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Food-derived nanovesicles as immunomodulators in cancer therapy

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ABSTRACT

Food-derived nanovesicles (FDNVs) have gained increasing attention as safe and natural nano-carriers with strong potential for cancer immunotherapy. These vesicles are obtained from edible plants and animal-based foods and show high biocompatibility, low toxicity, and the ability to deliver bioactive compounds such as lipids, proteins, metabolites, and microRNAs involved in immune regulation. Recent studies have shown that FDNVs can regulate important immune responses, including macrophage polarization, dendritic cell maturation, T-cell activation, and the reduction of tumor-related immunosuppression. This review presents a comprehensive overview of the immunomodulatory effects of FDNVs in cancer therapy and examines global research trends through a structured bibliometric analysis. Research output in this field has increased steadily since 2018, highlighting the growing interest in their therapeutic applications. Despite these advances, several challenges remain, including vesicle heterogeneity, the lack of standardized isolation methods, limited understanding of in vivo bioavailability, and difficulties in achieving large-scale and clinically approved production. In addition, recent findings indicate that the uptake pathways and therapeutic effects of FDNVs may vary depending on their composition and the target tissue environment, emphasizing the need for further mechanistic studies. Overall, FDNVs show considerable promise as natural immunomodulatory agents; however, their successful application in next-generation cancer immunotherapy will require continued scientific research and translational development.

1. Introduction

Cancer continues to be one of the most formidable health challenges of the 21st century, with global incidence and mortality rates steadily increasing (Bhawalkar et al., 2024; Torre et al., 2016). Despite advances in conventional therapies such as chemotherapy, radiotherapy, and targeted interventions, major limitations persist (Zafar et al., 2025). Drug resistance, off-target toxicity, and immune evasion often reduce long-term survival benefits, underscoring the urgent need for novel therapeutic strategies (Liu et al., 2024). Immunotherapy has emerged as a promising frontier, focusing on harnessing and modulating the host immune system rather than directly attacking tumor cells. However, the success of immunomodulatory strategies depends greatly on safe, effective, and biocompatible delivery platforms capable of modulating the tumor microenvironment (TME) (Zhang et al., 2025).

In recent years, naturally occurring extracellular vesicles derived from edible sources have attracted growing attention. These food-derived nanovesicles (FDNVs), including plant exosome-like nanoparticles, milk-derived exosomes, probiotic vesicles, and fungal or algal extracellular vesicles, are nanoscale lipid bilayer structures enriched with proteins, lipids, phytocompounds, and nucleic acids (Jung et al., 2025; Rivero-Pino et al., 2024). Unlike synthetic nanocarriers, they are inherently biocompatible, can be orally administered, and are capable of crossing biological barriers. Evidence from experimental studies indicates that ginger, grape, citrus, and dairy exosomes can modulate cytokine secretion, stimulate T-cell and natural killer cell activation, and influence macrophage polarization (Sundaram et al., 2022a). Several well-established studies illustrate the effects of plants or their component derived from nanovesicles. Ginseng-derived exosome-like nanoparticles (GDNPs) have been shown to shift macrophages

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from an M2 to an M1 phenotype through TLR4–MyD88 signaling, leading to suppressed melanoma progression (Cao et al., 2019). In their subsequent study, GDNPs conjugated with anti–PD-1 monoclonal antibodies were reported to remodel the immunologically 'cold' tumor microenvironment and generate sustained systemic anti-tumor responses (Han et al., 2022). Moreover, FDNVs exert anticancer effects by stimulating immune responses, triggering ROS-mediated apoptosis, and inhibiting tumor angiogenesis (Kim and Kim, 2022). Such properties make them highly attractive candidates for nutraceutical and therapeutic applications, particularly in the field of cancer immunotherapy.

