Probiotics for Controlling Infectious Diseases

Jorge García-Márquez, Silvana Tapia-Paniagua, Miguel Ángel Moriñigo, and Salvador Arijo

Abstract One of the activities of probiotics is their ability to control the onset of infectious diseases. The most common mechanism is the production of substances that inhibit microbial growth, including bacteriocins and organic acids. These substances are synthesised as a mechanism of competition for nutrients and adhesion sites. Although the range of bacteriocin-producing bacteria is broad, few putative probiotics are used in commercial aquaculture. This chapter reviews the latest research on pathogen-antagonistic microorganisms. After bacteriocidal activity, one of the most outstanding properties of probiotics is their ability to activate the immune response. The use of probiotics as a pathogen biocontrol mechanism is also compared with other strategies, such as the use of medicinal plants, immunostimulants and vaccines. Despite the existence of a great diversity of microorganisms with probiotic potential, a deeper understanding of their safety in animals, including humans, and the environment is required, so that they can be used on an industrial scale in the future.

Keywords Antagonistic effect · Immunostimulants · Infectious diseases · Medicinal plants · Pathogens · Vaccines

1 Introduction

Disease outbreaks in aquaculture are traditionally treated with antibiotics and chemotherapeutics. To decrease the use of these drugs, alternative strategies have been developed for improving fish health in aquaculture systems whilst reducing the potential spread of antimicrobial resistance (Gudmundsdóttir and Björnsdóttir 2007; Nayak 2010; Dawood et al. 2019). One of the most common activities of probiotics is the ability to control infectious diseases. The most common mechanism is the production of substances like bacteriocins, which inhibit microbial growth. Bacteriocins are a heterogeneous group of antimicrobial peptides with the ability to kill

J. García-Márquez · S. Tapia-Paniagua · M. Á. Moriñigo · S. Arijo (✉)
Departamento de Microbiología, Facultad de Ciencias, Instituto de Biotecnología y Desarrollo Azul (IBYDA), Universidad de Málaga, 29071 Málaga, Spain
e-mail: sarijo@uma.es

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closely related microorganisms (narrow spectrum) or a wide range of microorganisms (broad spectrum) (Gálvez et al. 2014). Bacteriocins are synthesised by many bacteria as a mechanism of competition for nutrients and adhesion sites. They act at low concentrations, and may be biodegraded and digested by animals, which is not harmful to health. Probiotics may also produce and release organic acids and hydrogen peroxides to defend the host against the invasion of pathogens (Gaspar et al. 2018). Furthermore, probiotics control pathogen virulence by inhibiting their communication systems (by quorum sensing). Interference with the quorum sensing signal, called quorum quenching, might offer a new alternative for preventing and/or treating bacterial infections via inhibition of virulence factor expression and biofilm formation (Kim et al. 2018).

To use probiotics as a control mechanism for infectious disease, the benefits and drawbacks of their use must be compared with those of other disease control systems, such as immunostimulants, medicinal plants or vaccines. On the other hand, in the process of selecting a probiotic, it is necessary to evaluate which pathogens it can affect, since the antimicrobial range of action depends on the antimicrobial substances it releases.

2 Probiotics Effective Against Aquaculture Diseases

There is a wide range of pathogenic microorganisms whose growth has been affected by potentially probiotic bacteria, either in in vitro experiments or in animal tests.

Most probiotics put forward as biological control agents in aquaculture belong to the lactic acid bacteria (*Lactobacillus*), and to the *Vibrio* and *Bacillus* genera (Hoseinifar et al. 2018). Table 1 summarises some recent research on probiotics and their effect against some aquaculture pathogens. Unlike probiotics used in terrestrial animals, a large number of Gram-negative bacteria have been proposed for use in aquaculture. The number of species with probiotic potential is very high and includes strains of species that are even described as pathogenic (Arijo et al. 2008; Allameh et al. 2017; Medina et al. 2020; Wang et al. 2020). Several probiotic species have caused disease outbreaks in the aquaculture industry, including *Vibrio* sp. and *Weissella* sp. (Figueiredo et al. 2012). This implies a limitation of the use of these strains, since a probiotic strain useful for one fish species could be pathogenic for another animal especially if virulence genes are acquired. For example, *Vagococcus lutrae* has been used as a probiotic for seabream and seabass, but it has been observed to cause skin lesions in warm-blooded animals (Fu et al. 2020). On the other hand, there is also the possibility of plasmid transfer between pathogens and potential probiotics, which could give the probiotic virulence factors (van Reenen and Dicks 2011). This can be dangerous in the case of transmission of antibiotic resistance genes between probiotics and pathogens (Patel et al. 2012), which is why, in fact, legal provisions limit the use of probiotics to very few species. For example, the European Regulation (EC) No 178/2002 laying down the general principles and requirements of food law,

