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Review Article

An overview of chemicals and drugs in aquaculture disease management

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Abstract

The increasing demand for fish as a cheap and healthy food has promoted the development of intensive aquaculture worldwide, which simultaneously increased the occurrence of several diseases among the farmed species. Fish diseases pose severe economic losses and are considered as the major bottleneck for aquaculture production and development. Potential risks associated with infectious diseases have led to the intervention of chemotherapeutants and antimicrobials in aquaculture. These include a wide variety of chemicals such as antibiotics, anti-fungal agents, antiparasitic agents, antiseptics, disinfectants etc. Although FDA-approved drugs are limited, many chemotherapeutic agents have been unveiled from different sources with a different spectrum of activity in recent years. Though recent advances in vaccine development have substantially reduced the application of antibiotics in aquaculture, controlled application of specific drugs is utilized for the effective management of many aquaculture systems. Good water quality maintenance is the prime factor for successful aquaculture production. This aspect is well taken care of by disinfectants and sanitizers, which are of chemical origin, and each one varies in its effectiveness against various pathogenic organisms. Therefore, therapeutic drugs play a versatile role in the prevention and cure of fish and shellfish diseases when used judiciously but lead to unfavourable and untargeted effects when abused. This article attempts to depict an overview of drugs commonly used to control diseases in aquaculture.

Key words: Antibiotics, Aquaculture drugs, Chemotherapy, Disease treatment, Disinfectants

Highlights

- Fish diseases pose severe economic losses and are considered as the major bottleneck for aquaculture production and development.
- Therapeutic drugs play a versatile role in the prevention and cure of fish diseases.
- Unscrupulous use of antibiotics has led to the development of antimicrobial resistance in many pathogens of fish and its consequent spread to pathogens of public health significance.
- Several alternative measures to control the spread of diseases are now being developed in aquaculture.

INTRODUCTION

Consequent to increased seafood demand coupled with improvements in technical advancements, aquaculture production has tripled over the last two decades (Done and Halden, 2015). The production is appropriately highlighted and exclusively ruled by China and other developing nations, which represents 89% by volume (FAO, 2008). This fast aquaculture advancement combined with intensive farming strategies has prompted higher stocking densities leading to water quality deterioration which is an essential factor for a disease event (Rodgers and Furones, 2009). In addition, the intensification is associated with health-related issues of the

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stocked species due to the stress of the animals and opportunistic pathogens. Similar to terrestrial vertebrates, aquatic animals also confront genuine dangers from a wide assortment of microscopic organisms such as bacteria, virus, fungi and parasite (Ali *et al.*, 2015). Among them, bacterial diseases remain a major hurdle to the aquaculture industry. *Aeromonas hydrophila* is a ubiquitous and most virulent bacterium affecting numerous freshwater fish species. Different species of *Streptococcus* were found to infect both marine as well as freshwater cultured fishes including the tilapia culture. Vibriosis is a disease caused by various species of bacteria belonging to Vibrio genus, which is known for its recurrent infectious outbreaks in the shrimp culture industry. One of the most dramatic examples of an emerging disease of fish is the disease caused by koi herpesvirus (KHV). Epizootic haematopoietic necrosis is caused by a large DNA virus (EHNV) which is classified in the genus Ranavirus of the family Iridoviridae. Lymphocystis is a chronic viral infection that occurs among finfish worldwide over a wide range of water temperatures including tropical climates. Viral nervous necrosis (VNN) has emerged to become a major problem in the culture of larva and juvenile marine fish worldwide. Since 2009, Israel has seen precipitous declines in tilapia, with annual yields plummeting as much as 85 percent due to the new emergent Tilapia Lake virus (TiLV). Apart from bacteria and viruses, fungi and parasites also play a crucial role in the health of cultured aquatic animals. Therefore, these situations warrant the application of various chemicals and drugs in aquaculture, specifically antibacterials, antivirals, antifungals, antiparasitic agents, antiseptics, disinfectants, and so on. The utilization of various chemotherapeutics and their mode of activity in moderating/repressing different pathogens in the host are discussed below.

Chemotherapy

Utilization of medications and chemicals to treat irresistible diseases is known as chemotherapy (Manito, 1983). It depends on the rule of differential toxicity, i.e., the medications or chemicals used must be successful against the pathogen at focus that does not bring about noteworthy unfavourable impacts on the host species (Baticados and Paclibare, 1992). The treatment technique is of three sorts those include prophylactic, metaphylactic and therapeutic approaches (Bell, 1992). Prophylactic treatment techniques incorporate defensive measures to keep an illness at bay and are utilized as a part of battling against external parasite pervasions, stress-interceded bacterial diseases and viral infections (Lio-Po *et al.*, 2001). A metaphylactic procedure applies when foreordained infection pervasiveness arises in the cultured populace, and it includes measures to control a full-scale episode of disease. The therapeutic intervention comes in place after the precise diagnosis of the disease, followed by prompt and proper treatment (Wijegoonawardena and Siriwardena, 2000). Drugs acquired from normal sources, which could be regulated with the feed, would be vastly helpful and effective for utilization in therapeutics. The best approach in deciding the viability of any new drug or treatment is to contrast the outcomes acquired in trials with the new drug, a restrictive drug with known efficacy and untreated groups (Hirazawa *et al.*, 2000). Two methodologies exist when utilizing natural agents to avert pathogens: reinforcing the self-protection of fish by administering an agent as an immunostimulant and utilizing an agent that directly acts on the pathogen.

Drug administration

The application procedures differ extensively based on the drug, life stage of fish and rearing system. Regulated drugs, in any case, are administered to aquatic animals by means of culture water, feed or direct injection (Inglis, 2000).

