

Chemotherapeutic Agents in Aquaculture Disease Management: Classification, Mechanisms, and Routes of Administration

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Abstract

The escalating demand for aquatic food products has driven the rapid intensification of aquaculture worldwide, simultaneously increasing the risk of infectious disease outbreaks caused by bacteria, fungi, viruses, and parasites. Chemotherapeutic intervention has become an indispensable component of disease management, playing a vital role in controlling infections and safeguarding aquaculture production. This review systematically classifies the principal groups of chemotherapeutic agents used in aquaculture, including antibacterials, antifungals, antiparasitic agents, antiviral compounds, anaesthetics, and disinfectants, with emphasis on their mechanisms of action, spectrum of activity, and practical applications in cultured fish and shellfish. The article also discusses the major routes of drug administration, including immersion, oral administration through medicated feed, injection, gavage, and topical application, highlighting their suitability according to disease type, fish size, and production system. Furthermore, it underscores the importance of the judicious use of chemotherapeutic agents to minimize the development of antimicrobial resistance (AMR), reduce drug residues in aquatic food products, and prevent environmental contamination. In addition, the article highlights emerging alternatives such as vaccines, probiotics, and immunostimulants as sustainable approaches for disease prevention and health management in aquaculture.

Keywords: Aquaculture, Chemotherapy, Antibiotics, Antifungals, Antiparasitic agents

1. Introduction

Global aquaculture production has expanded exponentially over recent decades, driven by declining wild catch fisheries and rising consumer demand for affordable, high-quality protein. Intensive culture practices involving high stocking densities and prolonged rearing cycles create conditions conducive to rapid pathogen transmission, opportunistic infections, and stress-mediated immune suppression in farmed species (Mishra et al., 2017). Bacterial diseases remain the dominant constraint, with pathogens such as *Aeromonas hydrophila*, *Vibrio* spp., *Streptococcus* spp., *Piscirickettsia salmonis*, and *Flavobacterium* spp. responsible for major production losses across species and regions (Noga, 2000). Viral diseases including Koi Herpesvirus (KHV), Viral Nervous Necrosis (VNN), Epizootic Haematopoietic Necrosis (EHN), and Tilapia Lake Virus (TiLV) have emerged as serious threats, while fungal infections caused by *Saprolegnia* spp. and parasitic infestations (ectoparasites such as sea lice, *Argulus*, *Lernaea*, and various protozoa) compound the disease burden (Dinesh et al., 2023).

Chemotherapy - the application of chemical compounds to treat, prevent, or control disease has been a cornerstone of aquaculture health management (Treves-Brown, 2000). It operates on the principle of differential toxicity: the agent must be sufficiently toxic to the target pathogen at concentrations that do not cause significant harm to the host or the surrounding environment. Chemotherapeutic strategies may be prophylactic (preventive), metaphylactic (applied at the onset of a disease event in a population), or therapeutic (applied after confirmed diagnosis) (Singh and Singh, 2018). Each approach demands precise knowledge of drug pharmacokinetics, pathogen susceptibility, and system-specific parameters. This article provides a structured review of the major classes of chemotherapeutic agents used in aquaculture, their modes of action, and the methods by which they are administered to aquatic animal.

2. Classification of Chemotherapeutic Agents

2.1 Antibacterial Agents

Antibacterial agents constitute the largest and most commonly applied class of aquaculture therapeutants. They are employed both therapeutically to treat confirmed bacterial infections and prophylactically, particularly in intensive hatchery and grow-out systems. Their mechanisms of action can be grouped into three broad categories:

Table. 1 Major categories of chemotherapeutic agents used in aquaculture disease management

Drug Category	Key Examples	Target Pathogen	Mechanism of Action
Antibacterials	Oxytetracycline, Florfenicol, Erythromycin, Amoxicillin	Bacteria (Aeromonas, Vibrio, Streptococcus)	Inhibit cell wall, protein, or DNA synthesis
Antifungals	Malachite green, Bronopol (Pyceze), Sodium chloride	Saprolegnia, Aphanomyces	Oxidation of thiols; disruption of energy metabolism
Antiparasitic	Praziquantel, Ivermectin, Trichlorfon, Diflubenzuron	Monogeneans, Copepods, Crustacean ectoparasites	Neuromuscular disruption; chitin synthesis inhibition
Disinfectants	Formalin, Chloramine-T, Hydrogen peroxide, BKC	Broad spectrum (bacteria, viruses, fungi)	Protein denaturation; oxidative damage; membrane disruption
Antivirals	Limited; Chloramine-T (indirect)	Fish viruses (IPNV, VHSV, KHV)	Suppression of viral replication cycles
Anaesthetics	MS-222 (Tricaine), Benzocaine, Carbon dioxide	N/A (handling aid)	CNS depression; loss of equilibrium and reflex

