

Microbial Diversity and Screening for Potential Pathogens and Beneficial Bacteria of Five Jellyfish Species-Associated Microorganisms Based on 16S rRNA Sequencing

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Abstract

Jellyfish, microorganisms, and the marine environment collectively shape a complex ecosystem. This study aimed to analyze the microbial communities associated with five jellyfish species, exploring their composition, diversity, and relationships. Microbial diversity among the species was assessed using 16S rRNA gene sequencing and QIIME analysis. Significant differences in bacterial composition were found, with distinct dominant taxa in each species: *Mycoplasmataceae* (99.21%) in *Aurelia coerulea*, *Sphingomonadaceae* (22.81%) in *Cassiopea andromeda*, *Alphaproteobacteria_unclassified* (family level) (64.09%) in *Chrysaora quinquecirrha*, *Parcubacteria_unclassified* (family level) (93.11%) in *Phacellophora camtschatica*, and *Chlamydiaceae* (35.05%) and *Alphaproteobacteria_unclassified* (family level) (38.73%) in *Rhopilema esculentum*. *C. andromeda* showed the highest diversity, while *A. coerulea* exhibited the lowest. Correlations among dominant genera varied, including a positive correlation between *Parcubacteria_unclassified* (genus level) and *Chlamydiaceae_unclassified* (genus level). Genes were enriched in metabolic pathways and ABC transporters. The most abundant potential pathogens at the phylum level were Proteobacteria, Tenericutes, Chlamydiae, and Epsilonbacteraeota. The differing microbial compositions are likely influenced by species and their habitats. Interactions between jellyfish and microorganisms, as well as among microorganisms, showed interdependency or antagonism. Most microbial gene functions focused on metabolic pathways, warranting further study on the relationship between pathogenic bacteria and these pathways.

Key words: jellyfish, microorganisms diversity, pathogenic bacteria, beneficial bacteria

Introduction

Microorganisms are closely related to the environment, and abnormal changes in the environment will lead to alterations in the composition and abundance of

microbial communities. Consequently, various microbial indicators are often regarded as environmental indicators. For instance, Foraminifera may serve as a biological indicator for monitoring transitional and marine ecosystems, and their significance in environmental

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monitoring studies is highlighted (Virginia Alves Martins et al. 2019). Additionally, multiple pathogenic bacteria, such as actinomycetes and proteobacteria in copper-contaminated rivers, were detected, posing long-term and potential threats to the ecosystem and aquatic organisms (Odhiambo et al. 2023). In terms of organisms, as mammalian hosts and their inherent gut microbiota co-evolved, they have formed a complex and stable relationship that prevents invading microbes from disrupting the gut environment (Schnitzlein and Young 2022).

The composition and function of the microbial communities between the water environment and aquatic organisms exhibit tissue-specificity, influenced by numerous environmental factors. At the same time, the composition and function of the microbial communities of aquatic species have a commonality (Sehnal et al. 2021). Cnidarians have become incubators for numerous marine organisms due to their viscous body fluids and unique biological structures. Within the phylum Cnidaria, jellyfish have gathered many microorganisms, displaying high host potential (Tinta et al. 2019). Although jellyfish are simple in structure, they play an essential role within the marine ecosystem and represent a micro-ecosystem collection. Various microorganisms inhabit their surfaces, internal structures, and surrounding environment (Liu et al. 2011). This micro-ecosystem contains bacteria, archaea, fungi, protozoa, and viruses. This symbiotic relationship is not merely parasitic but also interdependent and mutually beneficial (Li 2009), which has a profound impact on the growth, behavior (Weiland-Bräuer et al. 2020; Ohdera et al. 2022) and even the ecosystem. Microorganisms associated with jellyfish collectively form a miniature ecosystem whose stability is closely related to the health of jellyfish. Microorganisms also affect the jellyfish's ecological functions, such as nutrient absorption, reproduction, and pathogen resistance (Apprill 2017). Hence, the complexity of the symbiotic relationship between jellyfish and microorganisms remains a long-term focus of researchers. The diversity and complex structure of microbial communities present research challenges. We must delve deeper into the mechanisms of interaction between jellyfish and microorganisms and their state of equilibrium to better protect marine ecosystems' health. Marine microorganisms might serve as producers or contributors of certain natural active compounds. Investigating secondary metabolites and associated microorganisms expands our understanding of marine biology and holds significant potential for advancements in biomedical and biotechnological fields (Li 2009). This study aimed to analyze the potential pathogens and beneficial bacteria in five jellyfish species to offer novel strategies for marine ecosystem conservation, pharmaceutical exploration, and technological advancements (Waters et al. 2010; Qadri et al. 2020).

Experimental

Materials and Methods

Experimental subjects and acquisition methods.

Five jellyfish species including *Aurelia coerulea*, *Rhopilema esculentum*, *Phacellophora camtschatica*, *Cassiopea andromeda*, and *Chrysaora quinquecirrha* were obtained from an artificial aquarium in Shandong Province, China, and swiftly transported in 30‰ salinity artificial seawater to the laboratory in Naval Medical University (Second Military Medical University), Shanghai, China.

Sample preparation. Tentacle tissues from 20 jellyfish of the five jellyfish species (four jellyfish for each species) were cut, divided into five groups (each group contains four samples), flash-frozen in liquid nitrogen, and stored in a -80°C freezer. Microbial genomic DNA extraction from jellyfish samples was carried out using the FastDNA Spin DNA Extraction Kit (MP Biomedicals). Subsequently, the quantity and quality of extracted DNA were assessed using a Thermo Scientific NanoDrop™ 1000 Spectrophotometer (Thermo Fisher Scientific, Inc., USA) and agarose gel electrophoresis.

Bioinformatics analysis. We adopted the latest and better-performing QIIME 2 analysis process, calling DADA2 to denoise the data, remove redundancy, and obtain features. We identified the bacterial strains by comparing feature sequences with the database. Bioinformatics analyses primarily employed QIIME (version 1.9.1) and R packages (version 2.2.1) (Callahan et al. 2016; Bolyen et al. 2019). Alpha diversity indices, including Chao1, Shannon, and Simpson, were computed using QIIME to assess bacteria richness and evenness among different samples, reflecting species diversity. Beta diversity analysis encompassed Principal Coordinate Analysis (PCoA), Principal Component Analysis (PCA), and Non-Metric Multidimensional Scaling (NMDS), comparing differences in microbial community structure and species composition among samples. Random Forest methodology was employed to rank the top 20 most important microbial families (at the taxonomic level of the family) using mean decrease accuracy and mean decrease Gini indices. Utilizing the SparCC method, correlations among the top 20 dominant commensal microbial communities were determined by calculating abundance correlations between pairwise dominant species. Differential gene expression analysis of the top 20 KEGG Orthology (KO) annotations was conducted using Statistical Analysis of Metagenomic Profiles (STAMP) (Parks et al. 2014). KO feature functionality predictions were made using PICRUSt 2 (version 2.1.4) (Douglas et al. 2019). Graphs and charts were generated using GraphPad Prism version 9.0 (GraphPad Software, USA, www.graphpad.com)

and the Lianchuan BioCloud Platform (bioinformatic analysis was performed using the OmicStudio tools at <https://www.omicstudio.cn/tool>).

Statistical analysis. Differences in alpha diversity indices within sample groups were computed using Welch's *t*-test and Wilcoxon rank-sum test in the R environment. Tukey's honestly significant difference (HSD) test and Kruskal-Wallis *H* test were employed to assess differences in beta diversity indices among sample groups. Differences in microbial community structures among different samples were evaluated using Adonis (also known as Permanova, permutation multivariate analysis of variance) and Anosim (similarity analysis). All data were presented as mean ± standard deviation. One-way analysis of variance (ANOVA) determined inter-group differences. Statistical significance was set at **p* < 0.05, ***p* < 0.01.

Results

Microbial community structure and composition analysis. The five jellyfish species varied in shape and size (Fig. 1A). The abundance percentages of commensal microorganisms on the tentacles of the five jellyfish species were analyzed at the taxonomic level of the family, revealing significant differences in

microbial species composition among these jellyfish. Dominant microbial families varied across different jellyfish species: *Mycoplasmataceae* in *A. coerulea*, *Sphingomonadaceae* in *C. andromeda*, *Alphaproteobacteria_unclassified* (family level) in *C. quinquecirrha*, *Parcubacteria_unclassified* in *P. camtschatica*, and both *Chlamydiaceae* and *Alphaproteobacteria_unclassified* (family level) in *R. esculentum* (Fig. 1B). Furthermore, a shared and unique microbial community analysis at the family level indicated 23 families of microorganisms were common among the five jellyfish, while *A. coerulea* harbored 10 unique families, *C. andromeda* had 39 unique families, *C. quinquecirrha* had 46 unique families, *P. camtschatica* had 13, and *R. esculentum* had four unique families (Fig. 1C).

