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Antibiotic Resistance and Its Importance in Aquatic Organisms: A Review

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ABSTRACT: This review was carried out with the aim of investigating antibiotic resistance and its importance in aquatic animals. Literature review showed that resistance to antibacterial drugs is an inevitable phenomenon that occurs as a result of the specific nature or adaptation of bacterial cells to antibiotics and genetic changes. Resistance happens in two ways, natural and acquired. In this study, mechanism of acquired resistance including 1) Chromosomal resistance induced by spontaneous mutation, and 2) resistance induced by genetic exchanges was investigated. Also, types of resistance induced by plasmid transfer including transformation, mediated transfer and conjugation were focused. At the end of the paper, the importance of antibiotic resistance in humans was discussed.

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Today, aquaculture is one of the most important pillars in the field of food production in the world (Radkhah *et al.*, 2021). The ever-increasing growth of the population and the increasing human need for food, the limited natural resources of aquatic animals and attention to job creation, reveal the necessity of sustainable aquaculture development (Suthamathy and Ola, 2017). In order to develop the economy of reproduction and aquaculture, it is necessary to introduce more aquatic species to the aquaculture industry (Radkhah and Eagderi, 2021). The use of antibacterial drugs in the treatment of fish diseases has gained special importance due to the contact of the drug with the environment and the problems it causes in human health (Bojarski *et al*., 2020). This problem has caused the concern of those involved in the aquaculture industry in the world. Unfortunately, due to the young age of the aquaculture industry in Iran and the lack of necessary specialists in the field of aquatic health and diseases, the use of drugs and chemicals has increased (Kahn *et al*., 2012). These drugs and chemicals regardless of their pollution effects in nature and adverse effects of these substances on humans (such as toxic effects, hypersensitivity reactions, occurrence of secondary infections, metabolic disorders and ecological effects) are consumed (Boxall, 2004). In antibiotic resistance, there is a possibility of transferring resistant microbes to humans and jeopardizing the public health of society (Thornber *et al*., 2022). Therefore, the damage caused by this is inevitable. Microbial resistance causes the treatment of diseases to be disrupted and fish farmers suffer economic losses (Pepi and Focardi, 2021; Thornber *et al*., 2022). Antibiotics are mostly not toxic to the host, but their long-term, frequent, excessive and less than normal use in aquatic animals has caused the spread of resistant bacteria populations in fish, crustaceans and water microflora (Pepi and Focardi, 2021). The indiscriminate use of antibiotics, especially the types that are shared by humans, creates the basis for the development of bacterial resistance, endangering food security and public health, and the instability of food product exports (Fair and Tor, 2014). Today, the use of antibiotics has caused the creation of resistant bacterial strains and has caused many problems (Ventola, 2015; Fair and Tor, 2014).

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For example, the use of antibiotics causes diseases that are very difficult and in some cases impossible to treat. Finally, it causes the spread of the disease and the spread of an epidemic without treatment in the society. In the shrimp farming industry in Ecuador, the excessive use of antibiotics has caused antibiotic resistance against *Vibrio cholerae* in humans (Ferri *et al*., 2022). Of course, in these cases, the weakness of public health has played an important role in the disease epidemic. According to the above mentioned, this review was carried out with the aim of investigating antibiotic resistance and its importance in aquatic animals. It is hoped that the information presented can be used in order to understand the resistance caused by the use of antibiotics in aquaculture farms and reveal the different aspects of this ecological problem.

Mechanisms of drug resistance: Resistance to antibacterial drugs is an inevitable phenomenon that occurs as a result of the specific nature or adaptation of bacterial cells to antibiotics and genetic changes (Coculescu, 2009). Resistance is created in two ways, natural and acquired. Natural resistance is generally one of the basic characteristics of bacterial species and includes all individuals of a species. Natural resistance does not depend on previous exposure to antibiotics, but is caused by the inherent physiological, biochemical or morphological state of bacteria that prevents the effects of antibiotics (Apua, 2022). It is easy to detect this type of resistance, so that it can be identified in the short-term exposure of the organism to antibiotics. Examples of natural resistance include the exposure of *Pseudomonas aeruginosa* bacteria to tetracycline (Munita and Arias, 2016). Acquired resistance is the resistance that the bacterium was previously sensitive to the drug and became resistant to due to previous exposure. This exposure creates selective pressure, which causes excessive and rapid growth of resistant cells (Munita and Arias, 2016; Abdi *et al*., 2017). In Figure 1, a schematic diagram of Acquired resistance is provided.

