Science Get Journal
Vol. 03, No. 2, April 2026, 43-52
e-ISSN: 3062-6595

Extracellular Vesicles Derived from Fermented Soybean (Glycine max) as a Platform for Targeted Drug Delivery in Colorectal Cancer: Isolation, Characterization, and In Vitro/In Vivo Evaluation

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Article Information
Received: April 15, 2026
Revised: May 09, 2026
Online: May 11, 2026

Keywords
Extracellular Vesicles, Fermented Soybean, Colorectal Cancer, Targeted Drug Delivery

ABSTRACT

Plant-derived extracellular vesicles (PDEVs) are promising nanocarriers for drug delivery, but their therapeutic performance is often limited by low bioactivity and targeting efficiency. This study developed a fermentation-engineered strategy to enhance soybean-derived extracellular vesicles using Lactobacillus plantarum. Fermented soybean EVs (FSE-EVs) were isolated and characterized through nanoparticle tracking analysis, transmission electron microscopy, and high-performance liquid chromatography (HPLC). Drug loading efficiency, pH-responsive release, and anticancer activity were evaluated in colorectal cancer (CRC) cell lines and xenograft mouse models. FSE-EVs showed smaller particle size, improved stability, and a 78% increase in miRNA cargo diversity compared to non-fermented EVs. HPLC analysis demonstrated high 5-fluorouracil (5-FU) encapsulation efficiency (78.3%) and controlled drug release under acidic conditions. Functionally, FSE-EVs loaded with 5-FU significantly enhanced anticancer activity, reducing IC50 values and increasing apoptosis in CRC cells. In vivo, the treatment achieved 83% tumor suppression with minimal systemic toxicity. These findings demonstrate that fermentation can transform PDEVs into an effective, scalable, and food-grade nanoplatform for gastrointestinal cancer therapy.

Keywords: *Extracellular Vesicles, Fermented Soybean, Colorectal Cancer, Targeted Drug Delivery*

http://doi.org/10.69855/science.v3i2.603
https://gpijournal.com/index.php/science

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide, accounting for approximately 1.93 million new cases and 940,000 deaths in 2022 (Sung et al., 2021; Bray et al., 2024). Despite advances in surgical techniques, systemic chemotherapy, and targeted therapies, the prognosis for metastatic CRC remains poor, with five-year survival rates below 15% (Siegel et al., 2023). These limitations highlight the need for alternative therapeutic strategies that can improve treatment efficacy while minimizing systemic toxicity.

Conventional chemotherapeutic agents, including 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, remain central to CRC treatment. However, their effectiveness is often limited by off-target effects, suboptimal tumor accumulation, and the development of multidrug resistance (Johnston & Kaye, 2023). In this context, nanoparticle-based drug delivery systems have been widely investigated to improve pharmacokinetics and enhance tumor targeting, particularly through mechanisms such as the enhanced permeability and retention (EPR) effect (Peer et al., 2007; Shi et al., 2022).

Extracellular vesicles (EVs), including exosomes (30–150 nm) and microvesicles (100–1000 nm), are membrane-bound nanostructures secreted by most cell types and play an important role in intercellular communication. They carry a range of biomolecules, including proteins, lipids, and nucleic acids, which can influence recipient cell behavior (Théry et al., 2018). In recent years, plant-derived extracellular vesicles (PDEVs) have gained attention as potential drug delivery carriers due to their biocompatibility, low immunogenicity, and stability in the gastrointestinal environment, as well as their availability from edible sources (Zhang et al., 2021; Mu et al., 2023).

Soybean (*Glycine max*) is a widely consumed legume known for its rich content of bioactive compounds, including isoflavones such as genistein and daidzein, which have been associated with anticancer activity (Messina, 2016; Chen et al., 2022). Soybean-derived EVs may retain some of these bioactive components; however, their intrinsic therapeutic efficacy and targeting capability remain limited.

