Original Article

Investigating the effects of outer membrane vesicles derived from *Campylobacter jejuni* on the survival of HT-29 epithelial cells *in vitro*

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Abstract

Background: *Campylobacter jejuni* is an important pathogenic bacterium that is associated with diarrhea and gastroenteritis in several animal species and humans. The secretion of virulence factors is a crucial strategy that enteric bacterial pathogens use to interact with host cells, promote their survival, and damage the host. Many bacterial pathogens utilize outer membrane vesicles (OMVs) to deliver virulence factors into host cells. *C. jejuni* can produce nanosized OMV cargos, which have been proposed to have a key role in disease progression, pathogenesis, and immune system modulation. This study aimed to assess the effect of OMVs derived from *C. jejuni* on the survival of HT-29 intestinal cells *in vitro*.
Materials and Methods: In this work, *C. jejuni* clinical strain RIGLD 4-151 was used. *C. jejuni* OMVs were isolated using ultracentrifugation and were analyzed by scanning electron microscopy (SEM) and dynamic light scattering (DLS). HT-29 human colon cancer epithelial cells were treated with OMVs for 24, 48, and 72 hours. Cell viability of HT-29 cells exposed to OMVs was measured by MTT assay.
Results: Our results showed that *C. jejuni* strain RIGLD 4-151 released round-shaped nanovesicles ranging from 10 to 250 nm. The cytotoxicity assays unveiled a dose-dependent reduction in cell viability following exposure to various concentrations of *C. jejuni* OMVs.
Conclusion: The present study demonstrated that OMVs derived from *C. jejuni* strain RIGLD 4-151 can significantly affect viability of HT-29 cells. Further research is required to elucidate the definite role of OMVs derived from *C. jejuni* strain RIGLD 4-151 in the pathogenesis of *C. jejuni*.
Keywords: *Campylobacter jejuni*, Outer membrane vesicle, Cell viability, HT-29 cells

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Introduction

Campylobacter jejuni is a Gram-negative, slender, flagellate, spiral-shaped, motile, and microaerophilic bacterium that colonizes the human intestine[1, 2]. It is a frequent foodborne pathogen that commonly causes acute bacterial gastroenteritis in humans worldwide[3, 4]. *C. jejuni* infection is associated with different diseases that range from mild self-limiting, non-inflammatory diarrhea to severe inflammatory bloody diarrhea that may lead to pyrexia and bacteriaemia[5]. Additionally, *C. jejuni* infection can potentially play an important role in the development of chronic gastrointestinal disorders such as inflammatory bowel disease (IBD), colorectal cancer (CRC), and also is the major cause of peripheral neuropathies such as Guillain-Barré syndrome (GBS)[6-10]. *C. jejuni* can invade human intestinal epithelial cells (IECs) through paracellular or transcellular routes[11, 12]. *C. jejuni* lacks type III secretion system (T3SS), which many other enteropathogens use to transfer virulence factors into host cells. Instead, *C. jejuni* modulates host interactions for colonization and infection by secreting virulence proteins through the flagellar T3SS. The flagellar T3SS is a complex protein structure that not only aids bacterial motility by forming the flagellum but also secretes certain virulence factors. Unlike the non-flagellar T3SS, which functions primarily as a needle-like apparatus to inject proteins directly into host cells, the flagellar T3SS is involved in the motility and secretion of proteins necessary for infection. This dual functionality distinguishes the flagellar T3SS from the non-flagellar T3SS, which is specialized solely for protein injection into host cells. Additionally, outer membrane vesicles (OMVs) have been identified as another significant delivery system for virulence proteins produced by *C. jejuni*[13-16]. These OMVs are small, spherical proteoliposomes with bilayer structures formed by the blebbing of the outer membrane, which contains mostly lipopolysaccharides (LPS), outer membrane proteins (OMPs), periplasmic proteins and outer membrane lipids[17, 18]. Studies have illustrated that OMVs obtained from *C. jejuni* activate signaling pathways that cleave E-cadherin and occludin proteins and enhance bacterial invasion into epithelial cells[19]. The enigmatic nature of *C. jejuni* transcends acute gastroenteritis, with recent findings implicating its involvement in the pathogenesis of CRC, elevating its status from a mere foodborne pathogen to a formidable entity in the oncogenic landscape. Previous research suggests that toxins produced by *C. jejuni*, including cytolethal distending toxin (CDT), cause double-strand breaks in DNA and stimulate the growth of colorectal cancer. The present study aimed to investigate the effects of OMVs derived from *C. jejuni* strain RIGLD 4-151 on the viability of HT-29 cells, a human colorectal adenocarcinoma cell line with epithelial morphology.