Although the biological health-promoting activities of FDNVs are increasingly reported, the literature remains scattered across disciplines, including food science, nanotechnology, and oncology (Che et al., 2025). Prior bibliometric studies have mapped exosomes (EVs) in cancer and drug delivery, and a few have profiled plant-derived vesicles; however, none have systematically synthesized FDNVs across plant, dairy, microbial, fungal, and algal sources with a specific focus on immunomodulatory roles in cancer therapy (Ding et al., 2024; Wang et al., 2024; Yang et al., 2021). Traditional narrative reviews have summarized their biochemical characteristics and therapeutic promise. There is often a lack of a systematic assessment of how research in this domain has evolved, where scholarly attention is concentrated, and which themes are emerging. In the absence of structured bibliometric mapping, researchers face difficulty in discerning the intellectual organization of the field. This gap also obscures promising directions such as exploring the relationship between FDNVs and the gut microbiota or advancing their application in clinical studies.

Bibliometric analysis offers a robust means of addressing these gaps by quantitatively examining publication patterns, co-authorship networks, influential articles, and thematic clusters (Hassan and Duarte, 2024). Over the past decades, bibliometrics has been widely applied across diverse fields, including business, health sciences, data mining, and natural language processing, to identify emerging themes and guide strategic research directions (Chen et al., 2018; Sweileh, 2021). Applying this methodology to FDNVs in cancer immunotherapy provides a systematic overview of how the field has developed, which research clusters are gaining prominence, and where knowledge gaps remain.

By examining global publication trends and mapping conceptual structures, the present study seeks to clarify the current state of knowledge, highlight emerging hotspots, and outline translational directions for FDNVs as immunomodulators in cancer therapy. In doing so, it not only consolidates existing evidence but also positions FDNVs as a promising frontier in applied biomedical sciences, offering insights for both researchers and practitioners working at the interface of nutrition, nanotechnology, and oncology. Despite the rapidly expanding evidence base, no existing review offers an integrated, cross-domain bibliometric synthesis of food-derived nanovesicles (FDNVs) with a specific focus on their immunomodulatory roles in cancer therapy. Prior studies have evaluated plant-derived vesicles or general extracellular vesicles, but none have simultaneously mapped plant, dairy, microbial, fungal, and algal vesicles in relation to immune regulation, tumor microenvironment remodeling, and translational nanomedicine. This review fills this gap by combining descriptive bibliometrics with conceptual and intellectual structure mapping to reveal how the field has evolved, which scientific clusters drive current scholarship, and where the major mechanistic, methodological, and clinical gaps remain. In doing so, it offers the first systematic overview positioning FDNVs as a distinct and emerging platform in cancer immuno-immunotherapy. This study aims to (i) map global publication trends on food-derived nanovesicles in cancer immunotherapy, (ii) identify leading authors, countries, journals, and institutions contributing to the field, (iii) reveal conceptual clusters and emerging thematic trajectories through keyword co-occurrence and co-citation analyses, and (iv) highlight methodological and translational gaps limiting clinical progress. The following are the research questions being addressed in this study:

RQ1: How has research on FDNVs evolved over time, and what are the dominant sources of scientific productivity?
RQ2: Which conceptual themes and immunomodulatory mechanisms dominate the field?
RQ3: What gaps exist in methodology, translation, and clinical readiness?
RQ4: Which future research pathways are most critical for advancing FDNV-based cancer therapies?

2. Methodology

This review employed a structured bibliometric approach to systematically examine scientific research on food-derived nanovesicles as immunomodulators in cancer therapy, following established guidance on evidence synthesis and research mapping (Short, 2009). This review adopted a rigorous bibliometric methodology to systematically analyze global scientific output on food-derived nanovesicles (FDNVs) as immunomodulators in cancer therapy, following established guidelines for quantitative literature mapping (Hourigan et al., 2025). Bibliometric analysis was selected due to its demonstrated reliability in identifying intellectual structures, research clusters, and developmental trajectories across multidisciplinary scientific fields, especially those undergoing rapid conceptual expansion, such as extracellular vesicle biology and nanomedicine (Peng et al., 2024). This approach aligns with recommendations that bibliometrics offers an

evidence-driven foundation for assessing scholarly patterns and informing future research directions, particularly in emerging biomedical domains (Aria and Cuccurullo, 2017). The overall methodology was designed to ensure analytical rigor, reproducibility, and alignment with preferred practices for high-quality review research.

