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REVIEW PAPER

Best practices for fish biosecurity, well-being and sustainable aquaculture

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Abstract

Since its inception ~6000 years ago, aquaculture has evolved to enable its survival and growth to become a major contributor of protein of high nutritional value for human consumption, thereby improving food security and reducing poverty. Best practices have been established and updated to reflect developments as they occurred. Currently, best practices reflect all aspects of production from site selection and especially location in terms of proximity to other farms, construction and maintenance of the facilities, management practices, stock selection and acquisition, nutrition, biosecurity, disease control, and processing. Concerns about aquaculture continue to be addressed, and include the effects of pollution, such as from uneaten food and feces on the aquatic environment, and the needs of other users of waterways, such as for recreation/tourism. Best practices have been formalized into accredited standards, such as ISO 9000, and form the basis of Certification by the Global Seafood Alliance. With the intensification of aquaculture, the provision of total food requirements became necessary for the farmed stock. This has led to the development of feeds capable of providing all the nutritional needs of the farmed species. Concerns about the sustainability of some feed components, such as protein from trash fish, are ongoing. Disease management has progressed from a curative approach (= therapy) with chemicals/antibiotics to prophylaxis with vaccines, probiotics and plant products. Best practices encompass the most up to date technology, including engineering, life sciences and nanotechnology. For the future, aquaculture is likely to remain at the forefront of ingenuity with the goal of increasing its contribution to human nutrition.

Introduction

Aquaculture, which is the rearing of aquatic species in controlled conditions, originated in China around 6000 BC. Initially, common carp (*Cyprinus carpio*) and rice were produced together, with the fish derived from natural spawning, and fed naturally (Harland, 2019). Since then, aquaculture has increased enormously, such that in 2020, and despite the Covid-19 pandemic, 122.6 million tonnes of aquatic species were produced worldwide with a total value of US$ 281.5 billion. This quantity comprised 87.5 million tonnes of aquatic animals mostly for human consumption, 35.1 million tonnes of algae for human and non-food use, and 700 tonnes of shells/pearls for ornamental use (FAO, 2022). According to the FAO, the dominant position of fish production in freshwater fisheries has gradually decreased from 97.2% in 2000 to 91.5% in 2018, reflecting the strong growth of other animals, namely freshwater crustaceans (crab, crayfish and shrimps) in Asia. Furthermore, FAO underlined that the prominent aquaculture production in brackish water involved mollusks (17.3 million tonnes in 2018), followed by fish (7.32 million tonnes) and crustaceans (5.73 million tonnes). Marine fish ranked second by volume according to the 2018 statistics of FAO (2022). Fish farming, which is the most diverse sub-sector of aquaculture, encompasses the production of 27 species representing > 90% of the total fish produced in 2018, and the 20 most important species represent 83.6% of the total fish production. Compared to fish, fewer

crustaceans, mollusks, and other aquatic animal species are farmed (FAO, 2020). Moreover in 2023, the Food and Agricultural Organization of the United Nations called for a further expansion of aquaculture to supply the demand for aquatic foods. Since its inception, aquaculture has progressed from extensive systems with low stocking levels and natural feeding to intensive sites with high densities and the need to provide all feed. However, there are concerns about the availability of suitable locations, and further expansion may reflect the need to move away from the coast to offshore marine sites with the inherent difficulties of engineering, weather and predation (e.g, Galparsoro et al., 2020; Watson et al., 2022). Of course, consideration has to be given to environmental issues and the needs of other users, for example, tourism/recreation. Currently, aquaculture contributes approximately half of the total aquatic species used by human beings (FAO, 2022). In short, aquaculture is a major, vibrant contributor of highly nutritious protein for the masses, high value food – such as salmon and caviar – and components (e.g. pearls) for more affluent consumers, species for restocking of waterways, ornamentals for ponds and aquaria, and material destined for biotechnology (see Stickney, 2005). Overall, aquaculture has contributed significantly to improving food security and reducing poverty, environmental and social well-being while conserving biodiversity by protecting the aquatic ecosystem and reducing pollution, and has gained importance with the use of new technologies, i.e. the Blue Transformation (FAO, 2022).

Since the initial development of aquaculture, a wide range of effective methodologies has been developed to enable its current success of a major food contributor. Best practices have become established to support the development of infrastructure to support the rearing of aquatic animals, and include approaches to site selection, containment structures, stocking policies, nutrition, management of disease (involving use of medicinal plants, vaccines, biological control agents: phyto-, pro-, post-, syn-, para- and prebiotics, vitamins, bacteriocins and bacteriophages), optimizing water usage (i.e., filtration systems, disinfection systems), genetic improvements (breeder selection, sex control, polyploidy, marker assisted selection, [MAS], gynogenesis and androgenesis, nanotechnological techniques, such as supported by some other prophylactic methods, and mitigation of the effects of pollution. Best practices have been formulated into sets of guidelines that reflect the most appropriate ways to carry out an action, and are considered as better to alternatives, ensuring quality of the finished product. These practices form part of accredited standards, such as ISO 9000. Indeed, Best Aquaculture Practices form the basis of Certification by the Global Seafood Alliance (https://www.globalseafood.org), and seek to ensure that aquaculture is carried out responsibly. The Certification process verifies that producers use best practices involving every stage of production from hatcheries to processing, by considering safety, health and welfare, and environmental and social aspects. These aspects form the basis of the current review.

Current Status of Fish Production Technologies and Future Focus of Preventive Medicine

Aquaculture technologies (systems, applications and facilities) vary greatly around the world. In particular, there has been rapid and significant advances in the development of freshwater fish farming systems integrated with agricultural systems resulting in higher and better efficiency in the use of resources, and a positive impact on the environment (FAO, 2020). In this context, the current status of farmed aquatic species and known fish production technologies, i.e. extensive, intensive and super-intensive, with newly developed production technologies, namely Biofloc, Aquaponics, Integrated Multi-trophic Aquaculture (IMTA) and Aquamimicri, will be addressed.

Farmed Species

In marine and coastal aquaculture, production is focused mainly on crustaceans, mollusks and Atlantic salmon (*Salmo salar)*, production of which has increased significantly in Chile and Norway with governmental encouragement in identifying suitable areas in coastal waters. The interest in Mediterranean countries is in production of European sea bass (*Dicentrarchus labrax*) and gilthead sea bream (*Sparus aurata*), which have increased greatly over the past decade as a result of technological developments (FAO, 2002). Other important farmed species include Pacific threadfin (Moi; *Polydactylus sexfilis*) in Hawaii, sea bass and pompano (*Trachinotus* spp.) in the Mediterranean, yellowtail (*Seriola quinqueradiata*) in Japan, milkfish (*Chanos chanos*) in the Philippines, cobia (*Rachycentron canadum*) in Taiwan, and recently rainbow trout, i.e. "Turkish salmon", in the Black Sea.

In developing countries, except for shrimp, aquaculture production is dominated by omnivorous, herbivorous and/or filter-feeding fish (Araujo et al., 2022). These production systems and facilities are very diverse. Indeed, completely or partially artificial structures in areas adjacent to the sea, such as land-based ponds and closed lagoons along the coast, are used extensively.

The most cultivated species and their production technologies in aquaculture facilities have been included in Table 1 (see FAO, 2023). The top 5 species will be emphasized as they account for ~1000000 tonnes of production, and include grass carp (*Ctenopharyngodon idellus*), Nile tilapia (*Oreochromis niloticus*), Atlantic salmon (*Salmo salar*), milkfish (*Chanos chanos*) and rainbow trout (*Oncorhynchus mykiss*) (Table 1, FAO, 2023). Rainbow trout, considered as an important species for freshwater aquaculture, shows increasing success in brackish water conditions in the Black Sea, achieving harvest sizes of >2.5 kg in weight/fish (Yigit et al., 2023). In addition, barramundi/Asian sea bass (*Lates calcarifer*) production has undergone significant growth from 25000 tonnes to over 168000 tonnes in the last decade (China Fisheries Association, 2020). Similarly, pompano (*Trachinotus blochii*) and cobia, with production levels of 110194 tonnes and 50000 tonnes, respectively, are increasing substantially (McMaster & Gopakumar, 2016; Tveterås et al., 2019). All these species are considered as key players for the aquaculture industry leading to a beneficial economic impact from increased production and the use of appropriate, modern best practice production technologies (Table 1; Araujo et al., 2022). For the expansion of production for marine species, such as cobia, milkfish and pompano, further investigations are needed to focus on:

- new production technologies through the implementation of more efficient systems,
- investigation of environmental impacts, especially improvements in cage farming (off-shore and in-shore) and
- the commercialization of these products, with more emphasis on value-added by-products.

Concerns for the future expansion of Atlantic salmon production include the danger from the escape of specimens into the environment, the development and spread of resistance to diseases and pollution effects resulting from excessive use of nutrients and chemical products.

New species with less protein requirements and more sustainable production technologies could be considered for healthier and more sustainable production towards meeting food demand that is anticipated to increase even more in the near future. This goal may be achieved by international collaborations, which are necessary for the future of the global aquaculture industry that needs guidance and support by national and international policies. Strategic planning is needed to evaluate new production technologies, including the adoption of sensible locations,

medium stocking densities and appropriate feeding strategies, the benefit of which may be confirmed by low stress indicators, e.g. cortisol levels (Hanke et al., 2020). These criteria are directly related to the oxygen level and water quality of the culture environment. Therefore, aquaculture practices should be evaluated for all candidate species. FAO and other government organizations need to specifically support renewable energy and offshore farming.

Production Technologies

Although there is a variety of production technologies, they may be classified according to the intensity level of production, as follows:

- extensive
- semi-intensive
- intensive and continuous production systems
  - Extensive technologies assume that fish will only feed on natural food, zooplankton and bottom fauna. Thus, the cost of, for example, carp production, will be the lowest. The harvested fish may be referred to as "ecological", and production targets may not be predicted in advance.
  - Semi-intensive technologies assume that the fish are fed on natural food, and their energy needs are met by additional sources, such as carbohydrates in supplementary diets.
  - Intensive technology necessitates the need for feeding regimes with compound diets containing a high protein content, which allows a high productivity of 3-20 tonnes/ha in the case of carp. Although this system gives the highest performance, it requires the most costs. The ponds should be provided with additional aeration and good water flow to prevent the build-up of waste materials and the development of diseases.
  - Continuous Production Technology combines the intensive technology of fish grown in modern facilities with continuous technology, which is a simpler system for fish breeding. The technology is referred to as continuous because the production cycle is not interrupted by transportation from one site to another (Loboiko et al., 2021). This system is technically and economically viable, appropriate, socially acceptable and sustainable - in a three-stage system consisting of larviculture, pre-growth and final growth in cages – differently from the rainbow trout, sea bream and sea bass culture technique in Türkiye.

Cultivation at high densities may cause adverse environmental impacts, such as high chemical and biological loads, that in turn may result in the deterioration of water quality. Further impacts result in disease outbreaks, unsustainable nutrition, and competition for coastal space with harmful effects on the environment (Sun et al., 2021).

Jiang et al. (2022) developed a food-energy-water-carbon (FEWC) sustainability index from 0 to 100 to assess the global sustainability of aquaculture across countries. The results show that the overall sustainability of global aquaculture is low (mean score = 26); none achieved a high sustainability score (75-100); almost all aquaculture falls into the low sustainable range (0-50). Thus, there is great importance in using best practices to achieve sustainability in aquaculture production. A holistic approach to production is required by considering all aspects from production technologies to nanotechnology applications to achieve this.

