Veterinary Pharmacology and Therapeutics in Marine Aquaculture: Challenges and Solutions

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Abstract

Pharmaceuticals are largely utilized in fish farms for therapeutic purposes and are administered either directly into the water or mixed with fish feed to mitigate the risk of infectious diseases. The majority of medications are biodegradable in animal bodies, but some have comparatively extended biological half-lives. Used medicines, resulting from various anthropogenic activities, enter aquatic environments through consumption by animals and excretion, leading to significant environmental pollution. Antibiotic mixtures can alter medications by creating chemical complexes, potentially promoting resistant bacterial strains and causing fish death due to residual buildup in tissues. As contaminated river water eventually goes into the sea waste pharmaceuticals have an impact on marine habitats, including coastal zone waters. Alternative treatments like probiotics, essential oils, and plant extracts can reduce costs and more environment friendly because they are more biodegradable than synthetic molecules, and less likely to cause drug resistance in parasites. Strict controls, laws, and regulations regarding the use of antimicrobials in aquaculture should be devised and enforced. The presence of these contaminants in water systems is widely acknowledged as a severe hazard to aquatic ecosystems and human health, and minimizing their discharge into the environment is a top goal for international efforts.

Keywords: Pharmaceuticals, Aquaculture, Marine habitat, Antibiotics, Probiotics

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Introduction

Pharmacology is the science that broadly deals with the physical and chemical properties, actions, absorption, and fate of chemical substances termed as drugs that modify biological function. It is a field that works directly with toxicology and pharmaceutical studies, encompassing most aspects of both human and veterinary medicine. The definition of veterinary pharmacology is the study of pharmacological characteristics and all aspects of drug interactions with living things. Any biological agent used for medical treatment, prevention, diagnosis, cure, or physiological process regulation considered as drug (Kim et al., 2017).

Veterinary pharmacologists have a keen interest in studying the molecular composition of pharmaceuticals, the mechanisms by which drugs function, appropriate drug doses, potential adverse effects, the identification of novel drugs, innovative uses for current treatments, drug treatment procedures, and several other related subjects. Because pharmacology is applied to multiple species rather than a single one and because the responses of numerous animal species to medications are not well known, veterinarian pharmacology is far more complicated than human pharmacology (Kang et al., 2018).

Veterinary pharmaceuticals, which include antibiotics, anesthesia drugs, ectoparasiticides, endoparasiticides, and vaccinations, are widely utilized in coastal aquaculture. They are employed to manage microbial diseases and parasites, inside as well as outside the body. Shellfish farms do not typically use medicines, but fin fish farms can. Antibiotics, nevertheless, may be used in shellfish hatcheries to regulate water quality. The vast majority of marine finfish farms raise their fish in sea enclosures, and any chemicals used are released into the sediments as well as the water. The principal species implicated include Sea Bass (*Dicentrarchus labrax*), Rainbow Trout (*Oncorhynchus mykiss*), Atlantic Salmon (*Salmo Salar*) and Sea Bream (*Sparus auratus*) **(**Yang et al., 2020).

Use of Veterinary Medicine in Aquaculture

Veterinary treatment can be classified as therapeutic, prophylactic, or metaphylactic when it comes to livestock for food and aquaculture. The therapy of established infection is consistent with therapeutic use. The term "metaphylaxis" refers to group of medication methods that treat ill animals and also giving medication to other members of the group to avoid sickness. The proactive use of antimicrobials in people or communities in order to stop the spread of infections is known as prophylaxis. In fish farming, groups of fish sharing aquariums or enclosures are often given antibiotics, through the mouth at therapeutic dosages for brief periods of time. Any medication used lawfully in aquaculture has to be authorized by the government body in charge of veterinary medicine for instance, the Food and Drug Administration (FDA) in the USA. For example, oxytetracycline, florfenicol, and sulfadimethoxine/ormetoprim are among the antimicrobials that are permitted for use in aquaculture in the United States (Kemper, 2008). According to estimates, the annual global antimicrobial usage from the human, terrestrial, and aquatic food producing animal sectors is expected to reach 236,757 tons by the year 2030 (Figure 1).

