appropriate power calculations receiving greater emphasis. Statistical rigor was another key consideration, particularly the use of p-values to report the significance of findings. These quality considerations were applied during both the study selection and data extraction phases, and while not quantified using a formal scoring system, they informed the overall interpretation of the results.

Data Synthesis and Analysis

The data from the included studies were synthesized through a combination of narrative and qualitative approaches to evaluate the effects of nanoencapsulation on dietary supplements and nutraceuticals. A narrative synthesis was conducted to summarize the key characteristics and findings across studies, focusing on the nanoencapsulation methods, specific dietary supplements or nutraceuticals, and the primary outcomes reported. Given the variability in interventions, populations, and study designs, no quantitative meta-analysis was performed. Instead, the findings were synthesized narratively to provide a comprehensive overview of the existing evidence.

Limitations

While this systematic review was conducted with a rigorous and comprehensive approach, several limitations must be

acknowledged. First, the review was limited to studies published in English, which may have led to the exclusion of relevant studies published in other languages, potentially introducing language bias. Additionally, the search strategy, although exhaustive, may have missed some studies due to the limitations of database indexing and variability in keyword usage across different studies. The heterogeneity of the included studies, particularly in terms of the nanoencapsulation methods used, the types of dietary supplements and nutraceuticals studied, and the outcomes reported, made it difficult to directly compare findings across studies. Consequently, no quantitative meta-analysis was performed. Finally, the quality of the included studies varied, with some lacking detailed reporting on key aspects such as randomization, blinding, and sample size justification, which may affect the interpretation of the results. Despite these limitations, the review provides a comprehensive overview of the current evidence on the nanoencapsulation of dietary supplements and nutraceuticals, highlighting areas for future research.

RESULTS

Out of the 1,000 articles identified, 19 studies were selected for inclusion. These studies primarily consisted of 18 laboratory experimental research on animals (rats, mice, etc.) and one clinical trial involving patients with periodontitis. The interventions focused on various types of nanocapsules, such as nanomicelles and polymer nanoparticles, administered orally. Results indicate that the encapsulation efficiency (EE%) ranged between 90-100% in 8 studies and between 70-90% in 9 studies. In some studies, such as the study (15), the encapsulation rate of coenzyme Q10 varied with the type of nanoencapsulation (MSNs@CoQ10: 89.06%, DC-TPGS-LMSNs@CoQ10: 94.50%). Another study (7) reported encapsulation efficiency (EE%) of NP CVDL as 95.06 ± 0.4% and NP CVDL CHOL as 37.45 ± 1.8%.

Table 1: Overview of Encapsulation Efficiency (EE%) in Nanoparticle-Based Delivery Systems

N /27	Encapsulation Efficiency (%)
8	90-100
9	70-90
1	50-70
1	⩽50

Bioavailability data is highly heterogeneous. Some studies report increased bioavailability compared to non-encapsulated forms using a fold factor (e.g., for the study (1), relative Bioavailability: P/P-Nar NP: 4.73-fold increase compared to free naringenin suspension; Z/P-Nar NP: 1.89-fold increase compared to free naringenin suspension).

Others use percentages (e.g., Study (3): Bioavailability improved by 55% after nanoencapsulation compared to free sesamol solution), while others measure plasma accumulation (e.g., study (4): The study shows that LNCs significantly enhanced lutein bioavailability, with plasma levels of 67.6 nmol/mL at 1 mg/kg BW and 713.5 nmol/mL at 10 mg/kg BW compared to control levels <0.01 pmol/mL).

Overall, 12 studies clearly indicate increased bioavailability with improved clinical action and efficacy of nanoencapsulated components, while the remaining studies do not provide data on bioavailability.

Stability is a crucial criterion for assessing both the efficacy and safety of formulations. In this systematic review, various methods for evaluating stability were reported among the selected studies. Overall, stability was found to be better in most of the studies, one study did not provide information on stability.

Zeta potential: 10 studies assessed stability using zeta potential measurements. Among these, four studies reported values between ±30 mV and ±59 mV, indicating good stability and no aggregation (e.g., In the study (4): "The zeta potential of LNCs was +38 mV, indicating good stability and no aggregation."). 4 other studies showed zeta potential values ranging from ±15 mV to ±29 mV, which still indicated satisfactory stability with low aggregation (e.g., In the study (6): "Zeta potential: 20.4 ± 1.2 mV. Polydispersity index (PDI): 0.348 ± 0.044. These values indicate that the nanoparticles were stable with low aggregation."). Finally, 1 study observed zeta potential values below ±15 mV (e.g., In the study (7): "The zeta potential of NP CVDL: −2.04 ± 0.2 mV. The zeta potential of NP CVDL CHOL: −2.08 ± 0.1 mV. The nanoparticles showed good physicochemical stability over 7 weeks, with consistent particle size and zeta potential values.").