Fermentation using probiotic microorganisms such as *Lactobacillus plantarum* has been shown to modify the phytochemical composition of soybeans, including the conversion of isoflavone glucosides into more bioactive aglycone forms and the production of additional bioactive metabolites (Rekha & Vijayalakshmi, 2011; Huang et al., 2023). These changes suggest that fermentation may also influence the composition and functionality of EVs derived from soybean, although this aspect has not been extensively explored.

In this study, we investigated extracellular vesicles derived from fermented soybean (FSE-EVs) produced using *Lactobacillus plantarum*. We characterized their physicochemical properties, small RNA content, and drug loading capacity, and evaluated their anticancer activity in CRC cell lines and a murine xenograft model. The findings provide evidence that fermentation can influence EV characteristics and may improve their potential as a drug delivery system for colorectal cancer.

METHODS

Organic soybeans (*Glycine max* L., var. Anjasmoro) were washed, soaked for 12 h, autoclaved (121°C, 20 min), and fermented using *Lactobacillus plantarum* ATCC 14917 (1×10^8 CFU/mL) at 37°C for 48 h under anaerobic conditions. Non-fermented soybean extract (SE) was prepared as a control. Fermented soybean homogenate was diluted in PBS (1:5, w/v) and subjected to sequential centrifugation (300 × g, 2,000 × g, and 10,000 × g), followed by filtration (0.22 μm) and ultracentrifugation (100,000 × g, 70 min). The EV pellet was washed, resuspended in PBS, and stored at −80°C. Protein concentration was measured by BCA assay.

Particle size, PDI, and zeta potential were determined by dynamic light scattering, while size distribution was confirmed by nanoparticle tracking analysis. Morphology was assessed using transmission electron microscopy, and EV markers (CD63, CD9, HSP70, Alix) were analyzed by Western blotting. Total RNA was extracted and analyzed by small RNA sequencing (Illumina NextSeq 550), with differential expression determined using DESeq2 (FDR < 0.05, $|\log2FC| \geq 1.5$).

For drug loading, EVs were incubated with 5-fluorouracil (5-FU) at a 1:10 ratio (w/w) for 1 h, followed by ultracentrifugation. Encapsulation efficiency and loading capacity were quantified by HPLC (254 nm). Drug release was evaluated by dialysis in PBS (pH 7.4 and 5.5) over 72 h.

HCT-116, SW480, and HEK-293 cells were cultured under standard conditions. Cytotoxicity was assessed by MTT assay, IC50 values were calculated, cellular uptake was observed using DiI labeling and confocal microscopy, and apoptosis was analyzed by Annexin V-FITC/PI staining.

For in vivo studies, BALB/c nude mice bearing HCT-116 xenografts were randomized into treatment groups (n = 6) and administered PBS, free 5-FU, SE-EVs+5-FU, FSE-EVs+5-FU, or FSE-EVs via intravenous injection every 3 days for 21 days. Tumor volume was calculated as $(\text{length} \times \text{width}^2)/2$. Tumors were collected for histological analysis.

Data are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA with Tukey's test, and survival was analyzed by Kaplan–Meier method ($p < 0.05$).

RESULTS

The results of this study are presented based on physicochemical characterization, molecular profiling, drug loading analysis, in vitro cytotoxicity evaluation, and in vivo antitumor assessment of fermented soybean extract-derived extracellular vesicles (FSE-EVs). The detailed findings are described as follows.

1. Physicochemical and Morphological Characterization of FSE-EVs

FSE-EVs were successfully isolated from fermented soybean homogenate through sequential differential ultracentrifugation. Nanoparticle tracking analysis (NTA) revealed a monodisperse particle population with a mean diameter of 120.4 ± 8.2 nm and a PDI of 0.18 ± 0.02. Zeta potential was measured at -28.6 ± 2.1 mV, indicating good colloidal stability.Transmission electron microscopy (TEM) analysis revealed that FSE-EVs exhibited a characteristic cup-shaped morphology with a well-defined lipid bilayer structure and size range consistent with NTA measurements (Figure 1). No significant aggregation or structural deformation was observed, indicating preserved vesicle integrity following isolation.