From the 23 shared families of microorganisms, the top five families based on average abundance were selected for Circos plot analysis to illustrate the distribution proportions of predominant species across different sample groups: *Mycoplasmataceae* constituted approximately 99.21% of the microbial composition in *A. coerulea*, *Sphingomonadaceae* accounted for about 22.81% in *C. andromeda*, *Alphaproteobacteria_unclassified* (family level) represented roughly 64.09% in *C. quinquecirrha*, *Parcubacteria_unclassified* (family level) comprised approximately 93.11% in *P. camtschatica*, and *Chlamydiaceae* and *Alphaproteobacteria_unclassified*

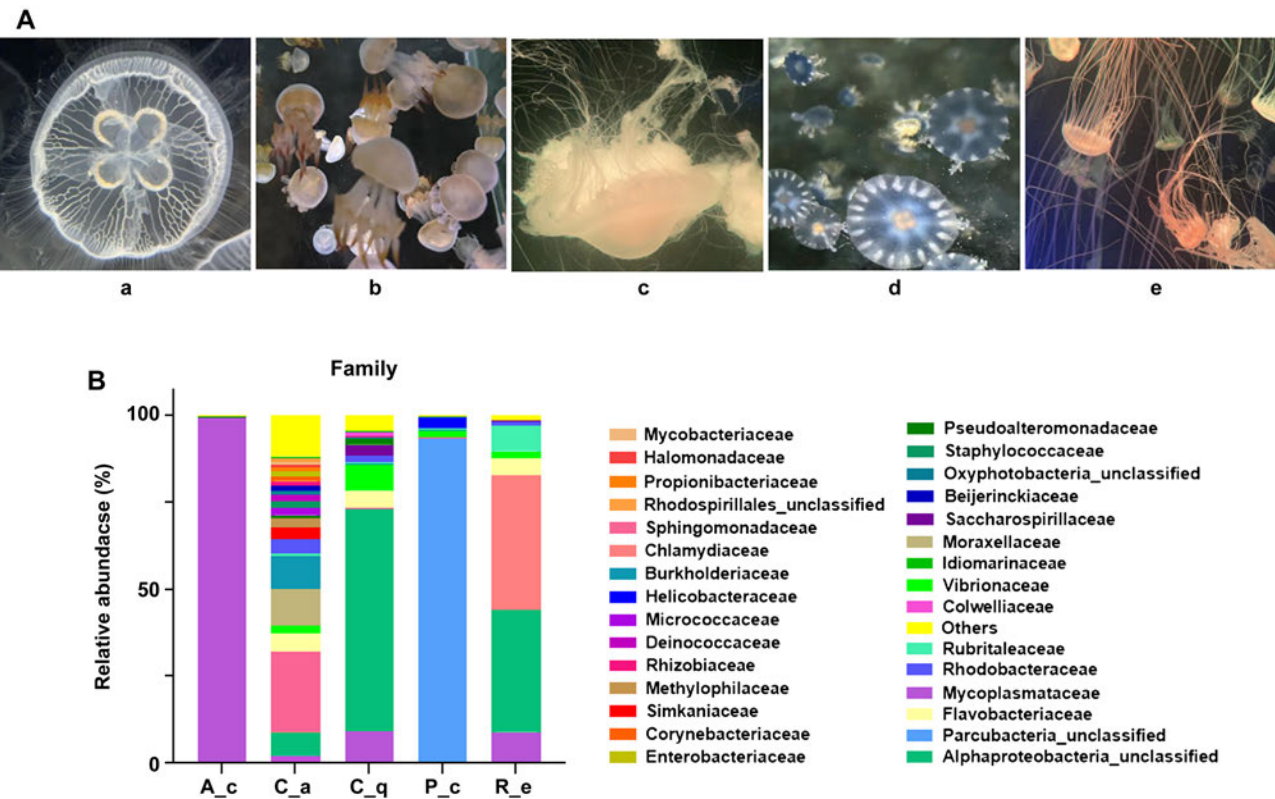


Fig. 1. Analysis of commensal microbial community compositions in five jellyfish species. A) From (a) to (e): *Aurelia coerulea*, *Rhopilema esculentum*, *Phacellophora camtschatica*, *Cassiopea andromeda*, and *Chrysaora quinquecirrha*; B) the microbial community compositions at the taxonomic level of the family for different jellyfish species.

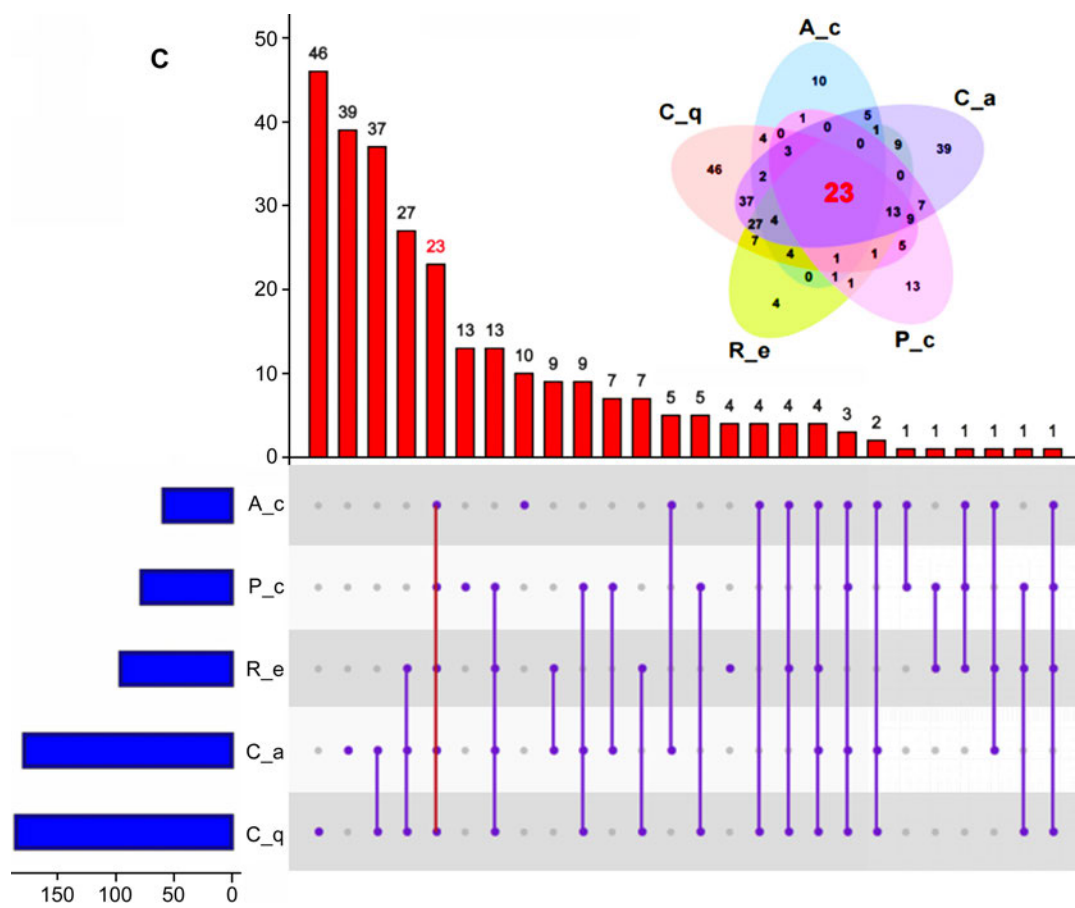


Fig. 1. Analysis of commensal microbial community compositions in five jellyfish species. C) the shared and unique counts of microbial families among different jellyfish samples at the family level.

(family level) constituted about 35.05% and 38.73%, respectively, in *R. esculentum* (Fig. 1D).

Microbial community diversity analysis. Alpha diversity measures the number of microbial species within an individual sample (species richness) and the proportion of each microbial species (evenness). Higher species richness indicates a greater variety of microbial species within a sample, while higher evenness signifies a more balanced proportion of each microbial species. Results from the Chao1 index indicated that *C. quinquecirrha* exhibited the highest microbial species richness, followed by *R. esculentum*, while *A. coerulea* and *P. camtschatica* showed similar and comparatively lower levels of microbial richness (Fig. 2A). However, considering the Shannon and Simpson indices, significant differences in diversity among the jellyfish groups were observed. Overall, microbial diversity was highest in *C. andromeda*, while *A. coerulea* displayed the lowest diversity when considering microbial richness and evenness together (Fig. 2B and 2C).

Beta diversity assesses differences in microbial community composition among different samples. Principal Component Analysis (PCA) demonstrates minimal differences in microbial community composition within the samples of *P. camtschatica* and *A. coerulea*. In con-

trast, other samples exhibited good similarity (Fig. 2D). Principal Coordinates Analysis (PCoA) and Non-Metric Multi-Dimensional Scaling (NMDS) based on Weighted UniFrac analysis revealed minimal variation in microbial community composition within *A. coerulea*, whereas *C. andromeda* exhibited the most significant differences in microbial community composition within its groups (Fig. 2E and 2F). This discrepancy in *C. andromeda* microbial diversity might contribute to these observed differences.

