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Mukta Singh
Department of Aquatic Health & Environment, College of fisheries, CAU, Lembucherra, Tripura, India

Paramveer Singh
Department of Applied Aquaculture and Zoology, Barkatullah University Bhopal, Madhya Pradesh, India

Correspondence
Paramveer Singh
Department of Applied Aquaculture and Zoology, Barkatullah University Bhopal, Madhya Pradesh, India

Drugs and chemicals applied in aquaculture industry: A review of commercial availability, recommended dosage and mode of application

Mukta Singh and Paramveer Singh

Abstract
This paper briefly reviews the application of different types of drugs and chemicals widely applied in aquaculture for treatment and preventive measures. 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. This review study provides 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. Emphasis is placed to give a clear picture of all approved drugs along with their recommended dosage to prevent the economic loss of fish farms due to disease outbreak or poor water and soil quality parameters.

Keywords: drugs, chemicals, recommended dosage, disease outbreak

1. Introduction
Global aquaculture has grown drastically in the previous 50 years to around 106 million tonnes in live weight, with a total estimated first-sale value of US$163 billion in the year 2015, comprising farmed aquatic animals, aquatic plants and non-food products (pearls and shells). Nonetheless, the worldwide population is expanding and, in order to maintain at least the current level of per-capita consumption of aquatic foods (19.7 kg in 2013, FAO, 2016) [12], the world will require an additional 23 million tonnes thereof by 2020. At present India contributes about 6.30% to the global fish production and 5% to the global fish trade. India is the second largest producer of aquaculture in the world (DADF, 2016) [9] and the country has plans to increase the annual growth rate mark by 8 percent in coming years by 2020 (Press Information Bureau, 2017) [21].

As there is limited scope for horizontal expansion, the current trend in aquaculture development is towards vertical expansion with the intensification of cultural practices. The vertical expansion of aquaculture practices with the introduction of diversified species and higher stocking density has resulted in more frequent incidence of disease outbreaks often leading to higher morbidity and mass mortalities with reduced overall production. In recent years, aquaculture has been adversely affected due to frequent occurrence of disease outbreaks mostly due to intensified culture system for higher economic gain (Walker and Winton *et al*., 2010) [29]. The diversity and number of species being produced has also resulted in new culture systems and practices, which themselves could influence the emergence and spread of pathogens (Murray and Peeler *et al*., 2005) [16].

Occurence of different fish microbial and parasitic diseases in India (Nayak *et al*., 2007; Sahoo *et al*., 2013) [17, 25] and other Asian countries (Bondad-Reantaso *et al*., 2005; Faruk *et al*., 2004) [4, 13] has led to enhancement in application of a wide range of aqua-medicines, drugs and chemicals in aquaculture to control production loss (Ali *et al*., 2014; Burridge *et al*., 2010; Chowdhury *et al*., 2012; Costello *et al*., 2001; Joshua *et al*., 2002; Pathak *et al*., 2000) [3, 6, 7, 8, 15, 19]. Various USFDA approved drugs to be applied in aquaculture are listed in Table 1 and 2 along with their recommended dosage. Along with their major role in fish health management, aquaculture drugs and chemicals are also used in various other aquaculture activities like pond preparation, soil and water management, natural aquatic productivity enhancement, feed additives and growth (Plumb 1992; Subasinghe *et al*., 1996; Gesamp, 1997; Alam *et al*., 2015) [20, 26, 14, 2]. Drugs and chemicals used in grow-out farms and hatchery operations in India can be classified into the broad categories as water/soil treatment products,

Disinfectants, piscicides, herbicides, therapeutants, anesthetics, feed additives, growth promoters, vaccines and probiotics. List of commercially available drugs and chemicals with their recommended dosage and trade names are given in Table 3.