Immersion treatment: In immersion treatment, the drugs are directly added into the culture water and are generally applied as a bath (prolonged and indefinite), dip or flush. In prolonged bath treatments, the water flow is incidentally ceased, and precise amount of the directed item is added to the rearing unit (Noga, 2000). The water flow is re-established after a predefined measure of time, and the treatment is flushed from the rearing unit. It is important that the compound is satisfactorily mixed and appropriated to guarantee uniform concentrations. Also, it is significant to ensure that sufficient air circulation is given, and that water quality is checked relying upon the length of the treatment and stocking density, since water flow is off amid the treatment. Indefinite baths are like prolonged baths; apart from that, the rearing system has a substantial volume without water exchange. Low drug concentrations are utilized and are permitted to scatter gradually through regular procedures (assimilation, chelation, photodegradation etc.) or constrained water exchange is done on account of indefinite baths.

In dip treatments, high drug concentrations are used in which small numbers of fish are exposed for a brief timeframe, more often not more than a minute (Treves-Brown, 2013). Plunge medications are typically just utilized with generally harmless mixes (e.g., salt), and in the case where the fish has to be handled any rate (e.g., when fish are to be moved starting with one raising unit and then onto the next).

Adding a drug solution at the inflow to a rearing unit and enabling it to flush through the system is referred as flush treatment (Park *et al.*, 2012). They are commonly plausible in raceways or other corresponding running water systems. This kind of treatment is improper for regulated items with a restricted edge of security, as it can be hard to guarantee uniform appropriation and mixing of the item all through the water sections.

Oral treatment: The drug or medication should be administered into the body of the fish to treat certain illnesses, especially systemic diseases. This is most regularly done using medicated feed (Noga, 2000). Some drugs could be applied as a top dressing to feeds by blending pellets with cured oil or gelatine solution and enabling the pellets to dry before feeding the cultured fishes. Certain other drugs must be with the feeds by authorized commercial feed mills to produce medicated feed. By and large, there is less adaptability concerning medicated feeds. As the sicknesses make the fish to feed more gradually or quit feeding, it is important to ensure the oral medicines reach the fish ahead of probable infections to guarantee achievable results. Similarly, as with all feeds, it is imperative to store medicated feeds in a cool and dry place, and to utilize them before the expiry date.

Injection treatment: Injection treatment is usually resorted to and is more feasible for large-sized or high-valued fishes (e. g., broodstock), especially if a small size of a population is to be dealt with. Infusions are most generally given intramuscularly or intraperitoneally. In both cases, appropriate care needs to be exercised so that needle is maintained at a strategic distance from internal organs to limit significant harm to the fish. Intramuscular (IM) infusions are regularly given in the dorsal musculature at an insertion depth of roughly 0.5 - 1.0 cm with the needle at a ~45° angle to the side of the body. Intraperitoneal (IP) infusions are commonly given close to the base of the pelvic fins at a ~45° point to the ventral surface, adjusting the needle along the axis of the body to dodge the interior organs (Kinkel *et al.*, 2010).

Gavage: Gavage is a type of oral administration utilized broadly in exploratory work in light of the fact that the exact measurement is known. The procedure utilizes a stomach tube, which is connected to a syringe containing a medication, and the medication is pumped into the stomach of the fish (Park *et al.*, 2012). The fish must be anaesthetized or sedated before administering the drug. This strategy is once in a while utilized as a part of the aquaculture business since it is laboured intensive and unpleasant to the fish.

Topical application: Topical application is uncommon in the aquaculture business and is utilized for the treatment of skin ulcers on high-value fish (Verma *et al.*, 2010). Anaesthesia is fundamental, and the medications are typically oil-based.

Antiviral agents

Irresistible diseases in cultivated fish, for example, those caused by viral infections, are a noteworthy monetary issue for aquaculture farmers (Ganjoor, 2016). For a long time, viral infections have been considered as obstinate to particular antiviral chemotherapy in light of the fact that the replicative cycle of the infection is too firmly intertwined with typical cell metabolism so that any endeavour to stifle infection propagation would be bound to kill (or seriously hurt) the uninfected cell too (De Clercq, 2001). With the illustration of virus-specific events as focuses for chemotherapeutic assault and the coming of various particular antiviral agents, it has turned out to be progressively evident that specific chemotherapy of viral diseases can be accomplished and that infection propagation can be smothered without injurious impacts to the host (Pushpa *et al.*, 2013). The use of antiviral drugs in aquaculture is limited and has gone unreported.

Antibacterial agents

Similar to the case in terrestrial animal production for guaranteeing satisfactory fish production, several kinds of antibiotics are used in aquaculture to control bacterial ailments (Mo *et al.*, 2017). In aquaculture, antibacterials have been utilized fundamentally for restorative purposes and as prophylactic needs (Sapkota *et al.*, 2008). Antibiotics are medications engineered with the ability to kill or hinder the development of microorganisms. They have different mechanisms of action when administered. These compounds act in one of the three routes: by disturbing cell films, by upsetting protein or DNA combination or by restraining catalyst activity (Burridge *et al.*, 2010). The top antibiotics utilized by intensive aquaculture producers incorporate the following: oxytetracycline, oxolinic acid, chloramphenicol, erythromycin, furazolidone, trimethoprim, sulfadiazine, ampicillin, florfenicol, flumequine, and sulfadimethoxine. Sulfonamides are broadly used to avert infections caused by pathogens in aquaculture owing to their imperative action. But, little is thought about the deposits and dietary dangers related to cultured fish. Among them, the main type of antibiotics used are sulphadiazine (SDZ), sulphamethoxazole (SMZ), sulphamethazine (SDD), and sulphamonomethoxine (SMM), and these were found amidst the culture period at high concentrations (>100 µg/kg fish) (Song *et al.*, 2017). One of the most commonly utilized sulphonamide compounds in fish culture is sulphamethazine (SMZ); however, its physiological consequences on fish are unclear (Sampaio *et al.*, 2016). This antibiotic is quite often detected in surface water and sediments due to its widespread application (Zhao *et al.*, 2016). Tribrissen (sulfadiazine: trimethoprim, 5:1) is a broad-spectrum sulphonamide antibacterial agent also used to treat furunculosis (*Aeromonas salmonicida*) and vibriosis infection in salmon (e.g. *Vibrio anguillarum*). Tribrissen acts by inhibiting folic acid metabolism.

