
Fish gut microbiota: a source of novel metabolites – A review article

Jisha, K.¹, Gayathri, G.¹, Gopikrishnan, V.², Song, J. J.³, Soyong, K.³ and Prabha, T. R.^{4*}

¹Department of Microbiology, Vels Institute of Science, Technology and Advanced Studies, Chennai- 600117, Tamil Nādu, India; ²Centre for Drug Discovery and Development, Sathyabama Institute of Science and Technology, Chennai- 600119, Tamil Nādu, India; ³Research Institute of Modern Organic Agriculture (RIMO), Faculty of Agricultural Technology, King Mongkut's Institute of Technology, Ladkrabang (KMITL), Bangkok, Thailand; ⁴Department of Biotechnology, Indian Institute of Technology Madras (IIT M), Chennai-600036, Tamil Nādu, India.

Jisha, K., Gayathri, G., Gopikrishnan, V., Song, J. J., Soyong, K. and Prabha T. R. (2023). Fish gut microbiota: a source of novel metabolites – A review article. *International Journal of Agricultural Technology* 19(2):459-474.

Abstract Similar to human beings, fish harbor microorganisms in their gastrointestinal tract (GIT). Fishes are diverse groups of gut microbiota, including protists, fungi, yeasts, viruses, bacteria, and archaea. In addition to serving as a barrier against infections, these microbes that inhabit the gastrointestinal tract of fish play a role in nutrition, physiology, immunity, and life span. All fish have gut microbiota; however, the makeup of these communities varies depending on the fish's life stages, the habitat they live in, their nutrition, the seasons, their trophic level, etc. For both recreational and commercial fisheries, it is crucial to comprehend the bacterial make-up of fish microbiomes. The gut microbiota aids in the development of methods for modifying the gut microbiota of the target fish species to enhance aquaculture quality. These gut microbes are an invaluable, essential source of novel, promising bioactive compounds with significant biological activity. The natural product secondary metabolites from specific strains of *Chaetomium* spp. may develop to be biomedicine for sustainable protection. This review provides a comprehensive knowledge of the composition of the gut microbiota of fish, their development, changes in the living environment, their modification, and their applications.

Keywords: Fish gut, Microbiota, Probiotic, Prebiotic, Synbiotic, Secondary metabolite

Introduction

Fish make up approximately half of all vertebrate varieties. There are over 34,000 different species of fish known. They play a significant role in aquatic systems. (Johny *et al.*, 2021, Kim *et al.*, 2021). Fish is the primary source of protein for humans across many regions of the globe. This is

* **Corresponding Author:** Prabha, T. R.; **Email:** drtrprabha@gmail.com

especially true in the majority of developing countries (Latha and Mohan 2013). Fish and other aquatic animals have a special and closely relationship with their surroundings and the microorganisms that live there. Microorganisms abound in the world's oceans According to studies, 3.6×10^{30} microbial cells account for more than 90% of all oceanic biomass. Fish can have a mutualistic or pathogenic relationship with the microorganisms in their environment (Gómez and Balcazar 2008; Sullam *et al.*, 2012). According to various research findings, microorganisms inhabit the digestive tract, gills, skin, and organs that emit light. Additionally, bacteria may be present in the fish internal organs like the liver, kidney, and spleen (Austin, 2002). The microbiota in the fish gut forms an intricate environment with a diverse spectrum of species. The habitat environment, together with other elements including the developmental stage, season, nutritional status, host genetics, and diet composition, has the potential to have a substantial impact on the microbiota (Kim *et al.*, 2021). Early in the 1930s, researchers started studying the fish gut and skin microbial communities to learn more about these intricate bacteria (Uma *et al.*, 2020). Previously, fish were found to have a small number of bacteria in their stomachs, which were thought to be from their environment or nutrition (Cahill, 1990; Ringø *et al.*, 1995). These conclusions were established after conducting experiments using culture-dependent methodologies. However, we now realize that in the laboratory conditions used at the time, only 10% of microbes might be isolated and cultured (Amann *et al.*, 1995). Since then, scientific methods have greatly improved, and today it is believed that cultivable bacteria make up less than 0.1% of the whole microbial population in the GIT of various fish species (Zhou *et al.*, 2014). Nevertheless, numerous current researchers continue to publish findings from culture-based methods, extrapolating microbiota function from information gathered from investigations of the growth of bacteria carried out in laboratory environments (Clements *et al.*, 2014).

For the analysis of fish microbiota, a broad range of culture-independent approaches are now accessible. They include clone libraries, quantitative real-time PCR (qPCR), finger-printing methods such as denaturing gradient gel electrophoresis (DGGE) and temporal temperature gradient electrophoresis (TTGE), and fluorescent in situ hybridization (FISH). These techniques are employed to ascertain the composition of the microbiota, measure overall microbial levels, quantitatively analyze taxa, ascertain the frequency of specific taxa, and assess host-bacterial relationships along the brush border mucosa (Zhou *et al.*, 2014; Wang *et al.*, 2018). The most recent molecular analysis technique, known as next-generation sequencing (NGS), is more routinely utilized in fish investigations. Over the past few decades, studies on fish gut microbiota have significantly risen as a result of the advancement of such

breakthrough molecular technologies and the explosive expansion of aquaculture. The fish gut microbiota is vital to the host survival since it actively participates in the metabolism of nutrients, the prevention of possible infections, and the immune system strengthening (Larsen *et al.*, 2015). More recent studies have shown that the bacteria found in fish guts are a promising source of enzymes, secondary metabolites, and aquaculture probiotics (Vignesh *et al.*, 2019).