Duration of stability: 5 studies mentioned stability over time, sometimes influenced by pH or temperature. For instance, in the study (3), stability exceeding six months was observed at 4°C without significant changes in particle size or polydispersity index. The study (11) showed that PPN-LPHNPs exhibited excellent stability in simulated gastric fluids (pH 1.2) and simulated intestinal fluids (pH 6.8), maintaining particle size for 180 days at various storage temperatures (4 ± 1°C, 25 ± 2°C, and 40 ± 2°C).

General stability: Some studies merely noted good stability without specific details. For example, study (1) indicated that the P/P-Nar NP formulation exhibited higher stability than Z/P-Nar NP, especially under simulated gastrointestinal conditions, with a more sustained release profile. Other studies utilized the polydispersity index (PDI) to assess stability, such as study (15), where a PDI of 0.687 indicated a fairly uniform distribution of nanoparticles, suggesting good stability.

Regarding tolerance: No adverse effects were reported or mentioned in the studies.

DISCUSSION

This systematic review highlights the significant advantages of nanoencapsulation in dietary supplements and nutraceuticals. Most studies reported an encapsulation efficiency exceeding 90%, demonstrating the method's high capability in preserving active compounds. Regarding bioavailability, a marked improvement was consistently observed, indicating that nanoencapsulation enhances the absorption of bioactive ingredients, a critical factor for the efficacy of many nutraceuticals.

In terms of stability, nanoencapsulation contributed to improve stability of nutraceuticals, supporting its role in extending product shelf life and maintaining potency. None of the studies reported any adverse effects, suggesting that nanoencapsulation is a safe approach. These findings underscore the potential of nanoencapsulation to significantly enhance the effectiveness of nutraceutical products, though further research could focus on long-term safety and specific applications across different formulations.