To ensure comprehensive coverage of global publications, data were retrieved from Scopus and Web of Science Core Collection, two of the most authoritative and widely used indexing databases for bibliometric studies (Singh et al., 2021). The use of multiple databases mitigates source bias and increases citation reliability, a methodological recommendation consistently emphasized in management, biomedical, and information science literature (Martín-Martín et al., 2018). Both databases were searched using a structured Boolean strategy incorporating terms related to food-derived nanovesicles, extracellular vesicles, edible exosome-like nanoparticles, plant- or milk-derived vesicles, immunomodulation, and cancer therapy, consistent with keyword formulation principles described in bibliometric research guidelines (Donthu et al., 2021). This approach ensured that the search strategy captured both foundational and cutting-edge studies across plant, animal, microbial, and algal vesicle systems, reflecting the interdisciplinary nature of FDNV science.

The retrieved records underwent a multi-step filtering and cleaning process, reflecting standard best practices in bibliometric workflows. Duplicate records across Scopus and Web of Science were removed manually and algorithmically, following recommendations for improving dataset reliability and eliminating redundancies that may distort citation counts or co-occurrence networks. Only original research articles and review papers were retained, in line with methodological guidelines advising bibliometric studies to focus on peer-reviewed scholarly outputs to maintain credibility and analytical consistency. Non-English records were excluded to maintain linguistic uniformity in metadata interpretation, a common practice in quantitative reviews requiring semantic precision. The final curated dataset served as the primary corpus for quantitative evaluation and visualization.

Descriptive bibliometric indicators—including annual scientific production, leading journals, most productive authors, and geographic distribution—were then computed to reveal macro-level publication patterns. Generating these performance metrics is central to bibliometric studies, as they provide insight into research dynamics, discipline maturity, and shifts in scholarly interest over time (Donthu et al., 2021).

The conceptual and intellectual structure of the field was examined using VOSviewer, a widely adopted bibliometric visualization tool known for its robustness in mapping co-authorship, co-citation, and keyword co-occurrence networks (Derviş, 2019). Such cluster-based mapping aligns with established literature demonstrating that keyword co-occurrence analysis is one of the most effective techniques for identifying conceptual hotspots, emerging research streams, and structural gaps in scientific domains (Sedighi, 2016).

To complement conceptual mapping, co-authorship patterns were analyzed to evaluate collaborative intensity and identify leading research groups contributing to FDNV literature. Strong research clusters frequently indicate disciplinary consolidation, while sparse networks reveal fragmentation or early-stage field development (Hassan and Duarte, 2024). These principles are well established in collaboration-focused bibliometric analyses, which demonstrate that robust co-authorship networks correlate with accelerated methodological innovation and more rapid translation of basic science findings. Keyword frequency thresholds were set to ensure meaningful cluster formation and prevent noise from low-frequency terms, following standard co-word analysis recommendations. Keywords appearing below the minimum threshold were excluded from visualization to preserve interpretative clarity.

Overall, this methodological design integrates database triangulation, structured search strategies, rigorous data cleaning, and advanced visualization techniques to generate a comprehensive, reliable, and analytically robust bibliometric assessment. By combining descriptive indicators, thematic co-word mapping, and structural network analysis, this methodology enables a nuanced understanding of how FDNV research has evolved and where scientific attention is now converging. This approach provides a strong foundation for interpreting the results and translating them into meaningful insights for future scientific and clinical applications.

3. Results and discussion

3.1. Annual publication trend

The bibliometric analysis demonstrated a steady increase in scientific output relating to food-derived nanovesicles (FDNVs) over the past decade, as illustrated in Fig. 1, which shows a clear upward trajectory in annual publication volume from 2015 to 2024. This upward trend is reflected in the increase from just one publication in 2015 to 64 publications in 2024, indicating a substantial expansion of the field. This growth aligns with broader trends in extracellular vesicle (EV) research, where edible vesicles have increasingly attracted attention due to their potential in immunomodulation, disease mitigation, and therapeutic delivery (Ali et al., 2022; Nguyen et al., 2023; Raimondo et al., 2022; Yang et al., 2020).