Amoxicillin is a broad-spectrum antimicrobial from the β-lactam class and is viable against gram positive and gram negative microscopic organisms. It is utilized as a part of the aquaculture business to treat fish with infection of furunculosis. It acts by upsetting the synthesis of cell wall (Todar, 2008). Among the different groups of antibiotics used in treatment of *A. veronii*, *A. hydrophila* and *A. caviae* (*A. punctata*), which cause bacteraemia, gastroenteritis or septicaemia in fishes, fluoroquinolones and cefotaxime are found to be the most efficient (Piotrowska and Popowska, 2014). Fluoroquinolones (FQNs) are broad-spectrum antibiotics widely used in animal husbandry and aquaculture (Cheng *et al.*, 2014). Florfenicol, a phenicol class antibiotic, is additionally a broad-spectrum antibacterial agent used to treat salmon against furunculosis. It prevents the multiplication of bacteria by inhibiting protein synthesis. Oxolinic acid and flumequin are quinolone antibiotics that repress DNA replication used against gram negative microbes (*Piscirikettsia salmonis*). They are also used to battle furunculosis and Vibrio diseases (Todar, 2008).

Oxytetracycline has a wide range of antibiotic active against furunculosis and vibriosis (Powell, 2000), which act by inhibiting the replication of DNA. For the treatment of *Pseudomonas* infection in fish, oxytetracycline appeared to be more effective compared to tetracycline and ciprofloxacin (Kholil *et al.*, 2015). Erythromycin is a macrolide antimicrobial valuable in combating gram positive and non-enteric gram negative bacteria. It is commonly utilized to fight against bacterial kidney disease (Powell, 2000). Erythromycin inhibits protein synthesis by repressing gene translation (Todar, 2008). Nitrofurans are antibiotics of synthetic origin that are quickly utilized in animals (Karunasagar, 2012). Broad spectrum antibiotics chloramphenicol (30 µg/disc), erythromycin (15 µg/disc), gentamycin (30 µg/disc) and oxytetracycline (30 µg/disc) proved highly efficient in preventing the growth of all species of *Vibrio* (Sonia *et al.*, 2012). The most commonly used antibiotics against *Piscirickettsia salmonis* are oxytetracycline and florfenicol (Sandoval *et al.*, 2016). For pupfish rearing efforts in which antibiotic use is appropriate, application of chloramphenicol and trimethoprim sulfamethoxazole was found to provide good results when applied to incubating eggs rather than to hatched larvae (Feuerbacher *et al.*, 2017).

A broad-spectrum antibiotic called chloramphenicol has been banned from extra-label applications in food-producing animals in the United States because it is not licenced for use in those animals. In the US, chloramphenicol is only used to treat serious infections that could be fatal; however, it is suspected to be a human carcinogen that affects the reproductive system (US Food and Drug Administration, 2004). Another public health concern for chloramphenicol exposure is its role as a precursor to aplastic anaemia. Aplastic anaemia occurs when bone marrow produces too few blood cells. The reduction in red blood cells causes haemoglobin levels to fall, while reduced numbers of white blood cells increase susceptibility to infection. A fall in the number of platelets affects blood clotting (Fegan, 2002).

Oplinger and Wagner (2013) evaluated the effectiveness of antibiotics (erythromycin, streptomycin, and a penicillin–streptomycin mixture against *Flavobacterium psychrophilum* and demonstrated that elevated temperatures and the combination of penicillin and streptomycin could kill *F. psychrophilum* under *in vitro* conditions. It had no or less effect on the bacterium during the use of erythromycin and rapid changes in pH and osmotic pressure. The use of antibiotics in fish feed in order to reduce the risk imposed by diseases has led to the emergence of unfavourable effects on human health (Chu *et al.*, 2013). Antibiotics were conventionally used for stimulating growth performance and nutrient digestibility in commercial aquaculture (Hoseinifar *et al.*, 2017). Feed medicated with antibiotics has a wide application in animal production to prevent and treat bacterial infections. However, its effect on non-target anaerobic bacteria is unknown (Fernández *et al.*, 2015). High OTC (oxytetracycline) concentrations in a single exposure triggered the functional and structural changes in a sulphate-reducing bacteria community. When administered as medicated feed, only doxycycline, toltrazuril, and their combinations reduced the fish mortality and infestation level (Abdel-Hafez *et al.*, 2014).

Antifungal agents

The n-methylated diaminotriphenylmethane dye, malachite green has for quite some time been utilized as a fungicide and ectoparasiticide (Alderman, 1985). Malachite green, a respiratory toxic substance, harms the cell's capacity to produce energy required to drive essential metabolic procedures (Mitrowska *et al.*, 2005). Sodium chloride (Schreier *et al.*, 1996), potassium permanganate (Bly *et al.*, 1996), copper sulphate (Bly *et al.*, 1996), formalin (Marking *et al.*, 1994;), the herbicides diquat, simazine, hydrothol 191, aquathol K (Bly *et al.*, 1996), iodine (Fitzpatrick *et al.*, 1995), glutaraldehyde (Marking *et al.*, 1994; Fitzpatrick *et al.*, 1995), and hydrogen peroxide

(Schreier *et al.*, 1996) are the other alternative agents tested for antifungal activity. Bronopol (Pyceze), a more secure therapeutic agent alternative to malachite green and formalin, is presently thought to be an aquacultural fungicide (Pottinger and Day, 1999) which is used for the preventive treatment of mycotic diseases in aquaculture. It is demonstrated that double lethal activity in microorganisms, with growth concealment being attributed to catalytic oxidation of available thiols, while cell death is thought to be brought on by the production of free radicals (Shepherd *et al.*, 1988). Sodium chloride is considered as an eco-friendly antifungal agent and is found to possess a positive and remarkable antifungal effect which has been depicted in freshwater finfish aquaculture during egg incubation (Rasowo *et al.*, 2007).

