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Exploring the Virulence Factors of *Campylobacter jejuni* Targeted by Quercetin: A Bioinformatics Approach

Sintice Dhea Valerie[1]*, Nawan Nawan[2], Ysrafil Ysrafil[3]
[1]Undergraduate Program of Medicine; [2]Microbiology Department, Faculty of Medicine; [3]Pharmacotherapy Department, Faculty of Medicine, Palangka Raya University. Jl. Hendrik Timang, Palangka Raya 73111, Indonesia.

Corresponding author*
sinticedheavalerie@gmail.com

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Abstract

Campylobacter jejuni is a major cause of bacterial gastroenteritis and continues to develop resistance to commonly used antibiotics, especially fluoroquinolones, creating a need for alternative therapeutic approaches. Quercetin, a natural flavonoid, exhibits antibacterial activity by disrupting membrane stability, inhibiting nucleic acid synthesis, and reducing virulence factor expression. This study aimed to predict the interaction between quercetin and essential proteins of *Campylobacter jejuni* and to identify virulence-associated proteins with immunogenic potential using a bioinformatics approach. The protein–compound interaction analysis was performed using STITCH, while virulence functions were predicted using VirulentPred and VICMPred. B cell and T cell epitope predictions were conducted using the IEDB Analysis Resources, and antigenicity was evaluated using VaxiJen. The results showed that quercetin interacts with key proteins such as ATP synthase, DnaK, catalase, and oxidoreductase, which contribute to bacterial survival through energy metabolism and oxidative stress regulation. Five virulence-associated proteins were identified with strong antigenicity and immunogenic potential, with most predicted to be located on the cytoplasmic membrane. These findings suggest that quercetin may function as a multi-target antimicrobial agent that interferes with essential cellular processes while promoting immune recognition, supporting its potential as a candidate for future therapeutic development against antibiotic-resistant *Campylobacter jejuni* infections.

Keywords: Antibiotic resistance; Bioinformatics; Campylobacter jejuni; Virulence factors; Quercetin.

INTRODUCTION

Campylobacteriosis is an infectious disease caused primarily by the bacterium *Campylobacter jejuni*, which is widely recognized as one of the major global causes of bacterial gastroenteritis. In 2010, approximately 96 million cases of campylobacteriosis were reported worldwide, making it one of the leading foodborne diarrheal diseases (Tobolowsky et al., 2024). In low- and middle-income countries, diarrheal disease contributes to around 78% of morbidity and mortality among children under five years old annually (Gahamanyi et al., 2020). *Campylobacter jejuni*, a Gram-negative and microaerophilic bacterium, is commonly transmitted through the consumption of undercooked poultry, contaminated drinking water, unpasteurized milk, and cross-contamination during food handling (Kaakoush et al., 2015).

Although many cases are self-limiting, antibiotic treatment such as fluoroquinolones and macrolides is required in patients with severe symptoms or immunocompromised conditions (Gahamanyi et al., 2020). Excessive and inappropriate antibiotic use in both humans and livestock has contributed significantly to the emergence of *Campylobacter jejuni* strains that are resistant to first-line antibiotics (S. Yanestria et al., 2024). One major mechanism underlying this resistance is the mutation occurring in the *gyrA* gene within the Quinolone Resistance-Determining Region (QRDR), which leads to high-level resistance against fluoroquinolones such as ciprofloxacin (S. M. Yanestria et al., 2024). These mutations have been detected in *C. jejuni* isolates from broiler chickens in Indonesia, reducing the effectiveness of commonly used therapeutic options in clinical settings (S. Yanestria et al., 2024).

This alarming increase in antibiotic resistance emphasizes the urgent need to develop alternative antimicrobial strategies. Natural bioactive compounds such as flavonoids have drawn rising scientific attention as potential therapeutic agents. Flavonoids possess a broad spectrum of biological activities, including antioxidant, anti-inflammatory, and antimicrobial effects (Mahmud et al., 2023). Previous studies have shown that flavonoids extracted from roselle exhibit antibacterial activity against methicillin-resistant *Staphylococcus aureus* (Ramadhani et al., 2024), while flavonoids from *Ziziphus mauritiana* leaves effectively inhibit the growth

of *Escherichia coli* by disrupting bacterial cell membranes (Mulyani et al., 2021).