The sharp rise in publications following 2018 corresponds with experimental breakthroughs demonstrating that plant-derived vesicles, such as those from bitter melon, ginger, grapes, tomato, and citrus, can influence inflammatory cytokines, modulate macrophage phenotypes, and alter intestinal and systemic immune responses (Garaeva

et al., 2024; Han et al., 2025; Raimondo et al., 2022; Sarwareddy et al., 2025; Yang et al., 2021). These findings parallel a surge in cancer immunology research, where modulating the tumor microenvironment (TME) has become a primary therapeutic target (Qiang et al., 2024). In this context, the growing interest in FDNVs reflects their promise as natural, biocompatible immunomodulators capable of influencing mechanisms central to tumor progression and immune escape (Cao et al., 2019; Karabay et al., 2025). The acceleration in publications after 2018 indicates that FDNV research has moved beyond exploratory isolation studies toward mechanistic and application-oriented investigations. However, the relatively recent surge and the absence of corresponding clinical output suggest that the field remains in an emergent developmental phase rather than a mature translational domain. This imbalance between laboratory expansion and clinical validation reflects a common trajectory in nanomedicine, where conceptual enthusiasm precedes regulatory and human-study advancement.

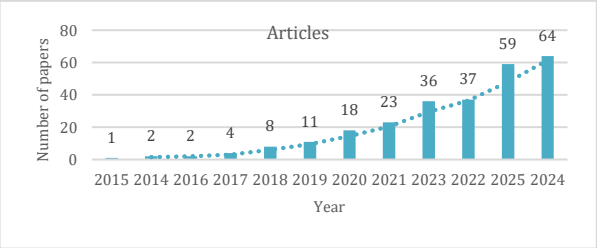

Fig. 1: Annual scientific production on food-derived nanovesicles (FDNVs) from 2015 to 2024

3.2. Journals

The distribution of publications across high-impact journals further reveals the scientific landscape and maturity of the field. Table 1 shows that journals such as Journal of Extracellular Vesicles, International Journal of Molecular Sciences, Scientific Reports, and Journal of Controlled Release have the highest citation impact. This pattern mirrors the centrality of EV biology within nanomedicine and highlights the alignment of FDNV research with established EV science. Journals in this list often publish foundational studies in vesicle biogenesis, cargo profiling, and immunoregulatory mechanisms, reinforcing the positioning of FDNVs within mainstream vesicle research. The presence of J Control Release and Molecular Therapy suggests ongoing efforts to translate dietary vesicles into delivery platforms, consistent with growing interest in exploiting their innate stability, low immunogenicity, and ability to withstand digestive conditions (Cabeza et al., 2020; Fang and Liu, 2022; Ronacher et al., 2025).

Complementing this, Table 2 illustrates journal productivity, with the highest number of publications originating from the International Journal of Molecular Sciences (17), Journal of Nanobiotechnology (11), and Pharmaceutics (8). The presence of articles in these journals suggests that current FDNV research is primarily driven by molecular-level investigations, nano–bio interactions, nanobiotechnology applications, and early-stage therapeutic exploration (Boggio et al., 2023; Sergazy et al., 2025). The presence of oncology-related journals such as Cancer Letters indicates that the field is increasingly intersecting with tumor biology. The preclinical investigations have demonstrated the capacity of edible vesicles to reduce inflammation, inhibit tumor growth, and reshape immune cell infiltration patterns in the TME (Aqil et al., 2019; Lucchetti et al., 2023). This journal distribution underscores the interdisciplinary nature of FDNV literature, integrating food science, nanotechnology, molecular biology, oncology, and immunology. These descriptive insights also support the interpretation of subsequent thematic and co-occurrence analyses. The concentration of publications in molecular biology and nanotechnology journals, rather than clinical oncology outlets, suggests that FDNV research is still primarily anchored in preclinical experimentation. This distribution signals strong mechanistic engagement but limited integration into clinical oncology discourse, further underscoring the early translational stage of the field.