Methods

Bacterial Strain and Growth Conditions: *C. jejuni* clinical strain RIGLD 4-151 used in this study was isolated from a fecal specimen of an Iranian patient suffering from acute gastroenteritis in the Research Institute of Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Briefly, Campylobacter charcoal cefoperazone deoxycholate agar (CCDA) (Merck, Darmstadt, Germany) enriched with 5% sheep blood and antibiotics including 10 µg/ml vancomycin (Vancoxir, Exir Pharmaceutical Company, Iran**)**, 50 µg/ml polymyxin B (Polymyxin B Sulfate, Darou Pakhsh Pharmaceutical Mfg. Co., Iran), and 5 µg/ml trimethoprim (Trimethoprim, Iran Daru Pharmaceutical Company, Iran) was used to culture the strain. The culture plates were incubated under microaerobic conditions of 85% N_2, 10% CO_2, and 5% H_2 (Anoxomat® Gas Exchange System, Mart Microbiology BV, Lichtenvoorde, Netherlands) at 42°C for 48 hours. Confirmation of *C. jejuni* colonies was conducted through their distinct morphology, Gram staining, and positive reactions for catalase, oxidase, nitrate reduction, and hydrolysis of indoxyl acetate. Furthermore, PCR amplification was performed using specific primers for *C. jejuni* 16S rRNA and the hippuricase (*hipO*) genes. The oligonucleotide primers are presented in Table 1[20, 21].

The isolation of OMVs from *C. jejuni* was carried out using a previously established protocol[22, 23]. A loopful of *C. jejuni* colonies grown on CCDA agar was suspended in Brucella broth medium (Merck,

Table 1. Characteristics of the primers used for PCR assay in this study.

Gene	Sequences	Product size (bp)
16S rRNA	F-GGATGACACTTTTCGGAGC R-CATTGTAGCACGTGTGTC	816
hipO	F-GAAGAGGGTTTGGGTGGTG R-AGCTAGCTTCGCATAATAACTTG	735

Darmstadt, Germany) for 42 hours at 42°C under microaerobic conditions. Then, the supernatant was concentrated using centrifugations at 10000 g for 20 min at 4°C to eliminate cell debris, membrane aggregates, and large proteins. The supernatant was cleared of residual bacteria and debris by sterile filtration through 0.22 and 0.45 µm filters (Sigma Aldrich, St. Louis, MO, USA). Subsequently, the pellet was obtained by ultracentrifugation (Optima XE-100; Beckman Coulter, USA) of 36 ml volumes of each supernatant at 130000 g for 3 hours at 4°C at the University of Tehran, Tehran, Iran. The pellet was washed by resuspending in phosphate-buffered saline (PBS, pH 7.0) and stored at -80°C for further analysis.

Characterization of OMVs: The protein concentration of OMVs was measured by a commercial bicinchoninic acid (BCA) assay kit (DNA biotech, Tehran, Iran).

Scanning electron microscopy (SEM): The SEM analysis was performed at the University of Sharif, Tehran, Iran, to determine the morphological changes of OMVs following a previously described method[24]. In brief, samples were washed using PBS and fixed with 4% paraformaldehyde and 1% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2) for 24 hours on a slide before being washed with PBS three times.

Size distribution of *C. jejuni*-derived OMVs: Using dynamic light scattering (DLS), we determined the size distribution of the extracted OMVs to examine their physicochemical properties (ZEN3600, Malvern Instruments, UK) at the University of Tehran, Tehran, Iran. Before DLS measurements, OMVs were diluted in 1 ml of PBS. The findings were represented as the average particle size and polydispersity index (PDI), a measure of the size distribution's width.