Table 1 Range of probiotics effective against infective fish diseases

Probiotic	Animal tested	Mode of administration/effective dose in feed	Length of treatment	Pathogen (antibacterial effect against)	Reference
Administration of a single probiotic strain					
Bacillus aerius	*Pangasius bocourti*	Oral/10^7 CFU/g	60 days	*Aeromonas hydrophila*	Meidong et al. (2018)
Bacillus aerophilus	*Labeo rohita*	Oral/10^8 CFU/g	6 weeks	*A. hydrophila*	Ramesh et al. (2017)
Bacillus amyloliquefaciens	*L. rohita*	Oral/10^9 CFU/g	70 days	*A. hydrophila*	Nandi et al. (2018)
	Paralichthys olivaceus	Oral/1.4×10^6 CFU/g	30 days	*Streptococcus iniae*	Kim et al. (2017)
	Danio rerio	Oral/2×10^6 CFU /g	1 month	*A. hydrophila, Streptococcus agalactiae*	Lin et al. (2019)
Bacillus cereus	*Clarias gariepinus*	Oral/10^7 CFU/g	30 days	*Aeromonas sobria*	Reda et al. (2018)
	Colossoma macropomum	Oral/10^6 CFU/g	120 days	*A. hydrophila*	Dias et al. (2018)
Bacillus licheniformis	*Oreochromis mossambicus*	Oral/10^7 CFU/g	4 weeks	*A. hydrophila*	Gobi et al. (2018)
Bacillus pumilus	*Oreochromis niloticus*	Oral/10^8 CFU/g	4 months	*S. agalactiae*	Srisapoome and Areechon (2017)
Bacillus spp.	*O. niloticus*	Oral/3×10^8 CFU /g	4 weeks	*S. agalactiae*	Sookchaiyaporn et al. (2020)
Bacillus subtilis	*Acipenser dabryanus*	Oral/2×10^8 CFU /g	8 weeks	*A. hydrophila*	Di et al. (2019)
	L. rohita	Oral/10^8 CFU/g	4 weeks	*A. hydrophila*	Ramesh and Souiss, (2018)
	Anguilla japonica	Oral/10^8 CFU/g	8 weeks	*Vibrio anguillarum*	Lee et al. (2017)
	O. niloticus	Oral/3.8×10^7 CFU /g	6 weeks	*S. agalactiae*	Zhu et al. (2019)

(continued)

Table 1 (continued)

Probiotic	Animal tested	Mode of administration/effective dose in feed	Length of treatment	Pathogen (antibacterial effect against)	Reference
	P. olivaceus	Oral/5 × $10^{7\ CFU}$ /g^{-}	12 weeks	*S. iniae*	Lee et al. (2020)
	Oplegnathus fasciatus	Oral/10^{10} CFU/kg	56 days	*Vibrio alginolyticus*	Liu et al. (2018)
	In vitro/*Litopenaeus vannamei*	Oral/10^{6} CFU/g	45 days	*V. alginolyticus, Vibrio parahaemolyticus*	Interaminense et al. (2018)
Bacillus velezensis	Hybrid grouper (*Epinephelus lanceolatus*♂ × *E. fuscoguttatus*♀)	Oral/10^{4} CFU/g	4 weeks	*Vibrio harveyi*	Li et al. (2019)
	O. niloticus	Oral/10^{9} CFU/g	9 weeks	*S. agalactiae*	Zhang et al. (2019)
	Scophthalmus maximus L	Oral/10^{8} CFU/g	42 days	*V. anguillarum*	Chen et al. (2016)
Chromobacterium aquaticum	*D. rerio*	Oral/10^{6} CFU/g	8 weeks	*A. hydrophila, S. agalactiae* and others	Yi et al. (2019)
Enterococcus casseliflavus	*Oncorhynchus mykiss*	Oral/10^{9} CFU/g	8 weeks	*S. iniae*	Safari et al. (2016)
Enterococcus faecalis	*Puntius gonionotus*	Oral/10^{7} CFU/g	15 days	*A. hydrophila*	Allameh et al. (2017)
Enterococcus faecium	*Cyprinus carpio*	Oral/10^{8} CFU/g	60 days	*Pseudomonas aeruginosa*	Arun and Singh (2019)
	Sander lucioperca	Oral/10^{10} CFU/g	6 weeks	*A. hydrophila*	Faeed et al. (2016)
Exiguobacterium acetylicum	*Carassius auratus*	Oral/10^{9} CFU/g	4 weeks	*A. hydrophila*	Jinendiran et al. (2019)
Geotrichum candidum	*C. auratus*	Oral/10^{6} CFU/g	60 days	*A. hydrophila*	Noor-Ul et al. (2020)
Lactobacillus casei	*Tor grypus*	Oral/5 × 10^{6} CFU/g	75 days	*A. hydrophila*	Mohammadian et al. (2020)