Quercetin is a flavonol-type flavonoid known for its broad-spectrum antimicrobial activity against both Gram-negative and Gram-positive bacteria, including drug-resistant strains. Its antibacterial mechanisms include damaging bacterial membrane integrity, inhibiting nucleic acid and protein synthesis, suppressing virulence factors, and preventing biofilm formation (Veiko et al., 2023; Ysrafil et al., 2023). Quercetin is also capable of reducing quorum sensing activity, a regulatory system important for bacterial virulence expression (Shastri et al., 2025). These characteristics make quercetin a promising antimicrobial candidate that may inhibit infection while reducing resistance development.

Advances in bioinformatics technology now enable comprehensive prediction of molecular interactions between antimicrobial compounds and bacterial proteins efficiently and cost-effectively, without relying solely on extensive laboratory assays (Sardi, 2022). In a bioinformatics study conducted by He et al (2020) demonstrated that quercetin effectively suppressed virulence properties of *Porphyromonas gingivalis*, including biofilm formation and pathogenic protein expression, indicating its potential to weaken bacterial infectivity. Similarly, the study conducted by Musini et al (2024) revealed that quercetin exhibited strong antibiofilm activity against drug-resistant *Staphylococcus aureus* and its interaction with target proteins was validated through molecular modeling. Therefore, this study aims to analyze the molecular interaction between quercetin and virulence-associated proteins of several *Campylobacter jejuni* strains using a bioinformatics approach, in order to identify potential protein targets that could contribute to efforts in overcoming antibiotic resistance.

MATERIALS AND METHODS

Study Design and Subject Retrieval

This research applied a computational in silico design utilizing bioinformatics-based analytical methods to explore molecular interactions and virulence profiles of pathogenic *Campylobacter jejuni*. The study focused on three reference strains such as, *C. jejuni* 414, 81176, and NCTC11168 to better understand their virulence mechanisms and identify potential therapeutic protein targets of quercetin. The subject of study consisted of quercetin and the protein sequences in FASTA format derived from *Campylobacter jejuni* strains 414, 81176, and NCTC11168. Only proteins predicted to interact with quercetin were selected for further bioinformatics analysis.

Bioinformatics Analysis

Compound–Protein Interaction Analysis

Interaction mapping between quercetin and target *Campylobacter jejuni* strain 414, 81176, and NCTC11168 proteins was performed using the STITCH v5.0 web server accessible through http://stitch.embl.de. Interaction networks were visualized in a three-dimensional diagram. The resulting protein candidates were then downloaded from NCBI in FASTA format for subsequent analysis stages.

Functional Classification

To classify their functional classification, the selected proteins were analyzed using VICMpred (https://webs.iiitd.edu.in/), which predicts protein involvement in cellular processes, metabolism, information pathways, or virulence.

Virulence Prediction

The VirulentPred website accessible on https://bioinfo.icgeb.res.in/virulent2/ was used to classify Quercetin-targeted *Campylobacter jejuni* proteins into virulent or avirulent categories based on predictive probability scores.

B-cell Epitope Prediction

The IEDB Analysis Resources using BepiPred v2.0 methods accessible on http://tools.iedb.org/bcell/ was employed to identify linear B-cell epitope regions within the predicted virulent proteins. Residues with prediction scores **>0.50** were considered potential epitopes and appeared as yellow peaks on the plot, while lower-scoring residues (**≤0.50**) were classified as non-epitopic.

T-cell Epitope Prediction (MHC-I and MHC-II)

T-cell epitope analysis was performed using IEDB MHC binding prediction tools for both $CD8^+$ (MHC-I) and $CD4^+$ (MHC-II) T lymphocytes. $CD8^+$ T-cell epitopes were identified via http://tools.iedb.org/mhci/ with a selection cutoff of percentile rank ≤ 2%, while $CD4^+$ T-cell epitopes were predicted using http://tools.iedb.org/mhcii/ with a percentile rank threshold of ≤ 10%. Epitopes meeting these thresholds were classified as strong-binding peptides and subsequently evaluated for antigenicity.