Development of fish gut microbiota

The intestinal microbiota of fish may originate from a variety of sources. It is commonly acknowledged that bacterial colonization mechanisms throughout the initial phases of larval fish development are complicated and reliant on the microbiota of eggs, the water used for larval rearing, and feeding habits. The original invading bacteria are now known to be species-specific, with variations in the glycoproteins present on the egg surface controlling variances (Larsen, 2014). Additionally, the microbial population of the water in the area determines which bacteria come into contact with the eggs and have a chance to colonize them. When sterile larvae hatch, they consume the chorion-associated bacteria, which are the first organisms to inhabit the developing GIT (Egerton *et al.*, 2018). The gastrointestinal tract of the freshly hatched larvae frequently has a few microorganisms in it. When fish larvae start drinking water to regulate their osmoregulation, they acquire subsequent bacterial habitats for the first time. Through feeding, the microbiota then diversifies even more. (Hansen and Olafsen, 1999).

Composition of fish gut microbiota

Fishes are a diverse group of gut microbiota, including protists, fungi, yeasts, viruses, bacteria, and archaea. However, the majority of the microbial community in the gut of fish is composed of bacteria and has so far been mainly studied in this area (Egerton *et al.*, 2018). In contrast to terrestrial vertebrates, fish have obligate anaerobes, facultative anaerobes, and aerobic bacteria as the main colonizers of the GIT (Llewellyn *et al.*, 2014). According to research, the fish gut contains between 10^7 and 10^{11} microorganisms per g^{-1} of intestinal material (Nayak, 2010). Proteobacteria, Firmicutes, Actinobacteria, Fusobacteria, Bacteroidetes, and Verrucomicrobia are some of the bacteria that inhabit the fish GIT, according to studies using NGS (Ringø *et al.* 2006; Desai *et al.*, 2012; Li *et al.*, 2013; Carda-Dieguez *et al.*, 2014). The most prevalent phyla of these are Proteobacteria,

Actinobacteria, Bacteroidetes, Firmicutes, and Fusobacterium (Figure 1). The majority of the microbiota in marine fish is composed of facultative anaerobes, including *Vibrio*, *Acinetobacter*, *Pseudomonas*, *Corynebacterium*, *Flavobacterium*, *Micrococcus*, and *Alteromonas*. Contrarily, *Aeromonas*, *Pseudomonas*, and Bacteroides type A predominate in the microbial community of species of freshwater fish, while Enterobacteriaceae: *Plesiomonas*, *Micrococcus*, *Clostridium*, *Acinetobacter*, Bacteroides type B, and *Fusarium* are less common species. (Wang *et al.*, 2018). Thirteen samples of fish from four different species in the Antarctic were studied for their fish gut microbiota, which was identified into 804 genera and 36 phyla. *Proteobacteria*, *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* are found to be the most prevalent phyla, and *Rhodococcus*, *Acinetobacter*, *Thermus*, *Mycoplasma*, *Propionibacterium*, and *Streptococcus* have also encountered the most prevalent species (Song *et al.*, 2016). According to cultivation-based approaches, Ascomycota and Basidiomycota were the two most often reported fungal phyla. Up to 10^7 CFU of yeasts were presented per gram of gut material. Protozoa and Archaea in fish intestines received little attention (Bruijn *et al.*, 2018).

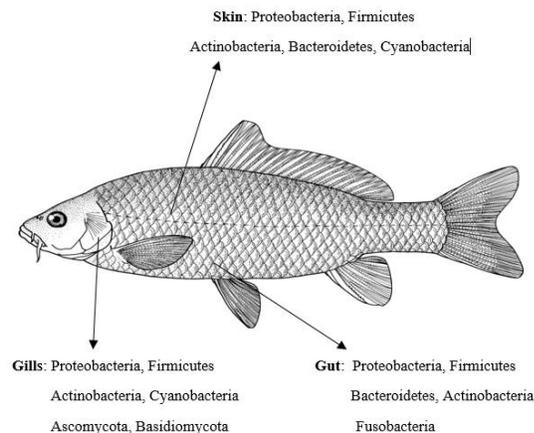


Figure 1. Composition of fish microbiota. Major phyla present in the gut, skin, and gills of fish (Source: Llewellyn *et al.*, 2014)

Factors affecting fish gut microbiota

Significant inter- and intra- species diversity has been identified in research on the fish gut microbiota. The age, weight, gender, diet, trophic level, habitat, season, phylogeny, and captive state, are some factors that affect this diversity (Hansen and Olafsen 1999; Clements *et al.*, 2007; Bano *et al.*, 2007; Dhanasiri *et al.*, 2011; Hovda *et al.*, 2012; Cordero *et al.*, 2015; Miyake *et al.*,

2015). The habitat, trophic level, and probably host phylogeny are the most likely contributing factors, in accordance with a recent meta-analysis of the factor determining the diversity of the fish gut microbiota (Sullam *et al.*, 2012). The scientific model species zebrafish is crucial because it is ideal for examining the dynamic variations in the gut microbiota that occur during development. While the relative quantity of the various groups of bacteria remained stable, the density and variety of the gut microbial population declined with age (Stephens *et al.*, 2016). Additionally, compared to adult fish, the composition of the gut microbiota in the early stages of development was more comparable to that of the aquatic environment, while in the adult forms, there was greater heterogeneity in the gut population across different fish (Bruijn *et al.*, 2018). The identification of a core microbiota in the intestines of wild and laboratory-raised zebrafish by Roeselers *et al.* (2011) offered proof of the importance of the host's genetic predisposition in determining the microbiome (Roeselers *et al.*, 2011). In the early phases of life, the water microbiome has a considerable impact on the gut microbiota, and host age promotes microbial diversity (Bledsoe *et al.*, 2016). Based on the host species and dietary habits, the structure of the gut microbiome and metabolite profiles might change dramatically (Li *et al.*, 2017). Non-adherent microbiota is far more diverse and dietary-reliant than adherent microbiota (Gajardo *et al.*, 2017). Additionally, a study by Li *et al.* (2016) discovered that the intestine microbial communities of male and female wild largemouth bronze gudgeon (*Coreius guichenoti*) differed significantly from one another (Li *et al.*, 2016). In a study with zebrafish, Stephens *et al.* (2016) demonstrated stage-specific signals and substantial inter-individual variability (2016). Water temperature and salinity are two key elements in the aquatic environment that influence fish GI microbiota (Stephens *et al.*, 2016). Carnivorous, omnivorous, and herbivorous fish can all have significantly different communities (Givens *et al.*, 2015; Miyake *et al.*, 2015). According to research, the diversity of bacteria in the guts of fish tends to decline as they transition from herbivores to omnivores, and carnivores have the least diverse gut bacteria (Wang *et al.*, 2018). Fusobacteria were more common in carnivorous fish species, while cyanobacteria were more common in filter feeders (Bruijn *et al.*, 2018). The makeup of the gut microbiota is substantially associated with salinity, according to a comparison of fish from freshwater, saltwater, or estuarine environments. According to principal coordinate analysis (PCoA), intestinal bacterial populations of freshwater and saltwater fish formed considerably different clusters. The greater proportion of operational taxonomic units (OTUs) from the bacterial orders Aeromonadales in freshwater fish and Vibrionales in saltwater fish was linked to these PCoA discrepancies (Wong