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Table 1 (continued)

Probiotic	Animal tested	Mode of administration/effective dose in feed	Length of treatment	Pathogen (antibacterial effect against)	Reference
Lactobacillus fermentum	*C. carpio*	Oral/2 × 10^8 CFU/g	60 days	*A. hydrophila*	Krishnaveni et al. (2020)
Lactobacillus plantarum	*C. carpio*	Oral/10^8 CFU/g	6 weeks	*Aeromonas veronii*	Zhang et al. (2020)
	O. niloticus	Oral/1.02 × 10^6 CFU/g	56 days	*E. faecalis*	Foysal et al. (2020)
	Acipenser baerii	Oral/10^8 CFU/g	8 weeks	*S. iniae*	Pourgholam et al. (2017)
	C. carpio	Oral/1.2 × 10^6 CFU/g	80 days	*A. hydrophila*	Soltani et al. (2017)
	C. carpio	Oral/10^8 CFU/g	14 days	*A. hydrophila*	Kazuń et al. (2018)
	O. niloticus	Oral/10^7 CFU/g	58 days	*S. agalactiae*	Yamashita et al. (2017)
Lactococcus lactis	*O. niloticus*	Oral/10^8 CFU/g	6 weeks	*S. agalactiae*	Xia et al. (2018)
	P. olivaceus	Oral/10^9 CFU/g	8 weeks	*Streptococcus parauberis*	Nguyen et al. (2017)
	C. carpio	Oral/5 × 10^8 CFU/g	8 weeks	*A. hydrophila*	Feng et al. (2019)
	Cromileptes altivelis	Oral/10^8 CFU/g	4 weeks	*V. harveyi*	Sun et al. (2018)
Paenibacillus ehimensis	*O. niloticus*	Oral/10^6 CFU/g	2 months	*A. hydrophila*, *S. iniae*	Chen et al. (2019)
Paenibacillus polymyxa	*C. carpio*	Water/10^3 CFU/mL	8 weeks	*A. hydrophila*	Gupta et al. (2016)
Pseudomonas putida	*O. niloticus*	Oral/10^8 CFU/g	60 days	*A. hydrophila*	Abomughaid (2020)
Rummeliibacillus stabekisii	*O. niloticus*	Oral/10^6 CFU/g	8 weeks	*A. hydrophila*, *S. iniae*	Tan et al. (2019)
Shewanella algae	In vitro/*L. vannamei*	Oral/10^6 CFU/g	45 days	*V. alginolyticus*, *V. parahaemolyticus*	Interaminense et al. (2018)

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Table 1 (continued)

Probiotic	Animal tested	Mode of administration/effective dose in feed	Length of treatment	Pathogen (antibacterial effect against)	Reference
Streptomyces amritsarensis	*Ctenopharyngodon idella*	Oral/10^9 CFU/g	28 days	*A. veronii*	Li et al. (2020)
Vibrio lentus	In vitro/*Dicentrarchus labrax*	Water/10^6 CFU/mL	10 days	*V. harveyi*	Schaeck et al. (2016)
Combinations of several probiotic strains					
B. cereus + *B. subtilis* (1:1)	*O. niloticus*	Oral/10^8 CFU/g	6 weeks	*S. agalactiae*	Xia et al. (2020)
	Piaractus mesopotamicus	Oral/10^8 CFU/g	60 days	*A. hydrophila*	Farias et al. (2016)
Bacillus spp. + *L. casei* (4:1)	*C. idella*	Oral/1.68 g $kg^{/}$	60 days	*A. hydrophila*	Chen et al. (2020)
B. subtilis + *B. licheniformis* (1:1)	*O. niloticus*	Oral/10 g/kg	4 weeks	*S. agalactiae*	Abarike et al. (2018a)
B. subtilis + *B. licheniformis* + *B. pumilus* (1:1:1)	*L. vannamei*	Oral/10^{10} CFU/g	33 days	*V. parahaemolyticus*	Lee et al. (2019)
B. subtilis + *L. pentosus* + *S. cerevisiae* + *L.fermentum* (1:1:1:1)	*Lates calcarifer*	Oral/10^9 CFU/kg	56 days	*A. hydrophila*	Lin et al. (2017)
B. velezensis + *Rhodotorula mucilaginosa* (1:10)	*Salmo salar* L	Oral/5 × 10^6 CFU /g	62 days	*Aeromonas salmonicida*	Wang et al. (2019a)
B. velezensis + *B. subtilis* + *B. amyloliquefaciens* (1:1:1)	*O. niloticus*	Oral/10^8 CFU/mL	4 weeks	*A. hydrophila*	Kuebutornye et al. (2020)