Antigenicity Assessment

Antigenicity of the selected proteins was evaluated using VaxiJen v2.0 (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html), was applied to classify predicted peptides as antigenic if ≥ 0.5 or non-antigenic if < 0.5. Only epitopes that were both strong binders and antigenic were shortlisted as vaccine candidates.

Subcellular Localization Prediction

PSORTb v3.0 accessible on the website https://www.psort.org/psortb/ was used to predict the cellular localization of each protein, enabling differentiation between cytoplasmic and membrane-associated proteins that are more feasible as therapeutic or vaccine targets.

RESULTS AND DISCUSSION

Interaction Analysis of Quercetin with Campylobacter jejuni Proteins

The interaction analysis using STITCH showed that Quercetin was associated with multiple essential proteins in *Campylobacter jejuni* strains 414, 81176, and NCTC11168. The majority of these interactions were clustered around ATP synthase subunits, including atpA, atpD, atpG, atpH, and atpC. Additional interacting proteins included DnaK, pglK and KatA, indicating the involvement of pathways related to stress response and energy metabolism. The diagram shown in Figure 1.

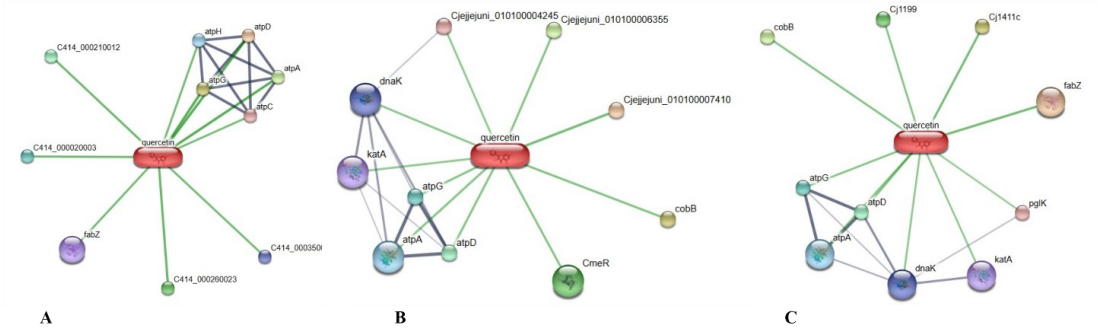

Figure 1. Quercetin Interaction Diagram with (A) Campylobacter jejuni 414 (B) Campylobacter jejuni 81176 (C) Campylobacter jejuni NCTC11168.

Functional and Virulence Classification

Further functional Functional classification using VICMPred indicated that the majority of Quercetin-associated proteins were involved in cellular and metabolic processes. However, virulence-based prediction revealed five proteins, such as C414_000260023, C414_000210012, Cjejjejuni_010100006355, CmeR, and Cj1199 with positive virulence characteristics that shown in Table 1.These virulent proteins were selected for antigenicity analysis.

Table 1. Analysis of Functional Classes and Virulence Prediction of Campylobacter jejuni strain 414, 81176, and NCTC11168 Proteins Interacting with Quercetin.

Organism	Identification Code	Proteins That React with Quercetin	Functional Class	Virulent Pred
Campylobacter jejuni 414	C414_000350068	Cytochrome P450 family protein	Metabolism Molecule	Non-virulent
	C414_000260023	Oxidoreducatse, 2OG-Fe(II) oxygenase family	Information and storage	**Virulent**
	fabZ	Beta-hydroxyarcyl-ACP dehydratase	Cellular process	Non-virulent
	C414_000020003	Hypothetical protein	Cellular process	Non-Virulent
	C414_000210012	Hypothetical protein	Cellular process	**Virulent**
	atpH	F-type ATPase subunit delta	Cellular process	Non-virulent
	atpG	F-ATPase gamma subunit	Cellular process	Non-virulent
	atpD	Putative ATP synthase F1 sector beta subunit	Metabolism molecule	Non-virulent
	atpA	ATP synthase F1 alpha	Cellular process	Non-virulent
	atpC	F-ATPase epsilon subunit	Cellular process	Non-virulent
Campylobacter jejuni 81176	Cjejjejuni_010100004245	ABC transporter, ATP-binding protein/permease MsbA	Metabolism Molecule	Non-Virulent
	Cjejjejuni_010100006355	Oxidoreducatse, 2OG-Fe(II) oxygenase family	Information and storage	**Virulent**
	Cjejjejuni_0101000074	cytochrome P450 family protein	Cellular process	Non-Virulent