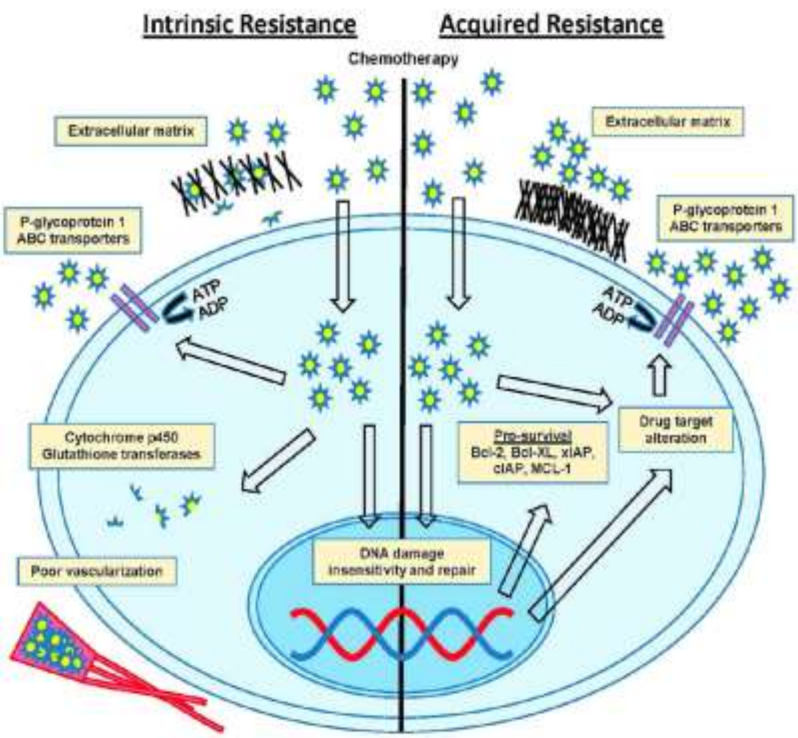

Fig 1: A schematic view of acquired resistance
(Modified from Cornelison *et al*., 2017)

Mechanism of acquired resistance: 1) Chromosomal resistance induced by spontaneous mutation: Mutation in the direction of antibiotic resistance occurs spontaneously and with a ratio of 10:10, which depends on the antibiotic bacteria (Aleksakhina *et al*., 2019). It is thought that chromosomal mutation is responsible for resistance to quinolone compounds, so that resistance to old quinolones such as nalidixic acid and oxolinic acid has been observed in pathogens such as *Aeromonas salmonicida*, *Vibrio anguillarum* and *Yersinia ruckeri* (Munita and Arias, 2016). New quinolones such as sarafloxacin and enrofloxacin are effective against multiple resistance of *Aeromonas* strains and *A. salmonicida* (Aleksakhina *et al*., 2019).

However, the exact molecular basis of the mutation that causes bacterial resistance remains unknown (Coculescu, 2009). One of the ways to prevent mutation and create resistance is to use medicinal compounds.

2) Resistance induced by genetic exchanges: Bacteria have two genetic structures called chromosomes and plasmids that play a role in resistance. Both structures have double-stranded DNA and are related to the inner membrane of the bacterial cell (Munita and Arias, 2016). Plasmid is not necessary for the survival of bacteria, but these components have genetic factors that are effective in the antibiotic resistance of bacteria (Bennett, 2008). Plasmids (R-Factor) contain 20-500 genes that have the ability to resist a large number of drugs. The importance of this type of resistance is because it occurs mostly among non-pathogenic bacteria (Ramirez *et al*., 2014). For example, *Aeromonas* in the water and on the body of the fish become resistant to the consumed oxolinic acid (Igbinosa *et al*., 2012). If this bacterium consumes contaminated water or fish, it transfers its resistance factor to an important human pathogen such as *Escherichia coli* (Kalter *et al*., 2010). This pathogen can cause an incurable infection in humans, which is dangerous in terms of public health. To create this type of resistance, the plasmid is transmitted in the following three ways (Abdi *et al*., 2017).

