DRUGS AND CHEMICALS APPLIED IN AQUACULTURE

Abstract

This chapter briefly reviews the application of various drugs and chemicals commonly applied in aquaculture for treatment and prevention of diseases. Main emphasis is given on different types of water/soil treatment products, disinfectants, therapeutants, anaesthetics, feed additives, growth promoters, vaccines, probiotics etc. along with their commercial availability and recommended dosage. It highlights a detailed summary of the current state of knowledge on the availability and mode of administration of chemicals or drugs applied in fish and shellfish aquaculture. The chapter entails a clear picture of all approved drugs along with their recommended dosage so as to prevent the economic loss of fish farms due to disease outbreak or poor water and soil quality management.

Keywords: Aqua-medicines; chemicals; drugs; growth promoters; antimicrobial agents; probiotics

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1. Introduction

In the context of food, nutrition, income, employment, and export revenues, aquaculture remains the world's fastest growing and most vibrant food producing sector. The prevailing propensity in aquaculture development appears in favour of vertical expansion leading to intensification of cultural practises, whilst leaving little scope for horizontal expansion. To address the rising demand for seafood or freshwater foods, as well as the challenges that result from the on-going internationalisation of trade, there has been observed intensification and diversification in aquaculture, advancement in technological innovations for food production, alterations in ecological systems and human behaviour, involving an increasing understanding of the urgency to preserve the environment, biodiversity, and health of the people. The aquaculture industry heavily relies on the use of chemicals, antibiotics, aquaculture drugs, and formulated diets. Drugs and chemicals employed in aquaculture are crucial in regulating fish health alongside boosting fish growth and production, fecundity, and lowering the risk of disease occurrence. Furthermore, they aid in reducing mortality losses through enhancing the overall production of fish and other aquatic organisms, improving reproduction through manipulation, promoting growth, processing, and adding value to the end product. Over the past twenty years, there has been an apparent spike in the usage of aqua-drugs worldwide, which has coincided with a shift in farming systems and an intensification of aquaculture practises. With the introduction of numerous species and increased stocking density, aquaculture practises have expanded vertically, which somewhat has heightened the frequency of disease outbreaks, increasing morbidity and mass mortality thereby leading to declining in overall production. The intensified culture system for higher economic gain has been the main driver behind the recurrent disease outbreaks that have adversely affected aquaculture in recent years (Walker and Winton 2010). According to Murray and Peeler (2005), the diversity and the number of species being produced have also led to the development of new culture systems and practises, which may have a profound effect on the development and dissemination of pathogens. Uncontrolled drug use in aquatic environments has resulted in environmental pollution, which is now a grave concern for aquaculture and human health. Various aqua-medicines, chemicals and drugs are being used more frequently in aquaculture to mitigate loss of production as a consequence of the prevalence of various fish microbial and parasitic diseases in India (Sahoo *et al*. 2013) and other Asian countries (Ali *et al*. 2014; Chowdhury *et al*. 2012). Frequently used chemicals typically include formalin, sodium chloride, methylene blue, malachite green, hydrogen peroxide, potassium, permanganate, and glutaraldehyde. Formaline, Chloramine T, Tricaine methanesulfonate, Oxytetracycline hydrochloride, injectable Chorionic gonadotropin, Florfenicol, Oxytetracycline dehydrate, and sulphamerazine are some of the FDA-approved medications that are most commonly used in aquaculture. Table 1 and 2 comprises a list of several USFDA-approved medications for use in aquaculture, along with recommended dosages. Drugs and chemicals play a vital role in regulating fish health; however, they are additionally utilised in preparation of pond, soil and water quality management, enhancing aquatic productivity, growth and feed additives (Alam *et al*. 2015). A great deal of farmers make use of these chemicals and medications at arbitrarily without understanding the requirement, safe dosage, potential side effects, optimal application technique, or drug dose regulating point. Farmers must exercise caution since they yielded output for consumption, even though the use of certain chemicals is common in contemporary culture practice. Chemical usage needs to be restricted to last resorts. According to studies conducted by Mishra *et al*. (2017), 364 aqua-medicines and chemicals were employed, with 216 of total being utilised in Andhra Pradesh, 98 in Odisha, 28 in Jharkhand, 22 in Chhattisgarh. The category which utilised the most aquaculture drugs and chemicals (i.e., feed supplements and growth promoters) accounted for 31% of these, followed by probiotics (24%), products which improve water quality (18%), antiseptics (13%), anti-parasitic drugs (10%), and antibiotics (4%). The responsible and prudent use of chemicals is crucial for aquaculture's success. Several international organisations have raised serious concern concerning the misuse or abuse of these chemicals, that often ends up in the emergence of antimicrobial resistance (AMR) and poses a risk to the public health (Romero *et al.* 2012). Water/soil treatment chemicals, disinfectants, piscicides, herbicides, anaesthetics, therapeutants, feed additives, growth promoters, vaccines, antibiotics, and probiotics are some of the broad categories under which chemicals and drugs used in farms and hatcheries in India can be categorised. Different commercially available chemicals with their recommended dosage are enlisted in Table 3.