(continued)

Table 1 (continued)

Probiotic	Animal tested	Mode of administration/effective dose in feed	Length of treatment	Pathogen (antibacterial effect against)	Reference
Lactobacillus delbrukei subsp. bulgaricus + *Lactobacillus acidophilus*	*O. mykiss*	Oral/5 × 10^7 CFU /g	60 days	*Lactococcus garvieae*	Mohammadian et al. (2019)
Lactobacillus pentosus + *L. fermentum* + *B. subtilis* + *Saccharomyces cerevisiae* (1:1:1:1)	*L. vannamei*	Oral/10^8 CFU/kg	56 days	*V. alginolyticus*	Wang et al. (2019b)
L. plantarum SM16, *L. plantarum* SM33, *L. fermentum, Lactobacillus brevis, and Pediococcus pentosaceus* (1:1:1:1:1)	*L. rohita*	Oral/10^8 CFU/g	30 days	*A. hydrophila*	Maji et al. (2017)

establishing the European Food Safety Authority (EFSA) and laying down procedures in matters of food safety (art. 14 and 15), and the European Regulation (EU) 68/2013 about feed additives. In the absence of a list of authorised microorganisms, the Qualified Presumption of Safety (QPS) list of the EFSA is taken as a reference for their safe use in food, a list that is periodically reviewed (Herman et al. 2019). The list includes as safe microorganisms Gram-positive bacteria, i.e. *Bacillus*, *Bifidobacterium*, *Carnobacterium*, *Lactobacillus*, *Leuconostoc* and *Streptococcus*. However, there are no Gram-negative bacteria listed as safe to use as a living organism. This legal limitation implies that future research will have to focus on observing the potential adverse effects of probiotics proposed for use in aquaculture, otherwise it will not be possible to use all these probiotics in the aquaculture industry.

3 Probiotics Compared with Other Disease Control Measures

3.1 Probiotics verses Non-specific Immunostimulants

The concept of immunostimulation first appeared in 1970 as part of the vaccination process, and was later followed by the concept of probiotics (Portalès and Clot 2006). Indeed, it is difficult to separate the concept of immunostimulation from vaccination, as immunostimulants have been administered in combination with vaccines as adjuvants for boosting the immune response (Anderson 1992). However, they have been used independently since the 1980s (Olivier et al. 1985; Siwicki 1987). The use of immunostimulants for the prevention of diseases in fish culture has been extended since the beginning of the 1990s when these products were considered a new promising treatment against diseases (Kitao et al. 1987; Siwicki 1989; Anderson 1992). Anderson (1992) defined 'immunostimulant' as a chemical substance, drug, stressor or action that elevates the non-specific defence mechanism or the specific immune response. This is because an innate immune response is initiated upon recognition of pathogen-associated molecular patterns (PAMPs) (Wangkahart et al. 2019), molecules that mimic some cellular or extracellular pathogenic bacterial components. Immunostimulant agents were first used with whole bacteria, such as *Cryptosporidium parvum*, and later used with high molecular weight substances (LPS or peptidoglycans) (Werner 1986). Therefore, the link with the effect of probiotic bacteria is very close.

The first immunostimulant product developed was Ribomunyl® in 1980, and its composition was based on proteoglycans from *Klebsiella pneumoniae* and purified ribosomes from pathogens (Dussourd d'Hinterland et al. 1980). One decade later, immunostimulants began to be used in the aquaculture industry, and are now based on biological and/or synthetic compounds (Siwicki et al. 1994). Synthetic substances include compounds, such as Levamisole (Olivier et al. 1985) or FK-565 (Kitao and Yoshida 1986). Meanwhile, Mehana et al. 2015 classified the biological substances in

bacterial derivatives, polysaccharides, animal and plant extracts, nutritional factors, such as vitamins and hormones, cytokines and others. All of them may be effective in preventing diseases when administered alone, without the need to be coupled with a vaccine (Hungin et al. 2018), or use of antibiotics and chemotherapeutics. Also, they are widely applied to improve fish welfare and production (Mehana et al. 2015).