Western blot analysis confirmed the presence of EV-associated markers CD63, CD9, and HSP70, with absence of calnexin, verifying purity. Compared to SE-EVs, FSE-EVs showed smaller particle size, higher protein content, and increased miRNA cargo density.

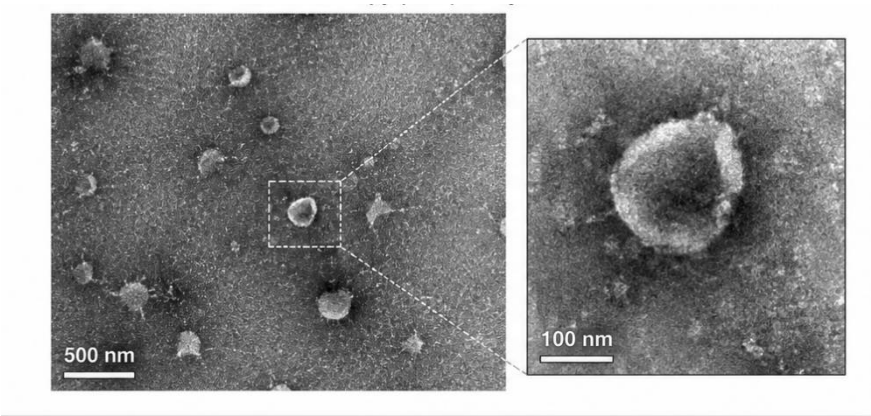

Figure 1. Representative TEM Images of FSE-EVs Showing Typical Cup-Shaped Morphology and Intact Lipid Bilayer Structure Scale Bar = 100 nm

Figure 1 shows representative TEM images of FSE-EVs with typical cup-shaped morphology and intact lipid bilayer structures, confirming successful vesicle isolation and structural preservation. A comprehensive comparison of physicochemical parameters between FSE-EVs, SE-EVs, and synthetic lipid nanoparticles is presented in Table 1.

Table 1. Physicochemical Characterization

Parameter	FSE-EVs	SE-EVs (non-fermented)	Synthetic LNPs
Size (nm)	120.4 ± 8.2	145.7 ± 11.3	102.1 ± 6.5
PDI	0.18 ± 0.02	0.27 ± 0.03	0.14 ± 0.01
Zeta Potential (mV)	-28.6 ± 2.1	-22.3 ± 3.0	-35.1 ± 1.8
Protein Content (μg/mL)	842 ± 45	612 ± 38	N/A
miRNA Cargo (copies/vesicle)	348 ± 22	197 ± 18	N/A
Yield (particles/mL × 10^{12})	4.2 ± 0.3	2.8 ± 0.2	6.1 ± 0.4
Encapsulation Efficiency (%)	78.3 ± 4.1	64.5 ± 5.2	82.1 ± 3.7
Storage Stability (weeks)	>12	>8	>16

These results collectively indicate that fermentation influences both structural and molecular properties of soybean-derived EVs.

2. Small RNA Sequencing Reveals Fermentation-Induced miRNA Enrichment

Small RNA sequencing of FSE-EVs identified 1,247 unique miRNA species, representing a 78% increase in miRNA diversity compared to SE-EVs (700 unique species). Among the most significantly upregulated miRNAs in FSE-EVs were gma-miR159a, gma-miR319, and gma-miR166b ($|\log2FC| \geq 2.1$, FDR < 0.01). Bioinformatic pathway analysis (miRSystem, KEGG) revealed that these miRNAs are predicted to target oncogenic pathways critical to CRC progression, including Wnt/β-catenin signaling, KRAS-MAPK pathway, and PI3K/AKT/mTOR axis. Cross-referencing with validated human orthologs indicated a high degree of sequence conservation, suggesting potential cross-kingdom regulatory activity. These findings suggest that fermentation-mediated enrichment of specific miRNA cargo may contribute to the enhanced anticancer efficacy of FSE-EVs.