Organism	Identification Code	Proteins That React with Quercetin	Functional Class	Virulent Pred
	10			
	cobB	NAD-dependent deacetylase	Virulence factors	Non-virulent
	CmeR	TetR family transcriptional regulator	Metabolism molecule	**Virulent**
	katA	Catalase	Metabolism molecule	Non-virulent
	dnaK	molecular chaperone DnaK	Cellular process	Non-virulent
Campylobacter jejuni NCTC11168	Cj1199	iron/ascorbate-dependent oxidoreductase	Cellular process	**Virulent**
	Cj1411c	cytochrome P450	Cellular process	Non-virulent
	fabZ	(3R)-hydroxymyristoyl-ACP dehydratase	Metabolism molecule	Non-virulent
	pglK	Flippase	Metabolism molecule	Non-virulent

B-Cell Epitope Prediction and Antigenicity

The analysis of B-cell epitopes was carried out following the prediction of functional classes and virulence attributes of Quercetin-targeted virulent proteins in *Campylobacter jejuni*. Linear B-cell epitope prediction using IEDB BepiPred revealed several amino acid regions with high potential to be recognized by B cells. In the generated graphs, yellow peaks represent epitope regions with scores above the prediction threshold, indicating their accessibility for antibody binding, while green regions are non-epitopic areas. Antigenicity analysis using VaxiJen confirmed that most yellow-highlighted epitopes possessed antigenicity scores ≥ 0.5, suggesting their potential to elicit humoral immune responses. These results are shown in Figure 2.