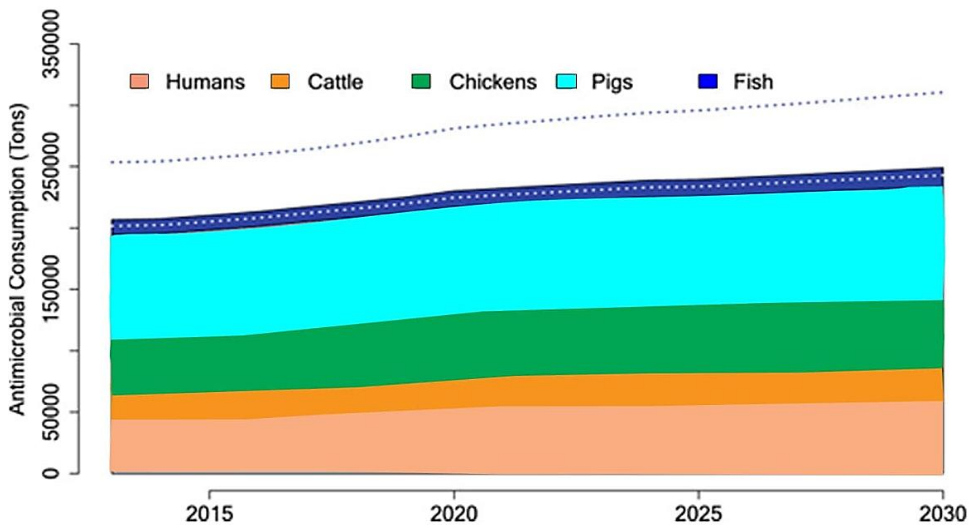

Fig. 1: Global antimicrobial consumption, 2013-2030. Dotted lines represent the 95% uncertainty interval for fish.

Both manufactured and natural antibiotics must be harmless for the host, allowing them to be used as chemotherapeutic agents to treat pathogenic bacterial infections. Because of the fish's immune system's effectiveness in eradicating the growth of bacteria and infection, the usage of preventative antibiotics has increased. Antibiotics are administered to fish via their food, and occasionally through baths and injections. The unconsumed food, and fish faeces, containing antibiotics spread the sediment at the bottom of the raising pens. The antibiotics seep into the sediment and are then carried by currents to other locations. These leftover antibiotics will continue to be present in the sediment, applying selection pressure that will alter the microflora's makeup and favor bacteria that are resistant to antibiotics (Hutchings et al., 2019).

It is possible for bacteria in the natural world, such as pathogens that affect humans and animals, to acquire the antibiotic resistance genes that have developed and been selected in this aquatic setting through horizontal gene transfer. The high levels of untreated effluent and agricultural and industrial effluent, pollution of freshwater and saltwater in developing countries have increased the possibility of these interactions in many aquaculture settings. These wastewaters contain pathogens that are typically immune to antibiotics as well as normal intestinal flora in livestock and humans. This is also true in environments where aquaculture and agriculture are combined, where it is common practice to use manure and other agricultural wastes as fish food (Singh et al., 2018).

Factors Affecting Antibiotics Use

While antibiotics are a highly helpful weapon to have in any fish health manager's toolkit, they are not "magic bullets." There are several elements that determine whether antibiotics can effectively eradicate a disease affecting fish. Does the issue contain a bacterial component? Are the selected antibiotics effective against the implicated bacteria? Are the right dosage and intervals between treatments being followed? Have there been any additional or decreased contributory stresses? Prior to using antibiotics, it is necessary to eliminate or minimize stressors including abrupt temperature fluctuations and low water quality, poor feeding, heredity, handling, and transportation. It's important to check the fish for parasites as well. Since bacterial infections frequently result from such management issues, any of these variables could be the main cause of the illness. By identifying contributory stressors and the extent of bacterial infection prior to the illness outbreak, contacting a fish health specialist can help lower the overall number of fish losses (Aly, 2014).

Guidelines for Therapeutic Application

While choosing the appropriate antibiotic is a crucial first step in managing bacterial infections, it's also critical to administer any antibiotic for the recommended number of days. A fish health expert should give instructions on the dosage, rate, and time of the antibiotic to be used. The withdrawal period, the amount of time needed from the moment the last antibiotic treatment is administered until the fish is sold, should be understood. It is important to ascertain an antibiotic's pharmacokinetics (Aly, 2014).

i. Before Treatment

To effectively treat fish, it's crucial to understand the chemical properties of the water supply and their impact on the treatment's toxicity and effectiveness. Preliminary tests on a limited sample of diseased fish are essential, as healthy fish are more tolerant. Cleanliness in raising facilities is essential, as contaminated raceways or tanks can absorb the treatment chemical. If the density of fish is high, it is advisable to decrease it, if feasible, before implementing static treatment. If necessary, further aeration should be administered. Administer treatments during low temperatures and avoid providing treatment within 4 hours after feeding. Prioritize gill parasite treatment due to potential respiratory impact. Assess dissolved oxygen levels before treatment. Administer a small group of fish and closely monitor for unforeseen death before using new drugs or formulations.

ii. During Treatment

Throughout treatment, keep an eye out for any indications of stress or unexpected toxicity in the fish. Throughout treatment, keep an eye on the dissolved oxygen levels. Following treatment, fish experience stress, which increases their oxygen requirement. Make sure you double-check your numbers every time (0.1X will not work, 1.0 will work, but 10X will be lethal). Have someone look over your figures if at all possible.