Types of resistance induced by plasmid transfer: Transformation (direct transfer): The simplest method of transfer is in which the bacterium transfers the naked DNA molecule that has been seen due to the lysis of the bacterial cell against penicillin. Gene transfer through transformation also happens in soil and oceans and plays an important role in genetic exchanges in nature (Darphorn *et al*., 2021).

Mediated transfer: Bacterial genes are transferred through viruses called bacteriophages that affect bacteria. In this method, due to the disturbances created in the life cycle of the virus, bacterial genes are added to the protein coat (capsid) of the phage, and then the gene-carrying viruses introduce them into another bacterium (Khan Academy, 2022). The amount of transferred DNA depends on the size of the virus and its life cycle stage (Brüssow *et al*., 2004).

Conjugation: Conjugation is the most important method of gene transfer in bacteria and is more similar to sexual mating. In this method, genetic information is exchanged through direct contact between two cells. The transfer is done by the donor cell (F^+ cell) in which a tube-like organ functions for the one-way transfer of DNA from the donor cell to the recipient. In this method, plasmid DNA is transferred alone or together with chromosomal DNA (Holmes and Jobling, 1996). In bacterial pathogenic agents, the occurrence of drug resistance due to plasmid is more common than the resistance induced by chromosomes. Plasmid genes are more mobile than chromosomal genes. The genes in the plasmid include specific characteristics such as drug resistance, metabolic enzymes and virulence factors. Transmission occurs mostly between Gram-negative bacteria and rarely between Gram-positive ones. The greatest efficiency of this type of resistance is gene transfer to a highly pathogenic agent such as *Escherichia coli* (Braz *et al*., 2020). Resistance due to plasmid transfer to four types of antimicrobial drugs has been observed in *Vibrio salmonicida*, *V. anguillarum*, *A. salmonicida*, *Edwardsiella tarda*, *Citrobacter freundii* and *Yersinia ruckeri* (Schulz *et al*., 2022). In addition to plasmids, genetic factors (transposons) are transposable DNA sequences that have the ability to transfer between two bacteria and between the host's chromosomes or in their own plasmid. Some researchers stated that transposons are the cause of bacteria resistant to a number of drugs (Partridge *et al*., 2018). Resistance to penicillin and tetracycline in bacteria is caused by this mechanism.

It is important to note that plasmid-induced resistance in fish pathogens to quinolones has not been reported, because these compounds inhibit plasmid processes. Among fish pathogens, beta (β)-lactamases have been widely observed in *Aeromonas* species (Piotrowska *et al*., 2017).

The importance of antibiotic resistance in humans: The creation of antimicrobial resistance is mostly related to the intestinal bacteria of warm-blooded animals, so that a person gets sick by feeding contaminated substances from water, meat, and etc. Some people believe that the possibility of transmitting zoonoses and food-borne diseases and even drug-resistant pathogens through fishery products is very low (Abebe *et al*., 2020). Published reports indicate the existence of a food-borne illness due to the consumption of raw fish (Iwamoto *et al*., 2010). The bacteria associated with this disease, which is sometimes found in shrimp and even other marine animals such as fish, is called *Vibrio parahaemolyticus* (Letchumanan *et al*., 2014). This bacterium causes food poisoning and digestive discomfort in humans. Currently, *V. parahaemolyticus* is responsible for 25% of food poisoning cases in Japan (Letchumanan *et al*., 2014). This bacterium can be isolated in hot weather from all kinds of aquatic animals, including fish, shrimp, oysters, and crabs. The symptoms of food poisoning with this bacterium in humans depend on the number of ingested bacteria in the intestine, which range from mild diarrhea with digestive pain and discomfort to pseudo-cholera disease. In America, only 10% of food-borne diseases are related to aquatic products, which is mostly the result of poisoning caused by consumption of fish living in coral islands (ciguatera), consumption of tuna and mackerel and raw molluscs and oysters (Ansdell, 2018). The basic problem is multiple resistance, so that bacteria resistant to one drug can also be resistant to other drugs that are similar in structure. *Salmonella* can be mentioned for this type of resistance (Abdi *et al*., 2017).