1.1 Water and soil treatment products

Pond preparation is an initial step towards enhancing of the fish production. Before stocking fish in pond, pond waters are treated for mineralization of organic matter, adjusting pH, and for disinfection. The chemicals used in this regard are lime in the form of lime stone ($CaCO_3$), slaked lime ($Ca(OH)_2$) or un-slaked lime (CaO). Aqua medicines like Geotox, Zeolite, Zeocare, Lime, Bio Aqua, Aquanone, Zeo prime are used for the pond preparation and water quality management. Disinfection and sterilisation of dried ponds are also done using active iodine or potassium permanganate ($KMnO_4$). Commercially available zeolite and porous aluminium silicate is applied along with lime for re-activating the soil to stabilize algal growth and to absorb fouling materials.

1.2 Disinfectants used in aquaculture

Disinfectants are used extensively worldwide in different aspects of aquaculture. The greatest quantities are used in intensive culture, particularly in finfish and grow-out facilities. They are used in site and equipment preparation, to maintain hygiene throughout the production cycle and, in some cases, to treat disease. Bleaching, Aquakleen, BKC, EDTA, Efinol, Formalin, Water clear are the drugs used for disease treatment. Formalin is also used to control protozoan disease. Most commonly used agent for controlling the bacterial disease is BKC (Benzal Konium Chloride) and to increase stress resistance, Efinol can also be used. Sodium hypochlorite, BKC, calcium carbide and Na-EDTA are some commonly used disinfectants. These are applied mostly in hatcheries and also in grow-out ponds, to a limited extent.

1.3 Piscicides and herbicides

In aquaculture practices, eradication of unwanted predatory fishes is a common pre-stocking management step. Most frequently used fish piscicides are mahua oil cake, tea seed cake, other plant derivatives and anhydrous ammonium substances.

Algicides and herbicides are applied to ponds to reduce the abundance of unwanted aquatic plants. Aquatic weeds are of common occurrence in fishponds in the country and are undesirable, as they pose serious problems by upsetting the oxygen balance and removing nutrients from the aquatic systems. Larger aquatic plants create dense communities that interfere with feeding and harvest. Herbicides used to control aquatic weeds are 2,4-D, Dalapon, Paraquat, Diuron, and many others ammonia derivatives.

1.4 Commonly applied therapeutants

Intensification has resulted in the incidence of several bacterial diseases in aquaculture leading to the increased application of antimicrobials agents (Defoirdt *et al*., 2011, 2007) [10, 11]. Antibiotics are frequently administered for short periods of time as therapeutics to groups of infected fish. Food and Drug Administration (FDA) has approved Florfenicol, Sulfamerazine, oxy tetracycline dihydrate, Oxytetracycline hydrochloride, as well as a drug combination of Sulfadimethoxine and ormetoprim for use in aquaculture as long as the fish contains less than a mandated maximum residue limit. Various vaccines have also been developed and commercialised for use in aquaculture against various bacterial and viral pathogens.

Parasitic infestations are widely distributed in freshwater fish which include single celled protozoan and multi-cellular trematodes, crustaceans and arthropods (Woo, 2006) [30]. The drugs and chemicals frequently used in aquaculture to control parasitic infestations included Nuvan, Butox Vet, Cliner, Ectodel (2.8%), Emamectin Benzoate (EB), Hitek Powder, Paracure-IV etc. Among these Butox Vet and Cliner has comparatively higher market demand than other products. However, there has been no official recommendation for use of such products in aquaculture, although many such products have been permitted for use in veterinary animals.

1.5 Anaesthetics used for Fish

Anaesthetics are chemical or physical agents used to calm animals and cause them to progressively lose their mobility, equilibrium, consciousness, and finally their reflex action. In fisheries and aquaculture, anaesthetics are helpful for reducing the stress caused by handling and transport. The use of anaesthetics in aquaculture in India is particularly in the long distance transport of brood-stock and fish seed. The most common anesthetic drugs used in fish are MS-222 (Tricaine), benzocaine, isoeugenol, metomi date, 2-phenoxyethanol, and quinaldine (Summer felt and Smith, 1990; Ross and Ross, 2008; Neiffer and Stamper, 2009; Ackerman *et al*., 2011) [27, 24, 18, 1].