2. Aqua-medicines, Drugs and Chemicals Use in Indian Aquaculture

A. Water and soil treatment products

The management the quality of the soil and water is key to achieving a profitable yield. Pond water and soil need to be treated during the pre-stocking phase followed by conditioning for optimum mineralization of organic matter, adjustment of pH, and disinfection. Lime in various forms such as agricultural lime ($CaCO_3$), slaked lime ($Ca(OH)_2$), or quick lime (CaO) are the most commonly used chemicals for this purpose. It works to regulate the pH of water and fix pond bottoms. Aqua medicines such as Zeolite, Geotox, Zeocare, Bio Aqua, Aquanone, Zeo prime are used for the preparation of pond and management of water quality (Sharker *et al.* 2014). Disinfection and sterilization of properly dried ponds are done using iodine or potassium permanganate ($KMnO_4$). For reactivating the soil, zeolite and porous aluminium silicate are applied along with lime so as to establish algal growth and for absorbing fouling materials. Farmers are towards the most widely used chemicals since they are cheap and efficient in managing water quality.

B. Disinfectants used in Aquaculture for Water Hygiene

Disinfectants have widespread application in several aquaculture domains across the globe. Huge amount are employed in intensive culture, especially in grow-out culture of finfishes. Several chemical components have been recommended for pond or hatchery disinfection. However, an excessive amount of organic material in the ponds may reduce the disinfectant's efficacy. They are used in site preparation, equipment maintenance, hygienic practices throughout the production cycle, and, in certain circumstances, for for the treatment of diseases. Water cleansers, EDTA, BKC, Aquakleen, bleaching, Efinol, and Formalin are a few of the medications used to treat diseases. Protozoan disease treatment involves the use of formalin. BKC (Benzal Konium Chloride), potassium permanganate is the most widely used drug for controlling the bacterial infecton; Efinol can also be used to promote stress resistance (Mukta and Paramveer 2018). Among the frequently employed disinfectants are BKC, sodium hypochlorite, calcium hypochlorite, calcium carbide, calcium oxide, and Na-EDTA. Chlorine is the active ingredient in most of these components. They tend be utilised in hatcheries and, to a lesser extent, in grow-out ponds.

C. Piscicides and Herbicides

A vital component of pre-stocking pond management is getting rid of undesired predatory fish and aquatic vegetation. Mahua oil cake (200–250 ppm), tea seed cake (75–100 ppm), derris root powder (5–10 ppm), and other plant derivatives as well as anhydrous ammonium compounds are the most commonly used fish piscicides (Mukta and Paramveer 2018). Nevertheless, the type of species, as well as its size and biomass, determine the dosage required to eradicate predators. Ponds are treated with herbicides and algaecide to diminish the undesirable aquatic vegetation. Since they disturb the oxygen balance and deplete the aquatic systems' nutrients, aquatic weeds are a regular sight in fishponds and should be eliminated. Dense colonies formed by larger aquatic plants obstruct feeding and harvesting. Herbicides such as 2,4-D, Dalapon, Paraquat, Diuron, Simazine, and numerous other ammonia derivatives at recommended doses are employed for controlling aquatic weeds. Aquanones also aid in the removal of undesirable fish and other harmful aquatic animals (Jilani *et al.* 2012).

D. Commonly Applied Therapeutants

A number of bacterial infections have become more common as a consequence of aquaculture intensification, necessitating more frequent administration of antimicrobial medicines (Defoirdt *et al.* 2011). Fish populations with infections are often treated with antibiotics for brief intervals of time. The Food and Drug Administration (FDA) has authorised the following medications for application in aquaculture: sulfamerazine, florfenicol, oxytetracycline hydrochloride, dihydrate, and sulfamerazine, as well as a combination of sulfadimethoxine and ormetoprim, provided that the fish have lesser residue than the regulated maximum residue limit (MRL). Additionally, number of vaccines against different bacterial and viral infections have been developed and made readily for aquaculture use. Drugs and chemicals such as Butox Vet, Nuvan, Ectodel (2.8%), Cliner, Emamectin Benzoate (EB), Dipterex, Hitek Powder, Paracure-IV, and others were frequently employed in aquaculture to combat parasitic infestations. Trifuralin is used to treat fish fungal infections. Compared to other products, Butox Vet and Cliner have a slightly higher market demand. Certain particular medications, such as copper sulphate (0.25–1 ppm) for filamentous bacterial illness and EDTA (10–15 ppm) for vibriosis-dip treatment @ 4-6 hours, Treflan for larval myosis @0.1-0.2 ppm-bath treatment, and Prefuran for bacterial necrosis @1 ppm are commonly used in hatcheries. Though many of these products have been approved for veterinarian animals, there hasn't been a formal recommendation for their adoption in aquaculture.

E. Anaesthetics used for Fish

Anaesthesia is crucial in aquaculture for minimising fish handling and transportation-related mechanical injuries and manipulation stress. In India, anaesthetics are not often used in aquaculture. They are used meticulously, especially when transporting fish seed and broodstock over large distances. Fish anaesthetics such as MS-222 (tricaine), isoeugenol, benzocaine, 2-phenoxyethanol, metomi date, clove oil, halothane, lignocaine, and quinaldine are among the most frequently employed medications. Currently, sodium chloride and MS-222 are approved by the USFDA for use on food fish in the United States, and after exposure, must be held for 21 days prior to harvesting and human consumption (Popovic *et al.* 2012). Various anaesthetics, such as isoeugenol, propofol, and propiscin (containing etomidate), have undergone experimental evaluation and are currently being utilised for research as well as non-food fish.