Integrated Multi-trophic Aquaculture (IMTA)

The discharge of wastewater, which is mainly attributed to the food sources that are used for fish production, may dramatically affect the

environment if not treated properly. Thus, the concept of IMTA (integrated multi-trophic aquaculture) was developed, which applies a simplified food web structure to a farming system involving feeding species, such as fish and shrimp, along with extractive organisms, such as mollusks and seaweed, that enable the absorption of particles and nutrients from the environment (Carballeira et al., 2021). Clearly, fish farmers need to consider many factors when designing a waste treatment unit particularly if recirculation (recirculation aquaculture system; RAS) is used and may utilize macrophytes or adsorbents to remove pollutants. The overarching aim is to reduce environmental pollution with appropriate treatment methods (Ahmad et al., 2022a).

The current knowledge available about RAS enables the production of high-value species that makes the system viable and economically feasible. However, other aquatic species may become sustainable with alternative applications, such as the incorporation of the green production of "aquaponics." Through research and field testing, more information about RAS technology is gathered, as well as a better understanding of the interaction between its complex components. RAS technology will continue to transform and modernize the aquaculture industry, including local production in or near metropolitan areas, as well as in places and countries with limited water resources where more traditional aquaculture systems will be implemented (Yue & Shen, 2022).

The nutrient-rich wastewater from rearing tanks of the most diverse cultivated marine species may be used for the cultivation of marine macroalgae. These algae have potential for the world food, pharmaceutical and energy industries with the latter focusing on production of biodiesel.

Biofloc Technology & Aquamimicry Concept

Even though the growth of aquaculture provides a significant amount of food for the growing world population, the control of waste from production facilities and the use of water resources especially in freshwater farms is of great importance. Thus, the water used for aquaculture may also be potential sources of potable drinking water for humans. The most rational approach is to re-use water in aquaculture as far as possible with the application of RAS (Austin et al., 2022). However, these systems need more investment, particularly regarding operating costs with the aim of devising cost-effective technologies. Therefore, the increase of production with less water should be the main goal for the future of aquaculture. Avnimelech (2012) underlined the essentials of increased food production with reduced water and land use. However, increased production will impact adversely on the generation of more waste. Also, the increase of biomass in aquaculture sites may affect the need for therapeutic agents, which could lead to the deterioration of water quality, and lead to more disease outbreaks (Deepak et al., 2020). Increased biomass and stocking densities necessitate the need for higher quantities of feed that may result in excessive total suspended solids (TSS) in the aquatic environment (Ebeling et al., 2006). The overall effect would be a reduction in water quality and possibly reduced fish growth in the long term (Vinatea et al., 2010).

Biofloc Technology (BFT)

The new approach of biofloc technology (BFT) has been introduced to achieve sustainable aquaculture that involves recycling nutrients, and providing food for fish while achieving the appropriate balance of carbon to nitrogen (C: N; Khanjani et al., 2022a). The main target of BFT is the production of suitable microbial populations (= flocs) with the cultured fish that requires only a minimum exchange of water. It may be emphasized that only 10% of the total daily water could be supported by fresh water entry for RAS, whereas BFT does not need the replacement of water if the C:N ratio is maintained properly. Hence, BFT would appear to be more efficient in cost and ecological approach compared to RAS. The

only source of energy in BFT would be the need for continuous aeration, which is essential to keep the microbial floc in suspension (Romano, 2017).

Aquamimicry Concept

The Aquamimicry concept has been introduced recently to Korean shrimp aquaculture, and is a method applied in ecological farming with the aim of harvesting animals with zero waste discharge from the production facilities (Cho & Yigit, 2022). The concept of "Aquamimicry" follows the harmony of nature with the development of copepods, that are valuable nutrients for shrimp. The Aquamimicry concept is strongly dependent on organic carbon with no external arrangement of the C:N ratio. According to Khanjani et al. (2022a), the concept is based on the natural inter-relation of prebiotics, such as oligosaccharides, which are naturally produced through the fermentation of a carbon source (e.g. rice bran) and a probiotic (e.g. *Bacillus* sp.) that may help trigger phytoplankton and zooplankton blooms. The latter provides healthy live food for cultivated shrimp. It has been reported that spreading productive bacteria in the Aquamimicry system supports the continuous production of healthy shrimp with good growth and commendable welfare in cultured conditions (Cho & Yigit, 2022).

Table 1. The most cultivated species and characteristics with production quantities and technologies in aquaculture facilities

Farmed species	**Production Tonnes*1000 / % (FAO, 2022)**	**Production Technologies**
Atlantic salmon, *Salmo salar*	2 719.6 32.6 %	RAS is used. Fish with an average weight of 40 to 120 g are transferred to the sea (= smolts). The cages can be square or circular and have different sizes, up to 24 m^2 or 100 m in diameter, and depths from 15 to 18 m (FAO, 2008) *Main advantage of production; Spawns in fresh water and growth in sea water*
Milkfish, *Chanos chanos*	1 167.8 14 %	In the Philippines, this species was traditionally cultivated in ponds with brackish water, but eventually expanded to fenced-in and marine cages (Philippine Council for Agriculture, 2016, de Jesus-Ayson et al., 2010, FAO, 2017) and is commonly performed in coastal marine waters. In this type of culture, different stocking densities are used, from 5 to 30 fish/m^3 (Lee et al., 1997). When comparing the operational procedures, as well as production costs in the intensive and semi-intensive systems in the milkfish cultivation in Taiwan, concluded that the semi-intensive or outdoor environments are profitable operations for the production of juveniles, when compared to intensive production (Lee et al., 1997) *Suitable for marine and brackish water fish, as well as fresh water*
Sea bream, *Sparus aurata*	282.1 3.4 %	Gilthead sea bream is a fish commonly cultivated in the Mediterranean Sea in marine cages (offshore and in shore) and RAS (hatchery production) (Seginer, 2016). Recently the fish have been cultivated in earthen ponds with between 5 and 15 ppt salinity.
Large yellow croaker, *Larimichthys croceus*	254.1 3%	The croaker is mainly limited to coastal waters of continental East Asia. The farming modes of the large yellow croaker include: framed floating sea-cage farming (sea-cage farming for short in the following), earthen-pond farming, subtidal-zone enclosure net farming (enclosure-net farming for short in the following); deep sea-cage farming, and inner bay-net barring farming. Sea-cage farming is simultaneously used to produce large-sized fry for other farming modes of this species and is the most important farming model for large yellow croaker (Chen et al., 2018).

Farmed species	**Production Tonnes*1000 / % (FAO, 2022)**	**Production Technologies**
European sea bass, *Dicentrarchus labrax*	243.9 2.9 %	European sea bass is commonly cultivated in marine cages (offshore and in shore), and RAS is used in hatchery production. Sites are mostly located in the Mediterranean area, principally in Turkey, Greece, Egypt and Spain (Vandeputte et al., 2019). Earthen ponds are also used as in sea bream culture.
Cobia, *Rachycentron canadum*	NA*	RAS for cobia hatcheries, generally the tanks are of small volume (~300 L) with some of the most popular species used for cage cultivation in the open sea (Carvalho, 2022) "In Taiwan, cultivation is carried out in two phases: fingerling hatchery, where nursery cages are used, and fattening, carried out in larger cages." (Liao et al., 2004) *Big increase in the last 20 years of production of Cobia. Rapid growth, high market value, good meat quality* *Cobia production in China, Taiwan, Panama, and Vietnam—the most important producing countries—is estimated to have been 53000 m.t. in 2020, an increase of only 3% from the previous year. Since 2010, production in these countries has fluctuated around levels of 40 to 50000 m.t. (Tveterås et al., 2019).
Barramundi, *Lates calcarifer*	105.8 1.3	In Asia, "farmed intensively in land ponds". In Australia, fish are stored in cages in fresh or brackish water environments, in marine waters, or in terrestrial recirculation systems. FAO, 2020. The fishing technique in the cage system is relatively simple. In the pond's cultivation system, it is more difficult, requiring the use of nets or mechanisms for water drainage (Rimmer, 1995; Sorphea et al., 2019) *Big increase in the last 20 years of production. High salinity tolerance and genetically resistant to vide range of environmental parameters*
Golden pompano, *Trachinotus blochii*	160 1.9	The mariculture of this fish is carried out in open sea cages, brackish water cages, and in ponds in China, India, Indonesia, Philippines, Taiwan, Thailand, and Vietnam. The methods for cultivation cages in open sea have been well-established in Vietnam (McMaster & Gopakumar, 2016) *Big increase in the last 20 years of production. Rapid growth rate, good meat quality and high market demand*

* NA: not available

Crustaceans

Common Name	**Production Tonnes*1000 / % (FAO, 2022)**	**Production Technologies**	**Source**
Whiteleg shrimp, *Penaeus vannamei*	5 812.2 51.7 %	Ongrowing techniques can be sub-divided into four main categories: extensive, semi-intensive, intensive, and super-intensive, which represent low, medium, high, and extremely high stocking densities respectively (Sun et al., 2023; FAO, 2023)	
Red swamp crawfish, *Procambarus clarkia*	2 469.0 22 %	RAS, BFT, and higher-place ponds (HPP) are considered as alternative technologies in addressing major environmental challenges linked to conventional whiteleg shrimp farming systems (Mazlum et al., 2020)	

Aquaculture inland

Common Name	**Production Tonnes*1000 / % (FAO, 2022)**	**Production technologies**	**Source**
Grass carp, *Ctenopharyngodon idellus*	5791.5 11.8 %	An omnivorous species, c*arp is one of the few fish for which a wide range of technologies has been developed: from extensive, with minimal human intervention in the formation of fish productivity of the reservoir, to intensive, with the most controlled production conditions (*Khan, 2003)	
Silver carp, *Hypophthalmichthys molitrix*	4896.6 10 %	*Since carp burrow in the pond bottom, have a broad environmental tolerance and an omnivorous feeding habit, they are a key species in integrated systems and for different breeding technologies.* (FAO, 2020)	
Common carp, *Cyprinus carpio*	4236.3 8.6 %	*Fish farming is now using continuous rearing technology*. (Chirwa et al., 2017); Loboiko et al., 2021) *The technology is called continuous primarily. Because, the cycle of carp rearing is not interrupted by transplanting it from pond to pond*	
Bighead carp, *Hypophthalmichthys nobilis*	3 187.2 6.5 %	*Big increase in the last 20 years of production of Catla*	
Catla (Indian carp), *Catla catla*	3 540.3 7.2 %	Today there are many technologies for growing carp. Extensive (grazing), semi-intensive, intensive, and continuous, as a different intensive technology for growing carp, is the most effective (Loboiko et al., 2021).	
Roho labeo, *Labeo rohita*	2 748.6 5.6 %		
Nile tilapia (*Oreochromis niloticus*)	4407.2 9 %	Nile tilapia *O. niloticus* cultivated in circular and quadrangular cages Tilapia tolerate low concentrations of dissolved oxygen in water (Araujo et al., 2011)	
Striped catfish, *Pangasianodon hypophthalmus*	2 520.4 5.1 %	The channel catfish are the most widely cultured catfish in China (Tran et al., 2017) African catfish, *Clarias gariepinus*, is a freshwater fish that widely cultivated in Indonesia. (Alawode et al., 2016)	
Clarias catfishes, *Clarias* spp.	1 249.0 2.5 %	Ponds, tanks (RAS is also used), cages (FAO, 2020) *Big increase in the last 20 years of production of both catfish*	

The main source of protein in feed destined for carnivorous species, e.g. trout, is an environmental challenge facing the industry (Martin et al., 2021). Hence, research on alternative protein sources in diets is important for the future of sustainable aquaculture. The over-exploitation of aquatic species as a source of fish meal and oil for incorporation into diets for carnivorous species is no longer sustainable (Austin et al., 2022).

There is concern about the effects of aquaculture on water quality. Fortunately, Aquaculture 4.0 computer programs (Biazi & Marques, 2023) may provide farmers with real-time monitoring of water quality and the conditions in the production sites (Araujo et al., 2022). In the near future, remote operated vehicles (ROVs), autonomous cage systems with robotic technologies for fish farming, drones that can view the farm site from the surface, and even dive for monitoring the facilities underwater, sensors for maintenance, and artificial intelligence systems for decision-making may become the focus for the sustainability of aquaculture.