- **Cell wall synthesis inhibition:** Beta-lactam antibiotics such as amoxicillin disrupt peptidoglycan cross-linking, causing osmotic lysis. Amoxicillin is effective against furunculosis caused by *Aeromonas salmonicida*.
- **Protein synthesis inhibition:** Tetracyclines (oxytetracycline) block ribosomal binding of aminoacyl-tRNA. Florfenicol (a phenicol antibiotic) and erythromycin (a macrolide) also act at the 50S ribosomal subunit, inhibiting translocation and peptide chain elongation respectively. Oxytetracycline has broad-spectrum activity against furunculosis, vibriosis, and *Pseudomonas* infections.
- **DNA replication inhibition:** Fluoroquinolones (enrofloxacin) and quinolones (oxolinic acid, flumequine) inhibit bacterial DNA gyrase and topoisomerase IV, preventing DNA uncoiling. They are effective against *Piscirickettsia salmonis* and gram-negative pathogens.

- **Folic acid synthesis inhibition:** Sulfonamides (sulfadiazine, sulfadimethoxine) and trimethoprim act synergistically to block sequential steps in folic acid biosynthesis. The combination Tribissen (sulfadiazine:trimethoprim, 5:1) is used against furunculosis and vibriosis in salmonids.

Chloramphenicol, once widely used, is now banned for extra-label use in food-producing animals in many countries due to its association with aplastic anaemia and carcinogenic potential in humans (Sapkota et al., 2008). Nitrofurans, including furazolidone, are also prohibited globally in food-fish production (USFDA, 2021).

2.2 Antifungal Agents

Fungal infections, particularly Saprolegniasis caused by *Saprolegnia parasitica*, affect salmonid eggs and juveniles and can cause significant losses in hatcheries. Key antifungal agents include:

- **Malachite green:** A triphenylmethane dye historically used as both a fungicide and ectoparasiticide. It acts as a respiratory toxin by disrupting mitochondrial electron transport. Although highly effective, malachite green is now banned in food-fish aquaculture in the EU, USA, and India due to its mutagenic and potentially carcinogenic metabolites (Sapkota et al., 2008).
- **Bronopol (Pyceze):** A safer alternative to malachite green and formalin, bronopol exerts its antifungal effect through dual mechanisms — catalytic oxidation of available thiols (inhibiting fungal growth) and production of free radicals (causing cell death). It is approved for use in several countries.
- **Formalin:** Used as an antifungal bath treatment for salmonid eggs at concentrations of 500-1000 mg/L for 15 minutes. Formalin acts by crosslinking proteins and nucleic acids, disrupting both structure and function.
- **Sodium chloride:** Considered an eco-friendly antifungal; effective during egg incubation in freshwater finfish hatcheries. It alters the osmotic gradient between the fungus and the aquatic environment.
- **Hydrogen peroxide:** Active against Saprolegnia; approved in several jurisdictions including the USA (35% PEROX-AID) for treatment of saprolegniasis in freshwater-reared salmonids and channel catfish (USFDA, 2021). It has low environmental persistence.

2.3 Antiparasitic Agents

Parasitic infestations including those caused by ectoparasitic protozoa (*Ichthyophthirius*, *Trichodina*), monogenean trematodes (*Gyrodactylus*, *Dactylogyrus*), crustaceans (*Lepeophtheirus*, *Argulus*, *Lernaea*), and endoparasitic helminths — represent a significant production challenge. Treatment agents include:

