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A REVIEW ON ANTIBIOTICS IN SEA FOODS AND THE CONSEQUENCE OF ANTIBIOTIC RESISTANCE

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ABSTRACT

Pharmacy is one of the healthcare professions that have significant role to play in health care system. India is endowed with a long coastline and hence offers scope for large exploitation of marine wealth. The occurrence of antimicrobials in fish and fisheries tissues has received broad interest over the last years. Reports recently published have demonstrated that continuous exposures to these compounds may result in accumulation of the parent compound, their metabolites or both in tissues of aquatic organisms. Antimicrobials (Tetracyclines, Sulphonamides, Chloramphenicol, Nitrofurans, Fluoroquinolones, Endosulphan and Nitroimidazoles) are widely prescribed for therapeutic and prophylactic reasons against microbial infections and also in animal farms as growth promoting agents. The presence of these drugs in animal tissues can have undesirable effects on consumer health, such as allergies, but that is not the main problem because there is a low incidence of such cases; the main problem is that uncontrolled ingestion of antimicrobials by consumer causes the development of bacterial resistance, which translates into a much bigger problem for consumers health when dealing with infections

Key words: Tetracyclines, Sulphonamides, Chloramphenicol, Nitrofurans, antibiotic resistance, sea foods.

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INTRODUCTION

A balanced and healthy diet is a prerequisite for good health. Fish and other seafood's are an important part of a balanced diet and contribute to a good nutritional status. Children, young people, pregnant women and New mothers in particular eat little fish. A good nutritional status is especially important for these vulnerable groups. Seafood contains high levels of many important nutrients that are not commonly found in other foods. It is an excellent source of proteins, very long-chain omega-3 fatty acids, vitamin D, vitamin B12, selenium and iodine. Fatty fish and certain fatty seafood products are the most important sources of marine omega-3 fatty acids and vitamin D in our diet. We know quite a lot about the health effects of isolated nutrients present in fish, but little about how the combined effects of nutrients in fish, i.e. fish as food, and contribute to better health.

As far as seafood is concerned, the health benefits of consuming the marine omega-3 fatty acids EPA and DHA that are the best documented

India is endowed with a long coastline and hence offers scope for large exploitation of marine wealth. Till a few years back, fishermen in India were involving themselves in traditional marine fishing. In the seventies fishermen started concentrating on catching prawns more commonly known as `prawns' due to high profitable return on the same on account of their export value. Brackish water prawn farming started in a big way during 91-94 especially in the coastal districts of Andhra Pradesh and Tamil Nadu.

The estimated brackish water area suitable for undertaking prawn cultivation in India is around 11.91 lakhs ha spread over 10 states and union territories viz; West Bengal, Orissa, Andhra Pradesh, Tamil Nadu, Pondicherry, Kerala, Karnataka, Goa, Maharashtra and Gujarat. Of this only around 1.2 lakhs hectare are under prawn farming now and hence lot of scope exists for entrepreneurs to venture into this field of activity (MPEDA & NACA Manual 2003)

Quality Control

Before harvesting or exporting, prawn should be examined for their health, hygiene quality and safety for consumers. Unhealthy prawns, which are easily recognized through their appearance, will not be acceptable by consumers and market value could be reduced. Unhealthy prawn should be treated before harvesting or removed during harvesting and processing if the proportion of unhealthy prawn in the stock is low.

Human pathogenic organisms could contaminate the prawn during harvesting, storage and processing. Therefore, samples of prawn should be sent to a reliable laboratory to conduct necessary test to certify the hygienic quality of the products, before exporting or sending them to market. The harvested prawn should also be checked for antibiotics and heavy metal residues before export. If the prawns have been treated for unhealthy conditions with antibiotics, the recommended withdrawal period should be followed (MPEDA & NACA Manual 2003)

Table-1 List of banned antibiotics, pesticides and Pharmacologically active substances in sea foods.