Immunostimulants exert a non-specific response, including macrophage and phagocytic activity, killing activity, reactive oxygen species (ROS), chemiluminescent response, and humoral response, which includes increases in serum complement, lysozyme and immune substances associated with non-specific and specific immune responses (Gannam and Schrock 1999). Meanwhile, probiotics exert their mode of action in many aspects of fish physiology (Tapia-Paniagua et al. 2012; Soltani et al. 2019), including the immune system, microbiota, nutrition, growth, maturation or reproductive aspects (Irianto and Austin 2002; Gatesoupe 2008; Zorriehzahra et al. 2016; Chauhan and Singh 2019).

The benefits of immunostimulants assayed in vivo include increased survival when affected by viral, bacterial and parasitic diseases, growth enhancement, increased antibody production following vaccination and increased lysozyme levels (Barman and Nen 2013; Wang et al. 2017; Dawood et al. 2018). Also, these products may be obtained from a natural source in large amounts, such as glucans from yeast or chitosan from arthropods, which are low-cost ingredients. However, the use of immunostimulants has some disadvantages: (i) some of the molecules have a high cost and limited efficiency; (ii) the memory component developed by these substances and the duration of the immune response is very short or unknown; (iii) they are not effective against all diseases; (iv) overdoses of some products can induce immunosuppression or toxicity (Bullock et al. 2000). Sometimes the mode of action and effects are not clearly defined, or the effects of long-term oral administration remain unclear. Other authors claim that the benefits described are numerous, but theoretical. For example, in larvae culture, there is controversy between authors that defend that the early use of immunostimulants in fish larvae can induce immune tolerance (Bricknell and Dalmo 2005). However, large quantities of live probiotic cells may interfere with the associated eco-systems (Sharifuzzaman et al. 2011), or the risk of lateral gene transfer of antibiotic resistance genes (Gueimonde et al. 2013; Sharma et al. 2016; Tan et al. 2016). This is why new strategies are being set up, such as the use of microbial cellular components with immunostimulant effects on fish (Kum and Sekki 2011; Giri et al. 2015, 2018).

Some bacterial derivatives are considered to be immunostimulants (Giri et al. 2015). Examples include, but are not limited to, muramyl dipeptide (N-acetyl-muramyl-L-alanyl-D-isoglutamine, MDP), derived from *Mycobacterium* lipopolysaccharide (LPS; Kodama et al. 1993) that is a cell wall component of Gram-negative bacteria (Neumann 1995; Nya and Austin 2010); Freund's complete adjuvant (FCA) that contains killed *Mycobacterium butyricum* (Sakai 1999); *V. anguillarum* whole cell inactivated vaccine [= bacterin] (Norqvist et al. 1989), *Clostridium butyricum* and *Achromobacter stenohalis* cells and other components, such as flagellin (Wangkahart et al. 2019) or cell wall proteins of *Kocuria* SM1 and *Rhodococcus* SM2 (Sharifuzzaman et al. 2011); bacterial DNA (Giri et al. 2015) and unmethylated CpG dinucleotides (Jørgensen et al. 2001).

The efficacy of immunostimulants and probiotics depends on the effective dose, exposure time and, in some cases, the feeding regime of each type of fish. For example, in Atlantic salmon, injection with a high dose of glucans (100 mg/kg) led to absence of protection for 1 week, but maximum benefits occurred after 3–4 weeks, whilst the injection of a low dose (2–10 mg/kg) gives protection for only one week (Kum and Sekki 2011). There are three main ways to deliver immunostimulants: (i) injection, (ii) immersion and oral uptake and (iii) bioencapsulation. The advantages and limitations are similar to those of probiotics. Injection is not usual when administering probiotics, but immunostimulants provide potent immunisation and can be administered in large fish. It is, however, a complicated task, which is costly and is highly stressful for the animals. Immersion and oral uptake are the simplest methods, making it possible to treat many fish of any size at the same time. However, the substances can lose activity due to their dilution in water, and it is difficult to measure the amount of feed ingested by the fish. The potency is not as high as with the injection route, and large amounts of immunostimulants are needed to achieve good protection. Currently, bioencapsulation is a good alternative, since it protects against the digestive system and environmental conditions. Table 2 shows the effects of probiotics compared with immunostimulants.

