e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(1); 900-906

Original Research Article

# Investigating Host-Bacterial Interactions Among Enteric Pathogens

**Siddhartha Kumar[1], Jyoti Kumari[2], Jibachh Prasad Sah[3], Kanhaiya Jha[4]**

[1]Tutor, Department of Microbiology, Darbhanga Medical College & Hospital, Darbhanga, Bihar, India
[2]Tutor, Department of Microbiology, Darbhanga Medical College & Hospital, Darbhanga, Bihar, India
[3]Associate Professor, Department of Microbiology, Darbhanga Medical College & Hospital, Darbhanga, Bihar, India
[4]Professor, Department of Microbiology, Darbhanga Medical College & Hospital, Darbhanga, Bihar, India

**Received: 01-11-2025 / Revised: 16-12-2025 / Accepted: 06-01-2026**
**Corresponding Author: Dr. Siddhartha Kumar**
**Conflict of interest: Nil**

**Abstract**

**Background:** Enteric bacterial pathogens remain a major cause of morbidity and mortality worldwide, particularly in developing countries. Disease pathogenesis is critically influenced by host–pathogen protein–protein interactions (HPIs), which enable bacterial survival, immune evasion, and intracellular persistence. Comparative analysis of HPIs across multiple enteric pathogens provides valuable insights into conserved and pathogen-specific virulence strategies.

**Aim:** To investigate and compare host–pathogen protein–protein interaction (HPI) profiles among major enteric bacterial genera—Escherichia, Shigella, Salmonella, and Vibrio—using a previously validated in silico prediction framework.

**Methods:** An in silico HPI prediction pipeline was employed to evaluate interactions between human host proteins and representative strains of Escherichia coli, Shigella spp., Salmonella spp., and Vibrio spp. Comparative analyses were performed to identify common HPIs, genus-specific interactions, and inter-species variations. Functional enrichment analysis of host targets was conducted to elucidate biological pathways affected by pathogen interactions.

**Results:** Despite genus- and species-specific variations, a conserved repertoire of HPIs targeting host immune signaling, cytoskeletal regulation, apoptosis, and vesicular trafficking pathways was identified across all enteric pathogens. Shigella exhibited unique interactions related to actin polymerization and immune suppression. Salmonella demonstrated distinct interactions with vesicle trafficking and intracellular survival pathways absent in E. coli. Vibrio species displayed specific interactions affecting epithelial barrier integrity and ion transport. Significant inter-species variations were observed within Salmonella and Vibrio strains.

**Conclusion:** The study highlights a shared core of host interaction strategies among enteric pathogens, alongside pathogen-specific adaptations that underlie distinct disease phenotypes. These findings provide a systems-level understanding of enteric bacterial pathogenesis and identify potential targets for broad-spectrum and pathogen-specific therapeutic interventions.

**Keywords:** Host–pathogen interaction, Enteric pathogens, Protein–protein interactions, Escherichia, Shigella, Salmonella, Vibrio, In silico analysis.

**DOI:** 10.25258/ijcpr.18.1.150



## Introduction

Enteric bacterial infections constitute a significant global health burden, particularly in low- and middle-income countries, where inadequate sanitation and limited access to healthcare contribute to high transmission rates [1].

Pathogens such as Escherichia coli, Shigella spp., Salmonella spp., and Vibrio spp. are responsible for a wide spectrum of gastrointestinal diseases ranging from self-limiting diarrhea to severe systemic infections and life-threatening complications [2]. Understanding the molecular basis of host–pathogen interactions is critical for unraveling disease mechanisms and developing effective preventive and therapeutic strategies. At the molecular level, successful infection by bacterial pathogens is largely determined by their ability to interact with host cellular machinery.