Analysis of microbial community differences. Beta diversity analysis revealed differences in microbial community composition within and among groups. Constructing an evolutionary branching diagram from phylum to family for the selected five microbial families showed their significant roles across the five jellyfish species, primarily classifying these important species at the family level (Fig. 3A). Moreover, the top 14 microbial families based on average relative abundance exhibited significant differences among the five jellyfish species (Fig. 3B). Results from random forest analysis emphasized the importance of five dominant families: *Mycoplasmataceae*, *Sphingomonadaceae*, *Alphaproteobacteria_unclassified*, *Parcubacteria_unclassified*, and *Chlamydiaceae*. Among these, *Mycoplasmataceae* and

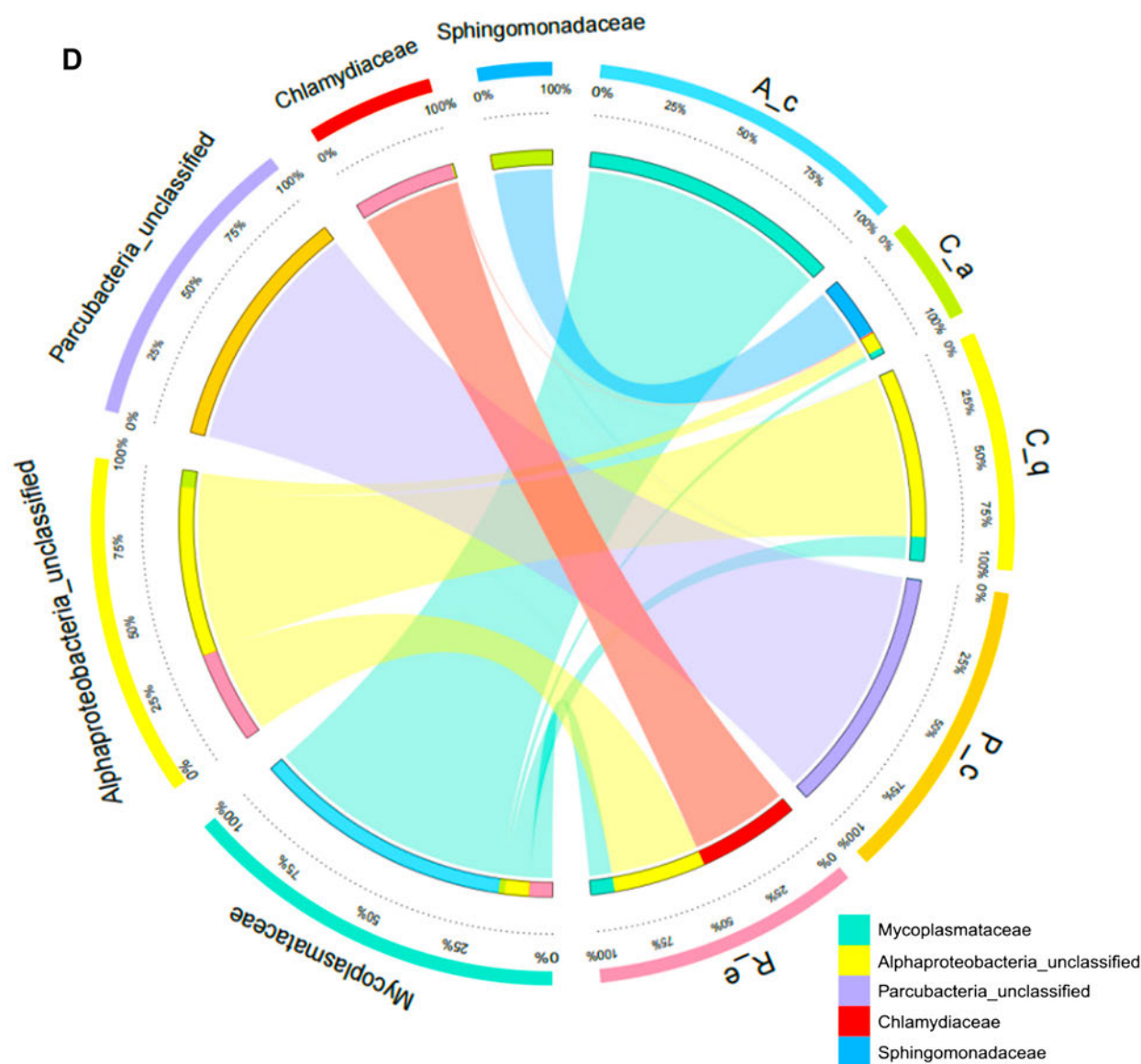


Fig. 1. Analysis of commensal microbial community compositions in five jellyfish species.
D) the Circos relationship diagram depicting the top commensal microbial families corresponding to different jellyfish species based on their abundance. We selected the top 30 bacteria with the highest abundance and drew these figures.

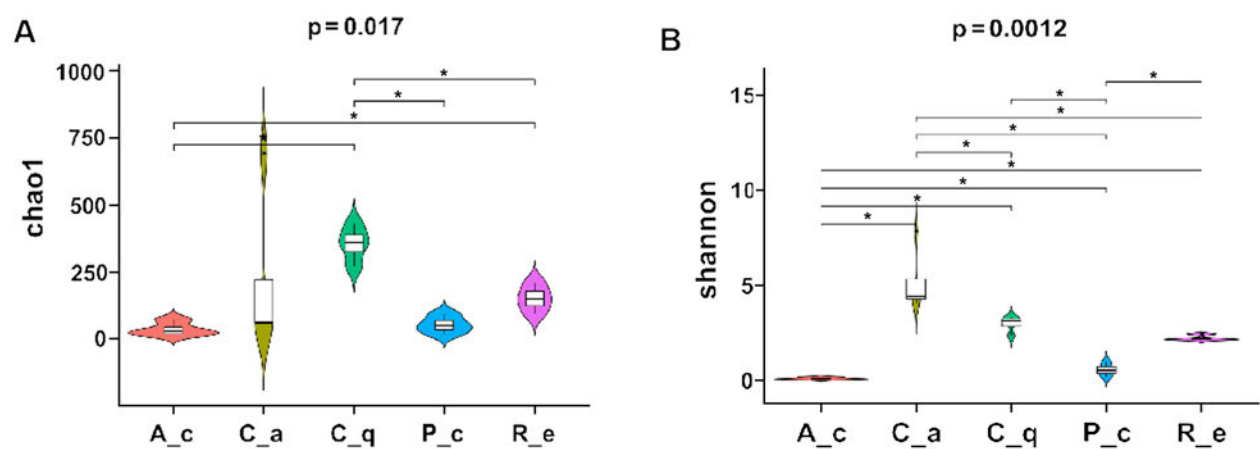


Fig. 2. Microbial community diversity analysis in five jellyfish species.
A) Alpha diversity based on the Chao1 index; B) alpha diversity based on the Shannon index.
* - $p < 0.05$, ** - $p < 0.01$

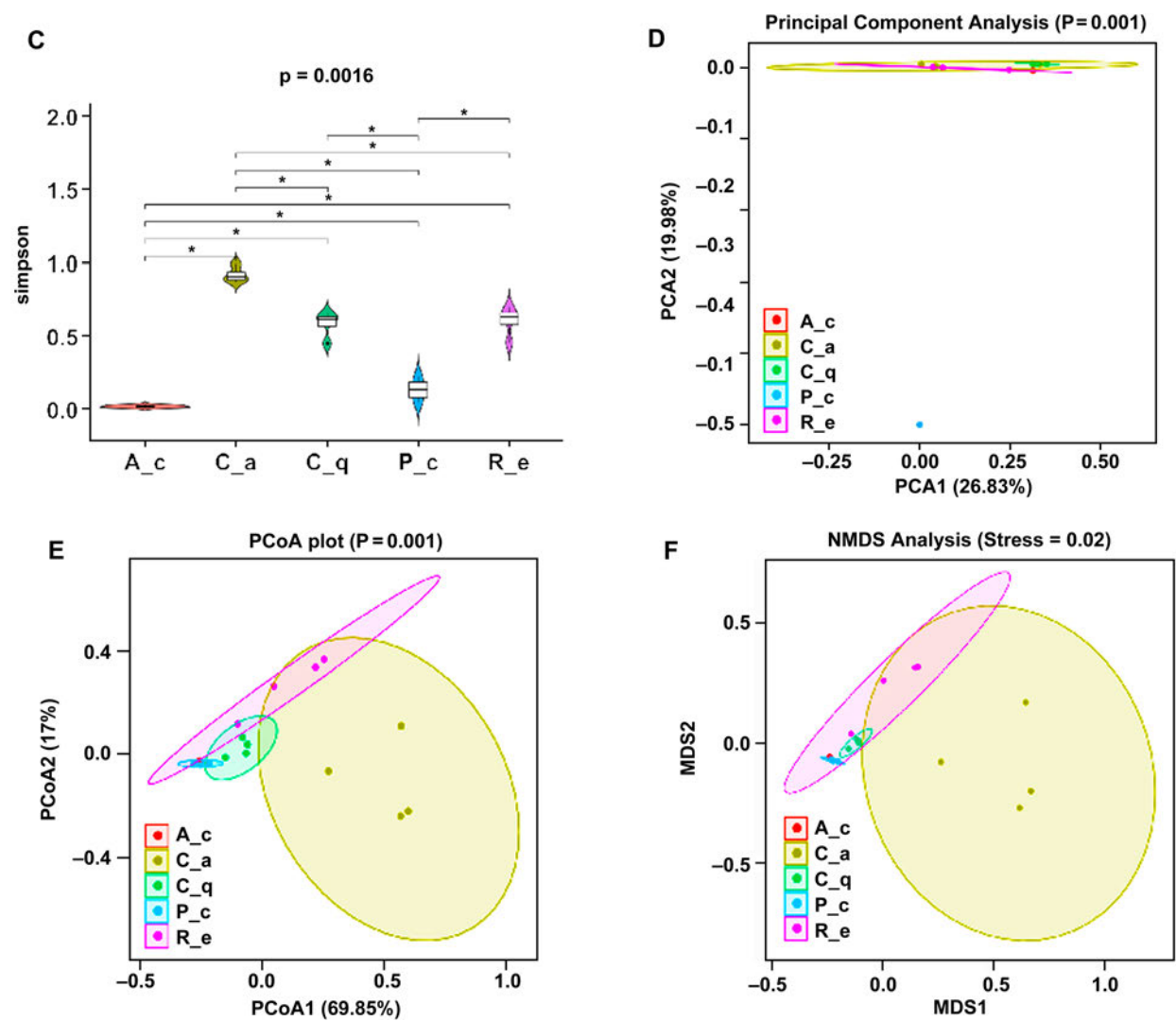


Fig. 2. Microbial community diversity analysis in five jellyfish species.
C) alpha diversity based on the Simpson index; D) within-group PCA analysis among different jellyfish species;
E) PCoA analysis among different jellyfish species; F) NMDS analysis among different jellyfish species.
* - $p < 0.05$, ** - $p < 0.01$