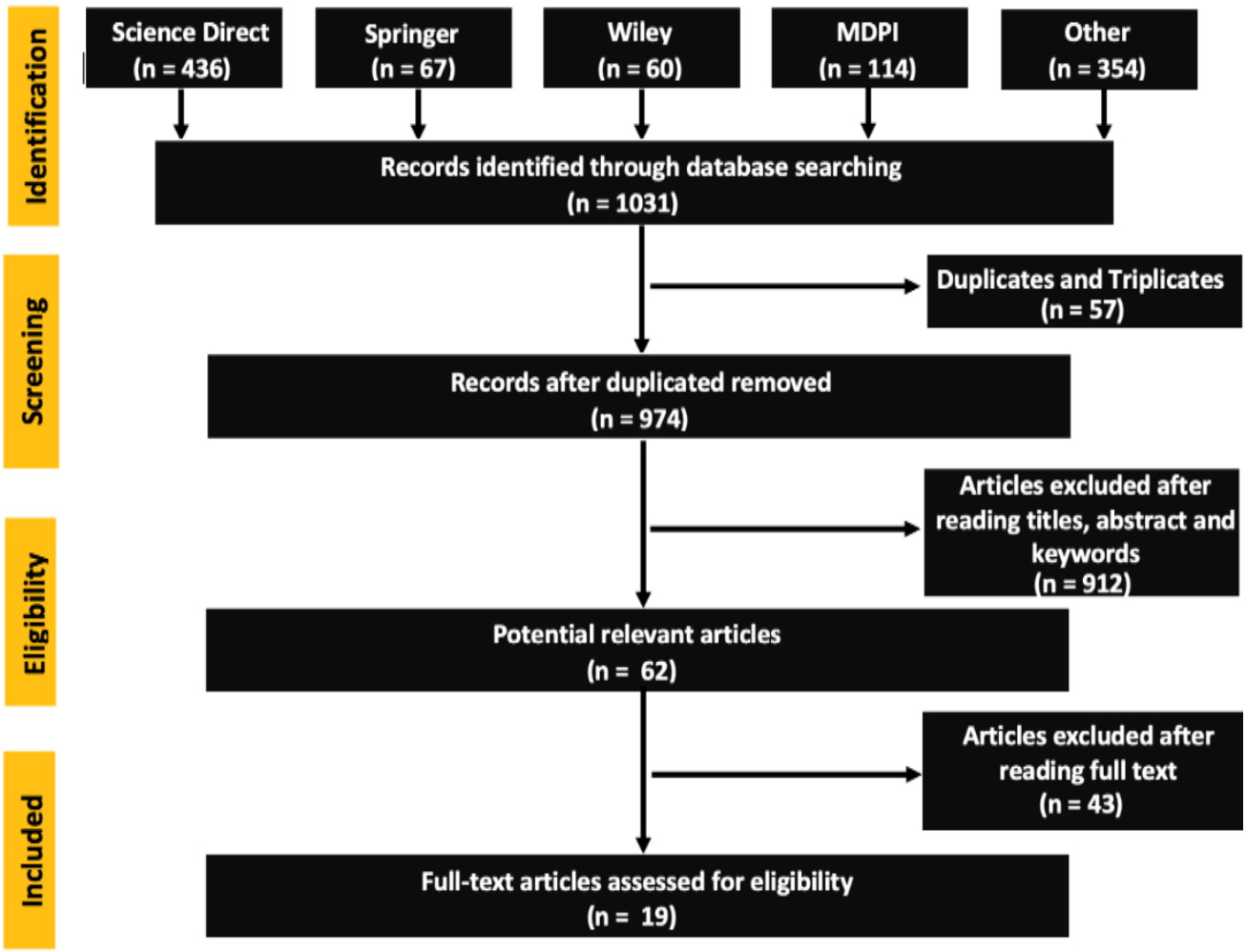

Figure 1: Flow Diagram of Study Selection Process for Systematic Review on Nanoencapsulation of Dietary Supplements and Nutraceuticals

Table 2: A Summary Table About Comparative Analysis of Delivery Vehicles and Efficacy in Nanoencapsulation Studies

Year	2022	2022	2021	2020	2019	2022
Substance administered	Naringenin	Alpha tocopherol	Curcumin	Lutein	Quercetin	Astaxanthin
Delivery vehicle	PLA/PVA and zein/pectin	Polycaprolactone	α-TM-VP-NVC	CS-SA-OA	Casein-HP-β-CD	Chitosan
Subject population	Rat	Rat	Rat	Rat	Rat	Rat
Trial Duration	24 hours	18 days	28 days	14 days (acute), 28 days (subacute)	48 hours	12 hours
Sample Size	18 rats	Groups of 5–7 rats	40 rats	30 rats (acute), 24 rats (subacute)	30 rats	Groups of 6 rats each
Encapsulation Efficiency (EE%)	P/P-Nar NP: 79.3 ± 5.2% Z/P-Nar NP: 62.5 ± 4.1%	Approximately 90%	88.5%	90%	Q-NP: 75.4% Q-HPCD-NP: 82.9%	63.9%
Treatment Group	P/P-Nar NP: 90 mg/kg, oral Z/P-Nar NP: 90 mg/kg, oral	Alpha-tocopherol-loaded PCL NPs: 100 mg/kg, oral	Nano-formulation: 10 mg/kg, oral	LNCs: 0.1, 1, 10, 100 mg/kg (acute); 1, 10 mg/kg (subacute), oral	Quercetin: 25 mg/kg, oral	/
Control Group	Naringenin: 90 mg/kg, oral. Naringenin in CMC solution, oral.	Alpha-tocopherol: 100 mg/kg, intraperitoneal	/	Nanocarrier (NCs) without lutein, oral	Quercetin in PEG400-water, intravenous. Quercetin in water, oral. Quercetin in PEG400-water, oral.	Free Astaxanthin, oral
Bioavailability	Improved bioavailability	/	Bioavailability improved by 55%	Enhanced bioavailability of	Improved bioavailability	/
Stability	Good stability	Good stability	Excellent stability	Good stability	Good stability	Moderate stability
Ref	(1)	(2)	(3)	(4)	(5)	(6)

Method of administration (Dosage, mode)

2022	2020	2022	2021	2023	2022	2020
Quercetin	Coenzyme Q10	Piperine	Anthrocyanin	Fucoxanthin	Curcumin	Carvedilol
Chitosan	Nano-micellar	Lipid polymer hybrid	Chitosan	Fucoidan	MSN-CCM	Chol-PLGA
Rat	Human	Rat	Rat	Rat	Mice	Mice
21 days	6 weeks	/	60 days	7 weeks	/	4 hours
25 rats	15 patients	Groups of 6 rats each	25 rats	48 rats	75 mice	60 mice
90.5%	99.4%	83.54%	70 ± 7%.	Low dose: 91.68% High dose: 89.94%	87.70 ± 0.05%	NP CVDL: 95.06 ± 0.4%. NP CVDL CHOL: 37.45 ± 1.8%.
Quercetin-NPs: 10 mg/kg/week (low), 20 mg/kg/week (high), oral	/	Piperine NPs: 20 mg/kg, oral	Encapsulated Anthocyanin-Chitosan NPs : 600 mg/kg,oral	Fucoxanthin nanoemulsion: 10 mg/kg/day (low), 50 mg/kg/day (high), oral	MSN-CCM: 5 mg/kg, oral. Rivastigmine: 2.5 mg/kg, oral	NP CVDL: 0.05, 0.1, 0.3 mg/kg, oral. NP CVDL CHOL: 0.05, 0.1, 0.3 mg/kg, oral. Free Carvedilol: 3 mg/kg, 0.3 mg/kg, oral.
Standard quercetin: 15 mg/kg/week , oral	Control Side: No treatment, only scaling and root planning, oral.	Free piperone, oral	Negative control: Standard diet, no treatment, oral.	Normal group: Normal diet, oral	Positive control: streptozotocin, intracerebro-ventricular.	Saline, oral. Positive control: Carrageenan, oral. Diclofenac-treated group (standard treatment), oral.
/	/	Improved bioavailability	/	/	Improved bioavailability	Improved bioavailability
Moderate stability	Excellent stability	Excellent stability	Good stability	Good stability	Bad stability	Bad stability
(14)	(13)	(11)	(10)	(9)	(8)	(7)