It's usually beneficial to wear gloves when making or giving any kind of medication to protect the user from exposure. Using antibiotics that are as recent as feasible and that have been stored correctly is crucial. Antibiotics that are used after their expiration date or stored in hot and humid settings will see a significant decrease in effectiveness and, in the worst case scenario, may be harmful.

iii. After Treatment

For future reference, keep records of all therapies, their purpose, and the outcomes.

Methods for Antimicrobials Application

1. Treatment in the Diet

Commercial feed with antibiotic additions is cost-effective and user-friendly, provided it is accessible. Medicated feed is highly storable and can serve as a substitute for the standard diet. Feed that has been medicated locally can be used in place of readily accessible medicated feed. If precautions aren't taken, water-soluble antibiotics like oxytetracycline may leak out of the diet. For the best results, put such medications in oil while making medicated feed (corn or soy bean oils work well, but cod liver oil seems to be more palatable) (Palme and Larsson, 2016).

2. Localized Applications

a. External

Applying localized skin treatments is only practical for important fish and bloodstock. The medication should operate immediately upon interaction, be comparatively insoluble in water, and being more sticky or heavier than water so the fish cannot brush it off.

b. Internal

Antibiotic injections can be utilized for a limited number of important fish, but they can be costly and laborious. Under the skin or intramuscular injections are inferior to abdominal injections. The fish should, if at all feasible, be held in the structure of a huge mesh net to render it immobile. It would be preferable to anesthetize the fish if struggling results in scale losses or other harm, or if they are just too big to handle. For this reason, carbon dioxide and MS-222 (tricaine methane sulfonate) have both been employed successfully. According to the stature of the fish, medication injections require small syringes and needles with a gauge of 20 to 26. Take a shallow position and insert the needle into the body wall right posterior to the pelvic girdle until the resistance abruptly stops. Don't put the needle in far enough to avoid rupturing the gonads or the gut (Broens & Geijlswijk, 2018).

c. Bath Treatments

Fish dipping is a quick bathing procedure that can take anywhere from a few seconds to five minutes (dip bath) or up to an hour (short bath), according to the chemical and dosage utilized. While using wood tubs is advised, plastic tubs prevent potential hazardous chemical interactions between chemicals used for treatment and zinc-plated metal. Bloodstock is frequently subjected to dip treatments. They work well, but they can be very stressful.

Mechanism of Action of Antibiotics

Antimicrobial medications can target various bacterial machinery components and possess a variety of chemical structures. Antibiotics often function through one of two ways (Figure 2):

i. An antibiotic has a bactericidal effect when it interferes with the bacterial cell wall development or contents, which leads to the death of the bacteria. Penicillin, metronidazole, and fluoroquinolones are a few examples.

ii. An antibiotic that prevents bacteria from growing by interfering with their ability to produce proteins, replicate DNA, or use other parts of their cellular metabolism is known as having a bacteriostatic effect. Tetracyclines, sulfonamides, chloramphenicol, and macrolides are a few examples (Upmanyu & Malviya, 2020)

Antibiotics such as glycopeptides and beta-lactams (penicillins, cephalosporins) can prevent bacteria from synthesizing their cell walls. By interacting with the enzymes necessary for the creation of the peptidoglycan layer, beta-lactam medications prevent the formation of the bacterial cell wall. By attaching to the terminal D-alanine residues of developing peptidoglycan chains, vancomycin and teicoplanin, on the other hand, block the cross-linking processes necessary for stable cell wall production. Antibacterial medications such as aminoglycosides, tetracyclines, chloramphenicol, and macrolides function by preventing the creation of new proteins.

By selectively inhibiting bacterial growth, these antibacterial medications take use of the structural variations between bacterial and eukaryotic ribosomes. The 30S subunit of the ribosome is bound by macrolides, aminoglycosides, and tetracyclines, while the 50S subunit is bound by chloramphenicol.