Table 1: Most influential journals publishing research on food-derived nanovesicles

Sources/journals	Articles published
Journal of Extracellular Vesicles	545
International Journal of Molecular Sciences	405
Scientific Reports	398
Journal of Controlled Release	381
Molecular Therapy	355
Biomaterials	277
Journal of Nanobiotechnology	273
PLOS ONE	245
Cancer Letters	203
International Journal of Nanomedicine	195

Table 2: Most productive journals in food-derived nanovesicle research (2015–2024)

Sources	Articles
International Journal of Molecular Sciences	17
Journal of Nanobiotechnology	11
Pharmaceutics	8
Journal of Controlled Release	7
International Journal of Biological Macromolecules	5
Journal of Extracellular Vesicles	5
Biomaterials Science	4
Cancer Letters	4
Cells	4
Frontiers in Pharmacology	4

3.3. Keyword co-occurrence analysis

This technique aligns with the recommendations of Paul and Criado (2020), who argue that thematic mapping allows researchers to classify knowledge domains into motor themes, niche areas, and emerging hotspots. VOSviewer's clustering algorithms enabled the identification of conceptual linkages between food-derived vesicles, immunomodulation pathways, and cancer-related

processes, thereby providing a comprehensive overview of the field's intellectual structure as depicted in Fig. 2. The modest but growing collaborative clusters in FDNV research, visible in VOSviewer network models, reflect a field in active development but not yet fully consolidated. The resulting clusters formed the basis for interpreting thematic structures and identifying scientifically significant pathways such as macrophage polarization, cytokine modulation, miRNA transport, and gut–immune regulation.

This analytical strategy revealed converging themes around immunomodulation, cancer therapy, oxidative stress, apoptosis, and microRNA cargo, consistent with known biological activities of food-derived vesicles and reveals several dominant clusters. The largest cluster centers on "extracellular vesicles," "nanoparticles," "immunomodulation," and "cancer," suggesting that immune regulation is the core intellectual axis of the field (Karabay et al., 2025). This cluster aligns with experimental evidence showing that dietary vesicles affect innate immune pathways, such as macrophage M1/M2 polarization and pattern-recognition receptor signaling, both of which are crucial for shaping antitumor immunity (Chen et al., 2023). Adjacent clusters include terms such as "apoptosis," "oxidative stress," and "inflammation," which reflect mechanistic pathways modulated by plant-derived vesicles, particularly those from ginger and citrus, known to modulate oxidative and inflammatory cascades in cancer models (Al-Ataby and Talib, 2022; Li et al., 2025). Another prominent cluster focuses on "microRNA," "delivery," and "bioavailability," consistent with growing research demonstrating that food-derived vesicles carry stable bioactive microRNAs that can influence gene expression across host tissues (Aqil et al., 2017; del Pozo-Acebo et al., 2021; Nathani et al., 2024). The dominance of immunomodulation and oxidative stress-related keywords, coupled with the relatively limited presence of pharmacokinetics, biodistribution, or clinical trial terminology, reveals a conceptual focus on biological plausibility rather than clinical feasibility. This pattern suggests that while the mechanistic foundation is strengthening, translational and regulatory pathways remain underdeveloped.

Fig. 2: Keyword co-occurrence network of food-derived nanovesicle research generated using VOSviewer

4. Discussion

4.1. Conceptual emphasis on dairy-derived vesicles and the gut–immune axis

The bibliometric findings highlight significant contributions from dairy-derived vesicles within the broader FDNV landscape. Milk-derived exosomes have been extensively investigated for their ability to enhance gut immunity, preserve epithelial barrier integrity, and deliver functional RNA cargo, as demonstrated in both animal and cell-based studies (He et al., 2021; Jabłońska et al., 2024; Wu et al., 2022). The clustering of keywords related to gut health and epithelial integrity in the thematic map indicates sustained scholarly attention to the gut–immune axis.