The question that arises is why the importance of antibiotic resistance in aquatic animals is insignificant. The answer should be found in the presence of natural factors and barriers in aquatic animals that prevent the transfer of resistance factors and the creation of resistant pathogenic bacteria in humans (Munita and Arias, 2016; Ferri *et al*., 2022). These factors are temperature, natural microflora, and developmental and physiological differences. The main natural obstacle is the temperature of the fish, whose body temperature is not constant and depends on the ambient temperature (Abdi *et al*., 2017). The temperature in fish is not suitable for most of the intestinal bacteria that cause infection in humans, because humans are warm-blooded like animals, and most pathogens from human food prefer warm temperatures similar to human body temperature. Among intestinal bacteria, only Listeria monocytogenes is able to reproduce at low temperature (Davis *et al*., 2019). Therefore, only a limited number of fish bacterial agents in temperate climates have the ability to cause disease in humans. In general, the risk of human disease from fish pathogens is reported to be low. In warm water fish farming, organisms such as *Aeromonas hydrophila* and *Edwardsiella* species are among the most important intestinal pathogens that can cause disease in humans (Leung *et al*., 2019). In hot months, *Vibrio* is one of the dominant species. Therefore, the seasonal outbreak of food-borne diseases in the consumption of raw fish and contaminated drinking water has a special appearance (Abdi *et al*., 2017).

The next natural obstacle is that reproduction in fish depends on temperature. At low temperature, the transfer of the resistance factor through transformation and conjugation is low (Pallares-Vega *et al*., 2021). Today, it has been proven that Mg and Ca present in seawater cause a severe decrease (90%) in the biological activity of oxytetracycline, quinolones and exolinic acid (Walden *et al*., 2021). Therefore, depending on the habitat of the fish, which is in the sea or fresh water, the bacterial strains accumulated in the intestines may become sensitive or resistant.

Another natural barrier that plays an important role in preventing the transfer of resistance is the variable nature of microflora in fish. The presence of bacteria in the digestive system of fish has a direct relationship with flora and food, and due to environmental or food changes, the microflora also changes (Talwar *et al*., 2018). In fact, fish that endure hunger for a long time have a sterile digestive system. Most human intestinal bacteria and other human pathogens lose the ability to accumulate in aquatic animals due to physiological and temperature conditions in cold-blooded vertebrates (Abdi *et al*., 2017; Talwar *et al*., 2018). Based on the information provided, the main risk of using drugs in aquatic animals on public health is limited to indirect contact with drugs (Radkhah *et al*., 2021). Therefore, applying treatment methods on water, which is one of the important ways of transferring resistant bacteria, reduces this risk. Otherwise, fish bacterial pathogens get used to an environment that has close contact with the human body and find the ability to survive in the intestine (Talwar *et al*., 2018). With the establishment of special laws in some countries, the use of microbial drugs in aquatic animals is limited, and as a result, public health is less threatened. In America, only oxytetracycline romet 30 is used, and in England, oxytetracycline, exolinic acid, amoxicillin and co-trimazine are used, while in some countries there is no effective monitoring system and fish farmers use any drug that they can prepare. Of course, this problem is not limited to fisheries and exists in all livestock breeding centers (Abdi *et al*., 2017).

Conclusion: The lack of reliable information about the medicinal agents used in the livestock industry and especially in the aquaculture industry creates the suspicion in the minds of whether the use of antimicrobial drugs is dangerous for the health of the society or not. Although it is very difficult to determine the prevalence of antibiotic-resistant bacteria in aquatic products that are consumed by humans, and to determine the origin of the bacteria and the route of transmission of resistance, obtaining information in this regard will end many speculations.

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