F. Feed Additives

Developments in aquaculture techniques lead to a significant transition from the use of supplemental fish feeds made of agricultural waste products to complete feeds that are nutritionally balanced and species-specific. The development of premium-grade feeds has been the main factor contributing to the rise of aquaculture. Feed additives enhance fish performance in context of growth and health (Bharathi *et al.* 2019). They have been used to increase productivity and upregulate resistance to various infectious illnesses, which would ultimately result in a sustainable aquaculture approach. In addition to protein, carbohydrates, and fat, artificial feeds additionally contain preservatives like mould inhibitors and antioxidants, as well as vitamins, minerals, phospholipids, carotenoid colours, and chemo-attractants. These additions help to improve the growth and survival of cultured fish (Bharathi *et al.* 2019). A variety of additives, including colours, vitamins, chemo-attractants, and preservatives including antioxidants and mould inhibitors, are incorporated in this balanced feed. The incorporation of these feed additives into diet formulas serves a specific purpose, and their nature and characteristics are fairly diverse. Certain additives, such as acidifiers and exogenous enzymes, have been used to promote the digestibility of feed ingredients or mitigate the adverse effects of anti-nutrients in order to improve fish performance. Additional supplements which improve gut health, stress tolerance, and disease resistance include probiotics, prebiotics, phytogenics, and immunostimulants (Mukta and Paramveer 2018). Furthermore, functional feed additives are safe for the environment and have no adverse effects on aquaculture.

G. Growth Promoters

Growth promoters typically result in improvements of body composition, net financial return, feed utilisation, and growth performances. Probiotics, prebiotics, acidifiers, synbiotics, and phytobioics such as Aqua Boost, Megavit Aqua, Biogen, Aqua Savour, Fibosoel, Grow Fast, Orgavit auqa, AQGrow-G, Fish vita plus, AQ Grow-L, Nature Aqua GP, Vitamix, F Aqua, ACmix, are some of the substances that have been used as growth inducing agents. However, probiotics are the most efficient, followed by prebiotics and acidifiers (Hussein *et al.* 2016). The immunostimulant such as Aqua boost strengthens fish's non-specific immunity. Several artificial larval feeds, such as shrimp flakes and micro-encapsulated diets, have been reported to be incorporated with antibiotics, such as oxytetracycline, oxolinic acid, and even chloramphenicol, as growth promoters.

H. Immunostimulants

Dietary supplements such as immunostimulants strengthen the body's innate (non-specific) defences against specific infections. Antibiotics, chemotherapeutics, and disinfectants are frequently employed in aquatic systems to combat disease, however this approach leads to drug resistance, human carryover, bioaccumulation, as well as substantial contamination of the aquatic environment. However, the most noticeable drawback of drug application is the emergence of antibiotic resistance in some pathogen strains as a result of overuse or misuse. Antibiotics can't get rid of infections completely, which leads to disease recurrence, hence, their residue could end up in fish flesh and surrounding areas. Thus, in order to alleviate this issue while ensuring a smooth aquaculture process, it is found that deploying immunostimulants rather than antibiotics to treat infectious diseases is preferable due to the former's lack of strain resistance and residue retention in tissues. Immunostimulants can be categorised under various agents regardless of their origin. These agents include bacterial preparations, polysaccharides, plant or animal extracts, dietary factors, and cytokines. A number of pathogens, including bacteria *Aeromonas salmonicida*, *A. hydrophila*, *Vibrio anguillarum*, *V. salmonicida*, *Yersinia ruckeri*, and *Streptococcus* spp., viruses that cause infectious diseases like hematopoietic necrosis, yellow head virus, viral hemorrhagic septicemia, and parasitic infestations like *Ichthyophthirius multifiliis*, have been effectively controlled in fish and shrimp using immunostimulants. Glucan, a commonly used immunostimulant, has been shown to boost aquatic species' non-specific defence mechanisms and enhance defence against bacterial infection. Hemocyte phagocytic activity has been demonstrated to be significantly increased by peptidoglycan. As a result, the growth statistics, survival, and feed conversion ratio of the treated animals showed an apparent improvement. In addition to peptidoglycan and glucan, additional commonly used immunostimulants in aquaculture include levamisole, yeast derivatives, vitamin A and C, carotenoids, lentinan, chitin and chitosan, Schizophyllan and oligosaccharide, and muramyl dipeptide.

I. Vaccines

Vaccines are developed from antigens that are extracted from pathogenic microorganisms and rendered inactive by suppressing their virulence in various way where they regulates fish immune responses and boosts their ability to fight against disease. The first fish vaccination against *Aeromonas salmonicida* infection was discovered in 1942 (Ayalew and Abunna 2018). Vaccination provides an approach to achieving protection. Furthermore, new vaccines are far easier to license and register than antibiotics (Ayalew and Abunna 2018). Commercial vaccines for infectious bacterial and viral fish diseases in aquaculture have become considerably easier to obtain in the recent years. According to a study, the bacterial vaccine that was initially commercialised for fish vaccinations was released in the USA in the late 1970s. These vaccinations were whole-cell immersion inactivated vaccines, and they were effective in preventing various bacterial infections. With the advancements in biotechnology and immunology, numerous fish vaccinations, including recombinant DNA vaccines, nano vaccines, genetically modified vaccines, and polyvalent vaccines, have been developed and brought to market (Dadar *et al.* 2017). The immersion method has demonstrated the efficacy of both live attenuated and inactivated bacterin vaccines. Additionally, safer live vaccinations with a high level of efficacy against furunculosis were tested using DNA vaccines; however, field approval for these vaccines has not yet been acquired (Muktar *et al.* 2016). Recombinant protein vaccines or inactivated virus vaccines are the commercial viral vaccines currently available for aquaculture (Muktar *et al.* 2016).