The mechanism by which fluoroquinolones inhibit DNA synthesis and induce deadly double-strand breaks in DNA replication is how they fight germs. For instance, topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are necessary for bacterial DNA replication, transcription, repair, and recombination, are inhibited by ciprofloxacin, which has bactericidal effects. DNA synthesis is ultimately inhibited by sulfonamides and trimethoprim (TMP), which disrupt the pathway for folic acid synthesis (Etebu and Arikekpar, 2016).

Two steps in the enzymatic route for bacterial folate synthesis are inhibited by the common antibacterial medication combination of sulfamethoxazole (SMX), a sulfonamide, and TMP, an analogue of folic acid. For instance, ormetoprim and sulfadimethoxine are two distinct antibiotics combined into one medication. Long-acting sulfonamide sulfadimethoxine and diaminopyrimidine ormetoprim share structural similarities with trimethoprim. Because they obstruct two sequential steps in bacterial folic acid synthesis, these antibiotics work in synergy to prevent bacterial thymidine synthesis (Sahu and Khare, 2023).

Sulfadimethoxine inhibits the enzyme dihydrofolate synthetase, preventing para-aminobenzoic acid from being converted to dihydrofolic acid. Ormetoprim inhibits dihydrofolate reductase, preventing the conversion of dihydrofolic acid to tetrahydrofolic acid. Overall, the result is a potentiated sulfa that has bactericidal rather than only bacteriostatic activity. One potential fifth, although less thoroughly studied, method of action could include disruption of bacterial membrane structure. Polymyxins are thought to accumulate in the bacterial cell membrane and increase the permeability of the membrane to cause their inhibitory effects. Daptomycin is a cyclic lipopeptide that appears to incorporate its lipid tail into the bacterial cell membrane, resulting in membrane depolarization and, ultimately, bacterial death.

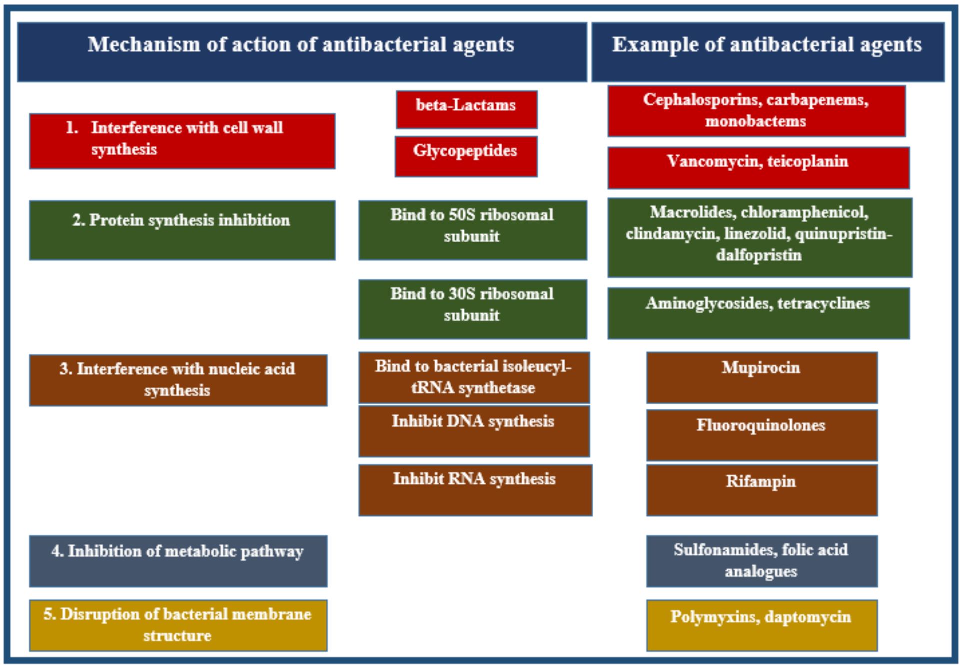

Fig. 2: Diagram showing the different mechanisms of action of antibiotics.

Consequences of Improper Treatment

Fish are susceptible to toxicity when doses are too high or treatment durations are too lengthy, which can often result in irreversible organ damage. The likelihood of the bacteria acquiring antibiotic resistance is significantly increased if the treatment period is too short or the antibiotic dose is too low. This is because the bacteria will not be sufficiently killed or weakened for the fish's immune system to remove them (Bellio et al., 2018).