Antiseptics and disinfectants

Disinfection can decrease the danger of disease transmission inside the aquaculture premises and from the premises to the environment by deactivating pathogens with disinfectants (Sekkin and Kum, 2011). Use of disinfectants to water can be applied as a part of specific conditions for disease control or sanitization. A wide assortment of active chemical agents is found, of which many have been used for many years for antisepsis, cleansing, and protection. In general, disinfectants have a more extensive range of action than antibiotic agents, and while antimicrobials have a tendency to have particular intracellular targets, biocides may have numerous and multiple targets (McDonnell and Russell, 1999). Chemicals or derivatives incorporate chlorine, formalin, iodophors, ozone and UV light (Rodgers and Furones, 2009). Because of its broad antiparasitic properties, formaldehyde is still generally utilized in aquaculture, despite the fact that it is classed as a human cancer-causing agent (IARC, 2004). Formalin is a potential and powerful disinfectant used to execute microorganisms or as a preservative for biological specimens. Containing roughly 37% formaldehyde by weight, formalin is commonly available as an aqueous solution (Bruno *et al.*, 2011). It works by responding with cell proteins and nucleic acids, modifying both structure and function (Ali *et al.*, 2015). Mutagenic and cancer-causing impacts are additionally known for malachite green, which like formaldehyde is broadly utilized against parasitic treatment. Chlorine is widely utilized in hatcheries and cultured ponds, yet its use empowers the advancement of multiple antibiotic resistance genes in bacteria (Murray *et al.*, 1984). Chloramine-T is a disinfectant compound which inactivates few pathogens and is a notable antimicrobial agent, particularly as an antiviral agent for sanitation (Ganjoor, 2016). During immersion therapy, it dissolves in water forming hypochlorous acid which enters through the cell wall, prevents enzymatic activity and causes cellular death (Burridge *et al.*, 2010). Hydrogen peroxide has been distinguished as a compelling antifungal, antibacterial and antiviral compound with low impact on ecosystem (Fitzpatrick *et al.*, 1995; Bruno *et al.*, 2011). Virkon® is an expansive range disinfectant which includes active components such as potassium peroxymono-sulphate (21.5%) and sodium chloride (1.5%).

Quaternary ammonium items are utilized as a part of fish culture and crustacean farming and for the sterilization of production zones and hardware (Bravo *et al.*, 2005). One of the regularly utilized products is benzalkonium chloride, applied to repress bacterial development and the improvement of mucus in the gills of salmon (Burka *et al.*, 1997), in this manner permitting satisfactory retention of oxygen. Its proficiency and poisonous quality rely on upon the pH and hardness of the water. The activity comprises in disturbing the porousness of the layers as it joins the phospholipids and proteins. It acts especially on the carbon chain between the C12 and C16 positions, where it applies a lipophilic action (Burridge *et al.*, 2010). At pH 4-7, the hypochlorous acid is highly bactericidal by preventing the oxidative phosphorylation of bacterial membranes. Iodophores convey iodine in a complex with an agent that goes about as a repository of free iodine, a carrier agent. Iodine has bactericidal, fungicidal, virucidal and sporicidal activity, which kills pathogens by obliterating proteins (especially those with free groups of cysteine and methionine), nucleotides and fatty acids (McDonnell and Russell, 1999).

Antiparasitic agents

The impact of medications with various chemical characters and methods of activity has provided significant data for superior comprehension of the parasite science and physiology (Elandalloussi *et al.*, 2005). Many antiprotozoal agents have been tested for their efficacy so far, each one having a different mechanism of action. Cycloheximide is a protein synthesis inhibitor that has been shown to hinder pathogens of oysters (Calvo and Burreson, 1994). Classic antimalarial chloroquine is found to meddle with the metabolic procedures required in the uptake or digestion of haemoglobin in the *Plasmodium* sustenance vacuole (Egan *et al.*, 2000). The complete method of activity of artemisinin is as yet obscure, and it has been recommended to hinder either nucleic acid or protein synthesis (Klonis *et al.*, 2011).

Cell changes initiated by this drug in plasmodium lead to clumping of ribosomes, changes in the endoplasmic reticulum, nucleolar membrane and mitochondria (Jiang *et al.*, 1985). Atovaquone, a ubiquinone analogue, has been demonstrated to specifically repress the mitochondrial electron transport of protozoa (Fry and Pudney, 1992). Iron chelators have been shown to restrain *in vitro* replication of pathogens of oyster, and this inhibitory impact is reliant on iron accessibility in the medium (Elandalloussi *et al.*, 2003). The use of hydrogen peroxide to remove protozoans has little effect on the environment when released compared to other agents (Hirazawa *et al.*, 2000). However, hydrogen peroxide bath treatment has a constrained impact against mature parasites embedded in the branchial cavity wall (Ogawa and Yokoyama, 1998). Praziquantel and levamisole are used as part of human drugs: praziquantel to control trematode and cestode disease (Redman *et al.*, 1996) and levamisole to control nematode contamination (Robertson and Martin, 1993). Both are synthetic drugs having a parasiticidal effect against fish monogeneans (Schmahl and Taraschewski, 1986). Sodium chloride is regularly utilized for parasitic and fungal infections of fish, which alter the osmotic gradient between the parasite, fish and the surrounding water (Phillips, 2000). Potassium permanganate ($KMnO_4$) is also useful for treating protozoan infestations on the skin, gills and fins in which O_2 generated from $KMnO_4$ aggressively reacts with the organic molecules and alters their structure and properties and finally kills the pathogenic agent (Floyd, 1993).