1.6 Feed additives

Advancement in aquaculture practices causes major shift from using supplementary fish feeds comprising of agricultural by-products to nutritionally balanced species specific complete feeds. These balanced feed contains various additives in the form of pigments, vitamins, chemo-attractants, and preservatives, like mould inhibitors and antioxidants. The nature and characteristics of these feed additives is quite diverse, and their application into diet formulations targets a specific purpose. Some additives, such as acidifiers, exogenous enzymes, are used to improve fish performance by providing enhanced digestibility of the feed materials, or counteracting the negative effects of anti-nutrients. Other additives, such as probiotics, prebiotics, phyto genics, and immune-stimulants target the improvement of intestinal health, stress and disease resistance.

1.7 Growth promoters for fish

There are different chemicals found in the chemical shops which are used as growth

enhancer including Megavit Aqua, Aqua Boost, Aqua Savor, Vitamin premix, Fibosoel, Grow fast, Orgavit auqa, AQGrow-G, Fish vita plus, AQ Grow-L, Nature Aqua GP, Vitamix, F Aqua, ACmix and many more. Aqua boost contains immune stimulant which enhances non-specific immunity in fish.

1.8 Probiotics used in fish farming

The common probiotics used in pond management are live bacterial culture (non-pathogenic organisms) and fermentation products rich in extracellular. Benefits of using probiotics in aquaculture ponds include enhanced decomposition of organic matter; reduction in nitrogen and phosphorus concentrations; better algal growth; greater availability of dissolved oxygen; control of ammonia, nitrite,

and hydrogen sulfide; lower incidence of disease and greater survival and fish production. However, studies have shown very few positive benefits resulting from the addition of probiotics (Boyd and Gross, 1998; Queiroz and Boyd, 1998; Queiroz *et al*., 1998) [5, 22, 23]. The probiotics contains mainly different concentration of beneficial bacteria which include *Bacillius* sp., *Rodobacter* sp., *Rodococcus* sp., *Streptococcus faecalis*, etc. No food and environment safety hazards are thought to be presented by addition of probiotics to aquaculture ponds.

2. Mode of drugs administration in aquaculture

Water medication and medicated feed are the two most common routes for the administration of antimicrobials in aquaculture. Medicating fish through the water is done when the fish biomass is small, such as with fry, and when adequate oral therapy is impractical. It is a simple method, in which only the volume of water needs to be known in order to calculate the final concentration of the medicine. Generally drugs of low molecular weight are recommended for water medication as they can be distributed thoroughly throughout the water. Drugs are absorbed by the fish through the gills epithelia, skin and mucosa and kills pathogens.

Medicated feeds are prepared by the addition of a small amount of the antimicrobial drug to a homogenised and extruded diet, or the drug may be sprayed or top-coated onto the feed. The benefits of in-feed medication include reduced wastefulness as compared to water medication. It also reduces undesirable exposure of the environment and other fish to the drug. This is a standard method to treat large population of diseased fish. Only limitation of this method is that the fish under treatment must be feeding actively.

Gavage method is used in experimental work as oral administration because the precise dose is known. This method uses a stomach tube, which is attached to a syringe containing a drug, and the drug is pumped into the stomach of the fish. Fish must be anaesthetised before administration of the drug. This method is rarely used in the aquaculture industry because it is labour intensive and stressful to the fish.

Injection methods are used extensively for vaccine administration and treating a limited number of fish or valuable fish, but they are labour intensive. The intramuscular, intra-peritoneal, and dorso-median sinus injections are common routes of injection for fish.