- **Antibiotic Resistance**

The emergence of antibiotic resistance in bacteria is a frequent phenomenon. Evolutionary processes are depicted by emerging resistance that occurs during the therapeutic use of antibiotics. As a result, resistant bacteria grow preferentially, while the medication prevents susceptible bacteria from growing. Bacteria frequently have inherited resistances that allow them to survive, but horizontal gene transfer causes the development of resistance to antibiotics (Figure 3).

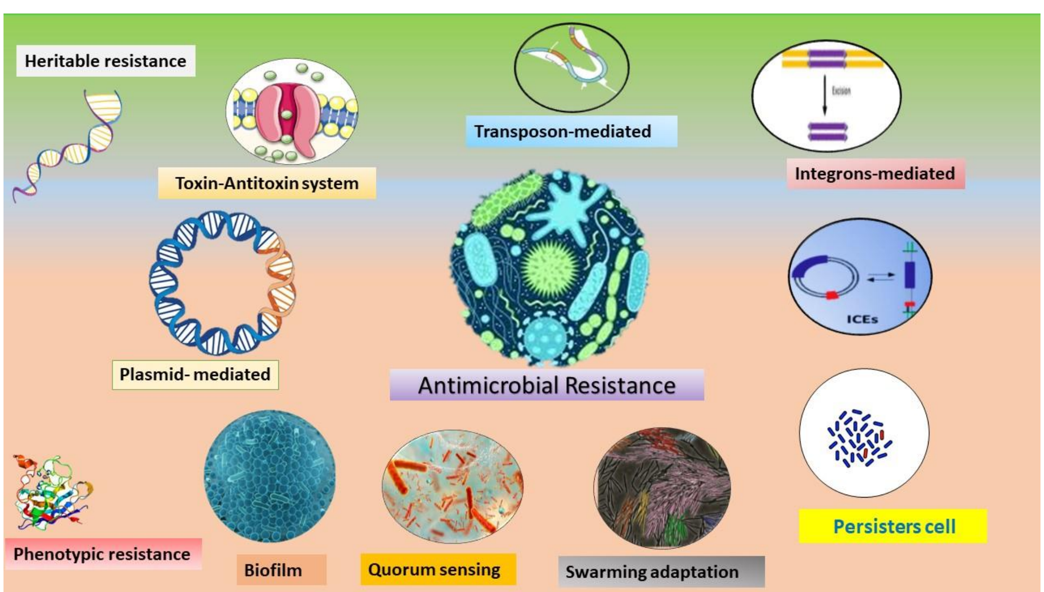

Fig. 3: Molecular mechanisms driving antimicrobial resistance. Image depicts heritable (blue framed) and phenotypic (orange framed) mechanisms of antimicrobial resistance in bacteria.

Unregulated Release of Antibiotics and its toxicity in Aquatic Environment

Antibiotics that can be introduced to fish, flow into the water bodies from a variety of sources, including industrial effluents and veterinary and human usage. Many kinds of antibiotics are found in freshwater worldwide, including nitroimidazole, quinolones, tetracyclines, sulfonamides, penicillin, macrolides, and cephalosporins. Among these are the quinolones, macrolides, tetracyclines, and sulfonamides cause aquatic toxicity, and are generally most commonly found in aquatic environments all over the region (Danner et al., 2019).

Sulfamethazine and sulfadiazine are mostly derived from animal husbandry, whereas sulfamethoxazole, tetracycline, doxycycline, and oxytetracycline are produced by household pollution and aquaculture. The characteristics of antibiotics in aquatic environments also vary based on their stability and chemical composition. The other elements that can reduce fish antibiotic accumulation are the salinity and sediments in the aquatic environment. A review of antibiotic concentrations in hospital effluents showed that ciprofloxacin, azithromycin, and clarithromycin were the antibiotics with the highest concentrations, and antibiotics ranging from 4886 ng/L in the summer to 322,735 ng/L in the winter (Aydin et al., 2019).

Veterinary antibiotics released into the aquatic environments are of great concern. The livestock industry frequently uses the ionophore antibiotic, an antibacterial drug that enhances the ionic permeability of the cell membrane. Manure, as well as transport and storage systems, contain large amounts of Monensin, an ionophore antibiotic utilized in ruminant feed. Maduramicin, also a kind of ionophore antibiotic utilized in the poultry sector, has been detected in surface water as high as 21.7ng/L in Spain (Walt et al., 2014).