J. Probiotics

Probiotics use in aquaculture is a well-recognized management technique for enhancing both environmental quality and gut health. Probiotics that are frequently utilised for pond management include fermented products that are high in extracellular components and live bacterial cultures, which are non-pathogenic organisms. Probiotic use in aquaculture ponds has several advantages, such as enhanced organic matter decomposition, increased dissolved oxygen availability, decreased nitrogen and phosphorus concentrations, improved algal growth, control over ammonia, nitrite, and hydrogen sulphide, decreased disease incidence, and increased fish survival and productivity. However, research has revealed that adding probiotics has relatively little beneficial effects. These probiotics mostly comprise various concentrations of good bacteria, such as *Streptococcus faecalis*, *Bacillus* sp., *Rodobacter* sp., and *Rodococcus sp*. etc. Probiotic applications can increase the advantages of this activity since, as this research demonstrates, they provide workable substitutes for producing animal products of superior quality in terms of size, production duration, and health. Probiotics are not believed to pose any risks to the environment or food safety when added to aquaculture ponds.

K. Antibiotics

The increased intensity of aquaculture has created an environment that is more conducive to the growth of certain illnesses and biofouling-related issues. The proverb "prevention is better than cure" is something to keep in mind, and it is undoubtedly feasible to focus more on preventing illness in fish. When fish are raised under optimum circumstances, the stock will almost certainly be in great condition and show no symptoms of illness (Austin and Austin 2007). Disease, however, is a part of fish welfare overall (Bergh 2007). An estimated 63,151 tonnes of antibiotics were used globally in 2010 to produce food animals and by 2030, that number is expected to rise to 105,596 tonnes, a 67% increase. As a result, a broad variety of chemicals some of which are not antibacterial agents are being employed in aquaculture, including hormones, insecticides, antibacterials, anaesthetics, mineral, and vitamin mixtures. In aquaculture, antibiotics are typically used extensively to prevent, treat, and manage bacterial infections. (Romero *et al.* 2012). Antibiotics are used worldwide not just in human health but also in aquaculture and livestock husbandry to treat bacterial infections and/or stimulate animal growth (Du and Liu 2012). Antimicrobial agents are often administered orally by mixing them with food, however larger fish may also get injectable therapy. The best chance of success for antibiotics is to give them early in the course of a disease. As the pathogenic load increases and sick fish typically refuse to eat, their effectiveness may diminish in later stages. Farmers in India utilise antibiotics under various brand names for disease management, both as preventative and control measures. Erythromycin, Nitrofurans (Furacin, Furanace), Oxytetracycline, Sulfamonomethoxine (Dimeton), Oxolinic Acid, Macrolides, Quinolones, Fluoroquinolones, and Sulfamonomethoxine (Dimeton) are among the most common ones utilised to treat bacterial infections such as red disease or ulcer disease, bacterial hemorrhagic septicemia, aeromoniasis, and enteric septicemia in catfish caused by *Edwardsiella ictaluri* strains (Lulijwa *et al.* 2020). In freshwater aquaculture and hatchery systems, the most widely used combination of chemotherapeutants were Oxytetracycline, Sulfadiazine, and Trimethoprim.

As the product becomes more widely used, there is an increasing concern regarding careless use, including the use of products that are prohibited, misdiagnosis leading to overuse, and abuse from not seeking professional assistance. Chemotherapeutic agents, which are antibacterials that are not too harmful to the host, are used to treat infectious diseases in humans, animals, and plants. Antibacterials are rarely used voluntarily as growth enhancers in any area of aquaculture. The hatchery, or the juvenile or larval phases of aquatic animal production, is where most preventive therapies are used. Additionally, it is believed that preventive care is more prevalent in small-scale production facilities that lack the resources to pay for or have access to medical guidance. Since no antibacterial drugs have been created especially for use in aquaculture, it is likely that this will always be the case due to basic economic factors. (Rodgers and Furones 2009). Although antibacterials are widely utilised in aquaculture facilities, little information is known on the dosages of antibacterials employed (Heuer *et al.* 2009). Compared to animals kept in aquariums or indoor facilities, those kept in net cages at sea will require different forms of care. An adequate treatment plan for aquarium fish or specific individuals from the broodstock may be prohibitively expensive or labor-intensive for commercial aquaculture operations. A treatment plan must also be viable. The necessity of treatment and its anticipated benefits must be weighed against the stress related to it (Smith *et al.* 2008).

3. Antibiotics Permitted for use in India

Not all antibiotics used in veterinary or human medicine can be used in aquaculture. The United States Food and Drug Administration (USFDA) are in charge of approving the antimicrobials that are appropriate for use in aquaculture. Authorities such as the MPEDA and CAA are crucial in India when it comes to establishing a list of safe antibiotics permitted for aquaculture use. Some of the antibiotics that are prohibited for use in shrimp aquaculture are listed in Table 4.

A. Legal use of antibacterial

It is against the law to employ antibacterial agents that are expressly prohibited in aquaculture (Lupin 2009). For the purpose of conducting such occupational safety assessments, the user safety data that is contained on labels and packaging inserts should be sufficient (Alderman 2009). Drugs must be evaluated for their effectiveness and environmental impact, as well as of their MRLs, prior to approval. Multiple agencies, including the EU and the FAO/WHO Codex Alimentarius Commission, which is governed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) provides scientific advice to the Commission, are responsible for producing MRLs. Especially in Europe and USA, regulations govern the use of antibacterial agents in food animal species, including fish. Pharmaceutical companies have occasionally shown little interest in creating and registering novel antibacterials due to the highly expensive and time-consuming approval process and the limited global sales potential of the aquaculture market (Rodgers and Furones 2009). Aquaculture antibacterials have a relatively modest market and a costly regulatory process when compared to their application in agriculture and medicine. The environment a fish lives in, particularly the temperature, can have a significant impact on how much of a medicine it excretes (Noga 2010). A general guideline known as "degree days" was proposed for determining the necessary withdrawal period due to the unpredictability in drug excretion, particularly with temperature.