Cell line and culture conditions: The HT-29 cell line, derived from human colorectal adenocarcinoma cells with epithelial morphology, was obtained from the Research Institute of Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The cells were cultured in 25 cm^2 tissue culture flasks using H-DMEM medium (Gibco-Invitrogen, Carlsbad, CA, USA) containing 10% inactivated fetal bovine serum (FBS) (Gibco-Invitrogen, Carlsbad, CA, USA), 1% non-essential amino acids (NEAA), and 100 U/ml penicillin-streptomycin (Gibco-Invitrogen, Carlsbad, CA, USA). The cells were passaged every 3-4 days after washing with PBS and incubation with a 0.25% trypsin-EDTA 1X (Gibco-Invitrogen, Carlsbad, CA, USA). The trypsinized cells were then incubated at 37°C with 5% CO_2 and 95% humidity for 5 minutes. A volume-equivalent amount of trypsinized cells was mixed with trypan blue (0.25%) and examined under a light microscope using a hemocytometer to estimate the number of viable cells during passage.

Cell viability analysis: The MTT assay was conducted using the Cell Proliferation Kit I (Sigma Aldrich, St. Louis, MO, USA) following the manufacturer's protocol to assess cell viability. In short, HT-29 cells were plated in 96-well plates at a density of 5×10^3 cells per well and exposed to various concentrations of *C. jejuni*-derived OMVs (5, 10, 20, 50, and 100 µg/ml) for 24, 48, and 72 hours. To begin the assay, the culture medium was replaced with a fresh medium containing 10% MTT solution (0.5 mg/ml in PBS) (Sigma Aldrich, St. Louis, MO, USA). The plate was then incubated for 4 hours at 37°C. Afterward, the supernatant was discarded, and the MTT-formazan was solubilized in 200 µl of dimethyl sulfoxide (DMSO), which was then added to each well. The absorbance was measured at 570 nm and a reference wavelength of 630 nm using a microplate reader (Eon, Biotech, USA). The percentage of HT-29 cell viability was calculated using the formula: cell viability (%) = (X-A/Y-A) × 100 was used to compute cell viability (%), where "X" represents the absorbance of treated cells, "Y" represents the absorbance of untreated cells, and "A" represents the blank absorbance.

Statistical Analysis: Statistical analysis was done using GraphPad Prism software version 8 (GraphPad Software, Inc., CA, USA). A one-way analysis of variance (ANOVA), followed by Tukey's post hoc test (for multiple comparisons between more than two groups), was used to calculate the statistical significance of the two groups. Unless otherwise stated,

results are presented as the average ± standard error of mean (SEM) of at least three experiments. Differences were considered statistically significant when $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, and $^{****}P<0.0001$.

This work does not contain any studies with human participants or animals. The Institutional Ethics Review Committee of the Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences approved the study (Project no. IR.SBMU.RIGLD.REC.1399.011).

Results

***C. jejuni* RIGLD 4-151 exhibits a remarkable ability to produce pleiomorphic OMVs of diverse sizes:** OMVs were meticulously isolated from *C. jejuni* RIGLD 4-151 cultures. The absence of cell debris was ensured through electron microscopy. Subsequent analysis via SEM (Fig. 1A) of purified OMVs revealed the presence of distinctive spherical vesicles encapsulating a pleiomorphic bilayer structure. The OMVs showcased a size spectrum ranging from 10 nm to 250 nm. Further characterization through DLS analysis divulged a nuanced size distribution profile, revealing that *C. jejuni*-derived OMVs contained particles spanning dimensions from 123.7 to 411.58 nm, with an average size of 255.4 nm (Fig. 1B).

Cell viability of HT-29 cells via MTT assay: The cytotoxicity effect of OMVs derived from *C. jejuni* strain RIGLD 4-151 on the viability of HT-29 cells was evaluated across 24, 48, and 72-hour intervals (Fig. 2).

The OMVs obtained from *C. jejuni* RIGLD 4-151 elicited distinct responses, as delineated in Fig. 2. Exposure to 5 µg/ml of OMVs led to a significant reduction in cell viability only after 72 hours ($P<0.05$). However, other concentrations including 10, 20, 50, and 100 µg/ml induced a notable decrease in viability across 24 ($P<0.01$, $P<0.0001$, $P<0.0001$, $P<0.0001$, respectively), 48 ($P<0.01$, $P<0.001$, $P<0.0001$, $P<0.0001$, respectively), and 72 hours ($P<0.001$, $P<0.001$, $P<0.0001$, $P<0.0001$, respectively) time point. Furthermore, it is noteworthy that OMVs did not reduce viable cells below 70%, a threshold deemed safe for further cell experiments.