Since most antibiotics are neither metabolized nor undergo absorption by the gut and end up in manure and are eliminated in feces and urine. Antibiotics are widely used in orchards and aquaculture in addition to their veterinary and human applications. One of the most important industries for supplying fish products for human consumption is aquaculture. Consequently, the global usage of antibiotics in aquaculture is rising. Various screening techniques using high-resolution mass spectrometry have been developed to identify different kinds of antibiotics present in these aquaculture products (Turnipseed et al., 2019).

- **Effects on Environmental Bacteria**

The gut microbiota and ambient bacteria may come into contact with the antibiotics found in hatchery wastes and fish farms when an antibiotic treatment (often administered via medicated feed) is initiated.

- **Effects on Host-Microbiota**

The microbiota found in the intestinal tracts of healthy fish has been studied by many authors since it is thought to be important for nutrition, disease prevention, and digestion. This potentially advantageous host-microbiota relationship could be altered by potential changes in the gastrointestinal microbiota brought on by antibiotic therapy and farmed fish have altered gut microbiota makeup, which results in decreased bacterial diversity. By eradicating normal microbiota microorganisms, antibiotic treatment promotes the growth of opportunistic bacteria by reducing competition.

Toxicity of Single and Combined Antibiotics

In aquatic environments, the ecotoxicity of antibiotic mixtures containing antibiotics from various classes as well as other PPCPs has been observed simultaneously. As a result, aquatic organisms may get exposed to these pharmaceutical mixtures; this should be considered while developing ERA strategies by assessing each antibiotic's individual effects and combined behavior (Valitalo et al., 2017).

Even at concentrations below the individual NOECs, the combined effects of antibiotics may cause toxicity to aquatic organisms significantly, even if the quantities of individual antibiotics in aquatic ecosystems may be too low to be detectable (Geiger et al., 2016). This could significantly underestimate the hazards posed by mixtures of antibiotics and other medications, as well as combinations with anthropogenic pollutants. Particularly, combinations of two or more antibiotics, such as trimethoprim and sulfamethoxazole, are occasionally administered simultaneously.

Toxic Effects of Antibacterial on Fish Organisms

The detrimental effects of human pharmaceuticals (diclofenac, clofibric acid, carbamazepine, and metoprolol) at environmentally relevant concentrations in the kidney, gills, and liver of Common Carp (*Cyprinus carpio*) and Rainbow Trout (*Oncorhynchus mykiss*) have been demonstrated by several studies. Tiny tears, edema, necrosis, and inflammation in the villi are among these alterations. Increased histological damage such as hypertrophy, vacuolization, and leucocyte infiltrations, in addition to alterations in metabolic processes and biochemical pathways, occurred (Bojarski et al., 2020).

- **Hematological and Blood Biochemical Changes**

Analyzing blood parameters is a crucial method for determining how toxic xenobiotics are to fish. Fish exposed to antibiotics may experience anemia or several hematological changes including an increase in red blood cell parameters (Hb, RBC, and Ht). Leukocyte counts can also go increase (occasionally) or decrease (frequently). Fish ALT and AST i.e., hepatic enzyme activities are frequently elevated, which in fish may be a sign of a hepatotoxic effect of the pharmaceuticals. Antibiotics may cause a stress response in fish, which is indicated by an increase in cortisol and hyperglycemia (Witeska et al., 2022).

- **Oxidative Stress Parameters**

The oxido reductive balance is altered when fish are exposed to antibacterial agents; the kind and degree of these modifications most likely rely on the type and dosage of the therapeutic agent used, the species of fish, and the stage of development of the fish. Lipid peroxidation (an increase in MDA levels) and the upregulation or inhibition of liver GST, GPx, CAT, and SOD are signs of oxidative damage. Furthermore, there was an upregulation of hepatic and intestinal caspase, indicating a rise in apoptotic activity. Additionally, there was an increase in the hepatic mRNA expression of lipase, aminopeptidases, carnitine palmitoyltransferase, and fatty acid synthase. The changes that have been found suggest that pharmaceuticals have disrupted liver functions and caused oxidative stress (Velazquez et al., 2022).

- **Histopathological Alterations**

Histopathological lesions may appear in fish exposed to different antibiotics. The liver, kidneys, and gills seem to be the organs that are most susceptible to the toxic effects of these compounds. Several histological changes were seen in the gills following acute exposure, including epithelial cell hyperplasia and mucous cell hypertrophy while epithelial lifting and lamellar fusion with chronic exposure. Hepatocyte hypertrophy and nucleus pyknosis, hepatocellular degeneration, vacuolation, and hemorrhage all occurred in the liver along with an increase in sinusoidal space. Hepatocyte vacuolation, sinusoid enlargement, hepatocyte degeneration, nuclear pyknosis, and hemorrhage are associated with changes after chronic exposure. Fish exposed to the veterinary antibiotic gentamycin showed signs of nephron neogenesis, suggesting nephrotoxicity of gentamicin to fish (Kitamura et al., 2022).