4. Route of Drugs Administration in Aquaculture

Antibacterials used to treat bacterial infections in intensive fish farming are typically administered intravenously, orally, or through water-borne ways (Zounkova *et al.* 2011). When administering treatment, fish should never be left unsupervised. If the fish exhibit any negative reactions, the medication should be stopped right away by shifting them to clean water or by diluting the water. Prior to treatment, a strategy for both detoxification and disposal of used drugs (e.g., ammonia and nitrite levels must be monitored closely during therapy) is a must as it's important to dispose of used medications properly.

A. Water Medication

The most popular way to treat fish is through the water, and it has several benefits, including being simple to use and comparatively less stressful. If the fish refuse to eat, application through the waterborne route becomes necessary, as they are unlikely to ingest any medicated food. This technique involve giving the fish a set amount of time to be exposed to medication solutions or suspensions. This could last anywhere from a few seconds (a "dip") to several minutes to several hours (a "bath") (Haya *et al.* 2005). When the biomass of the fish is low, as with fry, and when appropriate oral therapy is not feasible, fish are medicated through the water. This is a straightforward procedure that just requires the known volume of water in order to determine final concentration of the medicine. Fish absorb drugs that kill pathogens via the gills, epithelia, epidermis, and mucosa. Applying the medication to the water while treating fish helps prevent handling stresses. (Reimschuessel and Miller 2006). But there are drawbacks as well. Dosing is less accurate when compared to other treatment options (too little or too much). The antibiotic employed in baths and dips is often poorly absorbed internally, which makes them less effective than some other treatment approaches, especially for systemic illnesses. Water-borne treatments are mostly used to treat diseases that live on the skin and gills, such as bacteria, parasites, and water mould. Antibacterials that dissolve readily in water includes chloramines, enrofloxacin, dihydrostreptomycin, erythromycin, furpyrinol, flumequine, oxolinic acid, kanamycin, nifurpirinol, oxytetracycline, sulphadimidine, sulphadimethoxine, sulphanilamide, sulpha-monomethoxine, sulphapyridine, trimethoprim and sulphisomidine whereas chloramphenicol and gentamicin are not readily dissolved (Reimschuessel and Miller 2006). When compared to injections or oral (feed) therapies, more antibacterials are needed for bath-type treatments. Moreover, bath treatments are not recommended for aquarium settings with biological filters or recirculation systems. Less waste (and hence less expense) and less environmental contamination are the benefits of this kind of treatment. (Reimschuessel and Miller 2006).

B. Oral Medication

Many bacterial fish diseases in ornamental or food fish aquaculture can be effectively treated using medicated feeds, which is usually the recommended treatment method. Oral medicine is the most effective way to treat fish in ponds. Withholding food for 12 to 24 hours, however, may improve the acceptance of a medicated diet as unwell fish may not consume (Reimschuessel and Miller 2006). A small quantity of the antibacterial drug is added to a homogenised and extruded diet to produce medicated feeds. Alternatively, the medication can be sprayed or top-coated into the feed. One advantage of in-feed medication over water medication is less wastage. In addition, it minimizes the unwanted drug exposure to the environment and fish. This is a standard method to treat large population of diseased fish. The fish receiving treatment must be actively fed, which is the sole limitation of this method. The dosage required depends upon the original amount of active ingredient/kg fish body weight. The precise amount of antibiotics employed will determine the dosage rates, which usually depend on grams per 100 kg of fish each day. Antibacterial agents have been demonstrated to be less effective in seawater, which is connected to their decreased bioavailability and presents a challenge for the treatment of marine species. The dosage might vary based on the feeding rate and within certain limits. Other innovative oral delivery techniques, such as coated beads or microspheres, offer the possibility to convey delicate molecules up to their targeted sites in the gut while protecting them from deterioration in the gastric acids.

C. Injection

When treating bacterial infections, injections of antibacterial agents can be more successful than medicated feeds, especially in cases of advanced infection, and as the most reliable method of administering the recommended dose. (Douet *et al.* 2009). Although labour-intensive, injection methods are often employed for administering vaccines and treating few number of fishes. Fish injections frequently result in dorso-median sinus infections, intramuscular infections, and intraperitoneal infections. However, in large-scale fish production facilities, it is usually not feasible; rather, it is only feasible for individual fish, such as ornamental fish or broodstock. Drawbacks include the stress that comes with catching the fish and, in the case of tank fish, having to transport the fish to the clinic for each injection (Noga 2010). The most employed injection route is the IP route and this technique is only feasible to inject very small amounts (0.05 ml/50 grams of fish). The IM method has the drawback of potentially forming sterile abscesses and deteriorating carcass quality (Noga 2010).

D. Topical Application

Although it is uncommon, topical medication administration to fish is infrequently applied to treat skin ulcers on ornamental fishes. Topical treatments are usually applied for ornamental fishes or brood stock. Antibacterial ointments have occasionally been administered to the sutures and incision sites during fish surgery. Open sores or ulcers that are secondarily infected by bacteria or water moulds can also be treated.