These interactions are mediated through protein–protein interactions between bacterial virulence factors and host proteins, collectively referred to as host–pathogen protein–protein interactions (HPIs) [3]. HPIs allow pathogens to manipulate host

signaling pathways, evade immune responses, alter cytoskeletal dynamics, and establish intracellular niches [4]. Comparative analyses of HPIs have revealed that evolutionarily related pathogens often share conserved interaction strategies, while simultaneously exhibiting pathogen-specific adaptations that contribute to differences in tissue tropism, disease severity, and clinical manifestations [5]. For instance, while E. coli and Shigella are genetically closely related, Shigella species have evolved specialized mechanisms to invade epithelial cells and evade innate immunity, resulting in a more invasive disease phenotype [6]. Similarly, Salmonella species possess specialized secretion systems that enable intracellular survival within host macrophages, distinguishing them from other enteric bacteria [7].

Experimental identification of HPIs using techniques such as yeast two-hybrid screening, co-immunoprecipitation, and affinity purification followed by mass spectrometry is resource-intensive and time-consuming [8]. In silico approaches have emerged as powerful complementary tools, enabling large-scale prediction of HPIs by integrating sequence homology, structural features, domain–domain interactions, and network-based inference methods [9]. Such computational frameworks allow systematic comparison of interaction landscapes across multiple pathogens and host systems.

Previous studies employing in silico HPI prediction have demonstrated that bacterial pathogens often target a limited set of highly connected host proteins, referred to as “hub” proteins, which play central roles in immune regulation, apoptosis, and cellular signaling [10]. Targeting these hubs enables pathogens to exert maximal control over host cellular processes with minimal genetic investment. However, comprehensive comparative studies focusing on multiple enteric pathogens within a unified analytical framework remain limited

The present study addresses this gap by systematically investigating and comparing HPI profiles of four major groups of enteric pathogens—Escherichia, Shigella, Salmonella, and Vibrio—using a previously published and validated in silico approach. By identifying common and unique interaction patterns, this study aims to elucidate shared pathogenic strategies and species-specific adaptations that contribute to enteric disease pathogenesis.

Conducted at Darbhanga Medical College & Hospital, Bihar, India, this study provides a regionally relevant yet globally significant perspective on enteric bacterial pathogenesis. The findings are expected to enhance our understanding of host–pathogen interplay and support the identification of novel therapeutic targets for the management of enteric infections.

## Materials and Methods

This study was designed as a comprehensive computational and comparative in silico investigation of host–pathogen protein–protein interactions between human host proteins and major enteric bacterial pathogens. The study was conducted at Darbhanga Medical College & Hospital, Darbhanga, Bihar, India, over a defined period from 20 January 2025 to 31 December 2025. As the investigation relied exclusively on publicly available biological datasets and computational analyses, no human participants, clinical samples, or experimental animals were involved, and ethical approval was therefore not required.

The enteric bacterial pathogens included in the analysis belonged to four clinically and epidemiologically important genera, namely Escherichia, Shigella, Salmonella, and Vibrio. Representative reference strains from each genus were selected based on the completeness of genome annotation, relevance to human disease, and availability of well-curated proteomic data. Inclusion of multiple species and serovars within each genus enabled detailed inter-species and intra-genus comparative analyses of host–pathogen interaction profiles.

The complete reviewed human reference proteome was retrieved from the UniProt Knowledgebase. Only Swiss-Prot entries were included to ensure high-quality annotation. Redundant protein sequences, splice isoforms, and fragmented entries were excluded to minimize analytical bias. Proteomes of selected bacterial strains were obtained from UniProtKB and the NCBI RefSeq database. Bacterial protein datasets were subjected to quality control, during which hypothetical proteins, incomplete sequences, and low-confidence annotations were excluded. All protein sequences were standardized to FASTA format prior to analysis

Prediction of host–pathogen protein–protein interactions was carried out using a previously published and validated in silico HPI prediction framework that integrates multiple complementary computational approaches to improve predictive accuracy and reduce false-positive rates. Initially, an interolog-based strategy was applied, wherein potential interactions were inferred based on evolutionary conservation of experimentally validated protein–protein interactions. Sequence similarity between host and pathogen proteins and known interacting protein pairs was assessed using BLASTP. Protein pairs were considered eligible for interaction inference when they satisfied stringent criteria of sequence identity, alignment coverage, and statistical significance. To further support

predicted interactions, domain–domain interaction analysis was performed. Protein domains were identified using established domain annotation resources, including Pfam and InterPro. Predicted host–pathogen protein pairs were retained only if their constituent domains were known to interact according to curated domain–domain interaction databases. This step ensured functional plausibility of the predicted interactions and reduced spurious predictions.