Offshore aquaculture is a new enterprise that must include additional technologies, such as artificial intelligence and augmented reality that will remotely improve and automate numerous activities such as feeding, sampling, monitoring, and surveillance. There may well be use of ROVs, robotic cages for fish farming, drones capable of diving and monitoring fish ponds and cages, sensors to maintain sustainable aquaculture, and artificial intelligence for decision-making.

Prophylactic Nutrition - Critical Considerations

Quality feeds are branded not only for their pure nutritional characteristics, but also for their health-promoting and disease-preventing properties. How successful is a preventive (prophylactic) diet? The paramount importance of aquatic animal nutrition has been and will be noted at several points in this review, and is discussed extensively in recent reviews (e.g., Hayatgheib et al., 2020; Dawood, 2021; Rahimi et al., 2022; Skjærven et al., 2022): Appropriate nutrition strengthens the innate immune system and reproduction, promotes beneficial bacteria and the next generation(s), and ultimately drives evolution (Steinberg, 2018, 2022).

The majority of ingredients used in feed formulations serve to support nutritional requirements, whereas feed--additives are compounds that are incorporated into the diet for specific purposes other than meeting nutritional requirements, including improving the welfare of the cultured organism, the quality of the final fish product, and the physical and chemical properties of the feed (Bai et al., 2022). Feed additives are therefore referred to as ‘functional’ because they are intended to perform specific functions in the diet. There is a wide variety of functional feed additives used in aquaculture. Feed binders, stabilizers, antioxidants, and antimicrobial compounds are used in fish feeds to preserve the nutritional properties or the ingredients prior to feeding. Feed stimulants and attractants (e.g. betaine and nucleotides) are used to improve feed intake and palatability; colorants such as astaxanthin and other xanthophylls may help with the pigmentation of the final product; enzymes (e.g. phytate and amylase) and organic acids (e.g. butyric acid) may facilitate the digestive process and increase the availability of nutrients, resulting in improved growth performance. Another important group of additives includes immunostimulants, such as probiotics, prebiotics, and phytogenics. This group of feed additives is mainly used to improve the immune response of fish or the water quality of the farm (NRC, 2011; Encarnação, 2016). Taken together, feed additives comprise an integral part of modern feed formulations in aquaculture (Bai et al., 2022).

As one of several similar documents on the expected and realized beneficial effects of functional feeds in improving aquatic animal immunity, the recent study by Rahimi et al.

(2022) may be referenced. The authors conducted a meta-analysis on the effect of probiotics on immunological parameters in rainbow trout. The results of this analysis confirmed the beneficial effect of probiotics on immunity in rainbow trout by increasing serum lysozyme activity, serum ACH_{50} activity, plasma ACH_{50} activity, serum immunoglobulin, plasma immunoglobulin, serum total protein, serum complement activity, and phagocyte activity. However, some factors such as the duration of the experiment, fish size, and probiotic dosage may affect the results.

There is also a more general critical note to be made here: Despite the potentially beneficial contribution of functional supplements for prophylactic purposes, there are some drawbacks. These include the lack of accurate data on optimal dosages, especially the lack of toxicity studies, and insufficient data on the effects of these supplements at the biomolecular and other 'omics' levels. This is certainly due to the young age of this field of research, but applied science, such as preventive (prophylactic) nutrition of aquatic animals, cannot ignore the progress in basic biology.

When functional feeds are used as a means of counteracting and buffering future challenges, such as disease or abiotic stress situations, epigenetic mechanisms of action are at play (Anastasiadi & Piferrer, 2019; Saito et al., 2021; Piferrer & Wang, 2023). This is because, unlike genetic mutations, epigenetic changes, including epimutations, occur rapidly and are stress-induced and even directly targeted against the stressor (Ryu et al., 2020), rather than randomly, like real genetic mutations. Furthermore, most genetic mutations are at risk of extinction because most of the mutation products are highly inferior to conspecific competitors. Nutriepigenetics, which leaves DNA unaltered, is a young field of science that is gaining increasing attention.

In addition to this control variable in the appropriate use of feed to promote immunity and Darwinian fitness, there is another that is certainly as important as nutriepigenetics, but just as poorly understood: the role of the gut microflora (Baldassarre et al., 2022). More than a decade ago, Kiron (2012) pointed out the basis of preventive nutrition, the immune system, and summarized that knowledge of this system in fish is still fragmentary, except for a few species. This situation has not improved significantly to date. This is a limiting factor in any attempt to relate immune function to nutrient or additive intake. In addition, not all components of the immune system would respond equally to a given substance. Marginal deficiencies and nutrient imbalances would interfere with an optimal immune response. Very few attempts have been made to study the underlying mechanisms as influenced by a nutrient or its interactions with other nutrients/additives. The interaction between nutrition and the immune system of fish involves a myriad of physiological processes occurring in different organs under different levels of regulation. Since diets are complex mixtures that provide different nutrients and beneficial substances to support multiple physiological responses (Panserat & Kaushik, 2010), an integrative approach is required to analyze them. Recent approaches to understanding biological processes through gene expression, epigenetic fate of mRNAs, molecular interactions, and the cellular environment using high-throughput experimental techniques are contributing to a systematic build-up of an understanding of the immune system of prominent farmed fish (Kiron, 2012). Therefore, before advocating the use of feeds for specific health benefits, we need a better understanding of immune mechanisms to clearly explain the attributes associated with a nutrient or additive. This should include how individual variations in immune responses determine susceptibility to infection. In addition, we need to know how specific nutrients and their nutrient interactions are influenced by phenotypic, genotypic and epigenomic variations in fish populations. In addition, a compelling endpoint will be to know the extent to which any observed immune enhancement

translates into improved disease resistance and the fitness of offspring. In the future, these facts would help to better evaluate feed components to clarify their role in maintaining good health (Kiron, 2012). In addition to the incomplete but growing understanding of immunity in fish and invertebrates, there are even greater gaps in our knowledge of the role of gut microbiota, epigenetics, and prophylactic nutrition. Dawood (2021) and Baldassarre et al. (2022) point to the microbiota-mediated plasticity that allows organisms to cope with rapid environmental changes, including changes in alternative food sources. Although equally important, this aspect will not be pursued here. We will focus on epigenetics. Recently and for the first time, Marandel et al. (2022) highlighted that the global hepatic methylome in rainbow trout is affected by a plant-based diet, depending on its genetic background. Depending on the line, this latter effect appeared to be due to a decreased feed intake alone or combined with the effect of dietary composition *per se*. In addition, genes related to DNA (de)methylation processes have been shown to be sensitive to nutritional changes and for some of them in a line-dependent manner. Although the foundation is still fragmentary, the concept of preventive nutrition is gaining widespread acceptance in the aquaculture industry, as healthy fish and invertebrates would be able to resist pathogens, parasites, or other noxious agents and stressors.

Available reviews contain mostly successful examples; however, it remains unknown how many failed attempts preceded these examples, from which we could have learned if they had been published. To make a colloquial comment, the Nobel laureate in literature, Samuel Beckett, is quoted: '*Ever Tried. Ever Failed. No Matter. Try Again. Fail Again. Fail Better.'* Scientifically expressed: A guiding hypothesis for the development of preventive feeds does not yet exist.

All previous approaches follow the guidelines from the well-founded and justified perspective of food production, which is a less scientific but a more anthropocentric perspective:

a) What compounds are available as feed supplements; or

b) What can be valorized from agricultural waste; or

c) What compounds have successfully served human beings within the ethnopharmacological practice?

But are there really no innovative approaches from general biology or human medicine that are worthy of introduction into sustainable aquaculture? What could we gain by turning the tables and asking what and how the overall condition and health status of aquatic animals change when we feed them our newly designed, functional feed – other than the desired and projected life history traits in the organism, such as enhanced immunity and resistance to pathogens? Are there more objective life history traits or simply biomarkers than our more subjective, projected ones?

In human medicine, there is evidence that the effects of lifestyle and diet may be easily and seemingly reliably determined from an individual's methylome, also known as the epigenetic clock. The loss of epigenetic control with age is associated with progressive diseases of ageing, including cancer, immunodeficiency, and diabetes. Inappropriate diet or lifestyles, for example, accelerate this process (Strath et al., 2022). The close relationship between nutrition and DNA methylation makes epigenetic clocks ideal indices for modified and sustainability-related nutritional studies in aquatic animals. Although Horvath et al. (2012) initially developed the epigenetic clock to predict age, the discovery of its association with lifespan and health status has made it a hallmark of biological age, with an accelerated tick of the clock indicating a faster rate of degeneration (Lowe et al., 2018). Positive epigenetic age acceleration (i.e., epigenetic age greater than chronological age) indicates that the tissue

ages faster than would be expected, and has been linked with multiple age-related and stress conditions: such as obesity (Horvath et al., 2014; Nevalainen et al., 2017), reduced physical and cognitive fitness (Marioni et al., 2015), disease related cognitive functioning (Levine et al., 2015), diet, exercise, education, and lifestyle factors (Quach et al., 2017; Kim et al., 2022). In fact, the number of such papers has exploded since Horvath's (2013) first publication, and the idea is now entering forensics (Simpson & Chandra 2021), and the wild (De Paoli-Iseppi et al., 2017; 2019), including aquatics (Polanowski et al., 2014; Anastasiadi & Piferrer 2020, 2023; Tanabe et al., 2020).

The first piscine epigenetic clock (and the first one in poikilothermic vertebrates) has been developed in the European sea bass (*Dicentrarchus labrax*) (Anastasiadi & Piferrer, 2020). The authors showed that the epigenetic clock was precise and stable in this poikilothermic vertebrate. To pave the way for a broad application of epigenetic clocks, Anastasiadi & Piferrer (2023) provided a workflow for bioinformatic analysis of bisulfite sequencing data for epigenetic clock construction applicable to fisheries and aquaculture management. This method preferentially uses fin clips as specimens with the advantage that they are easy to access and collect, and are non-invasive and non-lethal (Piferrer & Anastasiadi 2023). It is well documented in aquatic animals that DNA methylation can be regulated by the environment and by nutrients – and it is likely that many environmental cues come through the diet. Although methodological challenges remain, the catalogue of aquatic vertebrates, and even invertebrates, is growing, so this approach, or another similar one, may put an end to the hypothesis-free period of trial and error in prophylactic nutrition.