3. Problems associated in use of aquaculture drugs

Various problems were recognized linked with the application of aquaculture drugs which included lack of proper knowledge regarding use of chemicals, lack of knowledge of the method of application of chemicals and antibiotics, indiscriminate use of drugs, lack of knowledge about residual effect and expiry date and lack of diagnostic facilities for proper disease diagnosis. Farmers usually do not maintain the recommended dose. Sometimes farmers apply a higher dose of drugs and chemicals than the recommended dose. This higher dose cannot be tolerated by other organisms which can result in serious biodiversity loss of aquatic organisms.

4. Conclusion

Considering the present scenario, it can be said that with the further development of the aquaculture industry, particularly in intensified system, the applications of chemicals would be increased. The present study described the different types of aquaculture drugs which are used in fish growth and health management by the fish farmers. However, researchers and policy makers should work together to address the issues of drugs use and abuse in aquaculture with the view to diminish the negative impacts. Therefore, both the government and nongovernment organizations should take initiative for better understanding of chemical and drug uses in aquaculture management.

Table 1: FDA approved aquaculture drugs (permitted for application in fisheries and aquaculture) **(**US FDA, 2017)

Sr. No.	Drug	Commercial Name	Usage	Approved Species
1.	Chorionic gonadotropin	Chorulon®	For improving spawning function in male and female brood finfish	Brood finfish
2.	Formalin	Formaldehyde solution	For the control of Protozoa and Monogenetic Tremetodes, and on the eggs of Salmon, Trout and Pike (esocids) for control of Fungi of the family Sapro-legniacea	Finfish and their eggs, Penaeid shrimp Salmon, Trout, Catfish and Bluegill
3.	Florfenicol	Aquaflor® Type A	For the control of mortality due to enteric septicemia of catfish. The tolerance for florfenicol amine (the marker residue) in muscle (the target tissue) is 1 ppm.	Channel catfish salmonids
4.	Tricaine methanesulfonate	Tricaine-S MS-222	It may not be used within 21 days of harvesting fish for food. The drug should be limited to hatchery or labo-ratory use.	Ictaluridae (catfish), Salmonidae, Esocidae and Percidae
5.	Oxytetracycline dihydrate	Terramycin® 200	For feed use. In Salmonids, 21 days; Catfish, 21 days; Lobster, 30 days. Oxytetracy-cline tolerance in the flesh is 2.0 ppm	Catfish, Salmonids, Lobster
6.	Oxytetracycline hydrochloride	Oxymarine™, Terramycin 343, Phennoxy 343, Tetroxy Aquatic	For feed use. In Salmonids, 21 days; Catfish, 21 days; Lobster, 30 days. Tolerance in the flesh is 2.0 ppm	Finfish fry and fingerlings
7.	Sulfadimethoxine/ Ormetoprim	Romet-30®	Withdrawal times are: Salmonids, 42 days; catfish, 3 days	Catfish, salmonids
8.	Sulfamerazine	Sulfamerazine	It may not be used within 21 days of harvest. Note: This product is currently not marketed	Trout (rainbow, brook, brown)
9.	Chloramine-T	Halamid® Aqua	-	Freshwater-reared salmonids, Freshwater-reared warm water finfish
10.	Hydrogen peroxide	-	-	Fin fish eggs, Salmonids, Cold freshwater reared finfish

Table 2: FDA low regulatory priority aquaculture drugs permitted for application in fisheries and aquaculture (US FDA, 2017).