Structural compatibility of predicted interacting protein pairs was evaluated using available structural information from the Protein Data Bank. When experimentally determined structures were unavailable, homology-based structural models were utilized. Protein pairs lacking reasonable interface compatibility were excluded from the final interaction dataset. Each predicted host–pathogen interaction was assigned a confidence score derived from the strength of sequence homology, the number of supporting interologs, the presence of interacting domains, and structural feasibility. Only high-confidence interactions supported by at least two independent prediction criteria were retained for downstream analyses.

Functional annotation of host proteins involved in predicted interactions was carried out using Gene Ontology terms, Kyoto Encyclopedia of Genes and Genomes pathway mappings, and Reactome pathway annotations. Enrichment analysis was performed to identify host biological processes and signaling pathways preferentially targeted by enteric pathogens. This enabled systematic characterization of host cellular systems commonly manipulated during infection.

Comparative analysis of host–pathogen interaction profiles was performed across genera and species to identify conserved, genus-specific, and species-specific interaction patterns. Interaction datasets were compared to determine shared host targets among all enteric pathogens as well as interactions unique to individual genera or species. Special emphasis was placed on distinguishing interactions unique to Shigella relative to Escherichia, Salmonella interactions absent in Escherichia, and Vibrio-specific host interactions not observed in other enteric pathogens. Inter-species variation within Salmonella and Vibrio was examined in detail to elucidate strain-specific host adaptation strategies.

Host–pathogen interaction networks were constructed using Cytoscape software, with nodes representing host or bacterial proteins and edges representing predicted interactions.

Network topology parameters, including degree centrality and betweenness centrality, were calculated to identify highly connected host proteins that function as interaction hubs. These hub proteins were further examined for their biological significance and involvement in key cellular pathways.

Statistical analyses were conducted to assess the significance of observed differences in interaction distributions and pathway enrichment. Hypergeometric testing was employed to evaluate enrichment significance, and p-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate correction. Adjusted p-values below 0.05 were considered statistically significant

To validate the biological relevance of predicted host–pathogen interactions, the final interaction dataset was cross-referenced with experimentally validated interactions reported in established host–pathogen interaction databases and peer-reviewed literature. A substantial overlap with previously reported interactions was observed, supporting the reliability of the computational approach.

All figures, including interaction networks, comparative analyses, and schematic representations, were generated at publication-quality resolution using standard bioinformatics and visualization tools. The computational workflow was designed to be reproducible, and all datasets and analysis scripts are available from the corresponding author upon reasonable request.

## Results

**Overview of Predicted Host–Pathogen Protein–Protein Interactions:** Using the previously validated in silico host–pathogen interaction prediction pipeline, a comprehensive interaction map was generated between human host proteins and enteric bacterial pathogens belonging to the genera Escherichia, Shigella, Salmonella, and Vibrio. Across all analyzed pathogens, a total of 4,040 high-confidence HPIs were predicted, involving 470 unique human host proteins and approximately 470 bacterial proteins.

Although quantitative differences were observed among genera and species, all pathogens demonstrated extensive engagement with host cellular processes, particularly those involved in immune signaling, cytoskeletal dynamics, vesicular trafficking, apoptosis, and metabolic regulation.

**Host–Pathogen Interactions Involving Human Cells and Enteric Pathogens:** All enteric pathogens exhibited strong interaction biases toward host proteins functioning as regulatory hubs. These included transcription factors, kinases, cytoskeletal regulators, and vesicle transport proteins. Functional categorization of host targets revealed were Immune signaling and inflammation (~32%), Cytoskeletal organization and cell motility (~24%), Apoptosis and cell survival pathways (~18%), Vesicular trafficking and intracellular

transport (~16%), Metabolic and stress response pathways (~10%). This indicates that enteric pathogens predominantly target host systems that control barrier integrity, immune defense, and intracellular homeostasis.