What about nutritional factors? Many B-vitamins are directly linked with DNA methylation by serving as substrates or cofactors in relevant pathways. In addition, several amino acids and fatty acids are known to play a role in the one-carbon metabolism and, in concert with acetyl-CoA, in epigenome modulations. Methionine, for example, is a major methyl donor; histidine also participates in the one-carbon metabolism, thus affecting DNA and protein synthesis as well as epigenetic pathways. Polyunsaturated fatty acids (PUFAs), such as arachidonic acid or linoleic acid, may interfere with the expression of genes that regulate homocysteine synthesis from methionine, indicating that dietary PUFAs affect the one-carbon metabolism (for details, refer to Steinberg, 2022). Acquired methylation patterns may even be passed on to subsequent generations, as shown in zebrafish with the widely used sunscreen ethylhexyl salicylate (Zhou et al., 2022). Actually, Saito et al. (2021) demonstrated the effect of micronutrient supplementation on hepatic transcriptional and epigenetic regulation in a dose-dependent manner in Atlantic salmon. Specifically, the authors elucidated the mechanisms of altered cell metabolism leading to improved growth performance by micronutrient surpluses at the level of gene expression and DNA methylation. The results indicated that micronutrient supplementation dose-dependently suppresses gene expression in lipid metabolism and broadly affects DNA methylation in cell adhesion and cell signaling. In particular, it increases DNA methylation levels at the *acetyl-CoA carboxylase alpha* promoter in a concentration-dependent manner, further suggesting that *acetyl-CoA carboxylase alpha* is an upstream epigenetic regulator that controls its downstream lipid biosynthetic activities. Taken together, this study demonstrates a comprehensive analysis to reveal an important role of micronutrients in lipid metabolism through epigenetic control of gene expression. Whether and how this DNA methylation pathway modulates epigenetic-to-chronological age discordance remains to be investigated. In a promising study, Bertucci et al. (2021) constructed an epigenetic clock in Japanese medaka (*Oryzias latipes*) capable of predicting chronological age. To test the role of

environmental factors in driving epigenetic age variation, the authors exposed medaka to chronic, environmentally relevant doses of ionizing radiation. Because most organisms share an evolutionary history with ionizing radiation, it has been hypothesized that exposure would provide fundamental insights into the interactions between environment and epigenetic ageing. Radiation exposure disrupted epigenetic ageing by accelerating and decelerating normal age-associated patterning and was most pronounced on cytosines that were moderately associated with age. These findings provide empirical evidence for the role of DNA methylation in the integration of environmental factors into ageing trajectories and open promising perspectives for nutritional issues. Other examples of successfully constructed epigenetic clocks in fish species are rapidly emerging, still somewhat crude, but with the potential for refinement: zebrafish (Mayne et al., 2020), Australian lungfish, Murray cod, and Mary River cod (Mayne et al., 2021), or two wild-caught Gulf of Mexico reef fishes (Weber et al., 2022). Although the exact method of using methylome modulations as a measure of nutraceutical suitability currently appears to be a light at the end of the tunnel, these few examples show that it is worth pursuing.

Disease Management

With the rapid expansion of aquaculture in the years after World War 2, disease control progressed from essentially a curative approach, i.e., therapy, to preventative (= prophylaxis). From the dominance of antimicrobial compounds, interest re-focused onto the development and use of vaccines, and a multitude of other approaches, including bacteriocins, bacteriophages, improved husbandry/management, non-specific immunostimulants, medicinal plant products, movement restrictions/slaughter, prebiotics, probiotics, synbiotics, paraprobiotics, postbiotics. quorum quenching, vaccines, vitamins and water disinfection, and use of genetically disease resistant stock. Antibiotics and other antimicrobial compounds were instrumental in combating bacterial diseases from the pioneering work of Gutsell (1946), who described the benefit of sulfonamides for the control of furunculosis in trout. This was followed by the demonstration of the effectiveness of oxytetracycline (= Terramycin) for use against ulcer disease in brook trout (*Salvelinus fontinalis*) (Snieszko & Griffin, 1951). This would have been the heyday of antibiotics, the success of which decreased research in other disease control methods, notably vaccine development. However, justifiable concern about the possibility of tissue levels and the development and spread of antibiotic resistance dampened enthusiasm for antibiotics (Mohan et al., 2019; Dawood et al., 2021). Consequently, attention focused on other methods of disease control:

Husbandry and Farm Management

The aquaculture facility and its management are the starting point for effective disease control. A "good" supply of chemically and microbiologically clean water is essential, and the site needs to be located at a distance from other aquaculture facilities and sources of pollution. Where possible, efforts need to be taken to prevent farmed stock from interacting microbiologically with wild animals, which could facilitate the movement of new and existing pathogens (Peeler & Ernst, 2019; Hinchliffe et al., 2021). Good management will include the use of certified-disease free stock, meaningful stocking levels, good quality feed kept in conditions to avoid contamination with micro-organisms including fungi and thus mycotoxins (Chizhayeva et al., 2022), feeding regimes to negate the accumulation of uneaten food in and around the stock, and attention to recognizing unhealthy conditions at an early stage. Biofouling communities, which may harbor pathogens and impede water movement in cage sites should be removed.

It is essential that disease is recognized as early as possible, which means that effective surveillance and communication are needed,

such that remedial action may be instigated as quickly as possible.

A Role for Inhibitory Compounds?

The dominance of antibiotics, which were regarded as the saviors of aquaculture in the 1960s-1970s, is clearly over as concerns mount about the impact of antibiotic resistance, tissue residues and the deleterious effects on the environment. It is difficult to foresee a long-term role for antibiotics in sustainable aquaculture except in special circumstances, such as the treatment of valuable individuals, which are housed in enclosed conditions leading to minimal discharge of bioactive compound into the aquatic environment. However, there will continue to be a role for other inhibitory compounds, such as disinfectants for controlling fungal infections of eggs, providing that consideration is given to minimize any potentially deleterious effects on the environment (Austin & Austin, 2016).

Movement Restrictions/Stock Destruction

For some diseases, their presence in aquaculture is regarded as so serious that movement restriction and/or slaughter would be the end result. This action would be covered by national legislation, and hopefully compensation to the aquaculturist. Movement restrictions would apply to diseases, such as bacterial kidney disease in salmonids and ostreid herpesvirus in *Crassostrea gigas* (Rodgers et al., 2019), whereby live animals would not be allowed to leave the site or exceptionally be transferred between infected farms. For the latter, which would apply to diseases, such as viral hemorrhagic septicemia, stock would be slaughtered, and destroyed by incineration or burying in quick lime.

Biological Control

The use of bacteriophages to attack bacterial fish pathogens, including *Aeromonas* and *Vibrio*, has shown promise for disease control in aquaculture, leading to reduced mortalities (Ninawe et al., 2020; Liu et al., 2022). In one example, bacteriophage FCL-2 was applied by bathing in a RAS containing rainbow trout to study the effect on populations of the causal agent of columnaris, *Flavobacterium columnare*. The outcome was that after a single application, the bacteriophage was detectable in the system for up to 3-weeks (Almeida et al., 2019; Kunttu et al., 2021). Bathing with bacteriophage suspensions before the onset of clinical disease was successful in preventing the development of columnaris (Kunttu et al., 2021). However, the approach of using bacteriophage therapy is still largely experimental and is unlikely to gain the widespread acceptability of some of the other possibilities discussed herein.

An exciting development involves the use of cleaner fish (notably corkwing wrasse, *Symphodus melops*), particularly in Norway and Scotland, to control sea lice, *Lepeophtheirus salmonis*, in Atlantic salmon facilities. Here, the wrasse feed on the sea lice that are present on the salmon (Gentry et al., 2020; Gonzalez & de Boer, 2021).

Medicinal Plant Products

A diverse range of plants, e.g., *Astragalus*, garlic *(Allium sativum*), ginger (*Zingiber officinale*), lavender (*Lavandula angustifolia*), rosemary (*Rosmarinus officinalis*) and stinging nettle (*Urtica dioica*), have been evaluated for use in aquaculture as feed supplements to improve growth and health of the recipient animals (Awad & Austin, 2010; Ozcelik et al., 2020; Zhu, 2020; Zhang et al., 2021). Research has involved the use of whole (dried) leaves and plant components, including carvacrol, curcumin, quercetin, silymarin or thymol, with data pointing to immunomodulation and protection against specific diseases (Soltani et al., 2021; Jeyavani et al., 2022). In one study, garlic fed at 0.5 and 1.0 g/100 g of feed improved growth, immunomodulation, and improved survival (relative percent survival = 95%) of rainbow trout after challenge with *Aeromonas hydrophila* (Nya & Austin, 2009). Subsequently, rosemary leaf powder was fed at 0-3% to common carp for 65 days leading to improved growth, and enhanced albumin, globulin, plasma total protein and lysozyme levels (Yousefi et al., 2019). Apart

from the whole plant, it has been demonstrated that components may be effective. For example, essential oils of ginger, lemon balm (*Lippia alba)* and peppermint (*Mentha piperita*) were fed for 30 days at 0.54 -2.88 g/kg of feed to tambaqui (*Colossoma macropomum*) leading to anthelminthic activity against the acanthocephalan, *Neoechinorhynchus buttnerae.* The most profound antagonistic activity was recorded with 0.54 g/kg of peppermint (inhibition of the parasite = 85.46%). Apart from a better growth rate, there was evidence of increased erythrocyte and thrombocytes number in the treated fish (Costa et al., 2020). Perhaps, it is not so surprising that because of all the research and the widespread availability of plants, many aquaculturists are including plant material in feed destined for use with their farmed animals

Probiotics and Bacteriocins

Probiotics, which are regarded as live microbial feed supplements, have gained widespread use in human and terrestrial animal medicine. For these uses, probiotics center on the lactic acid-producing bacteria, i.e., putative *Lactobacillus.* Certainly, probiotics have been introduced into aquaculture, and have met with great success in improving growth, immunomodulation, and protection against infectious diseases (Ringo et al., 2022). Indeed, there is evidence that some probiotics confer antimicrobial activity (e.g., Tesdorpf et al., 2022). For example, a tropodithietic acid producing isolate of *Phaeobacter piscinae* inhibited *Tenacibaculum maritimum, T. soleae* and some *T. discolor* isolates, which are the causes of tenacibaculosis in marine fish (Tesdorpf et al., 2022). However, the range of organisms considered for use as probiotics in aquaculture includes a diverse range of Gram-positive (*e.g., Arthrobacter, Bacillus, Bifidobacterium* and *Lactobacillus*) and Gram-negative bacteria (e.g., *Aeromonas, Pseudomonas* and *Vibrio*), yeasts and micro-algae. The viability of the preparation is not always essential insofar as inactivated cells (= paraprobiotics) may be effective (Choudhury & Kamilya, 2019; Wu et al., 2020). Also, subcellular components/metabolites of the probiotics (= postbiotics) may have beneficial effects on the host (Wu et al., 2020). Certainly, concern needs to be expressed over the use of some Gram-negative bacteria, especially from taxa associated with fish diseases. Here, the concern reflects the possibility that the probiotic could acquire virulence or antibiotic-resistance genes, although this scenario has never occurred. Paraprobiotics would negate this concern. In general, probiotics have been applied as single or two or more cultures at 10^7-10^9 cells/g of feed and fed for 7-14 days whereupon the recipient animals have been noted to have improved appetite, better growth and are protected against challenge with pathogens. There is often stimulation of innate and cellular immunity in finfish, including enhanced lysozyme, macrophage phagocytic and respiratory burst activities, serum alternative complement, and increased levels of erythrocytes and leukocytes (Austin & Sharifuzzaman, 2022). In shrimp (*Penaeus monodon* and *P. vannamei*), the use of probiotics has led to improved growth and survival, adherence to the cuticle and lining of the digestive tract, and higher levels of phenoloxidase and bactericidal activities (Apines-Amar et al., 2022; Rajasulochana & Gummadi, 2022; Ramirez et al., 2022). It is apparent that numerous probiotics have been commercialized and are available to aquaculture.

Interest has focused on the use of bacteriocins. These are antibacterial peptides/proteins associated often with lactic acid bacteria, which have an important role as probiotics, for disease control in aquaculture (Wang et al., 2019; Nayak et al., 2022; Pereira et al., 2022). In particular, vibriocin, which is produced by *Vibrio* spp., has been reported to inhibit pathogenic isolates of *V. alginolyticus, V. harveyi* and *V. parahaemolyticus* (Sheikh et al., 2022). However, it is relevant to question the relative advantage of using bacteriocins

rather than probiotics that produce these inhibitory compounds.