This prominence is consistent with emerging evidence in cancer immunotherapy demonstrating that microbiota–immune interactions influence patient responses to treatment (Tong et al., 2023). The observation that milk exosomes may modulate metabolic and immune pathways further positions them as potential adjuncts to oral immunotherapies

(Jiang et al., 2024). Importantly, the visibility of microbiota-related keywords suggests that FDNV research extends beyond conventional immune modulation to include host–microbial crosstalk. This aligns with recent findings that intratumoral and gut microbiota critically affect immunotherapy efficacy (Orefice et al., 2023; Zhang et al., 2024).

While this thematic concentration strengthens the biological rationale for oral and gut-targeted strategies, it also suggests that systemic immunomodulatory pathways and tumor-site biodistribution remain comparatively less explored within the current literature.

4.2. Geographic and institutional contributions

The bibliometric analysis indicates strong engagement from research institutions across Asia, particularly China and South Korea, where plant-derived vesicle characterization and engineering have advanced rapidly (Lian et al., 2022). This pattern aligns with broader nanomedicine trends, in which Asian institutions have demonstrated leadership in extracellular vesicle purification, cargo profiling, and nano–bio interface research (Fais et al., 2016).

European institutions also show notable contributions, particularly in dairy vesicle research and the development of vesicle-based oral delivery systems. The observed collaboration patterns are consistent with global extracellular vesicle research, where multi-institutional efforts have accelerated methodological refinement and interdisciplinary integration (Hassan and Duarte, 2024). However, the relatively limited multinational collaboration identified in the network analysis suggests that the field remains partially fragmented. Such fragmentation may slow harmonization of protocols and standardization efforts, which are critical for translational progress.

4.3. Thematic evolution toward functional and translational applications

The overlay visualization from VOSviewer indicates a discernible shift in thematic emphasis over time. Early studies were predominantly concerned with vesicle isolation, morphology, and bioavailability. More recent publications increasingly focus on immune modulation, cancer therapy, and engineered vesicle systems. This progression mirrors the broader trajectory observed in extracellular vesicle research, where structural characterization typically precedes mechanistic and translational exploration.

The growing presence of keywords such as “therapy,” “targeting,” and “clinical translation” reflects increasing interest in leveraging edible vesicles as carriers for small molecules, siRNA, and immunomodulatory agents (Karabay et al., 2025). In parallel, studies investigating engineered plant vesicles for targeted cancer delivery have expanded, aligning with wider nanomedicine trends toward hybrid biological–synthetic systems (Sethunga et al., 2025). These developments suggest that FDNV research is gradually transitioning from descriptive biological investigation toward functional application and therapeutic design.

4.4. Persistent translational and methodological constraints

Despite encouraging scientific momentum, several critical gaps remain. The limited presence of translational or clinical-trial terminology in the bibliometric mapping indicates that progression toward human application remains modest. This pattern reflects broader challenges within the extracellular vesicle field, including issues of standardization, reproducibility, and regulatory compliance (Théry et al., 2018).

Methodological variability in vesicle isolation, characterization, and batch consistency continues to limit reproducibility and cross-study comparability. In addition, the scarcity of keywords associated with large-scale vesicle production highlights unresolved challenges in achieving industrially viable yields. Without scalable manufacturing frameworks, clinical translation and commercial development remain constrained.

Pharmacokinetic and biodistribution-related terminology also appears infrequently, suggesting that in vivo profiling of dietary vesicle absorption, tissue distribution, and clearance remains underexplored. Such profiling is fundamental for any vesicle-based therapeutic strategy. Although the gut–immune axis is prominently represented, the molecular mechanisms underlying cross-kingdom RNA transport and vesicle uptake remain incompletely defined, reflecting ongoing debate within the extracellular vesicle community regarding uptake pathways and functional bioactivity (Gandek et al., 2023; Mulcahy et al., 2014).