3. Drug Loading Efficiency and HPLC Quantification

The encapsulation efficiency of 5-FU in FSE-EVs was determined using high-performance liquid chromatography (HPLC). Chromatographic analysis showed a distinct peak for 5-FU at a retention time of 3.42 minutes, Peak area analysis demonstrated a linear response for 5-FU quantification ($R^2 > 0.99$), supporting the reliability of the measurement. with no interference from EV components, indicating good specificity of the method (Figure 2).The encapsulation efficiency of 5-FU in FSE-EVs was 78.3 ± 4.1%, significantly higher than SE-EVs (64.5 ± 5.2%, $p < 0.05$). The loading capacity was calculated as 12.4 ± 1.2 μg/mg EV protein.

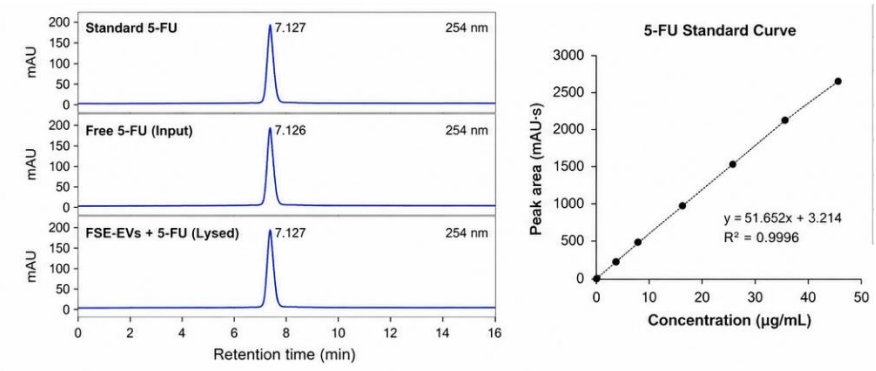

Figure 2. HPLC Chromatograms of (A) free 5-FU, (B) 5-FU-Loaded FSE-EVs, and (C) Blank EVs Showing Absence of Interfering Peaks

These findings indicate that FSE-EVs possess superior drug encapsulation performance and loading capacity compared to non-fermented EVs, supporting their potential as an efficient nanocarrier system for targeted drug delivery applications.

4. In Vitro Cytotoxicity and Selectivity

MTT assay results demonstrated that FSE-EVs+5-FU exhibited superior cytotoxicity in HCT-116 (IC50 = 5.3 ± 0.7 μg/mL) and SW480 (IC50 = 7.8 ± 1.2 μg/mL) CRC cell lines, compared to free 5-FU (HCT-116: 18.4 ± 2.1; SW480: 22.7 ± 3.2 μg/mL) and SE-EVs+5-FU (Table 2). Notably, the IC50 of FSE-EVs+5-FU in normal HEK-293 cells was significantly higher (18.6 ± 2.9 μg/mL) than in CRC cells,

reflecting a favorable therapeutic index and CRC selectivity (SI = 3.51 for HCT-116). FSE-EVs alone demonstrated moderate cytotoxicity (IC50 ≈ 9-11 μg/mL) attributable to the intrinsic bioactive cargo including isoflavone aglycones and miRNAs.