and Rawls, 2012). The isolated bacterial genera typically correspond to the fish's surroundings and vary depending on several variables, like salinity and the density of bacterial populations in the water. The microbiota in the gut is an example of microorganisms from the environment or the diet consumed that can endure and proliferate inside the gastrointestinal tract (Larsen *et al.*, 2015).

Functions of fish gut microbiota

The gnotobiotic zebrafish model system offers chances to investigate the molecular underpinnings of host-microbe interactions, such as the host-microbe metabolism and the immune system's synergistic evolution. According to research by Rawls *et al.* (2004), 212 genes, some of which are associated with enhancing innate immunity, increasing energy metabolism, and inducing epithelial growth, can be controlled by the fish microbiota. Accordingly, the lack of GI microbiota in fish may result in reduced physiological processes, including impaired nutrition absorption, metabolism, and immunological responses, as well as intestinal epithelial cell dysfunction. In the developing vertebrate intestine, it is hypothesized that the local intestinal microbiota boosts the integrity of b-catenin in the intestinal epithelium and fosters cell growth. Fish gut microbiota has enzyme-producing bacteria, which may play a significant role in metabolism (Ray *et al.*, 2012). These enzymes include lipase, amylase, proteases, cellulase, chitinase, and phytase. The GI bacteria have a significant impact on the development and maturation of gut-associated mucoid tissues (GALT), which in turn mediates a number of host immunological actions (Wang *et al.*, 2018).

Microbiota manipulation in fish gut

It is well established that there is an innate relationship between a host's microbial population and its state of health, many researchers are currently concentrating on strategies to manage this microbial community structure to promote host health. Interest in altering the gut microbiota of fish to enhance wellness and nutrition has increased with the development of the aquaculture sector. Modifying dietary lipids as well as proteins and also as including prebiotics and probiotics in the diet have been the main ways of gut flora management.

Proteins

Proteins serve as the body's structural constituents and have a variety of roles in numerous metabolic pathways and physiological processes. The source,

chemical composition, and quantity, of proteins can have an impact on microbial diversity and gut health (Kotzamanis *et al.*, 2007; Desai *et al.*, 2012; Geurden *et al.*, 2014). The reduced protein intake and a more diversified microbial population texture in the gut have been connected, according to previous research (Zarkasi *et al.*, 2016). Peptides and glycopeptides generated during hydrolytic breakdown influence the state and function of intestinal cells along with the nearby microbiota. Protein hydrolysates can modify dietary proteins in a way that both, directly and indirectly, alters the bacteria population in the host's gut. Short peptides can directly change the makeup of the bacteria in the gut by providing the bacteria with adequate substrates and promoting their growth (Kotzamanis *et al.*, 2007; Delcroix *et al.*, 2015). Some short peptides have antibacterial properties, which can aid in preventing the growth of harmful microorganisms. (Sila *et al.*, 2014).

Lipids

Fish require lipids as essential macronutrients in their diet. Increasing the level of fatty contents led to the production of a more diverse population of gut bacteria. The ability of fish to withstand pathogenic microorganisms can be increased by substituting plant oils for fish oils (Egerton *et al.*, 2018).

Probiotics

Probiotics are alive or dead components of microorganisms that help the host by boosting healthy intestinal bacterial species and enhancing the host's overall health (Ghanbari *et al.*, 2015). In the aquaculture sector, probiotics are usually added as feed or water supplements (Nayak, 2010). The most crucial probiotic organisms employed in aquaculture are *Bacillus* species and Lactic acid bacteria (Beck *et al.*, 2015; Chai *et al.*, 2016; Liu *et al.*, 2017]. *Saccharomyces*, *Clostridium*, *Enterococcus*, *Shewanella*, *Lactococcus*, *Leuconostoc*, *Aeromonas*, and *Carnobacterium* are the additional common probiotic organisms utilized in fisheries (Nayak, 2010). The first line of defense against the various pathogenic microorganisms that fish are vulnerable to is innate immunity. By being included in the diet, probiotics have a crucial function in enhancing fish immunological responses as well as the adaptive and innate immune systems (Cui *et al.*, 2022).

Prebiotics

Prebiotics are a novel approach that offers a dietary supplement to enhance immune function and growth by controlling gut bacteria (Gibson *et al.*,

2004). Prebiotics are frequently indigestible oligosaccharides that are supplemented with fish feed to encourage the development of particular beneficial microbes in the gut and hence improve host health (Gibson and Roberfroid, 1995). By raising the population of lactic acid bacteria, particularly *Bifidobacterium*, prebiotics can enhance the host's overall immunity by reducing the adhesion and colonization of harmful microbes in the digestive tract. According to several studies, prebiotics have been linked to immunological health, immune development, and the construction and variation of the gut microbiota in a range of fish species (Geraylou *et al.*, 2013; Hahor *et al.*, 2019, Hoseinifar *et al.*, 2013; Ali *et al.*, 2016; Guerreiro *et al.*, 2016). It is important to note that supplementing with prebiotics only helps when a moderate amount is given; prebiotics in large concentrations can harm the host. An imbalance in the gut microenvironment brought by many prebiotics may reduce the ability of fish intestines to digest food (Cui *et al.*, 2022).