E. Water Treatment

According to Treves-Brown (2001), antibacterial medications could trigger the filter to become inactive; hence it is not applicable to them.

F. Other Methods

Flushing is another method of administering medication to fish. In this method, the fish are submerged in flowing, non-recirculating water, like in a raceway. This technique is sometimes referred to as a "California flush," since it involves medicating the water by ceasing its flow, resuming it after a certain amount of time, and then draining the medicated water In experimental work, the gavage method is employed for oral administration because the exact dosage is known. This technique involves pumping a medication into the fish's stomach through a stomach tube connected to a syringe.

5. Problems Associated with Drugs and Chemical use in Aquaculture

The regulations pertaining to medicines mandate that the safety package assess the user's safety and that the product label provide caution and recommendations for safe usage. It is necessary to take into account any risks associated with feed medication as well as potential risks to the end user (the employees of the fish farms) (Alderman 2009). Most of the drugs use in aquaculture around the world are irrelevant to the categorization of the target bacterium or its susceptibility to the variety of antibacterial agents (Smith *et al.* 2008). There is also a need for assurance that it will not harm animals or humans. Aquaculture drug usage has been associated with a number of issues, involving improper knowledge, indiscriminate use, pressure from pesticide and pharmaceutical companies on farmers, awareness of the safety concerns when using hazardous chemicals, lack of information regarding potential hazards, ignorance of the residual effects on consumer health and the expiration date, lack of facilities for diagnosing fish diseases, and unregulated use of chemicals and drugs in excess of recommended dosages, which can lead to issues like excess drug tolerance by other organisms and drastically decrease aquatic biodiversity.

A. Toxicity to the Host

The most significant factor limiting drug dosage is direct host toxicity. Numerous detrimental effects on the host can result from antibacterial agents: (1) direct toxicity to the host (2) disruption of the metabolic processes of microbial flora in the digestive tract of herbivores (3) emergence of antimicrobial resistance (4) drug residues in animal products intended for human consumption (5) impairment of the host's immune system (Mulcahy 2011). However, oxytetracycline, the most widely used antibiotic in aquaculture, may impart genotoxic and ecotoxic implications in aquatic environments (Zounkova *et al.* 2011). Agents, such as betalactams, are generally considered to be safe, whereas aminoglycosides, are potentially toxic (Guardabassi and Kruse 2008).

B. Resistance of Aquatic Microbes

When exposed to antibacterial medications, aquatic bacteria respond similarly to other bacteria in most cases, and they have the ability to pass on genes that impart resistance to bacterial infections (Heuer *et al.* 2009). Antibacterial resistance in public health is a major issue as a result of the use of antibiotics in food fish, which appears to outweigh their application in human therapy in many countries (WHO 2011). Multiple resistant strains of harmful microbes are more likely to emerge in communities if subtherapeutic antibiotic dosages are continuously used to prevent disease. These could eventually lead to disease epidemics that antibacterial therapy is unable to control (Mulcahy 2011). Bacteria that infect humans and animals are becoming more resistant due to the overuse of antibacterials in fish aquaculture (Burridge *et al.* 2010; Defoirdt *et al.* 2011). Indirect contact with antibacterial agents, in addition to their direct therapeutic usage, may strengthen bacterial resistance: Resistance genes have been identified from ambient bacteria, animal-derived bacteria, and human infections without considering the sources of the bacteria (Martinez and Silley 2010). Antimicrobial resistance may be natural or acquired (Douet *et al.* 2009). Certain species possess inherent or intrinsic resistance to a particular agent due to their physiology or biochemistry, whereas others have developed resistance as a consequence of human use of antibacterial agents (acquired resistance) (Kümmerer 2008). Even after a considerable amount of time had passed since the use of antibacterials, tetracycline-resistant organisms from hatcheries have been released into streams. This suggests that there are reservoirs of organisms over and above the aquatic microbes and these bacteria act as reservoirs of resistance genes which are further disseminated (Stachowiak *et al.* 2010). In the end, human pathogens may come into contact with resistance genes from the aquatic environment, exacerbating the problem of antibiotic resistance in medicine (Heuer *et al.* 2009). Antibacterial-resistant microbes may enter receiving waters from commercial fish production facilities due to cross-resistance caused by biocides, even in situations when antibacterials are not actively used (Stachowiak *et al.* 2010). It has been demonstrated that the water and sediment related to aquaculture are more likely to harbour bacteria resistant to antibiotics. When medications were given as medicated feed, there was an increase in the percentage and level of drug-resistant bacteria. Furthermore, when medicated feed was used as the means of drug administration, the resistance persisted for a longer time. The maintenance of drug-resistant bacteria in sediment would be greatly influenced by the presence of feed residue in the aquatic environment (Yu *et al.* 2009). The proper use of antibiotics in livestock production will safeguard the antibiotics' long-term efficacy, promote the health and well-being of the animals, and reduce the likelihood that humans and other animals will become resistant to the antibiotics (Kemper 2008).

C. Aquatic Food Residues

The extensive therapeutic and prophylactic usage of antibiotics can result in higher antibacterial residues in ponds, marine sediments, aquaculture products and wild caught fish (Sapkota *et al.* 2008). Additionally, employing a lot of antibacterials to mix with fish meal poses challenges for industrial health and enhances the possibility that fish meat and fish products may contain residue antibacterials. Veterinarians can estimate residue-depletion times for antibacterial medicines that are provided above the authorised limit on the label with the help of the Food Animal Drug Avoidance Databank (FARAD) (Walker and Giguére 2008). The EU and other regulatory bodies across the world have set MRLs for antibacterial residues in animal products that are incorporated into the human food chain in order to safeguard human health (Cañada-Cañada *et al.* 2009).