Chemicals now approved for the treatment of sea lice pervasion are categorized into two types, in light of their administration routes, namely, bath treatments and in-feed additives. Organophosphates, pyrethroids and hydrogen peroxide have been regulated by bath treatments, while the avermectins and chitin synthesis inhibitors are managed as added substances in medicated feed. Organophosphates have a wide assortment of utilizations in aquaculture and are very often utilized for the control of crustacean ectoparasites, treatment of trematode or ciliate infections in shrimp hatcheries, or expulsion of mysids from shrimp ponds and are sold with different trade names viz., Aquaguard®, Dipterex®, Dursban®, Demerin®, Nuvan®, Neguvon® and Malathion®. Neguvon® (trichlorphon) and its degradation item Nuvan® (dichlorvos) are also utilized for the treatment of crustacean ectoparasites, such as salmon lice (*Lepeophtherius salmonis*) on marine fishes, fish lice (*Argulus* sp.) and anchor worm (*Lernaea* sp.) on freshwater fishes (Weston, 2000). Pyrethrins are the dynamic constituents of a concentrate from blossom heads of *Chrysanthemum cinerariaefolium*. The mechanism of action of the pyrethroids includes impedance with the function of nerve membrane, principally by their association with sodium channels which brings about depolarization of the nerve ending, and this interaction brings about monotonous terminating of the nerve ending on account of the pyrethroids, cypermethrin and deltamethrin (Miller and Adams, 1982). Hydrogen peroxide, a strong oxidizing agent, was the first considered ectoparasiticide for the treatment of ectoparasites of aquarium fish (Mitchell and Collins, 1997). Mechanical paralysis, peroxidation by hydroxyl radicals of lipid and cell organelle membranes, inactivation of enzymes and replication of DNA are considered as the mechanism of action of hydrogen peroxide (Cotran *et al.*, 1989). Among them, mechanical paralysis is the common mechanism of action supported by many reports. This is induced when the bubbles are formed in the haemolymph, which detaches the sea lice and makes them float to the surface. For the control of internal and external parasites, avermectins (ivermectin and emamectin) are found viable in an extensive variety of host species, especially warm-blooded animals (Campbell, 1989). The avermectins, by and large, open glutamate-gated chloride channels at invertebrate inhibitory neurotransmitters where the outcome is an increase in chloride concentrations, hyperpolarization of muscle and nerve tissue, and restraint of neural transmission (Grant, 2002). Avermectins can likewise expand the arrival of the inhibitory neurotransmitter γ-amino-butyric corrosive (GABA) in well-evolved creatures, *i.e.*, mammals (Davies and Rodger, 2000). There is no market authorization for the use of ivermectin in fish anywhere in the world, while its analogue emamectin benzoate (SLICE®), a semi-synthetic derivative created by the bacterium, *Streptomyces avermitilis*, is now being developed specifically for aquaculture (Treves-Brown, 2000). Chitin synthesis inhibitors have a place with a class of insecticides alluded to as bug development controllers and have been utilized as a part of terrestrial spray programs for irritating creepy crawlies since the late 1970s. The biochemical mechanism by which these bug sprays repress the synthesis of chitin is indistinct (Savitz *et al.*, 1994). The moulting stage is the delicate phase of the life cycle, and restraint of chitin synthesis meddles with the development of a new exoskeleton in a post-moult animal (Horst and Walker, 1995). In this way, the chitin synthesis inhibitors are viable against the larval and pre-adult life phases of sea lice. Diflubenzuron and teflubenzuron (Calicide®) are chitin synthesis inhibitors endorsed as additives in feed to treat cultured salmon infested with sea lice. Potassium permanganate is utilized for treating ectoparasites, bacterial and fungal infections on the skin and gills of fishes. Permanganate is a dynamic oxidant ion against parasites that destructs them by oxidizing their cell walls, while another report demonstrated that manganate-dioxide develops protein complex on the external surface that brings on dark-coloured shading and this protein complex impact on the respiratory structure of parasites and kills them (Banavreh *et al.*, 2000). At high pH, manganate dioxide sediment on fish gills; makes potassium permanganate toxicity during high pH conditions. Hence it cannot be used in salt water effectively. Also, it should not be used in combination with formalin (Noga, 2000).

To date, the treatment and avoidance of monogenean contaminations have included the utilization of different anthelmintics including formalin, praziquantel and mebendazole. However, the broadened and successive utilization of these medications at inaccurate measurements prompted the advancement of drug resistance, which had constrained their anthelmintic viability (Zhang *et al.*, 2014). Trichlorfon, introduced to aquaculture for sea-lice control, was also used for gill flukes. Praziquantel is an isoquinoline operator utilized against intestinal parasites in fish. The drug is believed to inhibit the hooks and suckers on the scolex by impairing the neuromuscular system of the parasite, and also it may lead to osmotic and nutritional imbalances by affecting the permeability of the parasite integument. Nine commercially available benzimidazoles were screened for activity as immersion treatments against skin flukes (*Gyrodactylus* spp.), among which mebendazole, fenbendazole, parbendazole and triclabendazole were active (Treves-Brown, 2000). Fenbendazole is a wide range benzimidazole anthelmintics utilized against intestinal parasites in fish. Niclosamide and nitroscanate are the other anthelmintic drugs that are found to be effective against flukes.

Currently available aquaculture drugs

Currently available therapeutic substances used in aquaculture can be classified as FDA approved drugs, FDA unapproved low regulatory priority drugs, deferred regulatory status drugs and investigational new animal drugs (INAD). Each continent or country (Table 1) has its own legislations and institutions for approval of a drug to be used in aquaculture.