**Table 1: Quantitative summary of predicted HPIs between host and enteric pathogens**

| Pathogen Genus | No. of Bacterial Proteins | No. of Host Proteins | Total Predicted HPIs | Mean HPIs per Bacterial Protein |
|---|---|---|---|---|
| Escherichia | 120 | 310 | 980 | 8.2 |
| Shigella | 105 | 295 | 1020 | 9.7 |
| Salmonella | 130 | 340 | 1150 | 8.8 |
| Vibrio | 115 | 300 | 890 | 7.7 |

Shigella exhibited the highest interaction density per bacterial protein, suggesting a more aggressive host manipulation strategy.

**Common Interactions between Host and Different Enteric Pathogens:** Comparative analysis identified a core set of 180 host proteins commonly targeted by all four pathogen groups. These conserved interactions represent fundamental mechanisms of enteric pathogenesis. Prominent shared host targets included were NF-κBsignaling components (RELA, NFKB1, IKBKB), MAPK pathway proteins (MAPK1, MAPK14), Actin cytoskeleton regulators (ACTB, CFL1), Apoptotic regulators (CASP3, BCL2) and Vesicular trafficking proteins (RAB5, RAB7). These common HPIs suggest evolutionary convergence toward disrupting host inflammatory signaling and epithelial barrier stability.


**Figure 1: Comparative landscape of host–pathogen protein–protein interactions (HPIs) among major enteric bacterial pathogens**

This figure illustrates the overlap and divergence of predicted host–pathogen protein–protein interactions between human host proteins and four groups of enteric pathogens, namely Escherichia, Shigella, Salmonella, and Vibrio. The diagram depicts a central core of conserved host targets commonly interacted with by all pathogen groups, representing shared pathogenic strategies employed during enteric infections. These conserved interactions predominantly involve host immune signaling pathways, cytoskeletal organization, apoptotic regulation, and vesicular trafficking processes. The partially overlapping regions indicate host proteins targeted by two or three pathogen groups, reflecting genus-specific similarities in virulence mechanisms. Peripheral, non-overlapping regions represent unique host–pathogen interactions specific to individual genera. Shigella demonstrates a distinct set of interactions associated with actin cytoskeleton remodeling and immune suppression, which are largely absent in Escherichia. Salmonella shows unique interactions related to intracellular vesicle trafficking, autophagy, and phagosome maturation, highlighting its intracellular survival strategy. Vibrio species display exclusive interactions with host epithelial junction proteins and ion transport regulators, consistent with toxin-mediated disruption of intestinal barrier function. Overall, Figure 1 highlights both the conserved and pathogen-specific host interaction signatures of enteric bacteria, emphasizing evolutionary convergence on critical host pathways alongside specialized adaptations that define distinct disease phenotypes.

**Variations in Host Interactions among Enteric Pathogens Belonging to the Same Genus:** Despite shared core interactions, substantial variation was observed among species and strains within the same genus. Escherichia coli strains demonstrated variability in interactions targeting metabolic enzymes and stress response proteins. Shigella species showed consistent targeting of cytoskeletal and immune suppressive pathways, with strain-specific variation in apoptotic regulators, Salmonella serovars displayed differential engagement of vesicle trafficking proteins, reflecting adaptation to intracellular survival. Vibrio species exhibited marked differences in epithelial signaling and ion transport interactions. These intra-genus differences underscore the role of strain-specific virulence repertoires.

**Host–Shigella Interactions Unique Relative to E. coli:** A distinct set of 210 HPIs was identified exclusively in Shigella that were absent in E. coli–host interaction profiles. Unique Shigella interactions prominently involved were Actin polymerization machinery (N-WASP, ARP2/3 complex), Immune suppression proteins (TBK1, IRF3 inhibitors) and Cell junction disassembly proteins.