1. Chloramphenicol	12.Endosulphan
2. Nitrofurans including Furazolidone, Nitrofurazone, Furaltadone, Nitrofurantoin, Furylfuramide, Nifuratel, Nifuroxine, Nifurprazine and all their derivatives	13. Sulfonamide (except approved sulfabromomethazine, sulfadimethoxine and sulfaethoxypyridazine)
3. Neomycin	14. Ronidazole
4. Nalidixic Acid	15. Ipronidazole
5. Sulphamethoxazole	16. Other nitroimidazoles
6. Aristolochia spp. and preparations thereof	17. Diethylstilbestrol (DES)
7. Chloroform	18. Dimetridazole
8. Chlorpromazine	19. Clenbuterol
9. Colchicine	20. Metronidazole
10. Dapsone	21. Fluoroquinolones
11.Nuvan	22. Glycopeptides

Applications of sulfonamides in veterinary medicine

More than 10 SAs are routinely used in veterinary medicines to treat a variety of bacterial and protozoan infections in cattle, swine, and poultry (1). Sulfamonomethoxine, sulfadiazine, sulfisoxazol and sulfadimethoxine are permitted and sold as veterinary medicines for marine products in Korea. However, the presence of sulfonamide residues in food is of toxicological and regulatory concern as some of them could be carcinogenic and cause allergic hypersensitivity reactions and therapeutic ineffectiveness in human beings. In recent years, both legislators and consumers have shown increased interest in the safety of food products. Events such as the appearance of drug residues in food of animal origin have impelled governments in the United States, the European Union, Japan, and many other countries in the world to set up monitoring program.

The European Union (EU) set a maximum residue limit (MRL) of 100µg/kgfor SAs in food of animal origin such as meat, milk, and egg (EU EMEA/MRL/026/95). The Codex Ali-mentarius Commission (CAC) set maximum residue limits (MRLs) of 25µg/kgand 100µg/kgfor SAs in cattle milk and animal origin (muscle, fat, kidney, and liver), respectively. Korea set a maximum residue limit (MRL) of 100µg/kgas sum of the 14 sulfonamides (sulfadiazine, sulfamerazine, sulfamethoxazole, sulfamethoxypyridazine, sulfadimethoxine, sulfathiazole, sulfaphenazole, sulfachloropyrazine, sulfachloropyridazine, sulfisoxazole, sulfadoxine, sulfamethazine, sulfamonomethoxine, and sulfaquinoxaline) in meat (muscle, fat, kidney, and liver) and milk. Korea also set a maximum residue limit (MRL) of 100µg/kgfor sum of the 14 SAs in marine products (2-5).

Applications of chloramphenicol in veterinary medicine

Chloramphenicol (CAP) is a potent, broad-spectrum antibiotic and potential carcinogen used in humans only at therapeutic doses for treatment of serious infections. Its use in meat producing animals, food producing insects, aquaculture, and animal-feed products has been banned in the United States, Canada and the European Union. However, the illegal use of CAP remains a possibility due to its broad activity, ready availability, and low cost. Even though use of CAP in meat producing animals and aquaculture is banned in the European Union (EU), Canada and United States, illegal use of CAP to treat seafood products remains a possibility due to its broad spectrum activity, ready availability and low cost (8). Both the EU and Canada have recently detected low levels of CAP in imported shrimp from China, Thailand and Vietnam (6). Canada's and EU's present methodology allow detection of CAP at 2.5 and 0.3 ppb respectively. The official method used by the U.S. detects CAP in shrimp at the 5 ppb level (FDA News, 2002); however, modifications and new methods should lower our detection limit to at or below 1 ppb (7). As of September 2002, there were over 24,000 references to CAP in the scientific literature with 4000 of these dealing with detection; however, only a few of these references dealt with detection of CAP in aquaculture.

Applications of nitrofurans in veterinary medicine

Nitrofurans were commonly employed as feed additives for growth promotion, and mainly used for livestock (i.e. poultry, swine and cattle), aquaculture (i.e. fish and shrimp) and bee colonies in the prophylactic and therapeutic treatment of bacterial and protozoan infections such as gastrointestinal enteritis caused by Escherichia coli and Salmonella spp., fowl cholera and coccidiosis black heads. In 1995, the use of nitrofurans for livestock production was completely prohibited in the EU (Commission Regulation, 1995) due to concerns about the carcinogenicity of the drug residues and their potential harmful effects on human health. Under EU regulation, countries with products intended for the EU are bound by the same regulations as locally produced food (Commission Decision, 2003), therefore food imported into the EU should be free of nitrofurans. The use of nitrofurans for livestock has also been prohibited in countries such as Australia, USA, Philippines, Thailand and Brazil. Contrary to the complete ban of nitrofuran use in livestock production, the drugs are readily available for veterinary and human therapy: nitrofurazone is used for topical application on infected burns and skin infections; furazolidone is available for the oral treatment of cholera, bacterial diarrhoea, and giardiasis; and nitrofurantoin is commonly used to treat infections of the urinary tract (9-15).