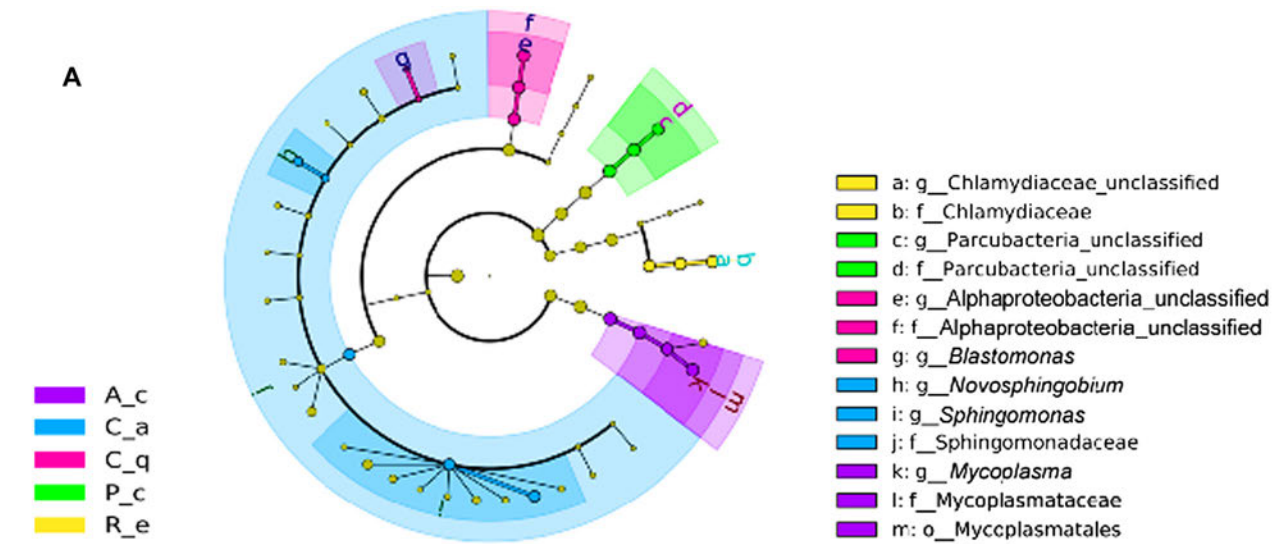


Fig. 3. Analysis of microbial community differences in the five jellyfish species.
A) Evolutionary branching of the most abundant commensal microbial species from the order to genera level across the five jellyfish species.

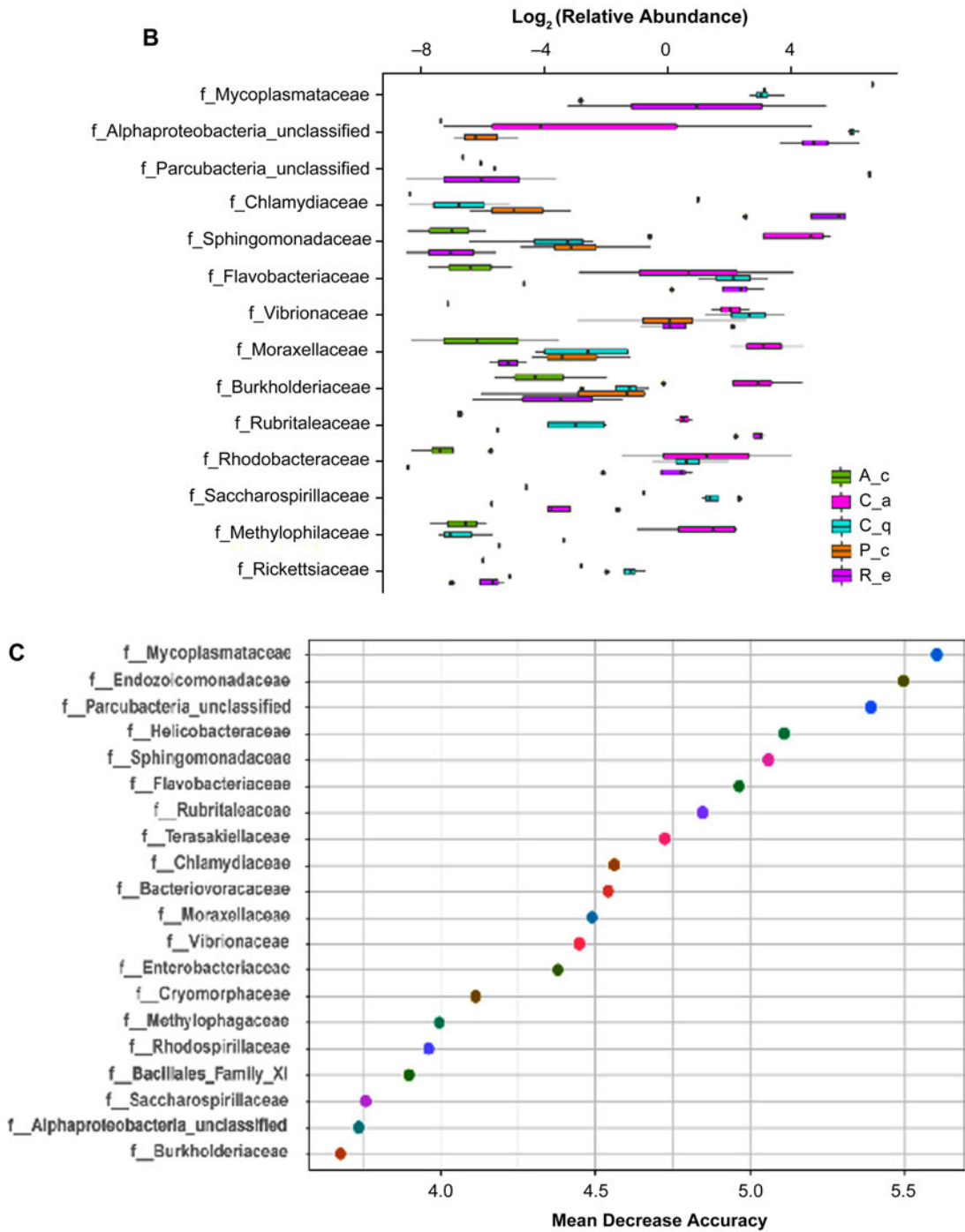


Fig. 3. Analysis of microbial community differences in the five jellyfish species.
B) comparative differences in relative abundance among the top 14 families of commensal microbes at the family level;
C) random forest analysis based on the mean decrease accuracy index.

Sphingomonadaceae appeared to play predominant roles based on their significance levels (Fig. 3C and 3D). Potential beneficial microbial families encompassed *Sphingomonadaceae*, *Endozoicomonadaceae* (Hochart et al. 2023), *Bacteriovoraceae*, *Rhodospirillaceae*, *Methylophagaceae*, *Burkholderiaceae*, while potential pathogenic microbial families comprised *Helicobacteraceae*, *Chlamydiaceae*, *Vibrionaceae*, *Enterobacteriaceae*, *Mycoplasmataceae*, *Cryomorphaceae*.

Microorganisms correlation analysis. *Alphaproteobacteria_unclassified*, *Parcubacteria_unclassified*, *Chlamydiaceae_unclassified*, *Sphingomonas*, and *Mycoplasma*, exhibited correlated microorganisms within their respective groups. These microorganisms also displayed inter-correlations, primarily negative, except for a non-significant positive correlation between *Alphaproteobacteria_unclassified* and *Chlamydiaceae_unclassified*. Among these, significant correlations existed between

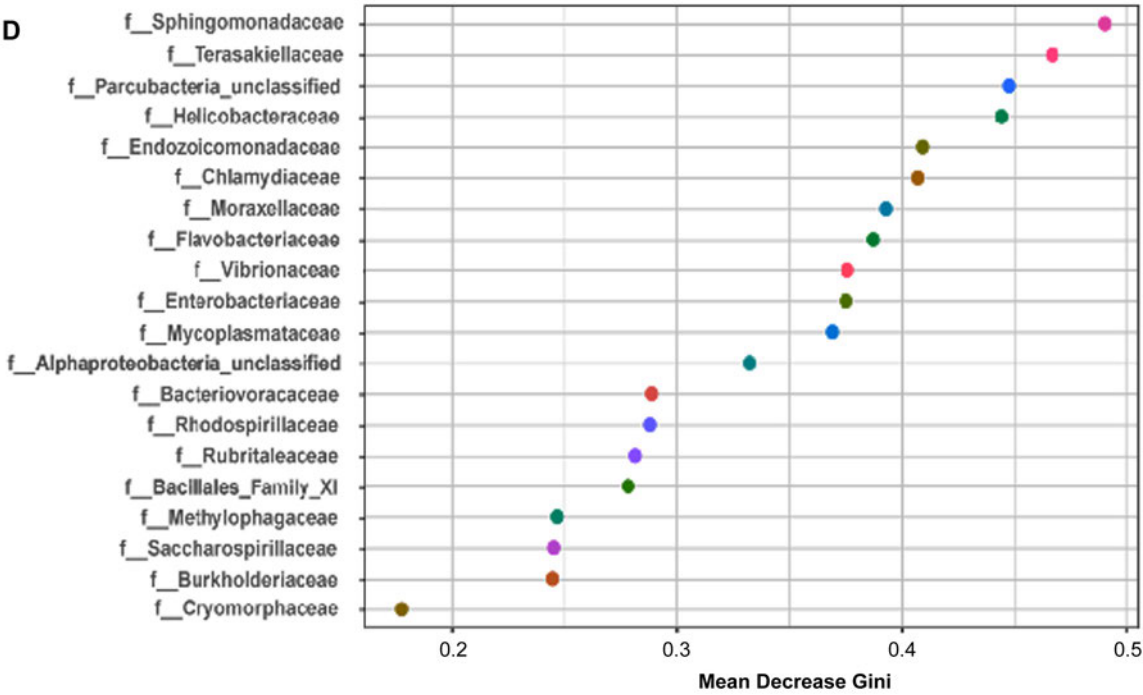


Fig. 3. Analysis of microbial community differences in the five jellyfish species.
D) random forest analysis based on the mean decrease Gini index. We selected the dominant bacteria and drew these figures.