Nonspecific Immunostimulants/Prebiotics

Prebiotics are (non-digestible) feed additives, notably carbohydrates (e.g. fructooligosaccharide, galactooligosaccharide, ß-glucooligosaccharide, mannanoligosaccharide), that act in the digestive tract to promote the development of beneficial micro-organisms to the detriment of potential pathogens and to stimulate innate immunity (Hasan et al., 2018; Mohan et al., 2019; Genc et al., 2020; Nababan et al., 2022). For example, ß-glucooligosaccharide, from barley glucan, was administered orally to juvenile olive flounder (*Paralichthys olivaceus*) at 0.1% for 8-weeks leading to slightly better growth, significantly enhanced lysozyme, respiratory burst and superoxide dismutase activities, and protection after challenge with *Streptococcus. iniae* compared to the controls (Hasan et al., 2018). In a comparison, mannanoligosaccharide when dosed at 2 g/kg of feed, led to better growth of African catfish in a RAS compared with fructo- and galactooligosaccharide with significant differences in monocyte numbers and alanine- and aspartate aminotransferase, but not so erythrocyte, leukocyte or lymphocyte numbers (Genc et al., 2020).

There is an overlap in the concept of prebiotics with nonspecific immunostimulants that boost immunoprotection of the host. Overall, a diverse range of bioactive molecules, including astaxanthin, chitosan, ß-(1-3)-glucan, vitamin C, lipopolysaccharides, and polysaccharides derived from plants, have been credited with immunostimulatory activity and the ability to enhance disease resistance when administered orally with or without probiotics to farmed stock (e.g. Mohan et al., 2019; Vijayaram et al., 2022; Rajan et al., 2023). Much interest has focused on ß-(1,3)-glucans, which are polysaccharides extracted from the cell walls of unicellular (= yeasts) and multicellular/mycelial fungi. Glucans may be administered orally, and have been linked with improved growth, immunomodulation involving cellular and innate immune responses, and protection against disease (e.g., Yano et al., 1989; Khanjani et al., 2022b). It is noted that some commercial fish diets contain ß-(1,3)-glucan.

Combinations of pro- and prebiotics (= synbiotics) have certain attractions, and may offer greater benefits in combination than used separately (Puri et al., 2023). For example, whiteleg shrimp were fed for 40-days with a probiotic, *Pseudoalteromonas piscicida* with and without fructooligosaccharide leading to improved growth, immunomodulation, i.e., total and differential hemocyte count, phenol-oxidase and respiratory burst activities, and immune-gene expression, and resistance to challenge with white spot syndrome virus and *V. harveyi* more so than when the pro- and prebiotic were used separately (Nababan et al., 2022).

Quorum Quenching

Quorum sensing, which is microbial cell-to-cell communication and may regulate virulence, could be disrupted (= quorum quenching [QQ]), and invoked for the biocontrol of disease. Indeed, a range of Gram-positive bacteria has been described with QQ potential. For example, a *N*-acyl-homoserine lactone (AHL) degrading *Bacillus* has been reported to control *V. harveyi* infections in post-larvae shrimp (*P. monodon*) by reducing the expression of virulence factors, i.e., including metallo- and serine-proteases and hemolysins, and inhibiting biofilm formation (Shaheer et al., 2021). Similarly, *Bacillus* sp. [including *Bac. firmus*; Li et al., 2019] has been linked with QQ and biofilm inhibiting activity, and the ability to inhibit a wide range of bacterial pathogens, including *Aeromonas* spp., *Edwardsiella tarda, Photobacterium damselae, Tenacibaculum maritimum* and *Vibrio* spp. (Santos et al., 2021). Other potentially beneficial AHL-degrading organisms include actinobacteria (James et al., 2023), *Enterococcus faecium* (Vadassery

& Pillai, 2020) and *Lactobacillus* (Haridas et al., 2022).

Vaccines

Vaccination is one of the most effective forms of prophylaxis for controlling infectious disease outbreaks in aquaculture and, in turn, reducing the use of antibiotics by fish farmers (O'Neill, 2015). Vaccine development started with the work of Duff (1942), who used a chloroform-inactivated preparation of *A. salmonicida* cells and succeeded in protecting cutthroat trout from furunculosis. Thirty years later, the first vaccines were commercialized for use in aquaculture, protecting rainbow trout against enteric redmouth (ERM; Busch, 1982) and farmed Atlantic salmon against vibriosis, and later furunculosis (Tebbit & Goodrich, 1982), whereas vaccines for Scottish and Scandinavian aquaculture were not commercialized until the following decade. These early vaccines were formalin-killed whole cell preparations (= bacterins) delivered by immersion. The furunculosis vaccine proved less effective, however, and an adjuvant was therefore added to the vaccine and administered by injection to improve its efficacy (Gudding et al., 1999). Commercial vaccines are now available for a variety of fish species, based mainly on formalin-killed whole-cell formulations (Adams, 2019). Live attenuated vaccines are, however, licensed for use in the USA, Chile, and Israel (Du et al., 2022), and recombinant and DNA vaccines for use in Atlantic salmon (Adams, 2019).

Vaccines are administered to fish by either intraperitoneal (IP) or intramuscular (IM) injection, immersion (dip or bath) or orally in their feed. Vaccination by IP injection is most frequently used as it confers longer-lasting protection than immersion and oral vaccination (Embregts & Forlenza, 2016; Kitiyodom et al., 2019). Most commercial vaccines are based on inactivated, whole-cell preparations, emulsified with an adjuvant, and administered by IP injection, some as micro-dose formulations (Adams, 2019). Conversely, immersion vaccination is widely used to vaccinate small fish. The cost of the vaccine for vaccinating larger fish via this route may be prohibitive, and immersion vaccination is associated with poor vaccine efficacy due to low antigen uptake through skin and gills, which in turn may lead to short durations of protection. Also, the procedure is stressful because of the need to crowd the fish in the vaccine bath. Oral delivery is an ideal method of vaccination because it is less stressful for the fish and does not have the same cost of administration that is associated with IP vaccination. One of the main problems with oral delivery is antigen degradation by gastric fluid in the stomach and the anterior gut of fish. Antigen microencapsulation has been suggested as a way of protecting the antigen during administration (Lakshmi et al., 2023).

Vaccines are now routinely used as part of fish husbandry for higher-value fish species, such as rainbow trout and Atlantic salmon (Adams, 2019). Vaccines for these species are often multivalent, protecting against several pathogens with only one vaccine application. Unlike antibiotics, the cost of vaccination may be calculated and incorporated into the production budget (Thorarinsson & Powell, 2006). Vaccines have been shown to increase the overall profitability of production by reducing fish mortalities, providing a better-quality product, and improving fish welfare. Since vaccines are applied prophylactically to prevent the disease from occurring in the first place, they help remove the need for antibiotic treatment. Often farmers of lower-value species, such as tilapia, find vaccines expensive and logistically difficult to administer. They prefer to use antibiotics than invest in vaccines because of their lower profit margins.

Commercial vaccines are not available for all fish pathogens, and fish vaccine research has become more sophisticated to develop vaccines for more problematic pathogens. Techniques, such as molecular sequencing of pathogens, reverse vaccinology and proteomics, allow targeted selection of

antigens for recombinant and DNA vaccine design, and artificial intelligence is being coupled with reverse vaccinology to predict immunogenic epitopes to include in recombinant and DNA vaccine formulations. New strategies are needed to design cheap, safe, and easy-to-deliver vaccines for lower-value species, such as tilapia, so farmers will be more willing to vaccinate their fish to reduce the reliance on antibiotics. There is a growing interest in the use of nanoparticles for immersion and oral vaccines for these species, but ultimately the vaccines need to be cheap enough so the farmers can afford to use them.

Optimizing Water Use

Disinfection Systems

The most common high-risk inputs into aquaculture systems are water, surfaces and equipment, stock and feeds. Different typologies of measures may be taken to minimize the likelihood of live pathogens in these farm inputs: monitoring and quarantine for stock; egg disinfection; heat treatments, high pressure or disinfection of feed; water disinfection. Different procedures, products and technologies are currently used to disinfect water, surfaces, eggs, zooplankton/feed and/or clothes (Table 2).

Table 2. Disinfection procedures used in aquaculture

	Main methods for disinfection
Surfaces	Chlorine/sodium hypochlorite, formalin, peracetic acid, hydrogen peroxide, quaternary ammonium
Effluent water	UV, chlorine/sodium hypochlorite, filtration, ozonation, formic or peracetic acid
Source water	UV, ozonation, filtration
Fish eggs	Iodophor, glutaraldehyde, ozonation, hydrogen peroxide
Zooplankton	Hydrogen peroxide

The choice of disinfection technique must consider the target (viruses, bacteria, fungi, yeasts, parasites), the object to be treated (water, eggs, surfaces, clothes, zooplankton), the expected log inactivation, the available concentration/radiation x time (*ct*) and the different sensitivity/tolerance of the target towards disinfectants used, and regulatory aspects. Disinfection performance is usually defined as log inactivation: Log inactivation = $\log_{10}$ (Example: 90% removal/inactivation is defined as 1 log, 99% as 2 log, 99.9% as 3 log). Effective chemical disinfection requires the maintenance of a specified concentration (*c*) of disinfectant and contact time (*t*), to achieve a target value for *ct* (Can et al., 2010). The effectiveness of UV disinfection depends also on the characteristic of surface/water, the intensity of UV radiation, adequate wavelengths, and the amount of time the microorganism are exposed to the radiation.

Disinfection systems must face new challenges which must be considered:

- Antibiotic and disinfectant resistance. There is a need for a paradigm shift from conventional disinfection, with the primary aim of inactivating pathogens, to effective damage to the DNA and resistance genes that could still be present after microbial inactivation.
- Disinfection by-products: we need to avoid or minimize their formation. From an environmental perspective, easily degradable chemicals, which do not form toxic disinfection by-products or accumulate in aquatic organisms, are preferred (Werschkun et al., 2014).
- Resilience. There is a need to optimize technologies and existing systems to maximize their resilience and what needs to be done differently to ensure that future services may cope with climate change's

impacts and increase food demand and production. For example, increases in algal or cyanobacterial growth linked to high levels of N and P and increasing temperatures may lead to increased levels of toxins in the water. Resilience also means adopting measures to avoid possible fluctuations in the prices of chemicals or their precursors, avoiding any problems in the supply chain related to war, disease, or other factors.

- One health approach. There is a need for an integrated, unifying approach to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent. The One Health perspective in Water Sanitation Hygiene (WASH) requires intervention in the human-animal interface to prevent and control zoonotic disease transmission.
- Efficacy extended to other agents that may impact health. If possible, there is a need to be effective against other pollutants or toxins that may be present in water (such as cyanotoxins) or on surfaces.
- Reducing water consumption through RAS (where possible) or reuse of wastewater in other processes (agriculture).
- Consider the links between disinfection systems, energy, and carbon footprint. Disinfection systems have an impact on energy consumption, on the production of CO_2 (for example for their production, their transport or for the production and disposal of their containers).

The choice of water disinfection procedures depends on the flow rates, the type of water to be treated (fresh- or seawater), organic matter, the presence of filtration systems or other treatment systems, pH, temperature, turbidity, presence of other oxidable elements (Fe, Mn, ammonia, nitrates, bromides, medicines, drugs, hormones and other micropollutants), the need to recirculate the water, the regulatory aspects and many other factors. In RAS, the disinfection strategy needs also to consider that the biological filtration unit depends on specific bacterial species to convert toxic fish metabolites (ammonia) to a less toxic form (nitrate), and these beneficial bacteria should not be severely impacted by the disinfection protocol (Eding et al., 2006; Pedersen et al., 2009).

It is advisable to provide water treatments in each phase of the production process:

a) pretreatment of influent water: filters or chemical oxidation/disinfection for protection of eggs, fish, crustaceans, mollusks, and the operators

b) treatment within the facilities (especially in RAS)

c) treatment of effluent water = protection of the environment and human health (zoonoses, antibiotic resistance bacteria or genes). Disinfection of wastewater is necessary to prevent contamination of the environment with pathogens. Electrolyzed salt water is easy to scale up, and can treat large volumes of water (Kasai, 2002; Yoshimizu, 2003). The advantage of electrolyzed salt water is that it uses precursors, such as sodium chloride and water (or directly seawater), to produce sodium hypochlorite or hypochlorous acid (depending on pH) on site.