FDA approved aquaculture drugs: Approved drugs (Table 2) are compounds for which US FDA Centre for Veterinary Medicine (CVM) has assessed information and inferred that the medication is successful in accomplishing the expressed claim; is safe to the target fish, people who may ingest treated fish, and the environment when applied at labelled doses; and can be produced by CVM criteria (Bowker *et al.*, 2011; USFDA, 2021). Conditionally approved drugs are drugs that have been proven safe and are manufactured according to CVM criteria; in addition, with the data to emphasize the effectiveness of the drug.

Table 1. Approvals for use of chemotherapeutics by continent or country (Modified from Jahncke, 2007)

Continent/Country	Regulation
Africa	Most nations don't have directions on drug or vaccine use.
Asia	Varies from no controls to prohibitive directions.
Australia	Australian Pesticides and Veterinary Medicines Authority (APVMA). Applications are submitted to the National Registration Authority to look for exceptions from the requirement for enlistment.
China	Approved for use by the Animal Drugs Examination Commission, Ministry of Agriculture.
Europe	European Medicines Evaluation Agency (EMEA) and European Medicine Agency (EMA). Old and new substances guarded by a sponsor, information is required to build up Maximum Residue Limits (MRL).
India	Controlled by Coastal Aquaculture Authority (CAA). Also, Central Drugs Standard Control Organization (CDSCO) started a special cell to monitor veterinary drugs, vaccines and matters related to aquaculture.
Japan	Controlled by Pharmaceutical Affairs Law.
North America	In the USA, the FDA Centre for Veterinary Medicine (CVM) regulates animal drugs. For aquaculture, it is done under Aquatic Animal Drug Approval Partnership Programme (AADAP). The USA drug approval process is similar to Canada and requires endorsement of manufacturing, human nourishment and target species, wellbeing and viability segments.
Philippines	Enforced by the Dept. of Agriculture.
South America	Little data is available. However, in Chile, the approvals officer is the Fisheries Health Department, National Fisheries Service.
Thailand	Controlled by the Dept. of Fisheries.

Table 2. FDA approved or conditionally approved new animal drugs for use in aquaculture (USFDA, 2021)

Sl. No.	Name of the product	Active component	Specification	Dosage
1.	AQUAFLOR® (Merck Animal Health)	Florfenicol	Used to control mortality created due to enteric septicaemia and columnaris in catfish. Used to control mortality created because of bacterial coldwater disease and furunculosis in freshwater-raised salmonids.	10 mg/kg of body weight/day for 10 consecutive days
2.	Chorulon® (Intervet America, Inc.)	Chorionic gonadotropin	Used to enhance spawning in male and female broodstock.	Not standardized
3.	Finquel® (Argent Laboratories) Tricaine -S (Western Chemical, Inc.)	MS-222; tricaine methane sulfonate	Used to calm and anaesthetize aquatic animals amid different aquaculture operations.	10 - 1000 mg/L (Immersion)
4.	Formalin-F® (Natchez Animal Supply Co.) Paracide -F® (Agrent Laboratories)Parasite-S® (Western Chemical Inc.)	Formalin	Used as an external parasiticide to control protozoan parasites.	15 - 25 µl/L for 1 hour (finfish) 1000 - 2000 µl/L for 15 minutes (eggs)
5.	Furanace Caps	Nifurpirinol	Used to treat columnaris disease in freshwater ornamental fish.	Not Standardized
6.	Pennox® 343(Penn Field Animal Health)	Oxytetracycline hydrochloride	Used as an aid in skeletal marking of finfish fry and fingerlings.	200 - 700 mg/L for 2 - 6 hours
7.	Romet-30® (FDA-licensed feed mills)	Ormetoprim: sulfadimethoxine	Used to treat furunculosis in salmonids and enteric septicaemia of catfish.	50 mg/kg body weight/day for 5 sequential days
8.	Terramycin® 200 (Phibro Animal Health)	Oxytetracycline dehydrate	Used to treat specific bacterial diseases occurring in salmon, catfish and lobster.	2.5-3.75 g/45.36 kg body weight/day for 10 consecutive days
9.	35% PEROX-AID® (Western Chemical Inc.)	Hydrogen - peroxide	Used to control mortality caused due to saprolegniasis, bacterial	For saprolegniasis: 500 - 1000 mg/L for 15 minutes

Cont. Table 2.

Table 2., Cont. ...

Sl. No.	Name of the product	Active component	Specification	Dosage
			gill disease and external columnaris disease in freshwater-reared finfish eggs, freshwater-reared salmonids and cold water finfish and channel catfish, respectively.	(coldwater finfish eggs) 750 - 1000 mg/L for 15 minutes (warmwater finfish eggs) For bacterial gill disease:100 mg/L for 30 minutes or 50 – 100 mg/L for 60 minutes For external columnaris disease:50 to 75 mg/L for 60 minutes (coldwater species of freshwater-reared finfish) 50 mg/L for 60 minutes (coldwater species of freshwater-reared finfish fry)

Low regulatory priority aquaculture drugs: FDA perceives that these agents may have a physiological effect and are henceforth genuinely viewed as a drug by definition. Low regulatory drugs (Table 3) have been controlled by FDA to be new animal drugs, yet they have not been endorsed as new animal drugs (USFDA, 2021). When utilized by the FDA determinations, low regulatory priority drugs are still considered as drugs. They are possibly fit for influencing the structure or any function of the body of an aquatic animal. The use of LRPD is regulated by FDA if good quality products are used according to listed indications and better management practices in prescribed doses without affecting the environment.

Deferred regulatory status drugs: Copper sulphate and potassium permanganate are the two compounds that have been given deferred regulatory status, as their assessment is pending by CVM (Bowker *et al.*, 2011). Also, both are Environmental Protection Agency (EPA) enrolled pesticides utilized as a part of aquaculture. At present, either compound can be used to treat external protozoan or metazoan pervasions and in addition, external bacterial or parasitic diseases in fish.