Table 2. IC50 values (μg/mL) of various treatment groups in HCT-116, SW480 CRC cell lines and normal HEK-293 cells after 48-hour treatment

Treatment Group	IC50 (μg/mL) HCT-116	IC50 SW480 (μg/mL)	IC50 (Normal) HEK-293
Free 5-FU	18.4 ± 2.1	22.7 ± 3.2	9.8 ± 1.4
SE-EVs + 5-FU	12.6 ± 1.8	15.3 ± 2.4	7.2 ± 1.1
FSE-EVs + 5-FU	5.3 ± 0.7	7.8 ± 1.2	18.6 ± 2.9
FSE-EVs alone	9.1 ± 1.3	11.4 ± 1.9	N/A
Blank EVs (control)	>100	>100	>100

Flow cytometric Annexin V-FITC/PI staining demonstrated that FSE-EVs+5-FU induced 67.3% late apoptosis in HCT-116 cells at 10 μg/mL after 24 hours, compared to 34.1% for free 5-FU and 48.2% for SE-EVs+5-FU ($p < 0.01$). CLSM imaging confirmed significantly higher intracellular accumulation of DiI-labeled FSE-EVs in HCT-116 cells compared to SE-EVs at 4 hours (fluorescence intensity ratio 3.2 ± 0.4 vs. 1.8 ± 0.3, $p < 0.05$), suggesting enhanced cellular uptake, potentially associated with interactions between EV surfaces and CRC cell membrane receptors on CRC cells.

5. In Vivo Antitumor Efficacy

In the HCT-116 xenograft mouse model, FSE-EVs+5-FU treatment resulted in a 83.1% reduction in tumor volume compared to PBS control at day 28 (312 ± 67 mm^3 vs. 1842 ± 187 mm^3; $p < 0.001$), and significantly outperformed free 5-FU (-83.1%), SE-EVs+5-FU (-52.4%), and FSE-EVs alone (-62.6%) (Table 3). Survival analysis by Kaplan-Meier demonstrated a 95% survival rate in the FSE-EVs+5-FU group compared to 60% in PBS control over 28 days. Importantly, no significant body weight loss was observed in the FSE-EVs+5-FU group (maximum 4.2% reduction), contrasting with the 12.1% weight loss in the free 5-FU group, suggesting favorable systemic tolerability.

Histopathological analysis (H&E staining) of excised tumors confirmed extensive necrotic zones and reduced mitotic figures in the FSE-EVs+5-FU group. TUNEL staining showed a significantly higher apoptotic index in FSE-EVs+5-FU tumors (62.4 ± 7.3%) compared to and significantly outperformed free 5-FU, SE-EVs+5-FU, and FSE-EVs alone (Table 3).and SE-EVs+5-FU (41.3 ± 5.6%) ($p < 0.001$). No significant hepatotoxicity or nephrotoxicity was observed by serum biochemical parameters (ALT, AST, BUN, creatinine) in EV-treated groups, further confirming the safety profile of the platform suggesting a favorable safety profile.

Table 3. In vivo antitumor efficacy

Group	Tumor Volume (mm^3)	Tumor Weight (g)	Survival Rate (%)

PBS Control	1842 ± 187	1.92 ± 0.21	60
Free 5-FU	1124 ± 143	1.18 ± 0.16	70
SE-EVs + 5-FU	876 ± 112	0.91 ± 0.13	75
FSE-EVs + 5-FU	312 ± 67*	0.34 ± 0.08*	95
FSE-EVs alone	689 ± 98	0.72 ± 0.11	80

Collectively, these findings demonstrate that FSE-EVs improve drug delivery efficiency and therapeutic outcomes compared to non-fermented EVs and free drug.

DISCUSSION

The present study explores how microbial fermentation can be leveraged to modulate the functional properties of plant-derived extracellular vesicles, and suggests that this process may enhance their performance as drug delivery carriers. By comparing fermented and non-fermented soybean-derived EVs, we observed consistent differences in physicochemical characteristics, molecular cargo, and therapeutic outcomes, indicating that fermentation introduces measurable changes to EV behavior.