2021	2022	2021	2023	2023	2023
Naringenin	Astaxanthin	Iron and Folic acid	Quercetin	Coenzyme Q10	
PLA/PVA and Zein/Pectin	Ethylene glycol chitosan	Bovin serum albumin	Zein	LMSNs	
Rat	Rat	Rat	Rat	Rat	
> 24 hours	> 60 hours	42 days	> 24 hours	> 24 hours	
18 rats	10 rats	36 rats	5 to 8 rats per group	/	
P/P-Nar NP: 79.3 ± 5.2% Z/P-Nar NP: 62.5 ± 4.1%	85.04%	95.78% for Fe and 97.54% for FA	90%	Q-NS: 82.3% Q-NC: 82.3%	
P/P-Nar NP: 90 mg/kg, oral. Z/P-Nar NP: 90 mg/kg, oral.	ASTA-PEG-g-CS nanoparticle: 8 mg/kg, oral	Stirred functional yogurt+ Fe + Folic acid@BSA-NPs, ascorbic acid (50 mg/kg Fe, 0.5 mg/kg FA, 125 mg/kg ascorbic acid), oral	Q-NS: 15 mg/kg, oral Q-NC: 15 mg/kg, oral	CoQ10-loaded DC-TPGS-LMSNs: 15 mg/kg, 30 mg/kg, oral	
Naringenin: 90 mg/kg, oral	Free astaxanthin: 50 mg/kg, oral	No supplementa--ion, oral	Control Formulation (Q): Quercetin with HP-β-CD, oral	Free CoQ10 solution, oral. CoQ10-loaded liposomes, oral. CoQ10- loaded MSNs (baseline control), oral.	
/	/	/	Bioavailability improved by 57%	/	
Good stability	Excellent stability	Excellent stability	/	Good stability	
(19)	(18)	(17)	(16)	(15)	

P/P-Nar NP: Naringenin-loaded PLA/PVA nanoparticles; **Z/P-Nar NP**: Naringenin-loaded Zein/Pectin nanoparticles; **CMC**: Carboxy methyl cellulose; **PCL**: Polycaprolactone; **Q-NP**: Quercetin-loaded nanoparticles; **Q-HPCD-NP**: Quercetin-loaded hydroxypropyl-beta-cyclodextrin nanoparticles; **CS-ZTO-SLN**: Chitosan-Zedoary Turmeric Oil solid lipid nanoparticles; **ZTO-SLN**: Zedoary Turmeric Oil solid lipid nanoparticles; **MSN-CCM**: Curcumin-loaded mesoporous silica nanoparticles; **TPP**: Triphenylphosphonium; **LMSNs**: Lipid-coated mesoporous silica nanoparticles; **ACNPs**: Anthocyanin-Chitosan nanoparticles; **HP-β-CD**: Hydroxypropyl-beta-cyclodextrin; **CS-SA-OA**: Chitosan-sodium alginate-oleic acid; **SLNs**: Solid lipid nanoparticles; **ASTA-PEG-g-CS**: Astaxanthin-PEG-grafted-chitosan; **PEG**: Polyethylene glycol; **α-TM-VP-NVC**: Alpha-Tocopherol Mesoporous Vesicle Nanoparticles with Polycaprolactone; **BSA-NPs**: Bovine serum albumin nanoparticles; **Fe**: Ferrous sulfate; **FA**: Folic acid; **CNPs**: Chitosan nanoparticles; **Q-NS**: Quercetin-loaded Zein nanospheres; **Q-NC**: Quercetin-loaded Zein nanocapsules; **CoQ10**: Coenzyme Q10; **NP CVDL**: Carvedilol-loaded nanoparticles; **NP CVDL CHOL**: Carvedilol-loaded cholesterol-functionalized nanoparticles

CONCLUSION

This systematic review demonstrates that nanoencapsulation offers significant benefits in the field of dietary supplements and nutraceuticals, particularly by enhancing encapsulation efficiency, bioavailability, and stability, without reported adverse effects. These findings support the growing use of nanoencapsulation as a promising strategy to improve the efficacy and safety of nutraceutical products.

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