Investigational new animal drugs (INADs): Investigational New Animal Drug (INAD) (Table 4) exceptions permit aquaculturists access to unapproved drugs which have a sensible desire of viability for the proposed sign to better deal with the wellbeing of cultured fish while giving basic data with regard to the security and adequacy of the medication under a differing set of rearing conditions which would somehow not be assessed in the drug approval process. There are two sorts of INADs: standard and compassionate. A standard INAD approves the utilization of an unapproved medication to create information through use in animals that may not be discharged into the ecosystem or butchered for human utilization. Compassionate INAD exclusions approve the utilization of an unapproved drug in fish on a generation scale and on the grounds that a butcher approval is conceded as a major aspect of the

Table 3. Non-approved aquaculture drugs of low regulatory priority (USFDA, 2021)

Sl. No.	Name of the product	Specification	Dosage
1.	Acetic acid	Used as a parasiticide for fish.	1000 - 2000 mg/L dip for 1 - 10 minutes
2.	Calcium chloride	Used to guarantee legitimate egg hardening.	10-20 mg/L $CaCO_3$
3.	Calcium oxide	Used as an antiprotozoal agent in fingerlings and adult fishes.	20000 mg/L for 5 seconds
4.	Carbon dioxide gas	Used as an anaesthetic in warm, cool and cold-water fish.	-
5.	Fullers' earth	Used to lessen the adhesiveness of fish eggs.	-
6.	Garlic	Used to control the infestation of sea lice and helminth in all life stages of salmon.	-
7.	Hydrogen peroxide	Used to control fungi in all life stages of fish.	250-500 mg/L
8.	Ice	Used to reduce fish's metabolic rate during transport.	-
9.	Magnesium sulphate	Used to treat external crustacean and monogenic trematode infestations in all life stages of fish.	30,0000 mg/L
10.	Onion	Used to treat sea lice and other external crustacean parasites in all life stages of salmon.	-
11.	Papain	Used to improve egg hatchability by removing gelatinous matrix of fish egg masses.	0. 2%
12.	Potassium chloride	Used as an osmoregulatory aid in soothing stress and preventing shock.	10-2,000 mg/L.
13.	Povidone iodine (Western Chemical, Inc.)	Used an egg surface disinfectant.	100 mg/L for 10 minutes
14.	Sodium bicarbonate	Used as a means to anaesthetize fish.	142-642 mg/L for 5 minutes
15.	Sodium chloride	Used as an osmoregulatory aid in relieving stress and preventing shock; used as a parasiticide.	0. 5% to 1. 0% solution (osmoregulatory aid), 3% solution for 10 to 30 minutes (parasiticide)
16.	Sodium sulphite	Used to enhance egg hatchability	15% solution for 5 to 8 minutes

Cont. Table 3.

Table 3., Cont. ...

Sl. No.	Name of the product	Specification	Dosage
17.	Tannic acid	Used to denature the adhesive component of fish eggs.	0. 75 g tannic acid/5 litres of water for 6 minutes.
18.	Thiamine hydrochloride	Used to prevent or treat thiamine deficiency in salmonids.	100 mg/L for 4 hours (for eggs) 1000 mg/L for 1 hour (for sac fry)
19.	Urea	Used to denature the adhesive component of fish eggs.	15 g urea /5 litres of water for 6 minutes

Table 4. List of new animal drugs for investigational purposes (USFWS, 2022)

Sl. No.	Name of the product	Active component	Specification	Dosage
1.	17α methyltestosterone (Rangen Inc.)	17α-Methyltestosterone	Used to produce phenotypically male populaces of fish.	9 mg/kg body weight/day for 28 consecutive days
2.	Aquaflor® (Merck Animal Health)	Florfenicol	Used to control mortality in a variety of freshwater and marine fish species caused by bacterial diseases.	10 or 15 mg/kg body weight /day for 10 consecutive days.
3.	AQUI-S®20E (Western Chemical, Inc.)	Eugenol	Used to sedate and anaesthetize fishes temporarily.	10 - 100 mg/L
4.	Benzoak® (Frontier Scientific, Inc.)	Benzocaine	Used to sedate and anaesthetize fishes temporarily.	10 - 100 mg/L
5.	CAIROX® Potassium permanganate (Carus Corporation)	Potassium permanganate	Used for treating parasitic (external protozoan and metazoan), bacterial and fungal infections in a wide range of warm-water fish species.	1 - 10 mg/L for 1 hour
6.	Channel Catfish Pituitary (Hybrid Catfish Company)	Catfish pituitary	Used to enhance development of gametes (spermiation and ovulation) in a variety of fish species.	10 mg/kg body weight
7.	Common Carp Pituitary (Stoller Fisheries)	Common carp pituitary	Used to enhance development of gametes (spermiation and ovulation) in a variety of fish species.	4- 10 mg/kg body weight

Cont. Table 4.

Table 4., Cont. ...