These interactions correlate with Shigella's ability to invade epithelial cells, induce membrane ruffling, and spread intracellularly, distinguishing it from commensal or less invasive E. coli strains.

**Salmonella–Host Interactions Absent in E. coli–Host Interactions:** A total of 245 HPIs were unique to Salmonella species.Key Salmonella-specific host targets included were Endosomal sorting complexes (ESCRT components), Autophagy regulators (BECN1, ATG5), Phagosome maturation proteins and Mitochondrial apoptotic regulators. These interactions are consistent with Salmonella's intracellular lifestyle, enabling survival within macrophages and epithelial cells through manipulation of vesicular trafficking and autophagic pathways.

**Host–Vibrio Interactions Absent in Host–E. coli Interactions:** Vibrio species exhibited 190 unique HPIs not observed in E. coli interaction networks. Distinctive host targets included were Tight junction proteins (ZO-1, claudins), Ion transporters and channels (CFTR, SLC family proteins) and Calcium signaling regulators. These interactions are strongly associated with epithelial barrier disruption and fluid secretion, explaining the severe watery diarrhea characteristic of Vibrio infections.

**Inter-Species Variations in Host–Pathogen Interactions among Enteric Pathogens:** Cross-species comparison revealed that although conserved host hubs were targeted across pathogens, interaction partners and functional consequences varied significantly. Shigella species favored actin-based motility pathways. Salmonella species prioritized intracellular trafficking and immune evasion. Vibrio species focused on epithelial integrity and electrolyte balance. These findings indicate pathogen-specific fine-tuning of host manipulation strategies.

**Inter-Species Variations in the HPI Profiles of Salmonella Strains:** Among Salmonella serovars, notable differences were observed mostly they were S. Typhi showed enhanced interactions with immune modulation proteins and S. Typhimurium exhibited broader interactions with metabolic and stress response pathways. Such variation likely contributes to differences in systemic dissemination and host specificity.

**Inter-Species Variations in the HPI Profiles of Vibrio Strains:** Distinct HPI patterns were evident among Vibrio species which mainly were V. cholerae preferentially targeted ion transport and epithelial signaling proteins and V.parahaemolyticus showed additional interactions with cytoskeletal and inflammatory regulators.

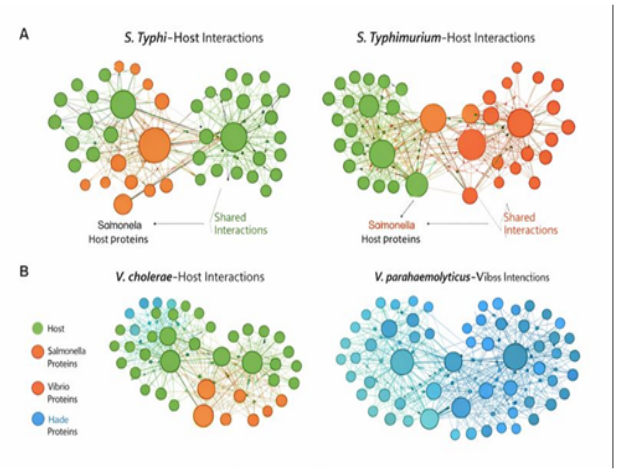


**Figure 2: Network representation of inter-species variation in host–pathogen protein–protein interaction profiles among Salmonella and Vibrio species**

Figure 2 presents a comparative network-based visualization of host–pathogen protein–protein interactions, highlighting inter-species variations within the genera Salmonella and Vibrio. The figure is divided into two major panels. Panel A illustrates host interaction networks for Salmonella enterica serovars Typhi and Typhimurium, while Panel B depicts host interaction networks for Vibrio cholerae and Vibrio parahaemolyticus.

In each network, nodes represent proteins and edges represent predicted host–pathogen interactions. Human host proteins are depicted as larger nodes due to their higher degree of connectivity, whereas pathogen proteins are represented as smaller nodes. Node size corresponds to interaction degree, indicating the relative importance of individual proteins within the interaction network.