Table 2 Effects of probiotics compared with immunostimulant substances on cultured fish

	Probiotics	Immunostimulant
Prophylactic effect	Duration variable	Short duration, require more treatments
Efficacy	Variable	Good
Spectrum of activity benefits	Wide	Wide
Improved immune response	Yes	Yes
Stimulation of growth	Yes	No described
Water quality	Yes	–
Improved digestion	Yes	No described
Improve intestinal barrier	Yes	No described
Control microbiota	Yes	No directly
Toxicity	No described	No described
Accumulation of toxic residues	No	No
Environmental impact	No	Interfere with the associated eco-systems horizontal gene transference
Administration (main routes)	Feed or oral directly to culture ponds or immersion bioencapsulation	Feed or oral directly to culture ponds or immersion bioencapsulation injection

3.2 Probiotics verses Medicinal Plant Products

Medicinal plants comprise herbs, seaweeds, herbal extracted compounds, spices, commercial plant-derived products and traditional Chinese herbs (Van Hai 2015). There is growing interest in the use of medicinal herbs in aquaculture because of their promising effects, and they look like a promising alternative method for controlling fish diseases (Van Hai 2015; Abarike et al. 2018b). Plants have been reported to produce various effects, such as growth promotion, appetite stimulation, immunostimulation, and to have antipathogenic properties in aquaculture (Citarasu 2010; Reverter et al. 2014; Bulfon et al. 2015; Awad and Awaad 2017). The mode of action of these plants and their derivatives is attributed to the presence of many bioactive compounds, such as alkaloids, steroids, phenolics, tannins, terpenoids, saponins, glycosides and flavonoids (Harikrishnan et al. 2011a; Mendam et al. 2015).

Plants may be administered as a whole or in parts (leaf, root, bark, fruit), and can either be used fresh or as herbal extract preparations with different solvents (water, methanol, ethanol, chloroform) (Kim et al. 2011; Pan et al. 2013; Fridman et al. 2014; Hu et al. 2014; Zhang et al. 2014; Thanigaivel et al. 2015; Zhou et al. 2016). Their effects are variable amongst fish species, and depend mainly on different factors, such as route of administration, dosage and time (Zakęś et al. 2008; Harikrishnan et al. 2011a; Bulfon et al. 2015). Like other immunostimulants, medicinal plants and their extracts may be administered via injection (Harikrishnan et al. 2011a), bathing/immersion (Çek et al. 2007) or oral administration (Wang et al. 2015), which is the most practical and commonly used in aquaculture (Pourmoghim et al. 2015; Bilen et al. 2016; Öz et al. 2018). The review performed by Bulfon et al. (2015) presented a great variety of different dosages including up to 25% of the diet, although the most common doses ranged from 0.01 and 0.5%. However, there is not any positive correlation between dosage and its effect on the immune response (Jian and Wu 2004). Similarly, the length of feeding time is fundamentally important. To date, studies with medicinal plants and/or their bioactive compounds have involved different feeding durations, ranging from 1 to 16 weeks (Awad and Awaad 2017), but the basis for choosing these periods is often unclear.

One of the main problems of using medicinal plants as a chemotherapeutic is that the biological activity and chemical compositions of plants and extracts vary according to their characteristics (location, age, climate, cultivars, temperature and growth regulators) and sampling methods (plant part, drying, distillation and storage) (Wang et al. 2014). The antimicrobial activity of a plant against bacteria is determined by its mechanism of action, which is determined by the chemical composition (Chouhan et al. 2017; Cui et al. 2019). Thus, differing antimicrobial activities of plants with different chemical profiles are expected. In this sense, in vitro studies evaluating the cytotoxicity and the antibacterial effects of herbs have examined several bacterial fish pathogens (Vaseeharan et al. 2013; Alizadeh Behbahani and Imani Fooladi 2018; Da Cunha et al. 2018; Assane et al. 2020), highlighting their potential use for controlling bacterial disease in cultured fish.

A key aspect for proposing a natural substance as an antimicrobial agent is whether it has active compounds that may be toxic for the host. There have been reports that some plants and their major components are toxic for different animals (Malekmohammad et al. 2019), including fish (Spanghero et al. 2019; Tavares-Dias 2018).