Also, the water in well boats used to transport fish to an aquaculture facility should undergo disinfection before addition to the well (= intake water) and with the discharge (= effluent water).

The main treatments of source water are UV, filtration and ozonation, and those for effluent are UV, chlorination, filtration, ozonation, formic or peracetic acid (Austin et al., 2022). Gram-negative bacteria and fish rhabdoviruses, herpesviruses and iridoviruses were killed when UV irradiated at the dose of 10^4 μ W·sec/cm^2. Standard, inexpensive UV lamps irradiate at that dosage, and may be suitable for hatcheries or

culturing stations that have problems caused by these microorganisms (Kasai et al., 2002). Water contaminated with Gram-positive bacteria, fish birnaviruses, fish reoviruses, fish nodaviruses and aquatic fungi that showed lower susceptibility to UV lamps should be disinfected with ozonation, or on site-hypochlorite/electrolization (Kasai et al., 2002). A summary of the main characteristics of the various disinfection systems is included in Table 3.

Table 3. Main characteristics of disinfection systems used in aquaculture

	On-Site Hypochlorite	**Commercial Hypochlorite**	**Chlorine gas**	**Chlorine dioxide**	**Peracetic acid**	**Ozone**	**UV**	**Filtration**
Capital Cost	Medium	Low	Low Medium	Low	Low	High	High	Medium High
Operational Cost	Low	Medium	Low Medium	Medium High	Medium High	Medium High	High	High
Effectiveness (bacteria/virus)	Very good	Very good	Very Good	Very good *1	Very good	Excellence	Good	Poor Very Good *2
Brominated byproducts	Possible *2	Possible	Possible	No	Possible	Possible *5	No	No
Chlorate formation	Low Medium *3	High	Negligible	Negligible Low	No	No	No	No
Chlorite formation	Possible *3	No	No	Possible	No	No	No	No
THM formation	Possible	Possible	Possible	Negligible *4	No	No	No	No
Residual disinfection	Yes	Yes	Yes	Yes	Yes	No	No	No

*1: Generally, chlorine dioxide is more effective as a disinfectant than hypochlorite at higher pH but similar or poorer at lower pH values (White, 1999). Studies show *ct* values higher than those of hypochlorite for some viruses

*2: Depending on the type of salt used

*3: Depending on the type of the cell coating and other factors

*4: Not produced directly

*5: Bromate formation

The re-used water, which characterizes RAS, leads to the accumulation of substances (e.g. dissolved solids, ammonia, and hormones) in the water (Mota et al., 2014), and may lead to the potential proliferation of pathogenic microorganisms, which are detrimental to the growth of reared organisms and the normal operation of the system (Blancheton et al., 2013; Vadstein et al., 2018). Ozone (O_3) addition and UV irradiation are the most commonly used methods of disinfection in RAS. However, UV disinfection is susceptible to water quality, and when bacteria or viruses attach to suspended particles in water, the particles protect them, thereby avoiding exposure to UV irradiation. So, the increase in the amount of particulate matter in water will reduce the sterilization efficiency of UV (Carré et al., 2018). Furthermore, most bacteria nay repair some of the damage caused by UV, and to block this self-repair mechanism, the dose of irradiation would have to be increased by three to four times to inactivate the overwhelming majority (99.9%) of the pathogenic microorganisms (Timmons and Ebeling, 2010). O_3 is a strong oxidizing gas that may be produced by air or oxygen as source, which must be dissolved in water in order to be used for microbial inactivation and oxidation of unwanted substances in RAS (Powell et al., 2015; Sharrer and Summerfelt, 2007). Studies have shown that the direct use of O_3 improves the productivity and welfare of reared animals, as well as improve water quality while reducing infections. Installing O_3 removal equipment could be required in RAS prior to use in culture tanks (Bullock et al., 1997). Because of the acute toxicity of residual O_3 and its by-products to aquatic animals, more attention should be given to the production of toxic by-products during ozonation in brackish water (Timmons & Ebeling, 2010). More recently, other disinfection methods, such as peracetic acid (PAA), have been applied to RAS. PAA

is a highly effective disinfectant widely used in aquaculture and sewage treatment plants (Pedersen et al., 2009). The disadvantage of PAA is that, because of the action of acetic acid, it will increase the content of organic matter in the system, which leads to microbial regeneration (Kitis, 2004; Pedersen et al., 2013). Furthermore, an excessive exposure to PAA may affect fish as shown by initiating a stress response in rainbow trout (Liu et al., 2017a) and common carp (*Cyprinus carpio*) (Liu et al., 2017b). The studies cited above indicate that there is species-specific PAA toxicity, which illustrates the need to test the PAA toxicity for each target species before its application.

The choice of surface disinfection procedures depends on the size, type and nature of the materials, the possibilities of implementing cleaning procedures and of disposing of the water deriving from disinfection processes, and the presence of biofilm (Can et al., 2012). Biofilms are complex microbial ecosystems formed by one or more species (mainly bacteria and fungi) immersed in an extracellular matrix composed of polysaccharides, such as cellulose, proteins and/or exogenous DNA. This matrix may be fixed to hard inert surfaces or to biological structures. Methods for biofilm detection, such as agar plating, are not effective due to the difficulty in culturing many biofilm bacteria because some foodborne pathogens, such as *Listeria monocytogenes*, are capable of entering into a 'viable but non-culturable' (VBNC) form with low metabolic activity. New techniques to detect biofilm include the use of the polymerase chain reaction (PCR; which is a technique for rapidly producing many copies of a fragment of DNA), the microtiter-plate test (MtP) and the Congo-red agar method (CRA). Biofilms physically protect embedded microorganisms against disinfectants.

It is necessary to consider the regulations present in different countries for the use and possible release of disinfectants into the environment (including by-products) or treatment plants after use. The disinfection procedures must be established after assessing the risks, namely microbiological, environmental and operator safety with the consequent definition of the treatment objectives and the correct procedures.

Filtration Systems

In aquaculture, water quality, namely temperature, salinity, ammonia, nitrites, carbon dioxide, chlorides, dissolved oxygen, pH, hardness, alkalinity, suspended and dissolved solids, and the presence of toxins or other contaminants, significantly affect the health of cultured species.

Types of filtrations

a) Gravitational separation
(i) Sedimentation
(ii) Channels. Channels with or without internal barriers, may be used to separate solid particles
(iii) Quiescent zones and trapping of solids within a raceway equipped with collection cones with valves at the bottom
(iv) Centrifugal concentrators - hydro clones or cones

b) Mechanical filtration

c) Biological filtration

In biological filters, bacteria are used to convert ammonia in various steps.

(i) Conversion of ammonium to nitrite

(ii) conversion of nitrite to nitrate and

(iii) Conversion of nitrate to molecular nitrogen

d) Chemical filtration

These disinfection and filtration methods are mostly incorporated with RAS.

To ensure environmental sustainability of aquaculture systems, it is important to obtain good quality water for farms because waste products (suspended and dissolved solids) are generated during metabolic activity. Suspended solids include uneaten feed, fish feces, growth of microalgae and bacteria, which may change pH levels, produce toxins,

and increase oxygen demand (Austin et al., 2022).

Removal of suspended solids, dissolved solids and organic matter from water flow is important in aquaculture particularly in relation to chemical or physical disinfectants (Schumann & Brinker, 2020).

In the case of using chemical disinfectants, the removal of suspended and dissolved solids allows reduction in the formation of [disinfection] by-products and the quantity of disinfectants to be used, whereas in the case of UV, the removal of suspended solids allows increases in the effectiveness of the treatment.

A key challenge RAS is the accumulation of particulate organic matter, especially the fine and colloidal fraction due to low removal efficiency of current technology (Fossmark et al., 2022). The choice of filtration technique must consider the target (suspended solids, dissolved solids, ammonia, nitrite, calcium, pollutants, contaminants, toxins), the water flow, feeding method, feed quality, rate of feeding, water exchange rate, the presence of RAS, tank hydrology, fish stocking density, dissolved oxygen level, and microplastics.

The primary biosecurity concern related to filtration is that, the organic and inorganic substances that build up within the filter structures may harbor disease-causing organisms, *i.e,* bacteria, parasites, fungi and/or viruses, which produce toxins or which generate biofilm and fouling thus prevent the proper functioning of the system.

Among the top emerging challenges that filtration systems face are those related to emerging contaminants and microplastics.

Emerging contaminant concern (ECCs) incoming and outgoing waters from aquaculture systems. These EECs enter the aquatic environment through various sources, such as domestic, pharmaceutical, and agriculture and farm industries. Also, the changes in aquacultural processes have led to the use of chemicals to boost production yield. These chemicals include hormones, antifungal compounds and antibiotics. Utilizing newly introduced chemicals leads to the release of compounds into wastewater. Recent studies reveal that increasing the concentration of multiple antibiotics has led to the proliferation of [antibiotic-]resistant bacteria in the environment. Moreover, the impact of antibiotic residues on the ecosystem has been recognized as a global threat (Ahmad et al., 2022b).

Microplastic ingestion by aquatic organisms has been confirmed in laboratory and field work, involving fish, bivalves, cephalopods and/or crustaceans. However, to date, the amounts of microplastics ingested by humans due to the consumption of seafood are unknown. In the future, in-depth studies will need to be carried out and possible technological solutions identified to address this problem.

Research needs to be focused on finding alternative energy sources, especially for RAS, to achieve optimal water use. Also, effective filtration and disinfection systems are important for welfare as aquatic species live in water. These issues are important economically and ecologically, and link into welfare and biosecurity concerns. Certainly, considerable progress has been achieved particularly in welfare, involving farming methods, transportation, pre-slaughter manipulations, and stunning/killing procedures (Daskalova, 2019).

Genetic Improvements in Aquaculture

Aquaculture has emerged as a significant contributor of protein, with global production reaching 87 million metric tonnes (Mt) in 2022. This figure represents a 2.7% increase compared to the previous year. Over the past decade, aquaculture has consistently experienced an average annual growth rate of 4.5%.

Nevertheless, the pace of aquaculture expansion witnessed a slowdown in 2022. This deceleration may be attributed to the widespread impact of the Covid-19 pandemic, which has unfolded over the past three years. The pandemic has disrupted global trade, caused supply chain disruptions,

and posed challenges to the efficient functioning of aquaculture operations. Consequently, the growth rate in aquaculture production was hindered, reflecting the broader consequences of the global health crisis. It is worth highlighting that despite the temporary setback in 2022, aquaculture remains a vital component in meeting the world's food requirements. The sector has consistently demonstrated its ability to contribute to food security and fulfil the increasing demand for animal protein. By leveraging technological advancements, sustainable practices, and continuous innovation, aquaculture holds the potential to enhance production further and play a crucial role in securing a stable and sustainable food supply for the growing global population (FAO 2022).

Genetic Resistance

The concept of selective breeding to improve disease resistance may be traced to the work of Embody & Hayford (1925), who researched controlling furunculosis in brook trout. Subsequent advances in genetics and genomics opened up the feasibility of developing disease-resistant stock (Doyle et al., 2019; Fraslin et al., 2022; Sciuto et al., 2022). Targets have included resistance to columnaris, furunculosis, infectious pancreatic necrosis, infectious salmon anemia, scuticociliatosis and eye fluke (*Diplostomum pseudospathaceum*) (Drangsholt et al., 2011; Karami et al., 2022; Zhang et al., 2022). Moreover, there is evidence that disease resistance is a heritable trait (Moraleda et al., 2021). A topical example concerns Egypt, where breeding programs have been aimed at improving disease resistance in Indian white shrimp (*Fenneropenaeus indicus*) and tilapia (Megahed, 2020). With the devastating effects of acute hepatopancreatic necrosis disease (AHPND) on shrimp production in Asia, considerable interest has focused on the obvious benefits of using disease-resistance stock (Tang & Bondad-Reantaso, 2019). An additional benefit is that resistant stock command a higher price, which leads to increased profitability as a result of improved survival (Delphino et al., 2022). In one study involving pond and cage culture of tilapia fingerlings with genetic resistance to streptococcosis caused by *Streptococcus agalactiae*, profitability was increased in areas where the disease was prevalent (Delphino et al., 2022). However, it should be emphasized that inbreeding may have the opposite effect of increasing susceptibility to disease (Doyle et al., 2019).