- **Impacts of Residual Pharmaceuticals on Fish Reproduction**

Reproduction is a biological process that relies on the neuroendocrine system's synchronizing actions. Many pharmaceuticals used in veterinary and by humans are discharged into urban wastewater, and these pollutants can harm fish and other aquatic life when they come into contact with them. The adult Fathead Minnow subjected to clofibric acid (a human medication) showed a decrease in sperm parameters. Fish exposed to pharmaceutical effluent downstream of the Dore River (France) exhibited altered enzyme activity, vitellogenin induction, intersex, and neurotoxicity. Several developmental abnormalities are seen in adult Zebrafish (*Danio rerio*) when subjected to acetaminophen, carbamazepine, acetaminophen, venlafaxine, and gemfibrozil mixture. These abnormalities include atretic oocytes, altered ovarian and kidney histology, and decreased embryo production (Yan et al., 2016).

- **Immuno Toxic Effects**

Toxic substances may have a direct impact on the immune system of fish and other species. The identification of drug residues in surface waters has raised questions about potential negative impacts on the freshwater biota. In fish and wildlife species, many ecological pollutants such as pharmaceuticals have been found to modulate immune systems, increasing an organism's susceptibility to pathogen infections. Research analysis has demonstrated how fish's immune system interacts with synthetic steroids. It additionally revealed how both natural and synthetic estrogens regulate fish immunomodulation functions by acting through microRNAs (miRNAs) as well as through estrogen receptors to regulate specific target genes (Perveen et al., 2019).

Risk Management Options

- **Policies and Legislation of Antibiotic Use in Aquaculture**

Antibiotic usage in aquaculture has been severely restricted in many countries due to the spread of antibiotic-resistant determinants from aquatic to terrestrial environments and antibiotic-resistant bacteria. The use of antibiotics for prophylactic in this context has been eliminated, and the use of antibiotics in therapeutics-which are still highly helpful in treating human infections-has been restricted. Other restrictions include tighter oversight over the prescription of therapeutic antibiotics. According to WHO estimates, 4.7 million deaths in Asia will be caused by antibiotic resistance by 2050. Together with the WHO, Sri Lanka created the National Strategic Plan (NSP) 2017–2022. The Global Action Plan's strategic objectives are in line with the five main strategies that form the framework of the NSP. It is therefore economically possible to develop a productive aquaculture industry without unnecessary use of these antibiotics as prophylactic measures. This increased control over antibiotic use, along with sanitary measures like vaccinations, has drastically reduced the use of antibiotics in the aquaculture industry of developed countries. Nonetheless, in countries like China and Chile where aquaculture has been growing, the use of quinolones and many other antibiotics is still unrestricted (Mo et al., 2017).

Long-term consumption of foods containing low levels of antibiotics may cause a rise in bacterial strains that are resistant to the drugs. To safeguard human health, the European Union has set safe maximum residue limits (MRLs) for these medications as well as other veterinary substances that are used in animal products that are eventually introduced in the human food chain (Hassan, 2013). EU Council Regulation 2377/90/EC, which outlines the process for establishing MRLs for veterinary medicinal products in products of animal origin, governs the use of veterinary medications. The European Union Council Directive 96/23/EC establishes MRLs for antibiotics in fish. It also provides comprehensive rules and processes for regulating veterinary drug residues in animals and obtained products. The use of growth-promoting substances such as β-agonists and hormones is prohibited in Council Directive 96/22/EC.

- **Alternative Treatments: Probiotics, Essential Oils, Phage Therapy, Vaccines, Phytochemicals**

Alternative treatments for bacterial infections in animal production, particularly in aquaculture, are required due to the growing concern over bacterial drug resistance and antibiotic residues on a global scale. In aquaculture, many antibiotic substitutes have been employed with success. Aquaculture has tested the use of benign microorganisms to prevent infections caused by bacteria in aquatic organisms. Here, we address some of the hypothesized mechanisms by which probiotics may inhibit aquatic pathogens and provide a brief overview of their application in aquaculture.