Synbiotics

Synbiotics are a term for the administration of prebiotics and probiotics together (Huynh *et al.*, 2017; Nayak, 2010). According to studies, synbiotics increase the probiotic bacteria's implantation, metabolism, and chances of survival in the gut (Cerezuela *et al.*, 2011). It has been demonstrated that synbiotics improve the host's ability to develop and use as food, which may be due to the host receiving more energy and nutrients from the organisms or to the host's body for improving the digestive processes (Ring ø and Song, 2016).

Fish gut microbiome and production of secondary metabolites

Pathogens have been reported to exhibit high resistance to numerous antibiotics due to mutations brought by the widespread and careless usage of antibiotics (Sharma *et al.*, 2016). The oldest and most common infectious agent is *Mycobacterium tuberculosis*, which causes tuberculosis (TB) (Hussain *et al.*, 2017). The emergence and spread of illnesses with extended-spectrum beta lactamases, such as those caused by Gram-negative bacteria such as *Acinetobacter baumannii*, *Escherichia coli*, and carbapenem-resistant *Klebsiella pneumonia* (CR-KP), pose a significant risk to public health (Schwaber *et al.*, 2008; Vatopoulos, 2008). To tackle multidrug resistance (MDR), novel antibiotics with specific molecular frameworks and distinctive modes of action are urgently required. Cancer continues to be one of the biggest health issues affecting people among lifestyle illnesses. Notably, the second-leading cause of

cancer fatalities in women after lung cancer is breast cancer. Combining surgical, radiological, immunotherapeutic, and chemotherapeutic methods is one of the therapeutic choices for cancer treatment (Maqsood *et al.*, 2018). Because of their variety of chemical structures, which cannot be equaled by any synthetic libraries, natural products are viewed as a wonderful repository for developing drugs (Rateb *et al.*, 2018).

However, our research findings found depsidones, known mollicellins E and J, and new mollicellins K-N from the fungus *Chaetomium brasiliense* expressed antimalarial activity against *Plasmodium falciparum*. It showed that compound new mollicellins K-N resulted in antimicrobial activities against *Candida albicans* and *Mycobacterium tuberculosis* causing tuberculosis. Moreover, all compounds expressed cytotoxicity to KB, BC1, NCI-H187 and five cholangiocarcinoma cell lines (Khumkomkhet *et al.*, 2009). *Ch. globosum* strain KMITL-N0802 recorded a novel anthraquinone-chromanone compound named chaetomanone and known compounds, chrysophanol, chaetoglobosin C, echinulin and iso chaetoglobosin D. With this, Chaetomanone and echinulin reported to be expressed antibacterial against *Mycobacterium tuberculosis* (Kanokmedhakul *et al.*, 2002). Our further research findings on the endophytic *Chaetomium globosum* 7s-1 isolated from a plant species, *Rhapis cochinchinensis* found a new xanthoquinodin B9, three epipolythiodioxopiperazines, chetomin, chaetocochin C, dethio-tetra (methylthio) chetomin, four other compounds, chrysophanol, two known xanthoquinodins, xanthoquinodin A1 and xanthoquinodin A3, emodin, and alatinone. It found that compounds xanthoquinodin A3, chetomin, chaetocochin C and dethio-tetra(methylthio) and chetomin expressed antimicrobial activity towards Gram positive bacteria at concentrations of 0.02 pM to 10.81 μM. Moreover, these metabolites also expressed cytotoxicity against a normal cell line (*Vero* cell) at IC₅₀ values of 0.04–3.86 μM and cytotoxicity toward KB, MCF-7, NCI-H187 cancer cell lines at IC₅₀ 0.04–18.40 μM (Tantapakul *et al.*, 2020). These natural products of secondary metabolites may possible to develop as biomedicine to control those pathogens.

Marine vertebrates have historically been found to be a rich resource of distinctive natural compounds, with a wide variety of biological activity. Recent research on microbial populations linked to vertebrates shows that microbes are the real source of many of these chemicals. The microbially rich habitat of the marine system has not been sufficiently studied to yield unique chemical substances such as antibiotics, enzymes, vitamins, medicines, and biosurfactants (Bhatnagar and Kim, 2010; Shekhar *et al.*, 2015). The ability of actinobacteria to produce a wide variety of secondary metabolites with fascinating potential bioactivities makes them well-known among marine

microbes (Vignesh *et al.*, 2021). Nineteen bacterial strains were discovered during the preliminary investigation of the intestinal flora of *Garra mullya* (Sykes), and they displayed a great range of enzymatic activity, morphology, and biochemical properties. The factors that control diversity as determined by analysis of principal components and correspondence analysis demonstrate that bacterial isolates have adapted to use a variety of resources, such as sugar and citrate, and also exhibit endurance to a variety of environmental factors, including pH, salinity, and bile in vitro conditions (Rudresh *et al.*, 2010). Actinomycetes found in Indian Mackerel (*Rastrellinger kanagurata Cuvier*) produce metabolites that prevent the growth of histamine-producing bacteria. These byproducts can be utilized to preserve seafood. (Choudhury *et al.*, 2008). In addition to having antibacterial action against ESBL *Klebsiella pneumonia* ATCC 13882 and *Mycobacterium tuberculosis*, the secondary metabolites from *Streptomyces enissoceasilis* SFA from shark fish also had anticancer activity against breast cancer cells (Vaishali *et al.*, 2021). Lipid-producing bacteria isolated from the guts of different freshwater and saltwater oily fish from the western coastal region of India have been found to produce PUFA (Masurkar *et al.*, 2014). n From the distal (DI) and proximal (PI) areas of the fish gut, Dutta and Ghosh (2015) isolated bacteria that produce extracellular enzymes. These strains may produce the extracellular enzymes lipase, cellulase, phytase, amylase, and xylanase. By using the cross-streaking and double-layer methods, additional research on antagonism against seven possible fish pathogens indicated some of the strains to be antagonistic against one or more pathogens (Dutta and Ghosh 2015). Study of *Streptomyces* spp. in the fish gut microbiota of three environmental biotopes, including fresh-water (*Cyprinus carpio* [common carp]), estuarine (*Oreochromis mossambicus* [tilapia]), and marine (*Epinephelus diacanthus* [grouper]), which have a greater relationship with muddy soils for the synthesis of antibacterial components against human pathogens *Vibrio cholerae* proved that these extracts have the capacity to produce effective antibacterial components against the pathogen (Deepa *et al.*, 2012). The actinobacterial strains from *R. kanagurta* showed antimicrobial and anti-quorum sensing, anticancer, and anti TB activity. The actinobacterial strains from *P. microdon* showed antimicrobial activity (Vignesh *et al.*, 2019). Due to significant financial loss, biofouling on ship surfaces poses a serious danger to the marine industry. Tributyltin has been used to combat biofouling, which is the root of the environmental problem. According to research, coral-associated marine bacteria and aquatic Actinobacteria have the ability to reduce the development of biofouling (Waturangi *et al.*, 2017).