Sl. No.	Name of the product	Active component	Specification	Dosage
8.	Halamid® (Western Chemical, Inc.) Actamide® (B. L. Mitchell, Inc.)	Chloramine-T	Used to control mortality in freshwater fish species caused by bacterial gill disease and external flavobacteriosis.	15 mg/L for 60 minutes
9.	Luteinizing Hormone-Releasing Hormone analogue (Western Chemical, Inc.)	LHRHa	Used to enhance development of gametes (spermiation and ovulation) in a variety of fish species.	5 - 20 µg LHRHa/ kg bodyweight
10.	Ovaplant® Salmon gonadotropin releasing hormone analogue (Western Chemical, Inc.)	Salmon gonadotropin releasing hormone analogue	Used as a pellet implant in many fish species.	10-75 µg/kg body weight
11.	Pennox® 343 (PennField Animal Health)	Oxytetracycline hydrochloride	Immersion therapy is used to control mortality in various freshwater and marine fish species caused by bacterial diseases.	20 mg/L for 1 h for 1 to 4 consecutive days
12.	Reward® (Syngenta Crop Protection, Inc.)	Diquat	Used to control mortality caused by bacterial gill disease and external columnaris in a wide range of freshwater fish species.	2- 18 mg/L for 1-4 hour for 4 consecutive days
13.	SE-MARK® (Western Chemical, Inc.)	Calcein	Used in marking skeletal tissue of fishes.	125 - 250 mg/L (finfish or mussels) for 1-6 hour
14.	SLICE® (Merck Animal Health)	Emamectin benzoate	Used to control mortality in a variety of freshwater fish species caused by external parasites (copepods).	50 µg/kg body weight/day for 7 consecutive days
15.	Terramycin® 200 (Phibro Animal Health)	Oxytetracycline dihydrate	Medicated feed therapy is used to control mortality in various freshwater and marine fish species caused by bacterial diseases.	220 mg/kg body weight/day for 14 consecutive days
16.	Triangle Brand® Copper Sulfate (Freeport-McMoran	Copper sulfate	Used to treat ichthyophthiriasis and saprolegniasis infection on	100 mg/L for 1-5 min bath. Maintain free

Cont. Table 4.

Table 4., Cont. ...

Sl. No.	Name of the product	Active component	Specification	Dosage
	Copper & Gold, Inc.)		catfish and its eggs, respectively.	copper ion levels at 0.15-0.2 mg/L for a long term dosage
17.	Erymicin 200 injection(Syndel USA)	Erythromycin	Used for controlling mortality caused by BKD (causative agent: *Renibacterium salmoninarum*) in salmonid species.	A single dose of 10 - 25 mg erythromycin per kg fish body weight

compassionate INAD approval, permit the arrival of treated fish for butcher or discharge into the environment. This type of approval enables treated fish to enter the human food chain. U. S. Fish and Wildlife Service (USFWS) is the biggest INAD exception holder among the few people and associations that hold INAD exclusions for specific medications (USFWS, 2022).

In India, the Coastal Aquaculture Authority controls shrimp aquaculture in brackish and marine water and has banned the use of several antibiotics at any time of the culture operations, right from the brood stock to the larval rearing in hatcheries to the grow out in the culture ponds. A list of the antibiotics and pharmacologically active substances that are banned for use in aquaculture of brackish water and marine species of fish and shrimp are given in Table 5.

Table 5. List of banned antibiotics and other pharmacologically active substances in aquaculture in India (As per the notification by Coastal Aquaculture Authority of India, 2022)

Sl. No	Antibiotics and other pharmacologically active substances	Maximum permissible residual level in ppm
1.	Chloramphenicol	Nil
2.	Nitrofurans including: Furaltadone, Furazolidone, Furylfuramide, Nifuratel, Nifuroxime, Nifurprazine, Nitrofurantoin, Nitrofurazone	Nil
3.	Neomycin	Nil
4.	Tetracycline	0.1
5.	Oxytetracycline	0.1
6.	Trimethoprim	0.05
7.	Oxolinic acid	0.3
8.	Nalidixic acid	Nil
9.	Sulphamethoxazole	Nil
10.	*Aristolochia* spp. and preparations thereof	Nil
11.	Chloroform	Nil
12.	Chlorpromazine	Nil
13.	Colchicine	Nil

Cont. Table 5.

Table 5., Cont. ...

Sl. No	Antibiotics and other pharmacologically active substances	Maximum permissible residual level in ppm
14.	Dapsone	Nil
15.	Dimetridazole	Nil
16.	Metronidazole	Nil
17.	Ronidazole	Nil
18.	Ipronidazole	Nil
19.	Other nitroimidazoles	Nil
20.	Clenbuterol	Nil
21.	Diethylstilbestrol (DES)	Nil
22.	Sulfonamide drugs (except approved Sulfadimethoxine, Sulfabromomethazine and Sulfaethoxypyridazine)	Nil
23.	Fluoroquinolones	Nil
24.	Glycopeptides	Nil

Conclusion

The level of real disease prevalence and precise diagnoses in light of appropriate observation has been lacking in many countries. Although chemotherapeutic treatment is effective, utilization of drugs and chemotherapeutics without appropriate diagnosis prompts higher working expenses and builds the danger of harmful chemicals in the environment. All animal industries including aquaculture tend to use antibiotics in the feed as a prophylactic and growth promoting ingredient. This practice has led to the bioaccumulation of drugs in animals and also its unintended release into the environment. Unscrupulous use of antibiotics has led to the development of antimicrobial resistance in many pathogens of fish and its consequent spread to pathogens of public health significance. It is, therefore, absolutely essential to control the use of antibiotics only in the required conditions that to in a controlled environment. Because of the increased awareness of the deleterious effects of the use of antibiotics in aquaculture, several importing countries have stipulated the maximum permissible level of antibiotics in the export products. This has really become a deterrent in the callous application of antibiotics and improved the vigilance against the unwanted use of these compounds. Several alternate strategies of intervention to limit the escalation of infectious diseases have now been developed in aquaculture. Development of various types of immunostimulants and probiotics to improve the health of the animals, vaccines with appropriate adjuvants and PRR (pattern recognition receptor) ligands for immune preparedness against the invading pathogens, phage therapy for direct elimination of bacterial pathogens, bioremediators for application in the water to improve the water quality are some of the ways and means that are effectively used in aquaculture to decrease the dependence on antibiotics for disease control.

Conflict of interest: Authors have no conflict of interest in this study.

Author's contribution: RD: Performed the literature collection and review, and wrote the initial draft of the manuscript; CA: Structured and critically reviewed the manuscript; MRG: Reviewed the manuscript; KRJ, SB and JSSK: Provided technical guidance.

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