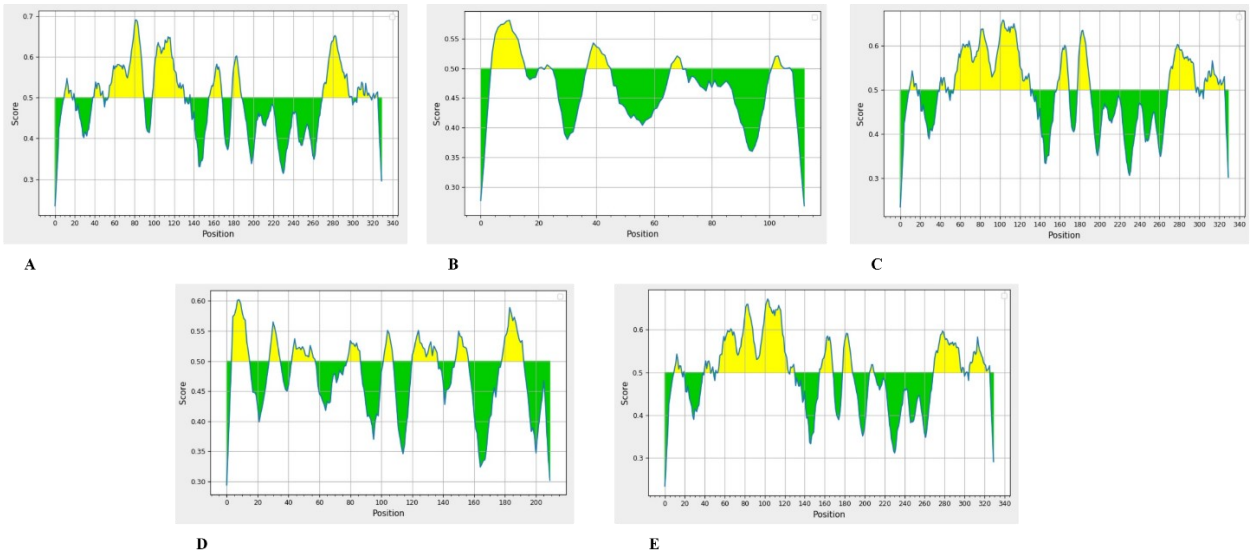

Figure 2. Result of B Cell Epitopes on (A) C414_000260023, (B) C414_000210012, (C) Cjejjejuni_010100006355, (D) CmeR, (E) Cj1199
Information*:*
Yellow peaks indicate sequences that have potential epitopes.
Green peaks indicate sequences that do not have potential epitopes.

T-Cell Epitope Prediction and Antigenicity

Furthermore, T-cell epitope prediction using the IEDB MHC-I ($CD8^+$) and MHC-II ($CD4^+$) binding tools identified multiple strong-binding peptide candidates, characterized by low percentile ranks and supported by favorable antigenicity values. Antigenicity assessment using VaxiJen confirmed that several epitopes achieved scores ≥ 0.5, categorizing them as antigenic with the potential to elicit effective cellular immune responses, while peptides with scores < 0.5 were classified as non-antigenic. The complete list of predicted T-cell epitopes is presented in Table 2 and Table 3.

Table 2. MHC I ($CD8^+$) Analysis.

Protein	Allele	Start	End	Length	Peptides	Percentile Rank	Vaxijen Score
C414_000260023	HLA-A*11:01	185	193	9	ITQGVGSHK	0.11	1.1723
	HLA-A*11:01	159	167	9	NAFDKLYGK	0.25	-0.1390
	HLA-A*11:01	38	46	9	GIDKNLNEK	0.34	1.7848
	HLA-A*11:01	25	33	9	ITSKIGFFY	0.35	0.1003
	HLA-A*11:01	175	183	9	IIHYPKSSK	0.39	-0.3784
C414_000210012	HLA-A*11:01	91	99	9	SIIRLSLNK	0.02	0.1294
	HLA-A*11:01	33	41	9	LLAKGSVMK	0.43	-0.2649
	HLA-A*11:01	20	28	9	ILIDDEHSK	0.64	0.6377
	HLA-A*11:01	103	111	9	VQRINAVLK	1.1	-0.1162
	HLA-A*11:01	6	14	9	WSKAEFYPK	1.2	-0.0187
Cjejjejuni_010100006355	HLA-A*11:01	133	141	9	LTWHKQTKK	0.1	0.2626
	HLA-A*11:01	185	193	9	ITQGVGSHK	0.11	1.1723
	HLA-A*11:01	38	46	9	SIDKNLNEK	0.16	1.4616
	HLA-A*11:01	175	183	9	IIHYPKSSK	0.39	-0.3784
	HLA-A*11:01	249	257	9	RVNLSPKER	0.61	0.8507
CmeR	HLA-A*11:01	162	170	9	AVLFCTMLK	0.1	0.3493
	HLA-A*11:01	49	57	9	NIYDGFKSK	0.12	0.3599
	HLA-A*11:01	148	156	9	QQNNSYMKK	0.13	0.8978
	HLA-A*11:01	21	29	9	VALELFLTK	0.14	0.9075
	HLA-A*11:01	114	122	9	IIYSQVYDK	0.17	0.5742
Cj1199	HLA-A*11:01	133	141	9	LTWHKQTKK	0.1	0.2626
	HLA-A*11:01	185	193	9	ITQGVGSHK	0.11	1.1723
	HLA-A*11:01	38	46	9	SIDKNLNEK	0.16	1.4616
	HLA-A*11:01	175	183	9	IIHYPKSSK	0.39	-0.3784
	HLA-A*11:01	249	257	9	RVNLSPKER	0.61	0.8507

Table 3. MHC II ($CD4^+$) Analysis.