Conclusion

Fishes have concerned with a wide variety of bacterial taxa and other microbes, which frequently mirror the microflora of the aquatic environment. The gut microbiota of fish can be considered as an organ, which is in charge of vital physiological processes essential to maintain the health of its host. Prior research had suggested that there were few bacteria in fish guts, but more recent research, using cutting-edge molecular methods like NGS technologies, has painted a different picture and revealed that there can be found as much as 10^9 CFU/g of bacteria cells in the gut of some species. Many of these fish-associated microorganisms play uncertain roles, and further research should focus on this area. The health and sustainability of aquaculture would be improved by our increased knowledge of the fish gut microbiota in relation to diet modifications and the effects of microbial ecology alterations on bioactivity research. For both recreational and commercial fisheries, it is crucial to comprehend the bacterial makeup of fish as it is proven to be a big impact on host health, resistance to diseases, and spoiling rates. Finding new bioactive compounds is crucial to combating the threat posed by bacteria that are multi-drug resistant. Because natural products include a variety of chemical scaffolding that cannot be equalled by synthetic libraries, they are regarded as a useful resource for drug development. At the moment, marine microorganisms are a priceless, important source of novel, and promising bioactive metabolites with significant biological activity.

References

- Ali, S. S. R., Ambasankar, K., Nandakumar, S., Praveena, P. E. and Syamadaya, J. (2016). Effect of dietary prebiotic inulin on growth, body composition and gut microbiota of Asian seabass (*Lates calcarifer*). *Animal Feed Science and Technology*, 217:87-94.
- Amann, R. I., Ludwig, W. and Schleifer, K. H. (1995). Phylogenetic identification and in situ detection of individual microbial cells without cultivation. *Microbiological reviews*, 59:143-169.
- Austin, B. (2002). The bacterial microflora of fish. *The Scientific World Journal*, 2:558-572.
- Bano, N., DeRae Smith, A., Bennett, W., Vasquez, L. and Hollibaugh, J. T. (2007). Dominance of *Mycoplasma* in the guts of the Long-Jawed Mudsucker, *Gillichthys mirabilis*, from five California salt marshes. *Environmental Microbiology*, 9:2636-2641.
- Beck, B. R., Kim, D., Jeon, J., Lee, S. M., Kim, H. K., Kim, O. J. and Song, S. K. (2015). The effects of combined dietary probiotics *Lactococcus lactis* BFE920 and *Lactobacillus plantarum* FGL0001 on innate immunity and disease resistance in olive flounder (*Paralichthys olivaceus*). *Fish & shellfish immunology*, 42:177-183.
- Bhatnagar, I. and Kim, S. K. (2010). Immense essence of excellence: marine microbial bioactive compounds. *Marine drugs*, 8:2673-2701.