Mycoplasma and *Alphaproteobacteria_unclassified*, as well as between *Sphingomonas* and *Mycoplasma*, with the negative correlation between *Mycoplasma* and *Alphaproteobacteria_unclassified* being notably pronounced. Furthermore, among these correlated microbes, potential pathogens included *Mycoplasma*, *Chlamydiaceae_unclassified*, *Vibrio*, *Acinetobacter*, and *Simkaniaceae_unclassified*, while the potentially beneficial microorganisms, *Sphingomonas*, stood out. Notably, the difference was most significant between *Mycoplasma* and *Acinetobacter*, demonstrating a positive correlation. *Sphingomonas*, a potentially beneficial genus, exhibited a positive correlation with the potentially pathogenic *Acinetobacter* but demonstrated negative correlations with other potential pathogens, mostly non-significant (refer to Fig. 4).

Environmental factor correlation analysis. This experiment's environmental factor analysis encompassed five species of jellyfish, examining the correlation between the top 10 abundant microbes categories from phylum to species levels and each jellyfish species. Most microorganisms demonstrated a negative correlation with *C. quinquecirrha*. However, microorganisms positively correlated with *C. quinquecirrha* were significantly influenced by *C. quinquecirrha*, resulting in lower sample similarity levels compared to other jellyfish. *A. coerulea* exhibited the highest sample similarity, with most commensal microorganisms displaying a negative correlation and experiencing minimal influence from *A. coerulea*.

A strong positive correlation was shown between *C. quinquecirrha* and the potential pathogens Proteobacteria but exhibited a negative correlation with other potential pathogens. Other jellyfish species displayed a lower positive correlation with other potential pathogens (Fig. 5A). A strong positive correlation was demonstrated between *C. quinquecirrha* and the potential pathogens belonging to the classes Gammaproteobacteria and Alphaproteobacteria, while a negative correlation was shown with other potential pathogens. Other jellyfish species displayed a lower positive correlation with other potential pathogens (Fig. 5B). At the order level, a strong positive correlation was exhibited with potential pathogens Vibrionales and Rickettsiales, while other jellyfish species showed a lower positive correlation with other potential pathogens (Fig. 5C). At the family level, a strong positive correlation was displayed between *C. quinquecirrha* with potential pathogen *Vibrionaceae*, whereas other jellyfish species exhibited a lower positive correlation with other potential pathogens (Fig. 5D). At the genus level, a strong positive correlation was showed between *C. quinquecirrha* with the potential pathogen *Vibrio*, whereas other jellyfish species exhibited a lower positive correlation with other potential pathogens (Fig. 5E). At the species level, a strong positive correlation was displayed between *C. quinquecirrha* with the potential pathogen *Vibrio* sp. PH1. Conversely, the potential pathogen uncultured *Vibrio* sp. exhibited a high negative correlation with all five jellyfish species, while other potential pathogens

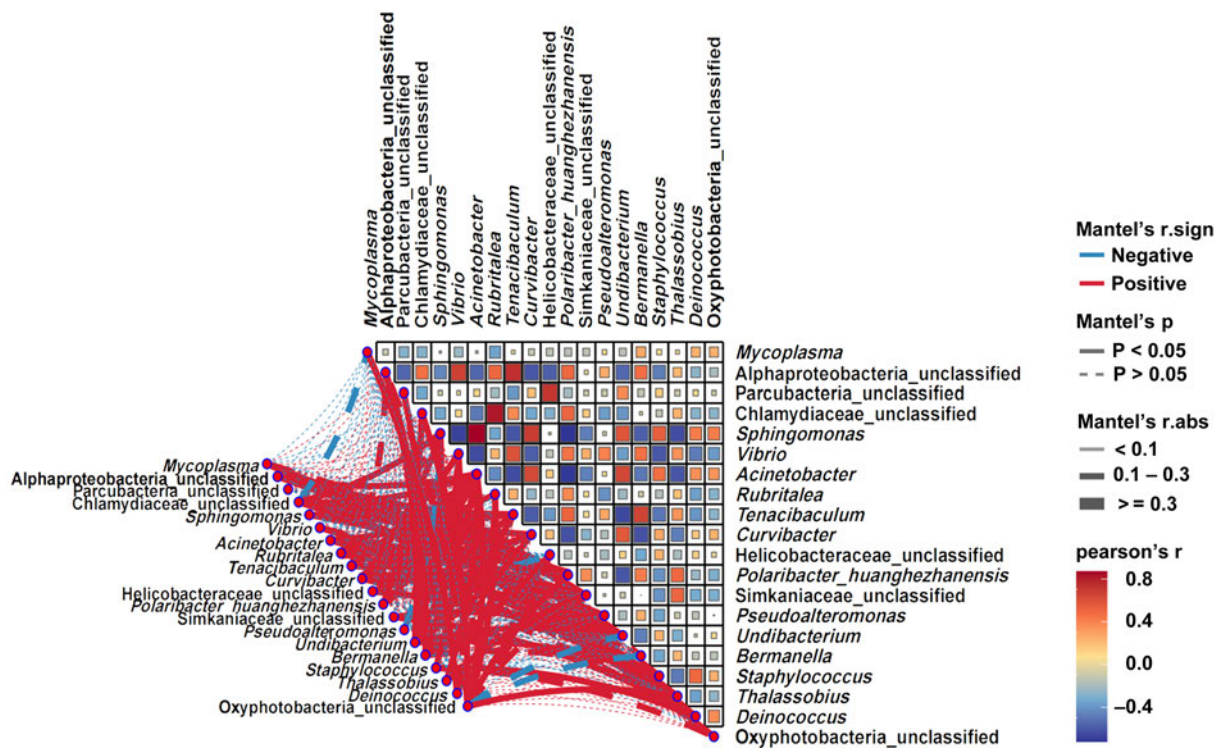


Fig. 4. The correlation network heatmap of commensal microbiota across the five species of jellyfish. (The red lines indicate positive correlations and blue lines for negative correlations). Solid lines represent significant differences, while dashed lines indicate non-significant differences. The thickness of the lines represents the relative abundance. We selected the top 20 bacteria and drew this figure.