Discussion

The present study aimed to investigate the effects of OMVs derived from *C. jejuni* strain RIGLD 4-151 on the viability of HT-29 intestinal cells *in vitro*. The role of OMVs in the pathogenesis of *C. jejuni* is increasingly recognized as a critical factor in understanding host-pathogen interactions. This study reveals that *C. jejuni* OMVs actively modulate the behavior of epithelial cells, particularly HT-29 cells, which serve as a model for intestinal epithelium. The ability of OMVs to influence epithelial cell responses highlights their potential as key players in the establishment and persistence of *C. jejuni* infection[26]. OMVs carry diverse molecules, including lipopolysaccharides (LPS), proteins, and nucleic acids, which can interact with host cells in various ways. For instance, specific proteins on OMVs may trigger signaling pathways in epithelial

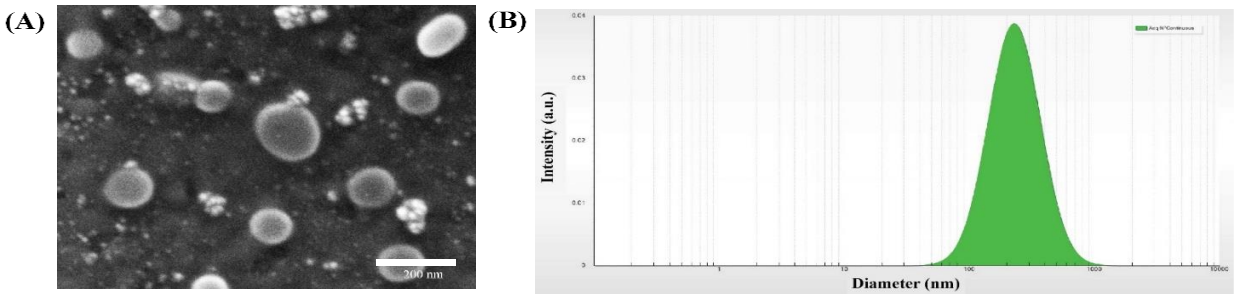

Figure 1. Morphological characterization of *C. jejuni* strain RIGLD 4-151 OMVs. **(A)** Scanning electron microscopy (SEM) images of OMVs indicated the spherical and double-layered vesicles in various sizes. Scale bars (lower right) represent 200 nm. **(B)** Size distribution by intensity of *C. jejuni* strain RIGLD 4-151 OMVs based on dynamic light scattering (DLS). Size distribution is determined based on the intensity of OMVs using the ultracentrifugation technique.

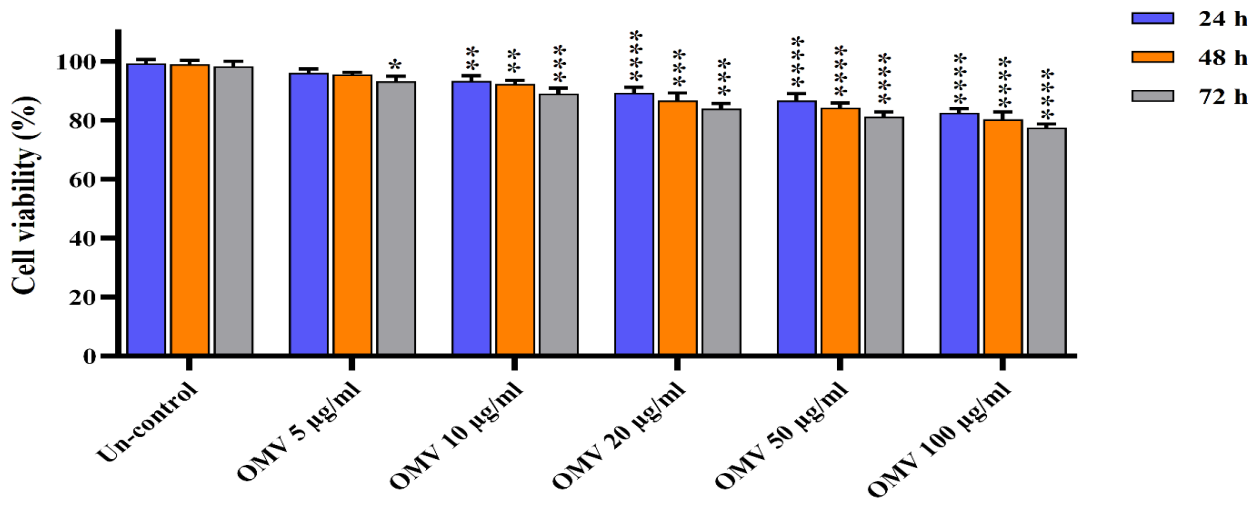

Figure 2. Cell viability of HT-29 cells treated with different concentrations of OMVs (5, 10, 20, 50, 100 µg/ml) isolated from *C. jejuni* RIGLD 4-151 for 24, 48, and 72 hours using MTT assay. Data are presented as mean ± SD from three independent experiments. A *P* value of <0.05 was considered significant (**P* <0.05; ***P* <0.01; ****P* <0.001; *****P* <0.0001) by ANOVA statistical analysis.