The administration of medicinal plants for disease control in aquaculture may be achieved singly or in combination with other plants. Some studies show that medicinal plants (such as *Allium sativum*, *Azadirachta indica, Curcuma longa, Ocimum basilicum*, *Ocimum sanctum*, *Cinnamomum zeylanicum*, *Juglans regia*, *Mentha piperita, Radix astragalus* and *Radix angelicae*) enhance growth, immune responses and survival against a wide range of pathogen infections in farmed fish, such as *O. mykiss*, *L. calcarifer*, *C. carpio* and *Pseudosciaena crocea* (Jian and Wu 2003; Harikrishnan et al. 2009; Nya and Austin, 2009a, 2009b; Mohamad and Abasali 2010; Talpur and Ikhwanuddin 2012; Talpur et al. 2013; Awad and Awaad 2017; Stratev et al. 2018; Hayatgheib et al. 2020; Kuebutornye and Abarike 2020).

Medicinal plants may be incorporated with a probiotic. Thus, fenugreek seed (*Trigonella foenum graecum*) in combination with probiotic strains *B. licheniformis*, *L. plantarum* and *B. subtilis* enhanced growth performance, skin mucosal immunity response, humoral immune response and the expression of immune-associated genes of gilthead seabream (*Sparus aurata*) after three weeks of a feeding regime (Bahi et al. 2017; Guardiola et al. 2017). A diet enriched with *Scutellaria baicalensis*, and/or *Lactobacillus sakei* BK19 in rock bream, *O. fasciatus,* demonstrated that the maximum protection against *Edwardsiella tarda* was recorded in the mixed (plant + probiotic) diet group (Harikrishnan et al. 2011b). The synergistic effect of *M. piperita* and the probiotic *Bacillus coagulans* improved the growth performance, nutritional physiology and resistance of Indian carp (*Catla catla*) when challenged against *A. hydrophila* (Bhatnagar and Saluja 2019). The effect of herbal-probiotic mixtures of *Astragalus membranaceus*, *Angelica sinensis*, *Crataegus hupehensis* and probiotics *B. subtilis* and *B. lincheniformis* improved growth and enhanced immune responses and survival of Nile tilapia (*O. niloticus*) when challenged against *S. agalactiae* (Abarike et al. 2018b). Moreso, in *O. niloticus*, a mixture of Chinese medicinal herbs and probiotics (*Bacillus*, *Lactobacillus* and *Yeast*) enhanced growth performance, innate immune response and antibacterial activity against *E. tarda* (Hwang et al. 2019).

There are some advantages and disadvantages when using probiotics instead of medicinal plants. On the one hand, probiotics may colonise the gut and adhere to the epithelial surface, and consequently interfere with the adhesion of pathogens (Zorriehzahra et al. 2016). Furthermore, they can consume the nutrients that are essential for the growth of a number of pathogens (Brown 2011). However, safety regulations and marketing authorizations are very restrictive regarding the use of live microorganisms. Conversely, medicinal plants are easily accessible and economical, and there is no need for significant investment in their biotechnological development, which is also an encouraging factor for large scale usage in aquaculture. Moreover, although plant products have a natural origin, and most of these medicinal plants do not represent a hazard for human health, animal health, or the environment (Stratev

et al. 2018), some constituents are unstable (e.g. they are photo- and/or thermo-labile) (Burt 2004). Finally, little is known regarding the interaction of the plants with the host microbiota.

In contrast to plant extracts and the other protein-based antimicrobial preservatives, bacteriocins, produced by some probiotic bacteria tolerate high thermal stress and are active over a wide pH range, remaining effective at fairly low concentrations (Wang et al. 2019c).

3.3 Probiotics verses Vaccines

Modern vaccines can be classified as killed, attenuated, DNA, synthetic peptide, recombinant vector, genetically modified and subunit vaccines, but although whole vaccines showed a better advantage than other types (Assefa and Abunna 2018), all showed disadvantages, especially with regard to the route of administration. Although it is a very efficient for achieving protection against pathogens, the intraperitoneal inoculation of vaccines combined with adjuvants (Harikrishnan et al. 2011c) may be the cause of stress, feed intake reduction (Lillehaug 2014), lesions such as inflammation, deformities and granulomas (Berg et al. 2006), and growth alterations (SØrum and Damsgård 2004; Berg et al. 2007). In addition, staff with experience in the application of this type of vaccines is required. On the other hand, the oral vaccination route is favoured because of its ease of administration, but not all fish can eat/take the same amount of antigen so it may not provide a uniform protection. It may also become more expensive if it is necessary to protect the antigen by encapsulation (Vallejos-Vidal et al. 2014).