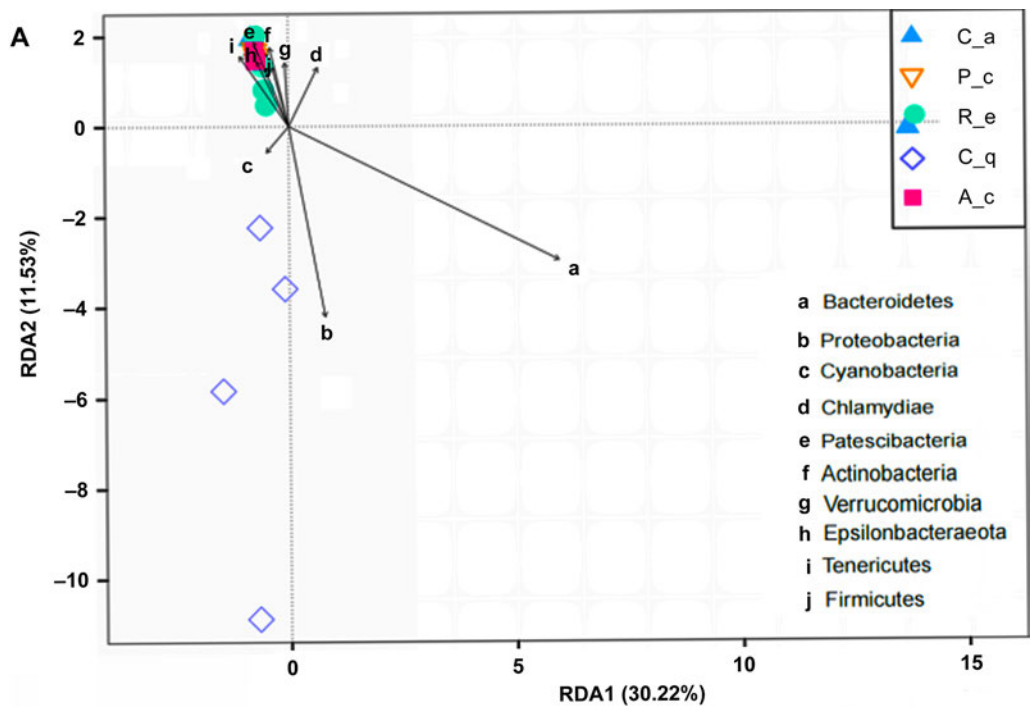
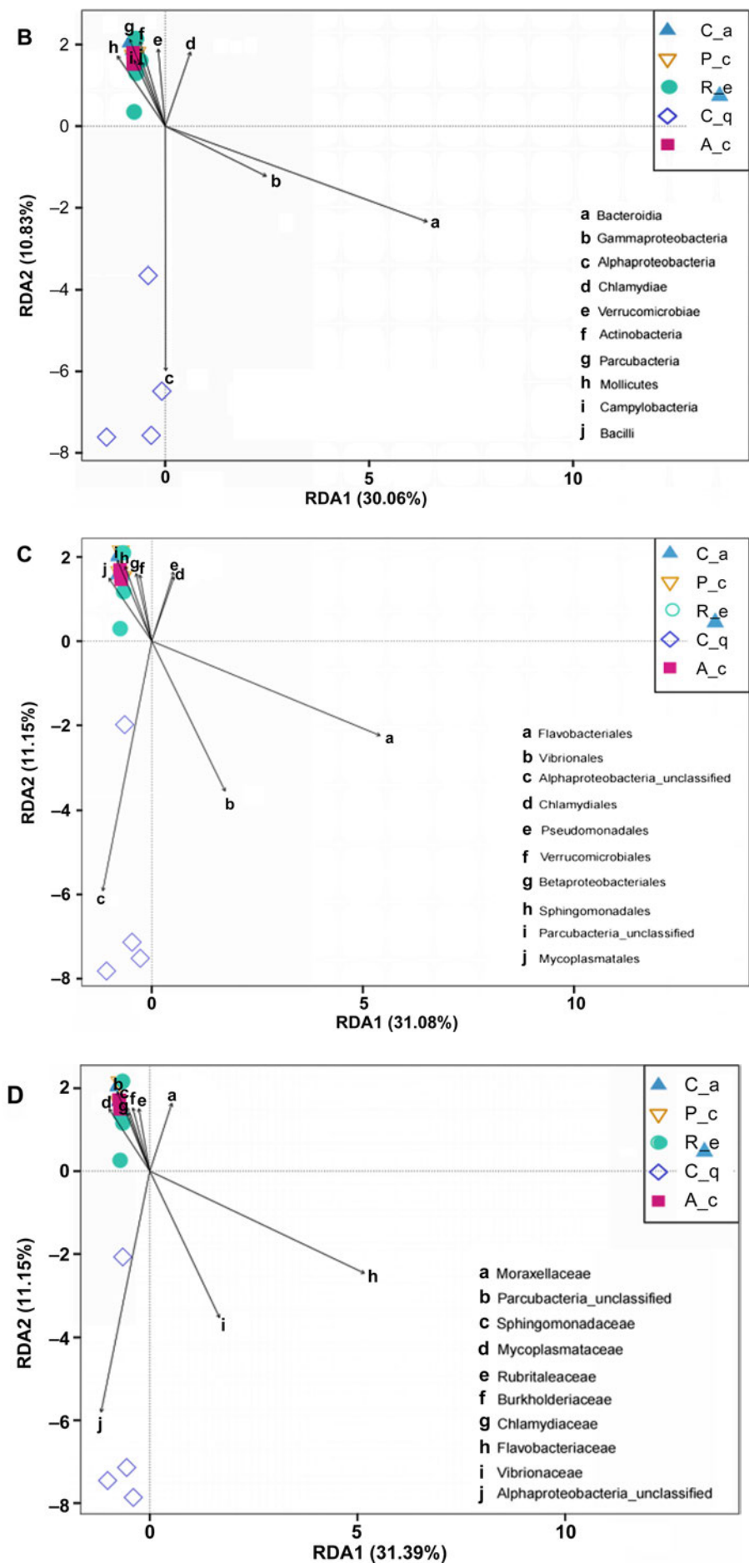


Fig. 5. Correlation analysis between the five jellyfish and their associated microbial communities. A-F) Correlation analysis between the associated jellyfish and microbial communities at different levels of taxonomical categories. RDA analysis was conducted using the top 10 abundant associated microbial communities across all samples.

showed a lower positive correlation with other jellyfish species (Fig. 5F).

Microbial community gene function prediction and screening for pathogenic and beneficial bacte-

ria. Five jellyfish species (*A. coerulea*, *C. andromeda*, *C. quinquecirrha*, *P. camtschatica*, and *R. esculentum*) were annotated with 466, 473, 1,082, 2,084, and 1,633 gene functions by 16S rRNA sequencing, respectively.



Among these, there were 62 genes shared among the five jellyfish (Fig. 6A). The expression levels of selected genes in the microbiota associated with *A. coerulea* were significantly lower than those in the other four jellyfish, especially in *C. andromeda* and *P. camtschatica*, where these genes were highly expressed. K03088, K01990, K01992, K06147, and K02003 exhibited relatively higher expression levels across the five jellyfish (Fig. 6B). We predicted the possible functions that microbial genes may carry based on KEGG (Table I).

According to the prediction of potential pathogenic bacterial phenotypes (Ward et al. 2017), *A. coerulea*,

C. quinquecirrha, and *P. camtschatica* showed higher pathogenic bacterial abundance compared to the other two jellyfish, with *R. esculentum* exhibiting the lowest pathogenic bacterial abundance (Fig. 6C). At the phylum level, the top five abundant potential pathogenic bacteria were Proteobacteria, Tenericutes, Chlamydiae, and Epsilonbacteraeota. The highest abundance of potentially pathogenic bacteria in *A. coerulea* was Tenericutes, in *P. camtschatica* was Epsilonbacteraeota, and in *R. esculentum* was Chlamydiae. The other two jellyfish showed the highest abundance of potentially pathogenic bacteria as Proteobacteria (Fig. 6D).

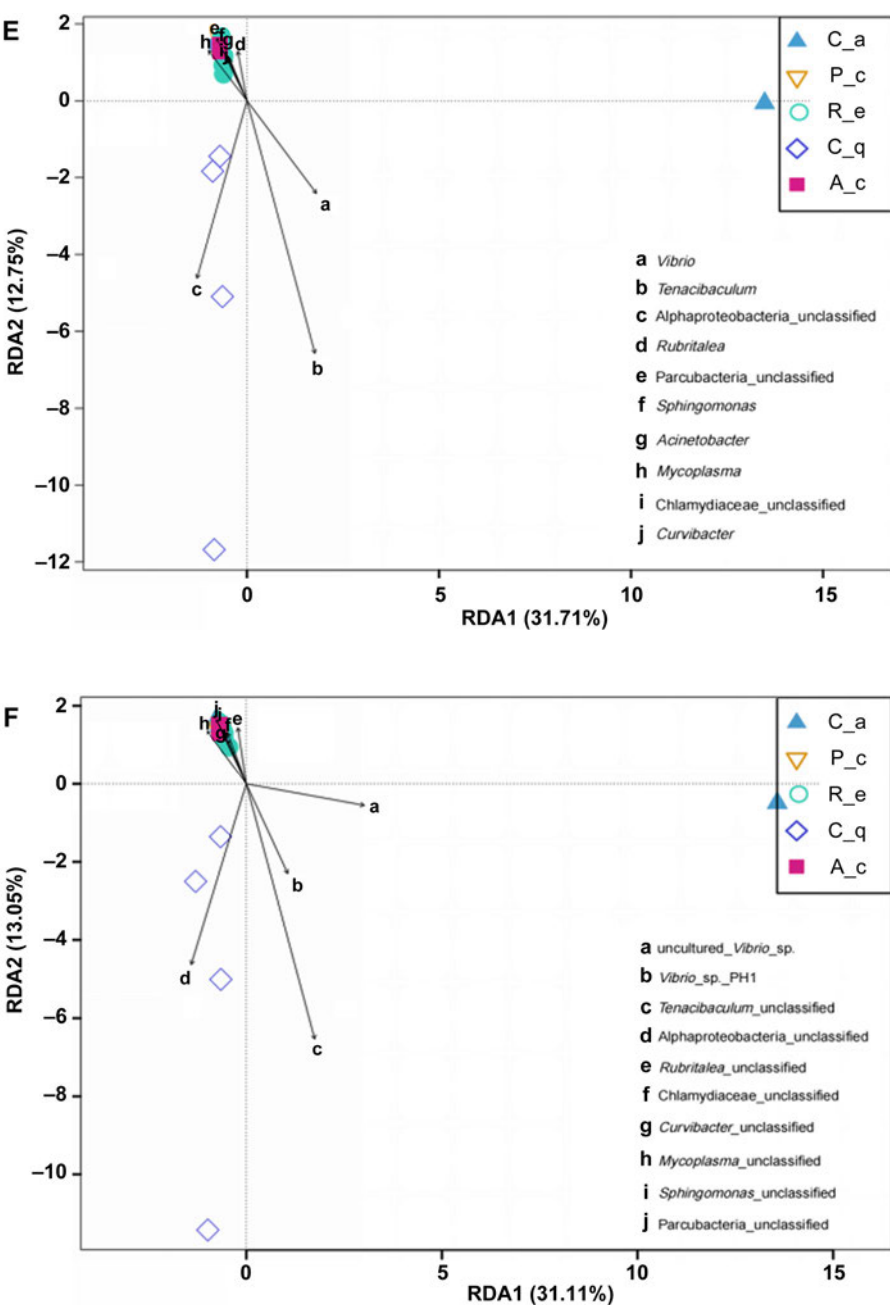


Fig. 5. Correlation analysis between the five jellyfish and their associated microbial communities. A-F) Correlation analysis between the associated jellyfish and microbial communities at different levels of taxonomical categories. RDA analysis was conducted using the top 10 abundant associated microbial communities across all samples.