Aquaculture species exhibit sufficient genetic variation to facilitate the adoption of selective breeding as an approach for stock improvement. Many species display additional biological characteristics that enhance the likelihood of favorable outcomes. The aquaculture industry needs to develop expertise and organizational frameworks to harness the potential of selective breeding. Furthermore, new genetic manipulation techniques in aquaculture species will offer more opportunities for stock development and enable the exploration of unique gene combinations in future selective breeding efforts (Gjedrem & Baranski, 2010; Gjedrem et al., 2012).

Sex Control and Manipulation in Aquaculture

In the past five decades, there has been significant progress in chromosome manipulation techniques in fish species. Pioneering efforts in ploidy manipulation and bisexual development have rapidly enhanced genetic traits in fish and shellfish with long-life cycles. Achievements include the production of sterile triploids, all-female populations, and clonal lines in numerous fish species, worldwide. Sterile triploids prevent unwanted reproduction, all-female populations enable selective breeding, and clonal lines propagate genetically superior individuals. Studies also explore higher polyploids and creating clones using non-reduced eggs, offering further opportunities for genetic improvement in aquaculture production (Arai & Fujimoto, 2018; Wan et al., 2023).

Controlling the sex ratio is a crucial aspect of finfish farming. Maintaining a balanced sex ratio is generally beneficial for managing broodstock and developing appropriate breeding strategies. However, producing mono-sex populations in certain species is desirable due to the value associated with specific sexes, such as differences in growth, sexual maturation, color, or shape. Unlike mammals and birds, fish exhibit a wide range of sex-determination mechanisms, and possess highly conserved master genes. Genetic variations and the involvement of multiple genes have been observed in fish sex determination and the genetic network responsible for gonad differentiation. Environmental factors and epigenetic mechanisms also contribute to establishing and maintaining sex differentiation pathways. Given the complexity of sex determination in fish, applying quantitative genetics and genomic tools is necessary for studying and implementing effective breeding programs. This has significant implications for aquaculture, where techniques, such as chromosome manipulation, environmental control, classical selection, and marker-assisted selection programs, are utilized depending on the species (Budd et al., 2015; Martínez et al., 2014).

Hormonal sex reversal is a common method used in aquaculture to control sex. It involves administering hormones during a critical developmental stage to convert one sex into the desired sex. Genetic manipulation is another method for sex control. Scientists use selective breeding or genetic engineering to identify and manipulate genes or genomic regions responsible for sex determination, influencing the offspring's sex ratio to favor the desired sex. Sex control in aquaculture offers advantages, namely optimizing production by eliminating the need to rear both sexes, improving resource utilization and leading to faster growth and higher uniformity in monosex populations. However, there are also challenges and limitations associated with sex control in aquaculture. The success and efficiency may vary among species, and the manipulation of sex can sometimes have unintended consequences on other traits or physiological processes (Budd et al., 2015; Wang & Shen, 2018).

Polyploidy: Diploidy and Triploidy

Polyploidy, a condition characterized by having more than two sets of chromosomes, is an important aspect of aquaculture research and breeding programs. One common application of polyploidy in aquaculture is the induction of triploidy, which involves the manipulation of the chromosome sets to produce organisms with three sets of chromosomes instead of the usual two sets (diploidy). Triploid individuals are typically sterile, which may be advantageous in aquaculture settings as it prevents energy expenditure on reproductive activities and allows for enhanced growth and meat quality. Triploid fish often exhibit reduced aggression, increased disease resistance, and improved fillet characteristics compared to their diploid counterparts. Triploidy induction is a favored approach, achieved by inhibiting second polar body release immediately following fertilization with normal spermatozoa. This process may be facilitated by subjecting the fertilized eggs to high temperature (heat), low temperature (cold), or high hydrostatic pressure shocks. These techniques interfere with the normal chromosome segregation process, leading to the generation of triploid individuals. Chemical treatments employing cytochalasin B and similar agents are not commonly utilized for the triploidization of finfish (Arai, 2001; Arai & Fujimoto, 2018; Piferrer et al., 2009).

Polyploidy has been successfully applied in various aquaculture species, including salmonids, carp, catfish, oysters, and shrimp. Natural polyploid fish species, such as common carp, gibel carp, crucian carp, salmon, and sturgeon, have been selected as important targets for aquaculture because of their valuable characteristics. Artificially induced polyploids, mainly derived from natural polyploid fish species of the

Cyprinidae and Salmonidae families, have been widely utilized in commercial aquaculture. In China, the mass production and improved economic traits in growth and flesh quality have made synthesized autopolyploid or allopolyploids from natural polyploid species of cyprinid fishes highly prevalent in aquaculture (Arai, 2001; Zhou & Gui, 2017).

Whereas polyploidy offers several advantages in aquaculture, there are challenges associated with its application. The induction of triploidy is not always 100% effective, and some individuals may revert to a diploid state. The induction process may stress the embryos, leading to reduced survival rates. The potential impact of triploid escapees on wild populations is also a concern, as in certain cases their sterility may be temporary or incomplete (Arai, 2001; Arai & Fujimoto, 2018; Piferrer et al., 2009; Zhou & Gui, 2017).

Continued research and refinement of polyploidy induction techniques, along with careful monitoring and risk assessment, are necessary to ensure polyploidy's responsible and effective use in aquaculture. When applied appropriately, polyploidy may contribute to aquaculture's sustainable development by improving productivity, reducing environmental impacts, and creating novel varieties of aquatic organisms with desirable traits (Piferrer et al., 2009).

Haploidy

Haploidy, the condition of having a single set of chromosomes, has gained attention in aquaculture as a technique for rapid genetic improvement and the development of novel traits. Haploidy may be achieved through various methods, such as gynogenesis, androgenesis, or spontaneous haploidy induction (Gjedrem & Baranski, 2010; Komen & Thorgaard, 2007). Spontaneous haploidy induction occurs naturally in some species, where some individuals are naturally haploid. These individuals may be identified and selectively bred to establish haploid lines, allowing for the exploitation of genetic diversity and the creation of novel traits (Bazylewska et al., 2015; Liu et al., 2016). Haploidy allows the rapid fixation of desirable traits, as only one generation is required to develop a fully homozygous population. Also, it enables the production of all-female or all-male populations, which enhance production efficiency, reduce reproductive competition, and facilitate the control of reproductive processes (Komen & Thorgaard, 2007). Haploid embryos are often more fragile and have lower survival rates than diploid embryos. The genetic instability of haploid genomes may also result in abnormalities and reduced viability. Furthermore, the limited genetic diversity in haploid populations may increase susceptibility to diseases and environmental stressors (Prigge & Melchinger, 2012).

Gynogenesis and Androgenesis

Gynogenesis and androgenesis are specialized breeding techniques used to rapidly produce genetically homogeneous populations. Gynogenesis involves using the sperm of a male without genetic contribution to initiate embryonic development, resulting in offspring that are clones of the mother. Androgenesis replaces the genetic material of the maternal egg with that of the father, generating offspring that are clones of the father. These techniques ensure uniformity in desirable traits, facilitating targeted trait improvement (Komen & Thorgaard, 2007). Gynogenesis is a gene manipulation technology that enables the production of all-female fish through asexual reproduction. This method involves activating the fertilization of eggs using sperm without the sperm contributing its DNA to the progeny. In gynogenesis, the sperm's DNA is denatured using UV or gamma rays. The denatured sperm activates the eggs, leading to fertilization. However, the sperm does not contribute its genetic material to the offspring. Only the genetic material from the female parent is inherited (Basavaraju, 2023; Donaldson & Devlin, 1996; Komen & Thorgaard, 2007; Paschos et al., 2001). Gynogenesis may be achieved through two methods: meiotic and mitotic gynogenesis.

The choice between these methods depends on the desired outcome and the fish species involved. Meiotic gynogenesis involves suppressing metaphase II in the second meiotic division, thus preventing the extrusion of the second polar body. This method produces offspring, known as meiotic gynogenesis. Administering a shock treatment immediately after fertilization, such as thermal or hydrostatic pressure shocks, induces meiotic gynogenesis by suppressing the metaphase II division and resulting in gynogenetic females with genetic material solely from the female parent. It is important to note that the timing of shock treatments may vary slightly between fish species. The optimal timing should be determined through experimentation and refinement for each species to achieve the desired outcome effectively (Basavaraju, 2023; Fopp-Bayat, 2010).

Androgenesis is a technique used to produce fish in which all nuclear genetic information originates from the male parent, whereas the mitochondrial DNA is maternally derived. This method involves irradiating the egg with gamma or UV radiation to inactivate the chromosomal DNA, followed by fertilization with normal sperm. The resulting zygote is haploid, containing a single set of chromosomes. Researchers have successfully used diploid sperm from tetraploid rainbow trout to fertilize gamma-irradiated ova, eliminating the need for pressure shock treatment to suppress the first cleavage division. Furthermore, fused sperm has been utilized to produce diploid androgenetic rainbow trout, presenting an alternative approach in the androgenesis process (Basavaraju, 2023; Das, 2014; Donaldson & Devlin, 1996; Normark, 2009)

Genetic Engineering and Manipulation in Aquaculture

Genetic manipulation, or genetic engineering or modification, involves inserting, deleting, or modifying specific genes within an organism's DNA to achieve desired traits or outcomes (Ansai et al., 2021). It is noteworthy that genetic manipulation in aquaculture is a topic of ongoing research and debate. Regulatory frameworks are in place in many countries to ensure the responsible and safe use of genetic manipulation techniques in aquaculture (Harrell, 2017). One of the advantages of most aquaculture species is their high fecundity and external fertilization, making them highly amenable to applying genetic improvement technologies. Among these technologies, CRISPR/Cas9-based genome editing holds significant promise. Improving disease resistance is a primary objective in aquaculture, and CRISPR/Cas9 presents exciting opportunities to address this challenge. It enables the correction of existing alleles associated with susceptibility, facilitates the transfer of beneficial alleles from wild populations or related species through introgression-by-editing, and creates entirely new alleles. A combination of *in vivo* and *in vitro* screening approaches may be employed to identify functional alleles that confer disease resistance. This approach holds the potential to pinpoint alleles that exhibit desirable functional traits, which may then be further tested and applied in downstream applications. Another promising avenue for using genome editing in aquaculture is the achievement of 100% sterility. This breakthrough has the potential to prevent interbreeding between farm escapees and wild stocks, safeguarding the genetic integrity of natural populations (Ansai et al., 2021; Luo et al., 2022).

Transgenic Fish

Transgenic fish are genetically modified organisms (GMOs) created by introducing specific genes from one species into the genome of another (Chen, 1995). An alternative successful method employed in transgenesis involves the utilization of fish sperm cells. These cells have the unique ability to remain dormant either within the seminal fluid or an artificial medium for extended periods, and they may be activated under suitable conditions without compromising the fertilization rate of the eggs. Moreover, it has been observed that

DNA may bind to the sperm during incubation. By employing such sperm cells for fertilization, it becomes possible to generate transgenic fish. In this process, the sperm acts as a carrier, facilitating the transgene transfer into the egg. Unfortunately, the frequency of these transfers is typically low. However, an intriguing observation indicates that the electroporation of sperm cells in the presence of DNA leads to a significant increase in the occurrence of transgenic individuals (Tsai et al., 1995).