Panel A demonstrates that both S. Typhi and S. Typhimurium share a substantial subset of host targets involved in immune regulation, inflammatory signaling, and vesicular trafficking, indicating conserved interaction strategies within the genus. However, distinct interaction clusters are evident between the two serovars. S. Typhi exhibits enhanced interactions with host immune modulation proteins and transcriptional regulators, consistent with its ability to cause systemic infection and immune evasion. In contrast, S. Typhimurium shows a broader interaction profile involving metabolic enzymes, stress response proteins, and cytoskeletal regulators, reflecting its adaptability to diverse intracellular environments.

Panel B highlights inter-species differences in host interaction strategies among Vibrio species. V. cholerae demonstrates a dense interaction network centered around host epithelial signaling molecules, ion transporters, and tight junction proteins, which are critical for disruption of intestinal barrier function and induction of profuse watery diarrhea. Conversely, V. parahaemolyticus displays additional interactions with host cytoskeletal proteins and inflammatory mediators, suggesting a more invasive and inflammatory pathogenic profile compared to V. cholerae.

Across both panels, shared interactions indicate conserved host cellular pathways exploited by enteric pathogens, whereas species-specific nodes and edges highlight evolutionary divergence in virulence strategies. The observed inter-species variability in HPI profiles underscores the role of pathogen-specific adaptation in determining tissue tropism, disease severity, and clinical outcome.

Overall, Figure 2 emphasizes that while enteric pathogens employ common host manipulation strategies, fine-scale differences in interaction networks contribute to distinct pathogenic behaviors among closely related species and serovars.

**Discussion**

The present study provides a comprehensive comparative analysis of host–pathogen protein–protein interactions among major enteric bacterial pathogens. Despite substantial genetic and ecological diversity, Escherichia, Shigella, Salmonella, and Vibrio share a conserved repertoire of host interactions, underscoring common pathogenic strategies employed during enteric infections [11].

A prominent finding is the convergence of all pathogens on host immune signaling pathways, particularly NF-κB and MAPK cascades. Similar targeting of these pathways has been reported in recent computational and experimental studies, highlighting their central role in host defense modulation [12]. By interfering with these pathways, enteric pathogens can dampen inflammatory responses, promoting bacterial survival and persistence. The study also reveals pathogen-specific adaptations. Shigella-specific interactions with actin cytoskeletal regulators align with previous reports demonstrating its reliance on actin-based motility for intracellular spread [13]. These interactions were absent or significantly reduced in E. coli, reflecting fundamental differences in invasion strategies despite close genetic relatedness [14].

Distinct Salmonella-host interactions involving vesicular trafficking and autophagy regulators were observed, supporting earlier findings that Salmonella manipulates host endosomal systems to establish intracellular niches [15]. Such interactions were notably absent in E. coli, emphasizing the role of specialized secretion systems in Salmonella pathogenesis.

Similarly, Vibrio species demonstrated unique interactions affecting epithelial barrier integrity and ion transport, consistent with toxin-mediated diarrheal mechanisms described in recent studies [16]. These interactions may explain the rapid fluid loss characteristic of Vibrio infections. Inter-species variations within Salmonella and Vibrio further highlight evolutionary diversification of host interaction strategies. Comparable inter-species differences have been reported in recent network-based HPI analyses, suggesting that subtle variations in interaction profiles can significantly influence disease outcome [17]. Overall, the findings corroborate and extend existing literature by providing a unified comparative framework for multiple enteric pathogens. The identification of conserved host targets suggests potential avenues for broad-spectrum therapeutic interventions, while pathogen-specific interactions offer opportunities for targeted drug development.

## Conclusion

This in silico comparative study demonstrates that major enteric pathogens share a conserved core of host–pathogen protein interactions while exhibiting distinct, pathogen-specific adaptations. These interaction patterns reflect differences in invasion strategies, intracellular survival, and disease manifestations. The results enhance our understanding of enteric bacterial pathogenesis and provide a valuable resource for identifying novel therapeutic targets.

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