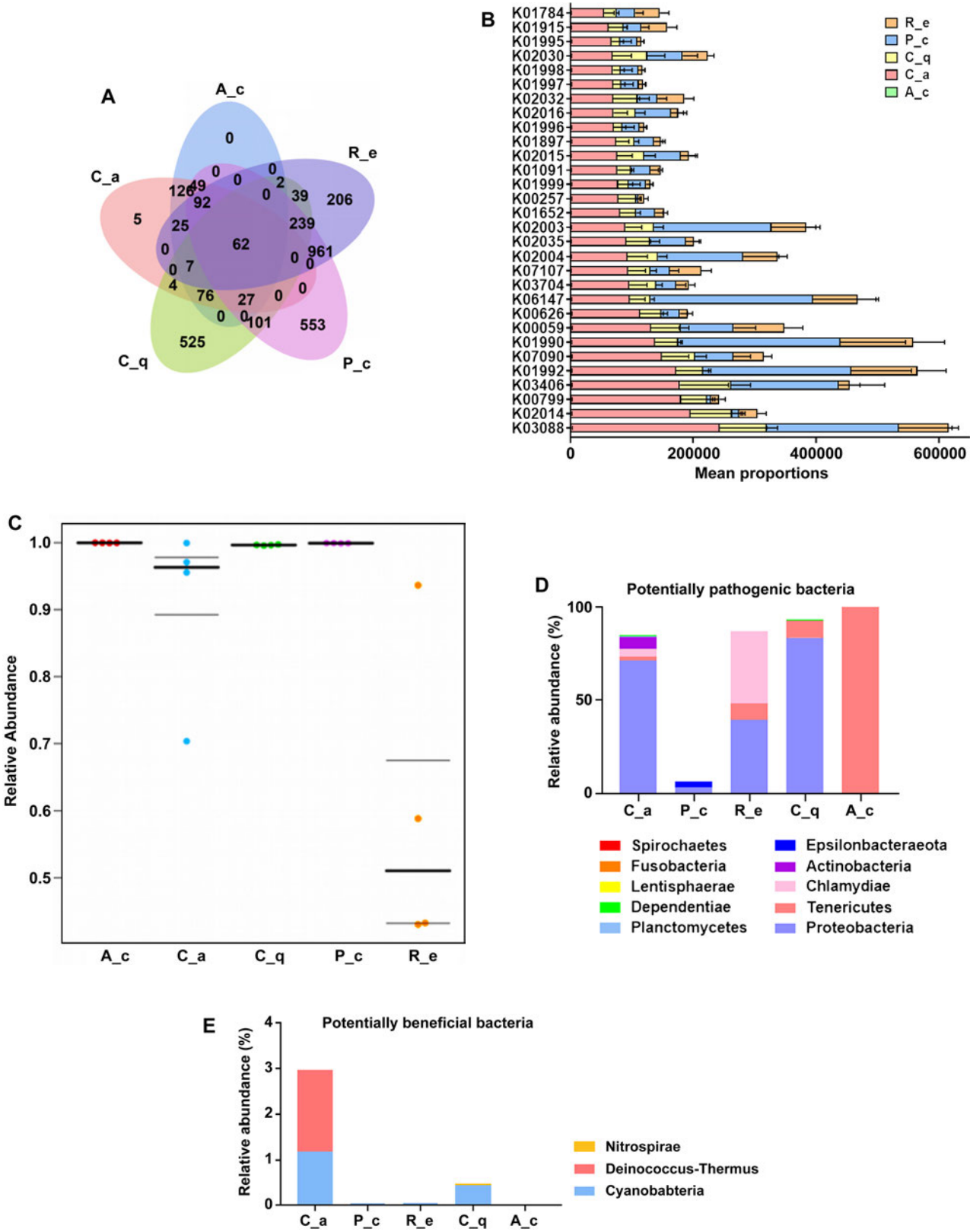


Fig. 6. Analysis of predicted gene functions and pathogenic phenotype prediction in microbial communities associated with five jellyfish species.

- A) Number of annotated genes unique and shared among different jellyfish samples;
B) predicted pathogenic phenotype in microbial communities associated with different jellyfish species;
C) differential analysis of predicted gene functions and metabolic pathways in microbial communities using STAMP analysis;
D) composition of potential pathogenic bacterial communities across different jellyfish samples;
E) composition of potential beneficial bacterial communities across different jellyfish samples.

We selected the dominant bacteria and the top 30 genes with total expression levels from shared expression genes to draw these figures.

Table I
Gene annotation and enriched pathways.

Entry	Symbol	Name	Pathway or Brite
K00059	FabG, OAR1	3-oxoacyl-acyl carrier protein reductase	fatty acid biosynthesis, prodigiosin biosynthesis, biotin metabolism, metabolic pathways, biosynthesis of secondary metabolites, fatty acid metabolism, biosynthesis of cofactors
K00257	mbtN, fadE14	acyl-acyl carrier protein dehydrogenase	unclassified: metabolism
K00626	ACAT, atoB	acetyl-CoA C-acetyltransferase	fatty acid degradation, valine, leucine and isoleucine degradation, lysine degradation, benzoate degradation, tryptophan metabolism, pyruvate metabolism, glyoxylate and dicarboxylate metabolism, butanoate metabolism, carbon fixation pathways in prokaryotes, terpenoid backbone biosynthesis, metabolic pathways, biosynthesis of secondary metabolites, microbial metabolism in diverse environments, carbon metabolism, fatty acid metabolism, two-component system, fat digestion and absorption
K00799	GST, gst	glutathione S-transferase	glutathione metabolism, metabolism of xenobiotics by cytochrome P450, drug metabolism-cytochrome P450, drug metabolism-other enzymes, metabolic pathways, platinum drug resistance, longevity regulating pathway-worm, pathways in cancer, chemical carcinogenesis-DNA adducts, chemical carcinogenesis-receptor activation, chemical carcinogenesis-reactive oxygen species, hepatocellular carcinoma, fluid shear stress and atherosclerosis
K01091	gph	phosphoglycolate phosphatase	glyoxylate and dicarboxylate metabolism, metabolic pathways, biosynthesis of secondary metabolites
K01652	ilvB, ilvG, ilvI	acetolactatesynthase I/II/III large subunit	valine, leucine and isoleucine biosynthesis, Butanoate metabolism, C5-branched dibasic acid metabolism, pantothenate and CoA biosynthesis, metabolic pathways, biosynthesis of secondary metabolites, 2-oxocarboxylic acid metabolism, biosynthesis of amino acids
K01784	galE, GALE	UDP-glucose4-epimerase	galactose metabolism, amino sugar and nucleotide sugar metabolism, O-antigen nucleotide sugar biosynthesis, metabolic pathways, biosynthesis of nucleotide sugars
K01897	ACSL, fadD	long-chain acyl-CoA synthetase	fatty acid biosynthesis, fatty acid degradation, metabolic pathways, fatty acid metabolism, quorum sensing, PPAR signaling pathway, peroxisome, ferroptosis, thermogenesis, adipocytokine signaling pathway
K01915	glnA, GLUL	glutamine synthetase	arginine biosynthesis, alanine, aspartate and glutamate metabolism, glyoxylate and dicarboxylate metabolism, nitrogen metabolism, metabolic pathways, microbial metabolism in diverse environments, biosynthesis of amino acids, two-component system, necroptosis, glutamatergic synapse, GABAergic synapse
K01990	ABC-2.A	ABC-2 type transport system ATP-binding protein	ABC transporters
K01992	ABC-2.P	ABC-2 type transport system permease protein	ABC transporters
K01995	livG	branched-chain amino acid transport system ATP-binding protein	ABC transporters, quorum sensing
K01996	livF	branched-chain amino acid transport system ATP-binding protein	ABC transporters, quorum sensing
K01997	livH	branched-chain amino acid transport system permease protein	ABC transporters, quorum sensing
K01998	livM	branched-chain amino acid transport system permease protein	ABC transporters, quorum sensing

Table I – Continued
Gene annotation and enriched pathways.

Entry	Symbol	Name	Pathway or Brite
K01999	livK	branched-chain amino acid transport system substrate-binding protein	ABC transporters, quorum sensing
K02003	ABC.CD.A	putative ABC transport system ATP-binding protein	ABC transporters
K02004	ABC.CD.P	putative ABC transport system permease protein	ABC transporters
K02014	TC.FEV.OM	iron complex outermembrane receptor protein	other transporters
K02015	ABC.FEV.P	iron complex transport system permease protein	ABC transporters
K02016	ABC.FEV.S	iron complex transport system substrate-binding protein	ABC transporters
K02030	ABC.PA.S	polar amino acid transport system substrate-binding protein	ABC transporters
K02032	ABC.PE.A1	peptide/nickel transport system ATP-binding protein	ABC transporters
K02035	ABC.PE.S	peptide/nickel transport system substrate-binding protein	ABC transporters
K03088	rpoE	RNA polymerase sigma-70 factor, ECF subfamily	transcription machinery (bacterial type)
K03406	mcp	methyl-accepting chemotaxis protein	two-component system, bacterial chemotaxis
K03704	cspA	cold shock protein (beta-ribbon, CspA family)	unclassified
K06147	ABCB-BAC	ATP-binding cassette, subfamily B, bacterial	ABC transporters
K07090	uncharacterized protein	uncharacterized protein	unclassified
K07107	ybgC	acyl-CoA thioester hydrolase	unclassified: metabolism

Table information reference from <https://www.genome.jp/kegg/>

Conversely, potentially beneficial bacteria only encompassed three phyla: Cyanobacteria, Deinococcus-Thermus, and Nitrospirae, primarily associated with *C. andromeda* and *C. quinquecirrha* (Fig. 6E). Overall, the relative abundance of potentially beneficial bacteria was considerably lower than that of potentially pathogenic bacteria.