4.5. Field positioning

Taken together, these findings depict a field that is expanding rapidly at the experimental and conceptual levels but has not yet fully transitioned into clinical or regulatory frameworks. The recurrent appearance of immunomodulation-, anti-inflammatory-, and oxidative stress-related keywords underscores the biological relevance of FDNVs in cancer and inflammatory contexts. However, the predominance of preclinical evidence suggests that clinical validation remains an important next step.

Simultaneously, the increasing emphasis on oral delivery, stability, and gastrointestinal uptake reflects sustained interest in positioning FDNVs as natural delivery systems. Moving forward, advancing FDNVs toward clinical integration will require coordinated interdisciplinary collaboration across extracellular vesicle biology, nanotechnology, immunology, oncology, and food science. Addressing methodological standardization, mechanistic

clarification, scalable production, and regulatory alignment will be essential for translating laboratory insights into clinically viable applications.

5. Future research directions

Despite the growing evidence supporting the therapeutic potential of FDNVs, several interconnected gaps continue to shape their translational trajectory in cancer immunotherapy. A central challenge lies in the lack of standardized isolation, purification, and characterization methods, as inconsistencies in vesicle yield and cargo composition still hinder reproducibility and cross-study comparability, making methodological harmonization an essential prerequisite for regulatory progress. Alongside these technical issues, the mechanistic understanding of how dietary vesicles modulate immune pathways remains incomplete. Although preclinical studies suggest they influence macrophage polarization, cytokine release, and dendritic cell activation, far more integrative multi-omics work is required to resolve the pathways through which FDNVs interact with innate and adaptive immunity. Also, cross-species RNA transfer, one of the most intriguing and debated mechanisms underlying dietary vesicle bioactivity, requires further molecular and *in vivo* validation before it can be reliably leveraged in cancer therapeutics. Future work should also focus on pinpointing and characterizing the key bioactive molecules within these vesicles. For example, grape-derived nanovesicles may contain specialized polyphenols, and ginger vesicles may carry anti-inflammatory compounds. Clarifying how such molecules are produced and regulated will help in tailoring vesicles with enhanced or targeted anticancer activity.

Emerging evidence also indicates that uptake mechanisms differ between tissues. Mu et al. (2014) demonstrated that PA (36:4) on garlic-derived nanovesicles binds to the BASP1 protein in microglial cells, suggesting that lipid–protein interactions can drive tissue-specific uptake (Sundaram et al., 2022b). Despite such insights, the broader *in vivo* fate of orally administered FDNVs remains poorly characterized. Only a limited number of studies have examined how orally administered vesicles withstand digestive conditions, enter systemic circulation, and reach target tissues, leaving major gaps in our understanding of their bioavailability, pharmacokinetics, and dose optimization in humans. At the same time, the current evidence base is heavily reliant on cell-based assays and small-animal models, highlighting the importance of transitioning towards more physiologically relevant systems (organoids, patient-derived xenografts, and immunocompetent tumor models) to capture better human tumor complexity and treatment response (An et al., 2025).

Despite this accumulating scientific momentum, clinical translation remains limited, as human studies evaluating safety, tolerability, and immunological endpoints are still scarce. Collectively, these interrelated limitations highlight the importance of coordinated advances in methodology, mechanistic research, *in vivo* modelling, and clinical assessment to fully realize the potential of food-derived nanovesicles as effective and safe immunomodulators in cancer therapy. While preclinical findings are promising, the existing evidence base presents several methodological constraints. A substantial proportion of studies rely on small-animal models without validation in immunocompetent tumor systems. Vesicle characterization frequently lacks comprehensive reporting of size distribution, purity markers, and cargo quantification in accordance with MISEV2018 recommendations. Furthermore, dose-response analyses and pharmacokinetic profiling remain limited, restricting accurate assessment of therapeutic thresholds and systemic behavior. The predominance of cytokine-based outcome measures without deeper multi-omics validation also limits mechanistic clarity. These methodological patterns indicate that experimental robustness must improve before clinical translation becomes viable.