- Bledsoe, J. W., Peterson, B. C., Swanson, K. S. and Small, B. C. (2016). Ontogenetic characterization of the intestinal microbiota of channel catfish through 16S rRNA gene sequencing reveals insights on temporal shifts and the influence of environmental microbes. *PloS one*, 11:e0166379.
- Cahill, M. M. (1990) Bacterial flora of fishes: a review. *Microbial ecology*, 19:21-41.
- Carda-Diéguez, M., Mira, A. and Fouz, B. (2014). Pyrosequencing survey of intestinal microbiota diversity in cultured sea bass (*Dicentrarchus labrax*) fed functional diets. *FEMS microbiology ecology*, 87:451-459.
- Cerezuela, R., Meseguer, J. and Esteban, M. A. (2011). Current knowledge in synbiotic use for fish aquaculture: a review. *Journal of Aquaculture Research & Development S*, 1:1-7.
- Chai, P. C., Song, X. L., Chen, G. F., Xu, H. and Huang, J. (2016). Dietary supplementation of probiotic *Bacillus* PC465 isolated from the gut of *Fenneropenaeus chinensis* improves the health status and resistance of *Litopenaeus vannamei* against white spot syndrome virus. *Fish & shellfish immunology*, 54:602-611.
- Choudhury, M., Kumar Sahu, M., Sivakumar, K., Thangaradjou, T. and Kannan, L. (2008). Inhibition of Actinomycetes to histamine producing bacteria associated with Indian Mackerel fish (*Rastrellinger kanagurata* Cuvier, 1816). *Journal of Fisheries and Aquatic Sciences*, 3:126-136.
- Clements, K. D., Pasch, I. B., Moran, D. and Turner, S. J. (2007). Clostridia dominate 16S rRNA gene libraries prepared from the hindgut of temperate marine herbivorous fishes. *Marine Biology*, 150:1431-1440.
- Clements, K. D., Angert, E. R., Montgomery, W. L. and Choat, J. H. (2014). Intestinal microbiota in fishes: what's known and what's not. *Molecular Ecology*, 23:1891-1898.
- Cordero, H., Guardiola, F. A., Tapia-Paniagua, S. T., Cuesta, A., Meseguer, J., Balebona, M. C. and Esteban, M. Á. (2015). Modulation of immunity and gut microbiota after dietary administration of alginate encapsulated *Shewanella putrefaciens* Pdp11 to gilthead seabream (*Sparus aurata* L.). *Fish & Shellfish Immunology*, 45:608-618.
- Cui, X., Zhang, Q., Zhang, Q., Zhang, Y., Chen, H., Liu, G. and Zhu, L. (2022). Research Progress of the Gut Microbiome in Hybrid Fish. *Microorganisms*, 10:891.
- de Bruijn, I., Liu, Y., Wiegertjes, G. F. and Raaijmakers, J. M. (2018). Exploring fish microbial communities to mitigate emerging diseases in aquaculture. *FEMS Microbiology Ecology*, 94:161.
- Deepa, S., Bharathidasan, R. and Panneerselvam, A. (2012). Studies on isolation of nutritional grouping streptomycetes from fishes. *Advances in Applied Science Research*, 3:895-899.
- Delcroix, J., Gatosoupe, F. J., Desbruyères, E., Huelvan, C., Le Delliou, H., Le Gall, M. M. and Zambonino-Infante, J. L. (2015). The effects of dietary marine protein hydrolysates on the development of sea bass larvae, *D icentrarchus labrax*, and associated microbiota. *Aquaculture Nutrition*, 21:98-104.
- Desai, A. R., Links, M. G., Collins, S. A., Mansfield, G. S., Drew, M. D., Van Kessel, A. G., *et al.* (2012). Effects of plant-based diets on the distal gut microbiome of rainbow trout (*Oncorhynchus mykiss*). *Aquaculture*, 350:134-142.
- Dhanasiri, A. K., Brunvold, L., Brinchmann, M. F., Korsnes, K., Bergh, Ø. and Kiron, V. (2011). Changes in the intestinal microbiota of wild Atlantic cod *Gadus morhua* L. upon captive rearing. *Microbial ecology*, 61:20-30.
- Dutta, D. and Ghosh, K. (2015). Screening of extracellular enzyme-producing and pathogen inhibitory gut bacteria as putative probiotics in mrigal, *Cirrhinus mrigala* (Hamilton, 1822). *International Journal of Fisheries and Aquatic Studies*, 2:310-318.

- Egerton, S., Culloty, S., Whooley, J., Stanton, C. and Ross, R. P. (2018). The gut microbiota of marine fish. *Frontiers in microbiology*, 9:873.
- Gajardo, K., Jaramillo-Torres, A., Kortner, T. M., Merrifield, D. L., Tinsley, J., Bakke, A. M. and Krogdahl, Å. (2017). Alternative protein sources in the diet modulate microbiota and functionality in the distal intestine of Atlantic salmon (*Salmo salar*). *Applied and environmental microbiology*, 83:e02615-16.
- Geraylou, Z., Souffreau, C., Rurangwa, E., De Meester, L., Courtin, C. M., Delcour, J. A. and Ollevier, F. (2013). Effects of dietary arabinoxylan-oligosaccharides (AXOS) and endogenous probiotics on the growth performance, non-specific immunity and gut microbiota of juvenile Siberian sturgeon (*Acipenser baerii*). *Fish & Shellfish Immunology*, 35:766-775.
- Geurden, I., Mennigen, J., Plagnes-Juan, E., Veron, V., Cerezo, T., Mazurais, D. and Panserat, S. (2014). High or low dietary carbohydrate: protein ratios during first-feeding affect glucose metabolism and intestinal microbiota in juvenile rainbow trout. *Journal of Experimental Biology*, 217:3396-3406.
- Ghanbari, M., Kneifel, W. and Domig, K. J. (2015). A new view of the fish gut microbiome: advances from next-generation sequencing. *Aquaculture*, 448:464-475.
- Gibson, G. R., Probert, H. M., Van Loo, J., Rastall, R. A. and Roberfroid, M. B. (2004). Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutrition research reviews*, 17:259-275.
- Gibson, G. R. and Roberfroid, M. B. (1995). Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *The Journal of nutrition*, 125:1401-1412.
- Givens, C. E., Ransom, B., Bano, N. and Hollibaugh, J. T. (2015). Comparison of the gut microbiomes of 12 bony fish and 3 shark species. *Marine Ecology Progress Series*, 518:209-223.
- Gómez, G. D. and Balcázar, J. L. (2008). A review on the interactions between gut microbiota and innate immunity of fish. *FEMS Immunology & Medical Microbiology*, 52:145-154.
- Guerreiro, I., Serra, C. R., Enes, P., Couto, A., Salvador, A., Costas, B. and Oliva-Teles, A. (2016). Effect of short chain fructooligosaccharides (scFOS) on immunological status and gut microbiota of gilthead sea bream (*Sparus aurata*) reared at two temperatures. *Fish & Shellfish Immunology*, 49:122-131.
- Hahor, W., Thongprajukaew, K. and Suanyuk, N. (2019). Effects of dietary supplementation of oligosaccharides on growth performance, gut health and immune response of hybrid catfish (*Pangasianodon gigas* × *Pangasianodon hypophthalmus*). *Aquaculture*, 507:97-107.
- Hansen, G. H. and Olafsen, J. A. (1999). Bacterial interactions in early life stages of marine cold water fish. *Microbial ecology*, 38:1-26.
- Hoseinifar, S. H., Khalili, M., Rostami, H. K. and Esteban, M. Á. (2013). Dietary galactooligosaccharide affects intestinal microbiota, stress resistance, and performance of *Caspian roach* (*Rutilus rutilus*) fry. *Fish & Shellfish Immunology*, 35:1416-1420.
- Hovda, M. B., Fontanillas, R., McGurk, C., Obach, A. and Rosnes, J. T. (2012). Seasonal variations in the intestinal microbiota of farmed Atlantic salmon (*Salmo salar* L.). *Aquaculture Research*, 43:154-159.
- Hussain, A., Rather, M. A., Shah, A. M., Bhat, Z. S., Shah, A., Ahmad, Z. and Parvaiz Hassan, Q. (2017). Antituberculous activity of actinobacteria isolated from the rare habitats. *Letters in applied microbiology*, 65:256-264.