- **Organophosphates (Trichlorfon, Dichlorvos/Nuvan):** Inhibit acetylcholinesterase, causing neuromuscular paralysis in crustacean ectoparasites. Used against sea lice (*Lepeophtheirus salmonis*), fish lice (*Argulus* spp.), and anchor worm (*Lernaea* spp.) via bath treatment.
- **Pyrethroids (Cypermethrin, Deltamethrin):** Interfere with voltage-gated sodium channels in nerve membranes, causing repetitive nerve firing and paralysis. Administered by bath for sea lice control in marine salmonids.
- **Avermectins (Emamectin benzoate/SLICE, Ivermectin):** Open glutamate-gated chloride channels in invertebrate inhibitory neurotransmitter synapses, causing hyperpolarization and paralysis. Emamectin benzoate is the only avermectin with market authorization for aquaculture use (medicated feed for sea lice control) (USFDA, 2021).
- **Chitin synthesis inhibitors (Diflubenzuron, Teflubenzuron):** Block chitin synthesis during moulting, preventing exoskeleton formation in larval and pre-adult sea lice. Administered as medicated feed additives.
- **Praziquantel:** An isoquinoline compound effective against monogenean, digenean (trematode), and cestode (tapeworm) infections. It impairs neuromuscular function in the parasite, disrupting suckers and hooks, and alters integument permeability.
- **Potassium permanganate (KMnO₄):** Broad-spectrum oxidant; used against protozoan and bacterial ectoparasites on skin and gills. It generates reactive oxygen that destroys cell walls and disrupts respiratory structures of parasites.
- **Hydrogen peroxide:** Used as an ectoparasiticide via bath treatment; causes mechanical paralysis through gas bubble formation in haemolymph and oxidative damage to parasite membranes.
- **Formalin:** Used as an external parasiticide against protozoa and monogeneans. FDA-approved at 15-25 µL/L for 1-hour immersion in finfish (USFDA, 2021).

2.4 Antiseptics and Disinfectants

Disinfectants are used to reduce pathogen loads in water, equipment, hatchery facilities, and on egg surfaces. Unlike antibiotics, which typically have specific intracellular targets, disinfectants act on multiple cellular components and have broader spectra of activity. Key agents include:

- **Chlorine compounds:** Chloramine-T releases hypochlorous acid in water, which enters bacterial cells, prevents enzymatic activity, and causes cell death. Effective as an antiviral and antibacterial agent, particularly for hatchery water treatment.
- **Formalin:** Broad-spectrum disinfectant effective against bacteria, viruses, fungi, and parasites. Acts by crosslinking proteins and nucleic acids. Despite being a known human carcinogen (IARC), it remains FDA-approved for aquaculture use due to limited alternatives (Sapkota et al., 2008; USFDA, 2021).
- **Hydrogen peroxide:** Acts as an antifungal, antibacterial, and antiviral compound; degrades rapidly in the environment making it an ecologically preferable option. Approved by the US FDA under the trade name 35% PEROX-AID (USFDA, 2021).
- **Iodophors (Povidone iodine):** Release free iodine which kills pathogens through destruction of proteins (particularly cysteine and methionine residues), nucleotides, and fatty acids. Used as egg surface disinfectants.
- **Benzalkonium chloride (BKC):** A quaternary ammonium compound; disrupts cell membrane permeability by interacting with phospholipids and proteins at the C12-C16 carbon chain positions. Effective against gram-positive bacteria and biofilm formation on gill surfaces.
- **Potassium permanganate:** Oxidizes organic material and cell walls of pathogens; used in hatchery disinfection and treatment of bacterial/fungal infections on skin and gills.
- **Virkon (Potassium peroxymonosulphate):** A broad-spectrum disinfectant used for equipment and facility sterilization.
- **Ozone and UV light:** Physical/chemical disinfection methods used in recirculating aquaculture systems (RAS) for pathogen reduction in incoming and outgoing water.

2.5 Antiviral Agents

Antiviral chemotherapy in aquaculture remains limited due to the fundamental challenge that viral replication is tightly coupled with normal host cell metabolism, making it difficult to suppress the virus without damaging the host (Treves-Brown, 2000). Unlike terrestrial

medicine, no antiviral drugs are currently approved specifically for aquaculture use. Chloramine-T has been shown to reduce fish mortality from viral infections (IPNV, VHSV) through its disinfectant properties in water (Dinesh et al., 2023). The primary strategy for viral disease management remains prevention through vaccination, biosecurity, and enhanced innate immunity via immunostimulants and probiotics.

3. Routes of Drug Administration

The route of administration is determined by the nature and severity of the disease, the drug's physicochemical properties, the target fish species and life stage, and the production system (Singh and Singh, 2018). Table 2 summarizes the principal administration routes:

Table 2 Drug administration routes in aquaculture with methods, suitable applications, and limitations

Route	Method	Suitable For	Limitations
Immersion (Bath)	Prolonged bath, dip, or flush; drug added directly to culture water	Ectoparasites, external bacterial/fungal infections; small fishes and eggs	Requires water flow cessation; uniform distribution critical
Oral (Medicated Feed)	Drug mixed with feed (top-dressed or incorporated by feed mill)	Systemic diseases; large populations	Ineffective if fish are anorexic; proper storage required
Injection (IM/IP)	Intramuscular (dorsal musculature) or intraperitoneal (near pelvic fins)	High-value broodstock; small populations	Labour intensive; risk of internal organ damage
Gavage	Stomach tube attached to syringe; drug pumped into stomach	Experimental/research settings for precise dosing	Requires anaesthesia; stressful; rarely used commercially
Topical	Oil-based drug applied directly to skin lesion	Skin ulcers in high-value fish	Requires anaesthesia; very limited application