6. Conclusions

Food-derived nanovesicles have emerged as a promising class of naturally occurring extracellular vesicles with significant immunomodulatory potential in oncology. The findings of this review demonstrate a marked and consistent rise in global scientific interest, driven by increasing recognition of the unique advantages that FDNVs possess over synthetic nanocarriers. Their biocompatibility, oral bioavailability, stability in the gastrointestinal tract, and ability to carry functional lipids, proteins, and microRNAs collectively position them as compelling candidates for next-generation cancer immunotherapies. Evidence across plant-derived, dairy-derived, and microbial vesicles reveals that these nanoscale structures can modulate key immune mechanisms—including macrophage polarization, cytokine secretion, dendritic cell maturation, and T-cell activation all of which are central to reshaping the tumor microenvironment and enhancing antitumor immunity.

The bibliometric mapping presented in this review highlights an expanding and increasingly interdisciplinary research landscape. High-impact journals in extracellular vesicles, nanotechnology, immunology, and oncology have contributed substantially to the knowledge base, reflecting growing scientific consensus on the therapeutic relevance of dietary vesicles. Thematic clusters reveal that FDNV research is shifting from foundational work on vesicle characterization and cargo profiling toward more advanced explorations of targeted delivery, molecular engineering, and translational applications. The emergence of themes related to microRNA cargo, oxidative stress regulation, drug delivery, and gut–immune

modulation underscores the multidimensional therapeutic potential of FDNVs in cancer contexts.

Despite these advances, variability in vesicle isolation methods, heterogeneity in particle composition, and incomplete understanding of vesicle biodistribution represent critical barriers to clinical deployment. Future research must prioritize methodological standardization, mechanistic clarity, and rigorous preclinical-to-clinical translation. Interdisciplinary collaborations across nanotechnology, food science, immunology, and oncology will be essential to advancing vesicle engineering strategies, optimizing delivery systems, improving cargo loading efficiency, and establishing robust manufacturing pipelines. Equally important is the need for carefully designed human clinical studies to assess safety, pharmacokinetics, immune responses, and therapeutic efficacy.

In conclusion, FDNVs represent a rapidly emerging and highly promising frontier in cancer immunotherapy. Their natural origin, biological compatibility, and inherent immunomodulatory capabilities make them strong candidates for safe, accessible, and effective therapeutic development. As research continues to accelerate and technological challenges are addressed, FDNVs have the potential to transform the landscape of immune-based cancer treatment and contribute meaningfully to the next generation of precision and nutritionally informed oncology.

This bibliometric review is limited by its reliance on Scopus and Web of Science, which may exclude non-indexed sources or recently published early-access articles. Citation-based metrics favor older studies, potentially underrepresenting emerging themes. The analysis depends on keyword quality, and variations in terminology (e.g., "edible nanoparticles," "exosome-like vesicles") may result in partial retrieval. Finally, bibliometric methods cannot evaluate experimental quality, requiring qualitative triangulation in future reviews.

List of abbreviations

BASP1	Brain acid-soluble protein 1
EV	Extracellular vesicle
FDNV	Food-derived nanovesicle
GDNPs	Ginseng-derived exosome-like nanoparticles
M1	Classically activated macrophage phenotype
M2	Alternatively activated macrophage phenotype
miRNA	MicroRNA
MISEV	Minimal information for studies of extracellular vesicles
MISEV2018	Minimal information for studies of extracellular vesicles 2018 guidelines
MyD88	Myeloid differentiation primary response protein 88
PA (36:4)	Phosphatidic acid (36:4)
PD-1	Programmed cell death protein 1
PRRs	Pattern-recognition receptors (not abbreviated in manuscript text)
RNA	Ribonucleic acid
ROS	Reactive oxygen species
siRNA	Small interfering RNA
TLR4	Toll-like receptor 4
TME	Tumor microenvironment

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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