- Huynh, T. G., Shiue, Y. L., Nguyen, T. P., Truong, Q. P., Chen, J. C. and Liu, C. H. (2017). Current applications, selection, and possible mechanisms of actions of synbiotics in improving the growth and health status in aquaculture: a review. *Fish & shellfish immunology*, 64:367-382.
- Johny, T. K., Puthusseri, R. M. and Bhat, S. G. (2021). A primer on metagenomics and next-generation sequencing in fish gut microbiome research. *Aquaculture Research*, 52:4574-4600.
- Kanokmedhakul, S., Kanokmedhakul, K., Phonkerd, N., Soyong, K., Kongsaree, P., & Suksamrarn, A. (2002). Antimycobacterial anthraquinone-chromanone compound and diketopiperazine alkaloid from the fungus *Chaetomium globosum* KMITL-N0802. *Planta medica*, 68:834-836.
- Khumkomkhet, P. Kanokmedhakul, S., Kanokmedhakul, K., Hahnvajjanawong, C. and Soyong, K. (2009). Antimalarial and cytotoxic depsidones from the fungus *Chaetomium brasiliense*. *Journal of Natural Products*, 72:1487-91.
- Kim, P. S., Shin, N. R., Lee, J. B., Kim, M. S., Whon, T. W., Hyun, D. W. and Bae, J. W. (2021). Host habitat is the major determinant of the gut microbiome of fish. *Microbiome*, 9:1-16.
- Kotzamanis, Y. P., Gisbert, E., Gatesoupe, F. J., Infante, J. Z. and Cahu, C. (2007). Effects of different dietary levels of fish protein hydrolysates on growth, digestive enzymes, gut microbiota, and resistance to *Vibrio anguillarum* in European sea bass (*Dicentrarchus labrax*) larvae. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 147:205-214.
- Larsen, A. (2014). Studies on the microbiota of fishes and the factors influencing their composition (Doctoral dissertation).
- Larsen, A. M., Mohammed, H. H. and Arias, C. R. (2015). Comparison of DNA extraction protocols for the analysis of gut microbiota in fishes. *FEMS microbiology letters*, 362(5).
- Latha, N. and Mohan, M. R. (2013). The bacterial microflora in the fish organs-a public health aspect. *Indian Journal of Advances in Chemical Science*, 1:139-143.
- Li, X., Yan, Q., Xie, S., Hu, W., Yu, Y. and Hu, Z. (2013). Gut microbiota contributes to the growth of fast-growing transgenic common carp (*Cyprinus carpio* L.). *PLoS One*, 8:e64577.
- Li, X., Yan, Q., Ringø E., Wu, X., He, Y. and Yang, D. (2016). The influence of weight and gender on intestinal bacterial community of wild largemouth bronze gudgeon (*Coreius guichenoti*, 1874). *BMC microbiology*, 16:1-8.
- Li, T., Long, M., Li, H., Gatesoupe, F. J., Zhang, X., Zhang, Q. and Li, A. (2017). Multi-omics analysis reveals a correlation between the host phylogeny, gut microbiota and metabolite profiles in cyprinid fishes. *Frontiers in Microbiology*, 8:454.
- Liu, L., Wu, R., Zhang, J., Shang, N. and Li, P. (2017). D-Ribose interferes with quorum sensing to inhibit biofilm formation of *Lactobacillus paraplantarum* L-ZS9. *Frontiers in Microbiology*, 8:1860.
- Llewellyn, M. S., Boutin, S., Hoseinifar, S. H. and Derome, N. (2014). Teleost microbiomes: the state of the art in their characterization, manipulation and importance in aquaculture and fisheries. *Frontiers in microbiology*, 5:207.
- Maqsood, M., Qureshi, R., Ikram, M., Ahmad, M. S., Jabeen, B., Asi, M. R. and Lilge, L. (2018). In vitro anticancer activities of *Withania coagulans* against HeLa, MCF-7, RD, RG2, and INS-1 cancer cells and phytochemical analysis. *Integrative medicine research*, 7:184-191.