Essential Oils are a natural plant component that is widely accepted as safe to use as an additional source of alternative treatments. These oils have antibacterial characteristics which make them potential substitutes for prophylactic and therapeutic substances in aquaculture. Phage Therapy has also drawn a lot of attention due to its benefits in controlling and preventing pathogen infections; aquaculture facilities have been effectively using phages since 1999.

Vaccines work by augmentation or modulation of the immune system. Depending on how well a host's immune system is stimulated or strengthened to fight against infection, vaccination can trigger inflammation, production of antibodies, activation of macrophages, and other well-known immunological responses. Globally, the prevalence of bacterial diseases has drastically decreased due to antibacterial vaccinations. Less erotogenic, cell-free vaccines composed of purified components, such as capsular polysaccharides and their conjugates to protein carriers, as well as inactivated toxins (toxoids) and proteins, have essentially replaced vaccines made from attenuated whole cells or lysates (Jia et al., 2018).

Phytochemicals can disrupt microbial membrane structures, alter the hydrophobicity of the surface of bacterial membranes, prevent the synthesis of peptidoglycans, and alter quorum sensing certain dietary supplements that are antioxidants such as grape seed extract also contain phytochemicals, or polyphenols which have been shown to have antibacterial activity in vitro (Figure 4). The possibility of novel antibiotics produced from plants is being studied in considering the rise in antibiotic resistance in recent years (Mostaghim, 2018).

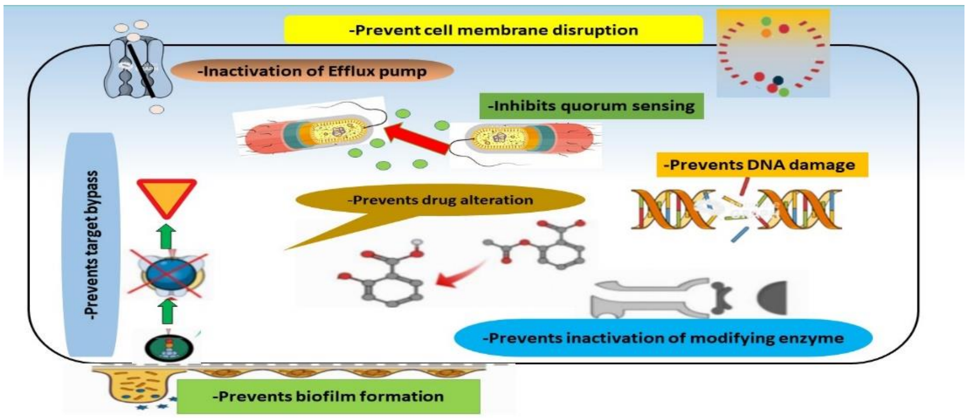

Fig. 4: Phytochemicals as antimicrobials, mode of action and their effectiveness against microbes.

Antibiotic Usage and Future

The 1930s brought the discovery and isolation of bactericidal substances produced by actinomycetes fungus, which marked the beginning of the antibiotic era. The next several decades are known as the "golden age of antibiotic drug discovery," during which at least 65 antibiotics from nine different classes were discovered and implemented into use in medicine. Unfortunately, as antibiotic resistance develops and spreads, the majority of antibiotics become less effective over +time. Many people who require them cannot afford the more expensive new antibiotics, particularly those in countries with low and middle incomes with high rates of infectious diseases. The most significant tool for retaining the effectiveness of antibiotics worldwide is not the development of new agents. It's critical to conserve complementary and effective technologies.

Conclusion

Bacteria and fish pathogens in the aquatic environment develop reservoirs of drug-resistant bacteria and transferable resistance genes as a result of the application of veterinary pharmacology in aquaculture. Some antibiotic-resistant pathogenic bacteria can be transmitted from the reservoir in the aquaculture environment to humans, but more significantly, resistance genes from bacteria in the aquatic environment can spread by horizontal gene transfer and end up as human pathogens. Although it hasn't been well studied, there is a likelihood that bacteria found in the aquatic environment, including fish pathogens, could cause horizontal gene transfer to human pathogens. There is a need to prevent the development and spread of antimicrobial resistance in aquaculture because of the industry's rapid growth and significance in numerous regions of the world, as well as the wide-ranging, intensive, and frequently unregulated use of antimicrobial agents in this type of animal production. The enhancement of management practices, regulatory oversight of antimicrobial agent use, application of sensible usage standards, and tracking of antimicrobial agent use and antimicrobial resistance should be the main objectives of these endeavors.

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