Protein	Allele	Start	End	Length	Peptides	Percentile Rank	Vaxijen Score
C414_000260023	HLA-DRB1*04:01	73	87	15	FRGYTSEGSEYTAGT	1.50	1.1860
	HLA-DRB1*04:01	70	84	15	QFRGYTSEGSEYTAG	1.80	1.1912
	HLA-DRB1*04:01	72	86	15	TKDYREQLDIGTERN	1.80	0.8536
	HLA-DRB1*04:01	87	101	15	RNAFKWDLNSPLWQR	1.90	1.0848
	HLA-DRB1*04:01	69	83	15	KRMIRSHPDVASIYH	2.10	0.2476
C414_000210012	HLA-DRB1*04:01	15	29	15	EVKINILIDDEHSKE	4.10	1.3665
	HLA-DRB1*04:01	14	28	15	KEVKINILIDDEHSK	6.50	1.0531
	HLA-DRB1*04:01	72	86	15	LDMISLEANMSHSLG	11	0.9089
	HLA-DRB1*04:01	90	104	15	DSIIRLSLNKLDKVQ	11	-0.0735
	HLA-DRB1*04:01	16	30	15	VKINILIDDEHSKEI	11	1.0829
Cjejjejuni_010100006355	HLA-DRB1*04:01	146	160	15	LLKAFAQVLDLPSNA	1.40	0.0683
	HLA-DRB1*04:01	147	161	15	LKAFAQVLDLPSNAF	1.60	0.2318
	HLA-DRB1*04:01	28	42	15	KIGFFYLINTSIDKN	1.80	0.8475
	HLA-DRB1*04:01	87	101	15	TKDYREQLDIGTERD	1.80	0.8701
	HLA-DRB1*04:01	306	320	15	KRMIRSHPDVASIYH	2.60	0.2476
CmeR	HLA-DRB1*04:01	70	84	15	KKHFHLIYSKTQEIK	1.40	0.7107
	HLA-DRB1*04:01	169	183	15	LKEPYHHLNVLINAP	1.60	0.1399
	HLA-DRB1*04:01	143	157	15	MGFFKQQNNSYMKKN	1.90	0.0179
	HLA-DRB1*04:01	170	184	15	KEPYHHLNVLINAPL	1.90	0.3052
	HLA-DRB1*04:01	96	110	15	GLAFIEIFNQPEAVA	2	-0.0867
Cj1199	HLA-DRB1*04:01	28	42	15	KIGFFYLINTSIDKN	1.80	0.8475
	HLA-DRB1*04:01	87	101	15	SKDYREQLDIGTERD	1.80	0.8694
	HLA-DRB1*04:01	306	320	15	KRMIRSHPDVASIYH	2.60	0.2476
	HLA-DRB1*04:01	29	43	15	IGFFYLINTSIDKNL	2.70	0.8122
	HLA-DRB1*04:01	86	100	15	GSKDYREQLDIGTER	2.90	1.0839

Subcellular Localization

Subcellular localization analysis using PSORTb showed that most virulence-associated proteins are located in the cytoplasm, while a few were classified as having unknown localization. The results are displayed in Table 4.

Table 4. Subcellular Localization Analysis.

Organism	Identification Code	Protein Name	Subcellular Location
Campylobacter jejuni 414	C414_000260023	Oxidoreductase, 2OG-Fe(II) oxygenase family	Cytoplasmic
	C414_000210012	Putative uncharacterized protein	Unknown
Campylobacter jejuni 81176	Cjejjejuni_010100006355	Oxidoreductase, 2OG-Fe(II) oxygenase family	Cytoplasmic
	CmeR	TetR family transcriptional regulator	Unknown
Campylobacter jejuni NCTC11168	Cj1199	iron/ascorbate-dependent oxidoreductase	Cytoplasmic

Discussion

Campylobacter jejuni is a major enteric pathogen responsible for global gastroenteritis burden, and rising antimicrobial resistance has complicated treatment outcomes, especially resistance driven by *gyrA* mutations in poultry-associated strains (S. Yanestria et al., 2024). This condition highlights the urgency to explore alternative antivirulence strategies using natural compounds such as Quercetin, which has been shown to disrupt membrane integrity, inhibit nucleic acid synthesis, reduce virulence expression, and suppress biofilm formation (Mahmud et al., 2023; Veiko et al., 2023).