- Masurkar, A. A., Datar, A. G. and Vakil, B. V. (2014). Screening and identification of PUFA producers from various fish of Indian coastal and fresh water habitats. *International Journal of Life Sciences Biotechnology and Pharma Research*, 3:181.
- Miyake, S., Ngugi, D. K. and Stingl, U. (2015). Diet strongly influences the gut microbiota of surgeonfishes. *Molecular ecology*, 24:656-672.
- Nayak, S. K. (2010). Role of gastrointestinal microbiota in fish. *Aquaculture Research*, 41:1553-1573.
- Rateb, M. E., Ebel, R. and Jaspars, M. (2018). Natural product diversity of actinobacteria in the Atacama Desert. *Antonie van Leeuwenhoek*, 111:1467-1477.
- Rawls, J. F., Samuel, B. S. and Gordon, J. I. (2004). Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota. *Proceedings of the National Academy of Sciences*, 101:4596-4601.
- Ray, A. K., Ghosh, K. and Ringø E. J. A. N. (2012). Enzyme-producing bacteria isolated from fish gut: a review. *Aquaculture Nutrition*, 18:465-492.
- Ringø E. and Song, S. K. (2016). Application of dietary supplements (synbiotics and probiotics in combination with plant products and β -glucans) in aquaculture. *Aquaculture Nutrition*, 22:4-24.
- Ringø E., Strøm, E. and Tabachek, J. A. (1995). Intestinal microflora of salmonids: a review. *Aquaculture Research*, 26:773-789.
- Ringø E., Sperstad, S., Myklebust, R., Refstie, S. and Krogdahl, A. (2006). Characterisation of the microbiota associated with intestine of Atlantic cod (*Gadus morhua* L.) - the effect of fish meal, standard soybean meal and a bioprocessed soybean meal. *Aquaculture*, 261:829-841.
- Roeselers, G., Mittge, E. K., Stephens, W. Z., Parichy, D. M., Cavanaugh, C. M., Guillemin, K. and Rawls, J. F. (2011). Evidence for a core gut microbiota in the zebrafish. *The ISME journal*, 5:1595-1608.
- Rudresh, B. S., Dahanukar, N., Watve, G. M. and Renukaswamy, N. S. (2010). Microbial gut flora of a freshwater fish *Garra mullya* (Sykes) from Mutha river, Northern Western Ghats, India. *Ecoprint: An International Journal of Ecology*, 17:53-57.
- Schwaber, M. J. and Carmeli, Y. (2008). Carbapenem-resistant Enterobacteriaceae: a potential threat. *Jama*, 300:2911-2913.
- Sharma, P., Kalita, M. C. and Thakur, D. (2016). Broad spectrum antimicrobial activity of forest-derived soil actinomycete, *Nocardia* sp. PB-52. *Frontiers in microbiology*, 7:347.
- Shekhar, S., Sundaramanickam, A. and Balasubramanian, T. (2015). Biosurfactant producing microbes and their potential applications: a review. *Critical Reviews in Environmental Science and Technology*, 45:1522-1554.
- Sila, A., Nedjar-Arroume, N., Hedhili, K., Chataigné G., Balti, R., Nasri, M. and Bougatef, A. (2014). Antibacterial peptides from barbel muscle protein hydrolysates: Activity against some pathogenic bacteria. *LWT-Food Science and Technology*, 55:183-188.
- Song, W., Li, L., Huang, H., Jiang, K., Zhang, F., Chen, X. and Ma, L. (2016). The gut microbial community of antarctic fish detected by 16S rRNA gene sequence analysis. *BioMed research international*, 2016.
- Stephens, W. Z., Burns, A. R., Stagaman, K., Wong, S., Rawls, J. F., Guillemin, K. and Bohannan, B. J. (2016). The composition of the zebrafish intestinal microbial community varies across development. *The ISME journal*, 10:644-654.
- Sullam, K. E., Essinger, S. D., Lozupone, C. A., O'CONNOR, M. P., Rosen, G. L., Knight, R. O. B. and Russell, J. A. (2012). Environmental and ecological factors that shape the gut bacterial communities of fish: a meta-analysis. *Molecular ecology*, 21:3363-3378.

- Tantapakul, C., Promgool, T., Kanokmedhakul, K., Soyong, K., Song, J., Hadsadee, S. and Kanokmedhakul, S. (2020). Bioactive xanthoquinodins and epipolythiodioxopiperazines from *Chaetomium globosum* 7s-1, an endophytic fungus isolated from *Rhapis cochinchinensis* (Lour.) Mart. *Natural product research*, 34(4), 494-502.
- Uma, A., Subash, P. and Abraham, T. J. (2020). Importance of gut microbiota in fish—a review. *Indian Journal of Animal Health*, 59:181-194.
- Vaishali, R., Ruchi, P., Subhashini, D. , Vignesh, A. , Manigundan, K. , Gopikrishnan, V., Revathy, K., Anbarasu, S., Radhakrishnan, M. and Joseph, J. (2021). Antibacterial, antitubercular and anticancer activity of gut-associated *Streptomyces enissoceasilis* SFA isolated from marine fish *Carcharhinus amblyrhynchos*. *Research Journal of Biotechnology*, 16(1).
- Vatopoulos, A. (2008). High rates of metallo-beta-lactamase-producing *Klebsiella pneumoniae* in Greece—a review of the current evidence. *Eurosurveillance*, 13:7-8.
- Vignesh, A., Ayswarya, S., Gopikrishnan, V. and Radhakrishnan, M. (2019). Bioactive potential of actinobacteria isolated from the gut of marine fishes. *Indian Journal of Geomarine sciences*, 48:1280-1285
- Vignesh, A., Gopikrishnan, V., Anbarasu, S., Radhakrishnan, M. and Joseph, J. (2021). Biomedical applications of fish gut associated *Streptomyces maritimus* IM20 isolated from *Rastrelliger kanagurta* (Indian mackerel). *Research Journal of Biotechnology*, 16:120-130.
- Wang, A. R., Ran, C., Ringø E., and Zhou, Z. G. (2018). Progress in fish gastrointestinal microbiota research. *Reviews in Aquaculture*, 10:626-640.
- Waturangi, D. E., Hariyanto, J. P., Lois, W., Hutagalung, R. A. and Hwang, J. K. (2017). Inhibition of marine biofouling by aquatic Actinobacteria and coral-associated marine bacteria. *Malaysian Journal of Microbiology*, 92-99.
- Wong, S. and Rawls, J. F. (2012). Intestinal microbiota composition in fishes is influenced by host ecology and environment. *Molecular Ecology*, 21:3100-3102.
- Zarkasi, K. Z., Taylor, R. S., Abell, G. C., Tamplin, M. L., Glencross, B. D. and Bowman, J. P. (2016). Atlantic salmon (*Salmo salar* L.) gastrointestinal microbial community dynamics in relation to digesta properties and diet. *Microbial ecology*, 71:589-603.
- Zhou, Z., Yao, B., Romero, J., Waines, P., Ringø E., Emery, M. and Merrifield, D. L. (2014). Methodological approaches used to assess fish gastrointestinal communities. *Aquaculture nutrition: Gut health, probiotics, and prebiotics*, 101-127.

(Received: 22 December 2022, accepted: 28 February 2023)