Marker-Assisted Selection (MAS) in Aquaculture

The use of markers in fisheries products to select desirable traits is known as Marker-Assisted Selection (MAS). MAS is a molecular approach that involves choosing parental lines for crossbreeding based on genotypic data and a selection index. This method improves upon the limitations of conventional breeding by offering enhanced efficiency and precision in trait selection. MAS allows combining target traits in a single genotype with fewer selection cycles and reduced unintentional losses. MAS shows promise in enhancing yield, combating biotic and abiotic stresses, and improving traits, such as stress resistance and quality attributes. To ensure practicality and success, MAS requires a strong correlation between the gene of interest and molecular markers, which should be stable, reproducible and easy to assay (Devi et al., 2017; Sonesson et al., 2007; Wakchaure et al., 2015). The initial molecular markers utilized in MAS were restriction fragment length polymorphisms (RFLP), identified in commercially significant species. Since then, considerable advancements have been made in developing new marker types, gene mapping, studying quantitative trait loci (QTL) and exploring the potential outcomes of MAS (Rothschild & Ruvinsky, 2007; Sonesson et al., 2007). Initially implemented in plants due to ethical considerations, these techniques have subsequently found applications in fisheries. Although MAS holds tremendous promise, there are limited studies showcasing its practical utility in reducing the frequency of recessive alleles responsible for genetic diseases, identifying simple Mendelian traits and enhancing various species. In fisheries, quantitative traits are often influenced by multiple genes, some of which interact with each other and are further influenced by environmental conditions. Consequently, relying solely on phenotypic measurements for selection may yield poor results when heritability is low. However, directly identifying and selecting the most valuable genotypes is very appealing. This approach may potentially enhance the efficiency of choosing quantitative and qualitative traits. Molecular markers, particularly those located within or near the gene of interest, have emerged as promising tools for genotype-oriented selection in fisheries (Dekkers, 2004; Rothschild & Ruvinsky, 2007).

Potential of Nanotechnology

The physicist, Richard Feynman initiated the concept of nanotechnology at the American Physical Society meeting in 1959 when he spoke about the manipulation and control of atoms and molecules. The name nanotechnology was coined by Norio Taniguchi over a decade later. Then, in 1981, the modern approach to nanotechnology began with the development of the scanning tunnelling microscope which enabled the study of individual atoms. Nanotechnology, which combines science and technology, is the processing of matter at a near atomic scale to produce new materials, structures and devices. It is promising as the technology of the future in many sectors, such as materials, medicine, energy, consumer products and manufacturing. Certainly, aquaculture has been fast in embracing the potential for nanotechnology for a wide range of applications, and it will undoubtedly contribute significantly to transforming the industry (Salem, 2023). Some of the most promising areas are in fish health management, nanoscale compounding, the use of nanotechnology in aquaculture feeds

and food packaging, and applications linked to value-added products, stress reduction and health management. Current applications include water purification, sterilization of pools, detection and control of pathogens, and the efficient distribution of nutrients and medicines (Huang et al., 2015; Luis et al., 2019; Fajardo et al., 2022).

Nanotechnology has a role to play in relation to providing new perspectives on disease diagnosis and health management in aquaculture (Handy, 2012). In particular, nanotechnology has been adopted in disease management, notably with diagnosis and control, including nanobioactive compounds, nanobubbles and nanovaccinology (e.g. Luis et al., 2019; Nasr-Eldahan et al., 2021; Dien et al., 2022). The technology has enabled the intact passage of bioactive substances through the stomach, and targeted delivery to key tissues. The outcomes include improved and sustained release of bioactive compounds, and reduction in the numbers of applications (Luis et al., 2019). The approach has led to improvements in oralizing vaccines, which hitherto may not have survived passage through the stomach. There has been considerable interest in nanoencapsulating essential oils for disease control. For example, nanoencapsulated essential oil of the tea tree *Melaleuca alternifolia* was bactericidal and gave total protection of the South American catfish *Rhamdia quelen* against challenge with *Pseudomonas aeruginosa*, compared with 70% protection when nonencapsulated essential oil was used (Souza et al., 2017). Moreover, poriferous nanomaterials, such as porous silica particles, may be used as a delivery matrix for the controlled release of pharmaceutical compounds (Stromme et al., 2009). Oral DNA vaccines using carriers, namely chitosan, liposomes or poly-lactide-coglycolide acid, have been evaluated for shrimp (Rajeshkumar et al., 2009) and fish (e.g. Li et al., 2013; Reyes et al., 2017). Moreover, the United States Department of Agriculture has trialed a system for mass vaccination of fish using ultrasound. Here, nanocapsules containing short strands of DNA were added to the water where they became absorbed into the fish. Ultrasound was then used to rupture the capsules, releasing the DNA and leading to an immune response (Mongillo, 2007).

Gold nanoparticles have found use in the diagnosis of shrimp diseases by means of a loop-mediated isothermal amplification system (Notomi et al., 2000). Currently, there is the ability to detect a wide variety of pathogenic organisms, such as single virus particles using electrical nanosensors (Patolsky et al., 2004).

There are applications of nanoparticles in aquatic feeds. Thus, nanoencapsulation technology have been proposed for vitamins, trace minerals, carotenoids and fatty acids to increase bioavailability (Bouwmeester et al., 2009; Acosta, 2009). The approach may be used to improve the delivery of micronutrients or unstable components as nanoparticles to fish feeds. Specifically, nanoencapsulation technology may be used for the delivery of minerals, fat-soluble vitamins and fatty acids (Handy, 2012).

Compared with other technologies, the transport of molecules with nanotechnology applications may be more effective for the prevention and treatment of diseases by reducing the risks related to health and environmental factors, and reducing the use of chemicals. Nanoparticles may allow for faster, non-intrusive, and more cost-effective new drug delivery methods (= nanodelivery) (Aklakur et al., 2016). Moreover, procedures that prevent diseases and combine diagnosis and treatment in a single step (= theragnostics) will increase the effectiveness and significantly reduce costs (Chen & Yada, 2011; Fajardo et al., 2022; Salem, 2023). Also, nanotechnology may be used to monitor nanosensors with locators that transmit data on geographic location and fish health status through the use of big data analytical technology that allows individual fish control and/or the development of smart cage systems (Sekhon, 2014).

Unicellular and multi-cellular organisms are used for biosynthesis of nano-particles. The

so-called green synthesis in nanotechnology is a sustainable and ecological protocol in materials science that provides reliable solutions for the non-toxic synthesis of numerous nanomaterials, such as hybrids, metal oxides, and biomaterials (Singh et al., 2018). Algae contain a variety of potentially useful compounds, such as vitamins, antioxidants, terpenes, flavonoids and various minerals. These compounds are used as biological reducing agents in nanobiotechnology. The potential use of these green agents as catalysts for biofuel production and cancer/gene therapy intensifies interest in algae (Mukherjee et al., 2021).

Using living organisms to create inorganic nanoscale particles is a potential new development in biotechnology. For example, algae have the ability to accumulate heavy metal ions at a high rate. This property makes it possible to process algal biomass under catalytic conditions with both downstream and upstream processes at an affordable cost. The capacity of algae to accumulate heavy metal ions and convert them into softer forms has made them model organisms for the production of biomaterials (Fawcett et al., 2017; Ponnuchamy & Jacob, 2016). Thus, for nanotechnology applications, algae have come to the fore (Jacob et al., 2021).

Nanoparticles may be synthesized extracellularly and intracellularly depending on the algal species. However, studies have shown that almost all algae, regardless of species, may be used to produce metallic nanoparticles (e.g. Abboud et al., 2014; Salem et al., 2020; Fatima et al., 2020; Alsaggaf et al., 2021). In particular, algae belonging to the families *Chlorophyceae*, *Cyanophyceae*, *Phaeophyceae* and *Rhodophyceae* have been used as nanomachines for intracellular and extracellular synthesis of gold, silver and other metallic nanoparticles. These may compete with standard drugs, and have anticancer, antibacterial, and antifungal activities.

Nanotechnology may have an important role in the development and sustainability of aquaculture notably in improving efficiency and environmental impact. Currently, most of these nanotechnological approaches are at an early stage of development, and the high cost is considered as the main limiting factor for widespread application. Any health and environmental concern need to be addressed. However, there are potential benefits of nanotechnology for aquaculture. For the future, the life cycle and shelf life of nanomaterials needs to be examined alongside consideration of the potential health and environmental risks associated with exposure, uptake, accumulation, release and accumulation (Handy, 2012).

Conclusions

Since its origins 8000 years ago, aquaculture has needed to be dynamic, adopting best practices resulting from advances in relevant knowledge to enable its survival as an industry, for growth and further development. Best practices have been included in formal standards requirements, such as ISO9000, and for purposes of certification by the Global Seafood Alliance. The approaches reflect all aspects of production from site selection and especially location in terms of proximity to other farms, construction and maintenance of the facilities, the need for a constant and adequate supply of clean water, availability of a workforce, and accessibility whether by land, water or air, management practices including the need for good hygiene, stock selection and acquisition, nutrition, disease management, processing, and impact on the environment, specifically negating the possible impact of pollution, such as from uneaten feed and feces. The question is: what will the future hold for aquaculture? All the signs point to a continued expansion in production to meet the growing need for aquatic foods. The balance of production is expected to shift from fisheries to aquaculture as wild stocks are plundered. The expansion of aquaculture will provide greater tonnage, and an increase in the range of

species involved. This will necessitate research to understand fully the biological needs of any newly introduced species. The industry will need to address the physical structures, focusing on recirculation systems for freshwater species to conserve water, and offshore rather than coastal sites for marine organisms. The challenge will be to solve the problems associated with offshore structures, which will need to be sufficiently resilient to withstand the effects of weather, tidal surges, pollution, e.g. oil spills, predation from large marine mammals, and damage caused by shipping. There have been advances in automation, including remote sensing and automatic feeders. Work is ongoing to design effective structures to minimize biofouling, which could impede water flow by allowing the build-up of organic material and reduced oxygen levels in and around the farmed species. The production cycle needs to be independent of collecting eggs/juveniles from the wild for ongrowing in aquaculture. This closed system works with many of the currently farmed species, but research will be necessary to more fully understand the biology of any newly introduced organisms. Best practices will include the availability of highly nutritious feed containing all the compounds necessary for the development and growth of the farmed species. Specifically, replacements are needed for the current use of fish meal derived from trash fish, which are caught from the seas. The management of disease continues to evolve from the former emphasis on therapy with antibiotics and other antimicrobial compounds to prophylaxis. The range of measures continues to increase, and includes vaccines, probiotics, plant products, nonspecific immunostimulants, bacteriophages and bacteriocins. The advent of nanotechnology is opening up other possibilities. It may be anticipated that interest in artificial intelligence will spread to aquaculture. In short, the future for aquaculture is bright, and the success reflects the adoption of best practices, which continually evolve to accommodate the latest developments.

Ethical approval

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed consent

Not available.

Conflicts of interest

There is no conflict of interests for publishing of this study.

Data availability statement

The authors declare that data are not available for this article.

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Author Contributions

Erkan Can: Conceptualization; supervision; writing the topic “Current Status of Fish Production…”, introduction, discussion and conclusion - original draft; writing - review & editing; Brian Austin: Conceptualization; supervision, writing the topic “disease management”, abstract, introduction, discussion and conclusion - original draft; writing - review & editing. Christian E.W. Steinberg: Conceptualization; writing the topic “Prophylactic nutrition” - original draft; writing - review. Cristian Carboni: writing the topic “Optimizing water use” - original draft-review. Naim Sağlam: writing the topic “Genetic Improvements” - review. Kim Thompson: writing (co-author of the topic “Disease management)-review. Murat Yiğit: writing the topic “Current Status of Fish Production…”-review. Şafak Seyhaneyildiz Can and Sebahattin Ergün: Writing the topic “Potential of Nanotechnology” - review.

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