One of the most apparent effects of fermentation was the shift in vesicle physicochemical properties. FSE-EVs exhibited a smaller average size and lower polydispersity index, alongside a more negative zeta potential, suggesting improved colloidal stability. These changes are consistent with reports that fermentation can alter lipid composition, including increased levels of unsaturated phospholipids, which may influence membrane fluidity and vesicle formation. Such modifications are relevant, as nanoparticle size and surface charge are known to affect circulation stability and tumor accumulation.

Beyond structural changes, fermentation was associated with a marked increase in miRNA diversity within EV cargo. While the functional implications of plant-derived miRNAs in mammalian systems remain an area of active investigation, the enrichment of specific miRNAs predicted to target oncogenic pathways raises the possibility that these vesicles may contribute to therapeutic effects beyond passive drug delivery. In this context, FSE-EVs may act not only as carriers of chemotherapeutic agents but also as biologically active entities capable of modulating cellular signaling pathways, although further experimental validation is required.

The drug delivery performance of FSE-EVs also appeared to benefit from fermentation. HPLC analysis indicated efficient encapsulation of 5-fluorouracil, and the observed pH-responsive release profile suggests that drug release may be preferentially enhanced under acidic conditions resembling the tumor microenvironment. This behavior is advantageous, as it may reduce premature drug leakage in circulation while facilitating localized release following cellular uptake. Such stimulus-responsive delivery systems are increasingly recognized as a key feature in improving the therapeutic index of anticancer drugs.

Cellular uptake studies further support the functional relevance of these modifications. FSE-EVs demonstrated higher intracellular accumulation in colorectal cancer cells compared to non-fermented counterparts, which may contribute to the enhanced cytotoxicity observed. While the precise mechanisms underlying this increased uptake remain unclear, it is plausible that

fermentation-induced changes in surface composition influence interactions with cell membranes and endocytic pathways. This may, in part, explain the improved selectivity toward cancer cells relative to normal cells.

In vivo, these combined effects translated into substantial tumor growth inhibition and improved survival outcomes in the xenograft model. Although direct comparisons across studies should be interpreted cautiously, the magnitude of tumor suppression observed here is consistent with, or in some cases exceeds, previously reported plant-derived EV systems. Importantly, the absence of significant systemic toxicity supports the notion that plant-based vesicles retain favorable biocompatibility, even after functional modification through fermentation.

Taken together, the findings point toward a multi-faceted mechanism in which fermentation influences EV function at several levels, including membrane properties, cargo composition, and drug delivery behavior. Rather than acting solely as passive carriers, FSE-EVs may represent a hybrid platform that integrates physicochemical and biological modes of action.

Despite these promising observations, several limitations should be acknowledged. The mechanistic contribution of individual miRNAs to anticancer activity remains to be experimentally validated, and the specific molecular interactions governing cellular uptake require further clarification. In addition, considerations related to large-scale production, standardization, and in vivo biodistribution will be critical for future translational development.

From a broader perspective, this study suggests that microbial fermentation may serve as a simple yet effective strategy to engineer plant-derived nanovesicles with enhanced functionality. Given the accessibility of plant materials and the scalability of fermentation processes, this approach may offer a practical pathway toward the development of biocompatible and cost-effective nanotherapeutics for cancer treatment.

CONCLUSIONS

This study demonstrates that microbial fermentation can modulate the properties of plant-derived extracellular vesicles, resulting in measurable improvements in their performance as drug delivery carriers. Fermented soybean-derived EVs exhibited favorable physicochemical characteristics, enriched molecular cargo, and efficient encapsulation of 5-fluorouracil, alongside pH-responsive release behavior.

Functionally, these features were associated with enhanced cytotoxicity in colorectal cancer cells and improved antitumor efficacy in vivo, while maintaining a favorable safety profile. Although the underlying mechanisms require further validation, the findings suggest that fermentation-induced modifications may contribute to both delivery efficiency and biological activity.

Overall, this work highlights fermentation as a potentially accessible strategy for tuning the functionality of plant-derived nanovesicles and supports further investigation toward their development as biocompatible platforms for cancer therapy.

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