cells that lead to altered gene expression, inflammation, or even apoptosis. Understanding these mechanisms is crucial for developing targeted therapies. Future research should focus on identifying the components of OMVs responsible for these effects, as this knowledge could inform the design of interventions to disrupt these interactions[27].

It has been demonstrated that OMVs can transfer bacterial virulence factors into host cells through receptor-mediated endocytic pathways or by fusion with the host cell's plasma membrane. Several bacterial pathogens, including enterotoxigenic *Escherichia coli* (ETEC), have been shown to bind their OMVs to lipid rafts[28]. OMVs isolated from *C. jejuni* RIGLD 4-151 in this investigation ranged in size from 10 to 250 nm. Previously, it was reported that OMVs isolated from *C. jejuni* strain 81-176 varied in size from 10 to 50 nm[29]. In the previous study, the isolation of OMVs of different sizes may be explained using a different growth temperature (42°C) and medium (Mueller-Hinton biphasic agar/broth). Indeed, the size range of OMVs isolated in this study is consistent with that of OMVs isolated from other Gram-negative bacteria[30]. Variation in the size, shape, and electron density of *C. jejuni* OMVs suggests that there may be differential sorting of OMVs cargo proteins, as is the case for *Porphyromonas gingivalis* OMVs[31]. In addition to the size determination of OMVs, our study also examined the cytotoxic effects of OMVs derived from *C. jejuni* strain RIGLD 4-151. The cytotoxic effects observed in our study align with those reported by Lindmark et al. (2009), who demonstrated that OMVs from *C. jejuni* can induce significant cytotoxicity in host cells. Taken together, these studies indicate that diverse bioactive components in the cargo of OMVs may enhance the cytotoxic effects of *C. jejuni*, leading to increased apoptosis and necrosis in HT-29 cells. This is in agreement with previous studies that have demonstrated the ability of *C. jejun* OMVs to provoke significant immune responses, including the release of proinflammatory cytokines like interleukin-8 (IL-8) from intestinal epithelial cells. These findings emphasize the need for further research on the specific mechanisms by which *C. jejuni* OMVs contribute to disease progression and host-pathogen interactions. The potential for targeting OMVs in therapeutic strategies is particularly promising[32]. By developing agents that inhibit OMV formation or block their interaction with epithelial cells, we could significantly reduce the pathogenicity of *C. jejuni*. Such strategies could include using small molecules that interfere with OMVs biogenesis or applying competitive inhibitors that prevent OMVs from binding to epithelial cell receptors.

Developing vaccines that elicit an immune response against OMV components could also provide a proactive approach to preventing *C. jejuni* infections[33]. The findings of this study also contribute to a broader

understanding of microbial pathogenesis. OMVs are not unique to *C. jejuni*; many Gram-negative bacteria utilize similar mechanisms to enhance their virulence. This raises important questions about the evolutionary advantages conferred by OMV production. One limitation of this study is using a single cell line, which may not fully represent the complexity of the human intestinal epithelium. Future studies should include multiple cell lines and *in vivo* models to validate these findings. Additionally, further research is needed to identify the specific components of OMVs responsible for the observed effects and to explore potential therapeutic interventions targeting OMVs. The findings of present study revealed that OMVs from *C. jejuni* significantly reduced the viability of HT-29 cells in a dose-dependent manner.

Conclusion

In conclusion, this study presents a viewpoint on the critical role of OMVs derived from *C. jejuni* in influencing the viability of HT-29 epithelial cells. An innovative method of reducing the consequences of *C. jejuni* infections might involve preventing OMVs from forming or preventing epithelial cells to attache these bacterial nanostructures. Therefore, by understanding the mechanisms of action and the implications for host-pathogen interactions, we can more effectively tackle the challenges posed by this important enteric pathogen. These findings provide a foundation for future research aimed at developing OMV-targeted therapies.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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