D. Environmental Impact of Antibacterial Use

The widespread application of veterinary medications is believed to pose a serious risk to public health since it can lead to various problems for humans, animals, and the environment in addition to the development and dissemination of resistant microorganisms (Kemper 2008). The most significant source of environmental resistance appears to be the introduction of resistant bacteria from various sources. Field soils have revealed the presence of multiple antibacterial classes, whose sorption behaviour and degradation have been thoroughly examined (Zounkova *et al.* 2011). The safety and nutritional value of farmed fish is generally comparable to that of wild-caught species; nevertheless, misuse, ignorance, and disregard for aquaculture technology can pose health risks to the population. Fish farming can produce significant volumes of dissolved effluents that may have an impact on the water quality nearby the farms (Holmer *et al.* 2008). Further, the application of antibacterials in livestock farms must be cautiously restricted so as to mitigate the potential dangers of antibacterials in environment. Wei *et al.* (2011) observed that sulphamethazine (75%), oxytetracycline (64%), tetracycline (60%), sulfadiazine (55%) and sulphamethoxazole (51%), were the most commonly found antibacterials. 500 metres from the source, antibacterials may be found in wastewater that enters receiving waters (Costanzo *et al.* 2005). Antibacterial resistance may arise from the simultaneous release of heavy metals, disinfectants, and antibacterials into water, which may cause harm to the aquatic environment (Baquero *et al.* 2008).

6. Conclusion

Disease outbreaks in aquaculture populations have significant adverse effects on the welfare of the afflicted fish and leave the well-being of those who are unaffected fish at risk. Given the intensive use of drugs and chemicals in aquaculture due to the industry's rapid global growth, further study needs to be done to comprehend the effects of employing large amounts of chemicals and drugs uncontrollably for animal production. Additionally, greater initiatives must be made to restrict the emergence and dissemination of antibacterial resistance in aquaculture. The chapter highlights the various drugs and chemicals which are employed for growth and health management. It focuses on the current trends of drugs and chemicals used in aquaculture sector and hinted on the issues regarding the meticulous usage by the farmers as well as supplier agencies. Along with advancements in husbandry and management that will lessen the need for those medications, safer, more effective medications need to be developed as well. However, a number of substitutes, such as probiotics, immunostimulants, vaccinations, and therapies, may lessen the negative effects of chemicals used in lieu of hazardous substances and drugs. To lessen the adverse effects, policymakers, scientists, and researchers should cooperate and work jointly to address the prudent issues of chemical usage in aquaculture. Fish farmers must also ensure that their fish are maintained in the best state of health and welfare conditions. Therefore, it is of the utmost importance that both governmental and non-governmental organisations take the lead in an effort to enhance awareness regarding the judicious application of chemicals and drugs in aquaculture management.

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Table 1: FDA approved drugs permitted for application in fisheries and aquaculture

Sr. No.	Drug	Commercial Name	Usage	Approved Species	Route of administration with recommended dosage
1.	Chloramine-T	Halamid® Aqua	Control of mortality due to bacterial gill disease and columnaris associated with *Flavobacterium* spp. in freshwater-reared salmonids	Freshwater-reared salmonids, Freshwater-reared warm water finfish	Immersion @20 mg/L for 60 minutes
2.	Chorionic gonadotropin	Chorulon®	For enhancing spawning function in male and female brood finfish	Brood finfish	Intramuscular injection Males: 50 - 510 IU chorionic gonadotropin/lb Females: 67 - 1,816 IU chorionic gonadotropin/lb Total dosage not to exceed 25,000 IU in fish
3.	Formalin	Formaldehyde solution	For controlling Protozoa and Monogenetic Tremetodes, and in Salmon, Trout and Pike (esocids) eggs of for controlling fungi (Family-Saprolegniacea)	Finfish, Penaeid shrimp Salmon, Trout, Catfish	Bath treatment Salmonids in tanks and raceways: Up to 170-250 µL/L for up to 1 hr Other finfish up to 250 µL/L for up to 1 hr
4.	Florfenicol	Aquaflor® Type A	For controlling of mortality in catfish due to enteric septicemia of catfish caused by *Edwardsiella ictaluri*, freshwater-reared salmonids due to coldwater disease caused by *Flavobacterium psychrophilum* as well as due to furunculosis caused by *Aeromonas salmonicida*.	Channel catfish, salmonids	Medicated Feeds @10 mg/kg fish/day for 10 days