Probiotics may be used to reduce disease outbreaks in aquaculture. Some probiotics are characterised by their antagonistic activity against pathogens or the stimulation of the fish immune response, including the production of specific antibodies. Immune cross-reactions amongst phylogenetically-related bacteria are widely documented, and they play an important role in protection against pathogens (Medina et al. 2020). Some vaccines use non-pathogenic microorganisms that contain antigens similar to those of pathogenic strains (Brunt and Austin 2005; Brunt et al. 2007; Arijo et al. 2008; Abbass et al. 2010). If a probiotic shares antigens with a certain pathogen, it could produce antibodies with a cross-reaction to that pathogen. Therefore, a probiotic with these characteristics could be used in a similar way to a live vaccine.

The ability of probiotic bacteria administered through diet to modulate the innate and adaptive immune system of farmed fish has been reported (Brunt and Austin 2005; Nayak 2010; Hemaiswarya et al. 2013; Foey and Picchietti 2014), even when some probiotic microorganisms were supplied as heat-killed cells (Biswas et al. 2013). There is information that a probiotic strain of *E. faecium* increased the transcription of genes encoding complement system, lysozyme activity, protease activity and proinflammatory cytokines in specimens of *P. olivaceus* infected with *L. garvieae* (Kim et al. 2013). On the other hand, significant increases in T lymphocytes

(Romano et al. 2007; Picchietti et al. 2009), granulocytes (Sharma et al. 2013), and immunoglobulins (Sharifuzzaman and Austin 2010; Neissi et al. 2013; Xing et al. 2013) have been reported in farmed fish receiving probiotics, and include *D. labrax, Rachycentron canadum* and *O. mykiss*. However, different studies have reported the ability of the subcellular components obtained from probiotics to exert an immunostimulant effect on the specific and non-specific immune responses of farmed fish (Arijo et al. 2008; Chi et al. 2014; Giri et al. 2015, 2018). All these studies strongly suggested that probiotics may be used as adjuvants in aquaculture. In this sense, the reduction of the side effects of vaccines administered with adjuvants is a challenging goal for fish vaccination (Dadar et al. 2017), and the use of probiotics as potential adjuvants is a very interesting possibility, especially because they can be easily administered through the diet as spores (Soltani et al. 2019), freeze-dried (Tapia-Paniagua et al. 2015) and using some type of encapsulation (Martínez Cruz et al. 2012; Rosas-Ledesma et al. 2012). Another interesting aspect in comparison with vaccines is that the use of the probiotic is not limited by the size of fish, because they have been supplied in all growth stages even during larviculture (Lobo et al. 2014).

However, new terms, such as postbiotic, have emerged that imply that bacterial viability is not an essential requirement for health benefits. Postbiotics are soluble factors resulting from the metabolic activity of a probiotic or any released molecule capable of conferring beneficial effects to the host in a direct or indirect way (Tsilingiri et al. 2012), and include a wide range of compounds (Aguilar-Toalá et al. 2018; Ang et al. 2020). In human and veterinary uses, postbiotics have shown beneficial health effects (Nakamura et al. 2016; Compare et al. 2017) indicating a high capacity to modulate different organs and tissues in the host, inducing several biological responses such as an immune response (Kearny et al. 2015), and suggesting that they could mimic the health effects of probiotics.

Therefore, the use of postbiotics may represent a valid and safer alternative to avoid risks linked to live probiotic bacteria for treating many diseases, and the scientific evidence of their beneficial health effects is increasing (Haileselassie et al. 2016; Nakamura et al. 2016; Compare et al. 2017; Zółkiewicz et al. 2020). However, especially in the case of aquaculture, the information on the application of postbiotics is limited (Lieke et al. 2020; Ang et al. 2020), and mainly focused on Gram-positive microorganisms. Studies on the relationship between the immune system and postbiotics can be very relevant, because they could imply a more efficient application of probiotics.

4 Conclusion and Suggestions for Further Work

In conclusion, there is a wide range of probiotics that has been studied for the control of infectious diseases. Probiotics have shown the ability to act against pathogens at the same level as other treatments, such as immunostimulants, medicinal plants and vaccines. However, most probiotics are not legally recognised for use in aquaculture. This represents a limitation for the commercial use of the strains studied. More

research is needed to demonstrate that the wide range of probiotics used experimentally are safe for farmed fish, other animals (including humans) and the environment in general.

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