Discussion

Composition of microbial communities associated with jellyfish and their influencing factors. The microbial communities associated with different jellyfish species and various parts of the jellyfish themselves exhibited differences in composition, species richness, and diversity (Kos Kramar et al. 2019; Liu et al. 2019). Liu et al. (2019) found that among four jellyfish species, *Phyllorhiza punctata*, *Cyanea capillata*, *Chrysaora melanaster*, and *Aurelia coerulea*, the relatively abundant top five families of microorganisms were *Staphylococcaceae*,

Mycoplasmataceae, *Moraxellaceae*, *Pseudomonadaceae*, and *Brucellaceae*. In our study, the five predominant microbial families were *Mycoplasmataceae*, *Sphingomonadaceae*, *Alphaproteobacteria_unclassified*, *Chlamydiaceae*, and *Parcubacteria_unclassified* within the five jellyfish species. A comparison of these two results reveals significant differences in the composition and abundance of associated microorganisms within jellyfish species, indicating that jellyfish species may be a critical factor determining the composition of commensal microorganisms, which is also identical with the results reported by Peng et al. (2023) On the other hand, alterations in the jellyfish community structure, particularly during jellyfish blooms, severely impact coastal facilities and marine ecosystems (Purcell et al. 2007; Fu et al. 2014). Consequently, the microbial communities associated with jellyfish undergo changes accordingly (Basso et al. 2019; Kos Kramar et al. 2019). Furthermore, variations in water quality conditions, such as fluctuations in temperature and salinity, also influence the abundance of marine microorganisms (Kim et al. 2023),

subsequently affecting the composition and abundance of microorganisms associated with the jellyfish.

Significant roles of commensal microorganisms in jellyfish life processes. Over the past few decades, research on pathogenic bacteria within marine microorganisms has increased (Little et al. 2020), exerting significant impacts on the stability of marine ecosystems and the regulation of jellyfish populations. Commensal microorganisms can influence jellyfish life cycle and growth. The absence of microbial communities reduced the number of early-stage ephyra in *A. coerulea* metamorphosis, while resettlement of microbial communities could restore their numbers (Peng et al. 2023). Weiland-Bräuer et al. (2020) also found that the native microbiome was crucial for offspring generation and fitness of *Aurelia aurita*. Additionally, metabolites from commensal microorganisms assist jellyfish in waste degradation, immune system enhancement, and food digestion. For instance, during the later stages of organic matter breakdown in jellyfish, the dominance of *Vibrionaceae* and *Alteromonadaceae* may aid in the accumulation of organic nitrogen compounds and inorganic nutrients during jellyfish dissolution (Tinta et al. 2023). Notably, *Vibrionaceae*, especially in *C. quinquecirrha*, exhibit a high relevance, suggesting a potentially crucial role in the life processes of *C. quinquecirrha*. Despite numerous studies on marine microbial metabolites, our understanding of the synthesis pathways and functions of commensal microbial products in jellyfish remains limited. In corals, metabolites from beneficial microorganisms provide nutrition, promote growth, and inhibit some pathogens, contributing to the balance and restoration of marine ecosystems (Peixoto et al. 2021). Two bacterial genera, *Polaribacter* and *Psychrobacter*, which produce physiologically active diketopiperazines, polyhydroxybutyrate salts (PHBs), bile acids, and other beneficial metabolites (Oppong-Danquah et al. 2023), are also present within the studied five jellyfish species. The products of these beneficial bacterial communities can serve as antibiotic alternatives, combating pathogens and protecting hosts from harm (Banerjee et al. 2007; Badhul Haq et al. 2012; Grotkjær et al. 2016). Therefore, the antagonistic effects of beneficial commensal microbes with jellyfish offer a promising approach for eradicating pathogenic microbes in aquatic environments.

On the contrary, potential pathogenic commensal microorganisms with jellyfish may exert detrimental effects, leading to diseases. In this study, potentially pathogenic bacteria were screened, including *Helicobacteraceae*, *Chlamydiaceae*, *Vibrionaceae*, *Enterobacteriaceae*, *Mycoplasmataceae*, and *Cryomorphaceae*. *Vibrio splendidus* and *Vibrio neptunius* from *Vibrionaceae* can cause umbrella tissue lysis in reared *A. aurita* (Chi et al. 2018). The combination of other pollutants

and pathogens in the ocean intensifies the threat to jellyfish. For instance, widespread microplastics in marine environments readily adhere to various microorganisms, including pathogens (Sun et al. 2023), and can easily attach to the jellyfish mucus containing a glycoprotein, potentially infecting the jellyfish (Ben-David et al. 2023). The presence of pathogenic microbes within jellyfish may affect their growth, survival rates, and the health of predators, consequently disrupting the marine food chain and ecological balance. When numerous environmental pathogens are present, they could doubly impact near-shore aquaculture during jellyfish blooms (Clinton et al. 2020). Accumulation of pathogenic microorganisms within jellyfish triggers specific defense mechanisms, which is significant for studying jellyfish immune mechanisms (Weiland-Bräuer et al. 2019).

In addition, the symbiotic microorganisms associated with jellyfish have certain potential for biotechnology utilization. Specifically, bioremediation: some microorganisms associated with jellyfish may have unique abilities to degrade pollutants or decompose organic matter. Biopharmaceuticals: microorganisms associated with jellyfish may produce bioactive compounds with potential medicinal applications. Biotechnology experts can separate and characterize these compounds for drug development. Enzyme production: some microorganisms associated with jellyfish may produce enzymes with special functions. Probiotics: although microorganisms associated with jellyfish may include pathogens, they may also contain beneficial microorganisms used to improve intestinal health or enhance immune function in humans or other animals (Dong and Shang 2021).

Jellyfish provide a suitable substrate for the growth and metabolism of bacteria; for example, jellyfish mucus is rich in proteins and lipids, providing high-quality energy for bacteria. Bacteria associated with jellyfish are involved in the carbon-nitrogen, sulfur, and phosphorus cycling (Lee et al. 2018), indicating a symbiotic relationship. Proteobacteria can participate in the synthesis and metabolism of a variety of biomolecules, such as *Kiloniellaceae*, which are producers of antibiotic compounds (Wiese et al. 2009). It has been shown that *Tenericutes* is a potential endosymbiotic bacterium in jellyfish (Weiland-Bräuer et al. 2015). *Chlamydiae* are intracellular bacteria with potential pathogenic ability that threatens human health because of the lack of effective vaccines (Elwell et al. 2016). As photosynthetic microorganisms, Cyanobacteria provide nutrients for both themselves and their hosts (Mulikidjanian et al. 2006).

Our data also includes related gene expressions. The gene expression of substrate transport systems can reveal how bacteria meet their growth and metabolic needs by acquiring nutrients provided by jellyfish. At

the same time, they may reflect the nutrient acquisition strategies of bacteria within jellyfish, as well as their symbiotic or competitive ways (Onyeabor et al. 2020) with jellyfish. The expression of perceptive and adaptive genes, such as methyl receptive chemotactic proteins and CspA family proteins (Yamanaka et al. 1998), may demonstrate how bacteria perceive and adapt to chemical signals and temperature changes in jellyfish. The expression patterns of these genes may reflect bacterial responses to jellyfish immune systems, physiological conditions, and competition with other bacteria. Transcriptional regulation of gene expression, such as RNA polymerase sigma factor (Campbell et al. 2008) expression, can reveal how bacteria regulate gene transcription in jellyfish to adapt to different external signals and environmental conditions. The expression of antioxidant and detoxification genes, such as coacyl-CoA thioester hydrolase genes (Black et al. 2000), may reflect the ability of bacteria to cope with internal oxidative stress and toxin loading in jellyfish. The expression patterns of these genes can reveal how bacteria respond to host immune system attacks or other environmental pressures. In summary, the expression patterns of these genes can provide insights into the survival of bacteria in jellyfish and their interactions with them, thereby helping to understand the dynamics and complexity of the symbiotic relationship between jellyfish and microorganisms.

Potential health impacts of commensal microorganisms. Jellyfish blooms are frequent and widespread in recent years, and jellyfish may act as vectors of bacterial pathogens in coastal areas, responsible for severe gill diseases of farmed fish (Ferguson et al. 2010; Stabili et al. 2020). Wound infection may occur in the victims stung by box jellyfish (Thaïkruea and Siririyaporn 2015; Thaïkruea 2023). Marine *Vibrionaceae*, as a main potential pathogenic microbial family found in our study, was reported to cause severe necrotizing fasciitis of the extremities and diarrhea in patients (Jiang 1991; Joynt et al. 1999). Changes in the abundance or location of these potentially pathogenic bacteria may influence the health status of humans and also of marine organisms. Further studies are needed on this issue. In addition, due to the accumulation of certain pathogenic bacteria in the body of some edible jellyfish, there is a risk of infection when consumed by humans without proper cooking, which has potential negative impacts on human health (FAO 2022).

Due to the lack of commensal microbial community genome data, this study does not systematically explore how the imbalance of commensal microbial communities affects the host. To expand this research, subsequent studies could employ metagenomics and metatranscriptomics to determine the genomic composition and expression data of commensal micro-

bial communities (Segata et al. 2011; Douglas et al. 2019), thereby accurately investigating the potential mechanisms by which commensal microbial communities affect hosts (Oppong-Danquah et al. 2023). Conducting metabolomic profiling and studying the metabolites and antibacterial activity of microorganisms will be crucial. Metabolites represent one of the primary means through which commensal microbial communities influence hosts. Associating commensal microbial community data with metabolomic data will facilitate a multidimensional explanation of the interaction between commensal microbial communities and hosts. Conducting causal validation experiments by transplanting commensal microbial communities into germ-free mice to verify phenotypic changes would directly demonstrate the causal relationship between commensal microbial communities and diseases.

Ethical statement

The experimental animals in this study did not involve ethical review.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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