In the present study, interaction analysis using STITCH demonstrated that Quercetin targets multiple key proteins involved in bacterial survival and pathogenicity, including ATP synthase components and stress-response regulators. By interfering with ATP production, Quercetin may impair fundamental metabolic and energy-driven cellular processes (Ravera et al., 2023). This cascade can compromise protein refolding mechanisms regulated by DnaK, weaken biofilm assembly pathways, and reduce bacterial capacity to overcome host-induced oxidative stress, particularly through suppression of KatA catalase activity (Chivu et al., 2025). These findings support the notion that Quercetin exhibits multitarget inhibition capable of reducing *C. jejuni* colonization and virulence potential in a synergistic manner.

Functional and virulence prediction using VICMpred and VirulentPred further confirmed that several Quercetin-targeted proteins contribute to cellular regulation, adaptation, and host interaction pathways associated with pathogenicity. Such virulence-associated proteins are promising candidates for antivirulence therapy and selective immune targeting, since suppressing them can weaken disease severity without exerting strong selective pressure for antimicrobial resistance (Pecoraro et al., 2023).

Evaluation of humoral immune induction revealed multiple B-cell epitopes with strong predicted antigenicity, indicated by BepiPred threshold-exceeding regions. These epitope sites represent surface-accessible antigenic portions capable of provoking antibody-mediated neutralization (Jespersen et al., 2017). Meanwhile, T-cell epitope analysis demonstrated the presence of strong MHC-I and MHC-II binding peptides, characterized by low percentile ranks and antigenicity scores ≥0.50, indicating their ability to activate cytotoxic and helper T lymphocytes (Doytchinova & Flower, 2007; Paul et al., 2017). Together, these findings highlight immune-recognizable regions that could be integrated into an epitope-based vaccine strategy.

Although most virulence-associated proteins identified in this study were localized within the cytoplasm, their predicted strong epitopes remain relevant immunologically, as cytoplasmic proteins are processed via MHC pathways during infection and are common targets for T-cell–dependent vaccines against intracellular bacterial pathogens (Nguyen & Bhattacharya, 2022). The ability of Quercetin to penetrate bacterial cells and interfere with intracellular systems further supports its compatibility in combination with immunotherapeutic approaches (Yang et al., 2020).

Overall, these findings suggest that Quercetin not only attenuates bacterial virulence through multitarget metabolic and stress-response disruption, but also facilitates the identification of antigenic virulence-associated proteins that may serve as candidates for epitope-based vaccine development. Combining Quercetin-driven antivirulence therapy with immune-targeted strategies warrants further investigation as a complementary approach to combat antimicrobial-resistant *C. jejuni* infections.

CONCLUSIONS

This bioinformatics study on the antivirulence mechanism of quercetin against *Campylobacter jejuni* strains 414, 81176, and NCTC1168 demonstrates that quercetin interacts molecularly with virulence-associated proteins critical for the pathogen's survival and infectivity. Functional analysis revealed that these target proteins play major roles in energy metabolism, stress response, and regulatory pathways that contribute to bacterial virulence.

Epitope prediction confirmed the presence of B-cell and T-cell epitopes with strong antigenic potential, while subcellular localization analysis indicated that most virulent proteins were positioned within the cytoplasmic membrane, making them more accessible to immune system recognition. These findings suggest that quercetin may inhibit essential pathogenic processes while

enhancing host immune responses. Further experimental studies are necessary to confirm these bioinformatic predictions and to assess the potential of quercetin as an adjunct candidate for antimicrobial or vaccine strategies targeting antibiotic-resistant *Campylobacter jejuni*.

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Authors' Contributions: Sintice Dhea Valerie & Nawan designed the study. Sintice Dhea Valerie & Ysrafil Ysrafil analyzed the data. Sintice Dhea Valerie, Nawan Nawan & Ysrafil Ysrafil wrote the manuscript. All authors read and approved the final version of the manuscript

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