Sr. No	Name of the Drug	Recommendations
1.	Acetic acid	1000 to 2000 ppm dip for 1 to 10 minutes as a parasiticide for fish
2.	Calcium chloride	Used to increase water calcium concentration to insure proper egg hardening.
3.	$CaCO_3$	Used up to 150 ppm indefinitely to increase the hardness of water for holding and transporting fish in order to enable fish to maintain osmotic balance
4.	Calcium oxide	Used as an external protozoacide for fingerlings to adult fish at a concentration of 2000 mg l^{-1} for 5 seconds
5.	Carbon dioxide Gas	Anesthetic purposes in cold, cool, and warm water fish
6.	Fuller's Earth	To reduce the adhesiveness of fish eggs to improve hatchability
7.	Garlic (Whole Form)	Used for control of helminth and sea lice infestations of marine salmonids at all life stages
8.	Hydrogen peroxide	Used at 250-500 mg l^{-1} to control fungi on all species and life states of fish, including eggs
9.	Ice	Used to reduce metabolic rate of fish during transport
10.	Magnesium sulfate	Used to treat external monogenic trematode infestations and external crustacean infestations in fish at all life stages. Fish are immersed in a 30,000 mg, MgSO4 l^{-1} and 7000 mg NaCl l^{-1} solutions for 5 to 10 minutes
11.	Onion (Whole Form)	Used to treat external crustacean parasites, and to deter sea lice from infesting external surface of salmonids at all life stages
12.	Papain	Used in a 0.2% solution to remove the gelatinous matrix of fish egg masses in order to improve hatchability and decrease the incidence of disease
13.	Potassium chloride	Used as an aid in osmoregulation; Relieves stress and prevents shock. Dosages used would be those necessary to increase chloride ion concentration to 10-2000 mg l^{-1}
14.	Povidone iodine	Used in a 100 mg l^{-1} solution for 10 minutes as an egg surface disinfectant during and after water hardening
15.	Sodium bicarbonate	Used at 142 to 642 mg l^{-1} for 5 minutes as a means of introducing carbon dioxide into the water to anesthetize fish
16.	Sodium chloride	Used in a 0.5% to 1.0% solution for an indefinite period as an osmoregulatory aid for the relief of stress and prevention of shock; and 3% solution for 10 to 30 minutes as a parasitide

Table 3: List of chemicals used in aquaculture along with thir trade names and recommended dosage

Sl. No.	Trade Name	Active Ingredients	Dosage	Manufacturer
1.	Super Zeolite	SiO2, Al2O3, Fe2O3, CaO, MgO, LoI, K2O	20-30kg/acre	Avon Animal Health
2.	Aquanone	Rotenone	5-7kg/acre	Square Pharmaceuticals Ltd.
3.	Aqua Lime	CaCO3, Ca(OH)2	1–2 kg/dec	ACI Animal Health
4.	BKC	Benzal konium chloride	Spread with water, 0.5 ppm	Chemical seller
5.	Formalin	38% Formaldehyde	1–3 ppm	Chemical Seller
6.	Lenocide	Ankul benzyl dimethyl ammonium chloride + poly-2 deoxy-2 amino glucose	500–1000 ml/acre	Nature care
7.	Aquakleen	Tetradesail Tri-methyl Amonium bromid, BKC	0.5-1 L/acre	Square pharmaceuticals Ltd.
8.	Oxymax	H_2O_2 10%	250-500 gm/acre (1 m deep water body)	Eon animal health products Ltd.
9.	Oxy flow	H_2O_2 10%	General dose 250–350 gm/acre. In case of high deficiency 500 gm/acre in same water body	Novartis Pharmaceuticals Ltd.
10.	Registrol	Betain, Calcium, P, Vit-C	5-10ml/kg feed	Square pharmaceuticals Ltd.
11.	Oxysentin 20%	Oxytetracycline HCL BP	50–100 gm/100 kg feed, 5–7 days (for treatment)	Novartis pharmaceuticals ltd.
12.	Megavit Aqua	Vitamin, mineral and amino acid supplement	100 g/100 kg feed	Novartis pharmaceuticals ltd.
13.	C-150	Coated Vit-C	5 g/kg feed	CP Aquaculture
14.	Super Biotic	*Bacillus sp.*	1–2 kg/ acre	CP Aquaculture
15.	Super PS	*Rodobacter sp. Rodococcus sp.*	4–6 L/acre	CP Aquaculture
16.	Aqua boost	Organic acid, ß-glucan	500 g/mt feed	Novartis pharmaceuticals ltd.
17.	Pond D tox	Pracoccus pantotrophus	4 ppm	Fish tech.(BD) Co. Ltd.

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