5.	Hydrogen peroxide	35% PEROX-AID®	Controlling of mortality due to bacterial gill disease caused by *Flavobacterium branchiophilum*, external columnaris disease caused by *F. columnare*	Finfish eggs, Cold freshwater reared finfish, Salmonids	Bath treatment Coldwater finfish eggs: 500 - 1,000 mg/L for 15 min in a continuous flow system once daily on consecutive or alternate days Warmwater finfish eggs: 750 - 1,000 mg/L for 15 min in a continuous flow system once daily on consecutive or alternate days
6.	Oxytetracycline dihydrate	Terramycin® 200	For controlling of gaffkemia caused by *Aerococcus viridans*, in freshwater-reared salmonids due to coldwater disease cauded by *Flavobacterium psychrophilum*, in freshwater-reared *Oncorhynchus mykiss* due to columnaris caused by *Flavobacterium columnare*.	Catfish, Salmonids, Lobster	2.50-3.75 g/100 lb fish
7.	Oxytetracycline hydrochloride	Terramycin343; OxymarineTM, Oxymarine™, Phennoxy 343	For feed use. Tolerance in the flesh is 2.0 ppm	Finfish fry and fingerlings	Immersion @200-700 mg/L water for 2-6 hours
8.	Sulfadimethoxine/ Ormetoprim	Romet-30®	1. For controlling of furunculosis in salmonids (trout and salmon) caused by *Aeromonas salmonicida*. 2. For controlling of bacterial infections in catfish caused by *Edwardsiella ictaluri* (enteric septicemia of catfish).	Catfish, salmonids	Medicated feeds @50 mg/kg fish BW for 5 days consecutively
9.	Sulfamerazine	Sulfamerazine	Not to be used within 21 days of harvest. Not currently marketed	Trout (rainbow, brook, brown)	-

10.	Tricaine methanesulfonate	Tricaine-S, MS-222	Not to be used within 21 days of harvesting fish for food. Limited to hatchery or laboratory use.	Salmonidae, Ictaluridae (catfish), Esocidae and Percidae	Fish: 15 - 330 mg/L Other poikilotherms: 1:1,000 1:20,000

Source: US FDA, 2020. Approved Aquaculture Drugs, U.S. Food and Drug Administration

Table 2: FDA low regulatory priority drugs

Sr. No.	Drug	Recommendations
1.	Calcium chloride	Used for increasing calcium concentration in water to insure proper egg hardening
2.	$CaCO_3$	Used up to 150 ppm for increasing the water hardness
3.	Calcium oxide	Used as an external protozoacide @2000 mg/l for 5 seconds
4.	Carbon dioxide Gas	Used for anesthetizing cold as well as warm water fish
5.	Hydrogen peroxide	Used @250-500 mg /l for controlling fungi in life stages of fish, including eggs
6.	Potassium chloride	Used as an aid in osmoregulation; relieves stress and prevents shock.
7.	Sodium bicarbonate	Used @142-642 mg/l for 5 minutes to introduce carbon dioxide into the water for anesthetizing fish

Source: US FDA, 2020. Approved Aquaculture Drugs, U.S. Food and Drug Administration

Table 3: Chemicals applied in aquaculture

Sr. No.	Trade Name	Active Ingredients	Dosage
1.	Super Zeolite	SiO_2, Al_2O_3, Fe_2O_3, CaO, MgO, LoI, K_2O	20-30kg/acre
2.	Aquanone	Rotenone	5-7kg/acre
3.	Aqua Lime	$CaCO_3$, $Ca(OH)_2$	1–2 kg/dec
4.	BKC	Benzal konium chloride	Spread in water @0.5 ppm
5.	Formalin	38% Formaldehyde	1–3 ppm
6.	Aquakleen	Tetradesail Tri-methyl Amonium bromid, BKC	0.5-1 L/acre
7.	Oxymax	H_2O_2 10%	250-500 g/acre
8.	Registrol	Betain, Calcium, P, Vit-C	5-10ml/kg feed
9.	Oxysentin 20%	Oxytetracycline HCL BP	50–100 g/100 kg feed, 5–7 days (for treatment)
10.	Aqua boost	Organic acid, ß-glucan	500 g/mt feed
11.	Pond D tox	Pracoccus pantotrophus	4 ppm
12.	Frankzole	Vitamin-A, D3, E, K3, C, Folic acid Biotin, DL-methionine, L-Lysine, Inositol, Zn, Se, SiO_2	1 k/acre
13.	Star Shrimp	Growth promoter of essential macro and trace minerals in organic form (Ca, P, K, Na, Mg, Zn, Fe, Cu, Mn)	Shrimp: 10 g per 1 k feed. Fish: 500 g - 2 k/ton feed
14.	K-Max	Enriched Potassium, Chloride and other nutrient	10 to 20 k/ha/week
15.	Growel	Vitamins like A, E, D3, B1, Niacin, Pantothenic acid, Folic Acid, Vitamin-C etc.	Shrimp- 5 to 8 g/k of feed regularly
16.	Paramed	Pentapropyl methyl-thio-benzimidazole carbamate 5%	1-1.2 k/ton feed for 3 Days
17.	Copper (II) Sulfate pentahydrate pure	Copper sulphate	1:2000 with water/acre
18.	Potassium permanganate	Potassium permanganate	20 g/10l water and spray or dip treat
19.	Malachite green (M.S)	Malachite Green	Dip: 66.7-100 mg/l
20.	Aqua kleen	Brominated Organic Salts, Amino Nitrogen, Benzalconium	0.5-1 litre/acre

Source: Mukta and Paramveer 2018; Roy *et al*. 2021

Table 4: Antibiotics and pharmaceutically active ingredients that are prohibited for use in shrimp farming

Antibiotics and other ingredients
Chloramphenicol
Nitrofurans including: Furazolidone, Furaltadone, Furylfuramide, Nifuratel, Nifuroxime, Nitrofurantoin, Nitrofurazone
Neomycin
Nalidixic acid
Sulphamethoxazole
Chlorpromazine
Colchicine
Dapsone
Dimetridazole
Metronidazole
Ronidazole
Ipronidazole
Other nitroimidazoles
Diethylstilbestrol (DES)
Fluroquinolones

Source: Coastal Aquaculture Authority