3.1 Immersion Treatment

Immersion is the most widely applicable and practical route for treating aquatic animals. The drug is dissolved directly in the culture water and administered as a prolonged bath (water flow stopped for a defined period), an indefinite bath (low concentration maintained over an extended period), a dip (high concentration for very brief exposure, typically under a minute), or a flush (drug solution added at inflow and allowed to pass through). Drugs of low molecular

weight are preferred as they distribute uniformly through water and are absorbed efficiently via the gill epithelium, skin, and mucosa. Adequate aeration during treatment is essential, especially when water flow is interrupted.

3.2 Oral (Medicated Feed)

Medicated feed is the standard route for treating systemic infections in large fish populations. The drug is incorporated into the feed either as a top dressing (mixed with oil or gelatine and allowed to dry) or produced by licensed commercial feed mills. The major limitation is that diseased fish often exhibit reduced appetite, meaning treatment must begin before anorexia sets in to ensure adequate drug intake. Medicated feeds must be stored properly (cool, dry conditions) and used before expiry. Florfenicol, oxytetracycline, and sulfadimethoxine/ormetoprim are commonly administered via medicated feed.

3.3 Injection Treatment

Injection - intramuscular (IM) or intraperitoneal (IP) - provides the most predictable and measurable dose but is labour-intensive and stressful to fish. It is reserved for high-value individuals such as broodstock or for vaccine administration. IM injections are administered in the dorsal musculature at approximately 0.5-1.0 cm depth at a 45° angle; IP injections are given near the base of the pelvic fins, directing the needle along the body axis to avoid internal organs.

3.4 Gavage and Topical Application

Gavage involves passing a stomach tube attached to a syringe directly into the fish's stomach, ensuring precise dosage delivery. This method requires anaesthesia and is confined to experimental research settings. Topical application of oil-based drugs is used for wound treatment in high-value fish; anaesthesia is also required.

4. Antimicrobial Resistance and Emerging Alternatives

The indiscriminate and prophylactic use of antibiotics in aquaculture has contributed substantially to the emergence of antimicrobial-resistant (AMR) strains of fish pathogens, with significant implications for public health (Sapkota et al., 2008). Residues of antibiotics such as oxytetracycline, sulfonamides, and fluoroquinolones have been detected in fish flesh, sediments, and surrounding water bodies, creating reservoirs of resistance determinants (Burrige et al., 2010). Chlorine-based disinfectants have also been implicated in the advancement of multiple antibiotic resistance genes in bacteria.

In response, several alternative strategies have gained traction in sustainable aquaculture:

- **Vaccines:** The development of effective immersion, oral, and injectable vaccines have substantially reduced antibiotic use in salmonid aquaculture. Vaccines with pattern recognition receptor (PRR) ligands as adjuvants are being developed for improved efficacy.
- **Probiotics and prebiotics:** Beneficial microorganisms supplemented in feed or water to enhance gut microbiota diversity, immunity, and competitive exclusion of pathogens. *Bacillus*, *Lactobacillus*, and *Saccharomyces* species are commonly employed.
- **Immunostimulants:** Beta-glucans, nucleotides, and herbal extracts that enhance non-specific immune parameters including lysozyme activity, respiratory burst, and phagocytic activity.
- **Phage therapy:** Bacteriophages targeting specific fish pathogens offer highly specific, residue-free alternatives to broad-spectrum antibiotics.
- **Bio-remediators and water quality management:** Improved pond management, biosecurity, and probiotic-based water remediation reduce pathogen load and disease pressure, decreasing the need for chemotherapeutic intervention.

5. Conclusion

Chemotherapeutic agents remain an essential component of aquaculture health management, spanning antibacterials, antifungals, antiparasitic compounds, disinfectants, and anaesthetics. Each class operates through distinct mechanisms and requires careful selection based on pathogen identity, drug pharmacology, fish species, and production context. The route of administration immersion, medicated feed, injection, or topical further influences efficacy and must be matched to the disease presentation and operational feasibility. However, the escalating problem of antimicrobial resistance and environmental contamination demands that chemotherapy be used only when necessary, at appropriate doses, and ideally following laboratory-confirmed diagnosis. The integration of preventive strategies vaccines, probiotics, immunostimulants, and good aquaculture practices offers the most sustainable path forward for disease management in the global aquaculture industry.

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