Antibiotic resistance

It is a specific type of drug resistance. Antibiotic resistance evolves naturally via natural selection through random mutation, but it could also be engineered by applying an evolutionary stress on a population. Once such a gene is generated, bacteria can then transfer the genetic information in a horizontal fashion (between individuals) by plasmid exchange. If a bacterium carries several resistance genes, it is called multiresistant or, informally, a superbug which- Causes antibiotic resistance can also be introduced artificially into a microorganism through transformation protocols.

This can be a useful way of implanting artificial genes into the microorganism. Antibiotic resistance is a consequence of evolution via natural selection.

The antibiotic action is an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will be a fully resistant generation. Several studies have demonstrated that patterns of antibiotic usage greatly affect the number of resistant organisms which develop. Overuse of broad-spectrum antibiotics, such as second- and third-generation cephalosporins, greatly hastens the development of methicillin resistance. Other factors contributing towards resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients, and the use of antibiotics as livestock food additives for growth promotion. Researchers have recently demonstrated the bacterial protein LexA may play a key role in the acquisition of bacterial mutations. Resistant pathogens Staphylococcus aureus (colloquially known as "Staph aureus" or a Staph infection) is one of the major resistant pathogens. Found on the mucous membranes and the skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was the first bacterium in which penicillin resistance was found in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity. MRSA (methicillin-resistant Staphylococcus aureus) was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of blood poisoning in the UK in 1999, up from 4% in 1991.

Tetracyclines Resistance

Energy dependent efflux of antibiotic mediated by resistance proteins in the bacterial cell membrane resulting in concentrations of antibiotic in the cell that are too low for ribosomal binding to occur. This mechanism is plasmid mediated and occurs as a result of the complete or partial loss of the gene coding for the membrane poring proteins via which tetracyclines enter the cell.

Ribosomal protection where tetracyclines can no longer bind to the ribosomal sub-unit, despite intracellular tetracycline concentrations that are normally lethal in unprotected cells.

Chemical modification of tetracycline by oxygen requiring chemical reaction that occurs in the cytoplasm rendering the drug inactive as a protein synthesis inhibitor. The inactivated drug then diffuses out of the bacterial cell. This mechanism is rare because foci of infection are usually poorly aerated (16-18)

Sulfonamides resistance

Sulfonamides were the first drugs acting selectively on bacteria which could be used systemically. Today they are infrequently used, in part due to widespread resistance. The target of sulfonamides, and the basis for their selectivity, is the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway. Mammalian cells are not dependent on endogenous synthesis of folic acid and generally lack DHPS. Instead, they have a folate uptake system which most prokaryotes lack. Laboratory mutants in the dhps (folP) gene can be easily isolated and show a trade off between sulfonamide resistance and DHPS enzyme performance. Clinical resistant mutants, however, have additional compensatory mutations in DHPS that allow it to function normally. In many pathogenic bacteria sulfonamide resistance is mediated by the horizontal transfer of foreign folP or parts of it. Clinical resistance in gram-negative enteric bacteria is plasmid-borne and is effected by genes encoding alternative drug-resistance variants of the DHPS enzymes. Two such genes, sul1 and sul2, have been sequenced and are found at roughly the same frequency among clinical isolates. Remarkably, the corresponding DHPS enzymes show pronounced insensitivity to sulfonamides but normal binding to the p -aminobenzoic acid substrate, despite the close structural similarity between substrate and inhibitor (19)

Chloramphenicol resistance

There are three mechanisms of resistance to chloramphenicol: reduced membrane permeability, mutation of the 50S ribosomal subunit and elaboration of chloramphenicol acetyltransferase. It is easy to select for reduced membrane permeability to chloramphenicol *in vitro* by serial passage of bacteria, and this is the most common mechanism of low-level chloramphenicol resistance.

High-level resistance is conferred by the *cat*-gene; this gene codes for an enzyme called chloramphenicol acetyltransferase, which inactivates chloramphenicol by covalently linking one or two acetyl groups, derived from acetyl-S-coenzyme A, to the hydroxyl groups on the chloramphenicol molecule. The acetylation prevents chloramphenicol from binding to the ribosome. Resistance-conferring mutations of the 50S ribosomal subunit are rare.

Nitrofuran resistance

Resistant mutants are rare, and clinical resistance emerges slowly. Among themselves, nitrofurans show complete cross-resistance, but there is no cross-resistance with any other antibacterial agents. Because of very slight water solubility, the nitrofurans are used either PO or topically. No nitrofuran is effective systemically. They are either not absorbed at all from the GI tract or are so rapidly eliminated that they reach inhibitory concentrations only in the urine. Toxic signs seen with excessive doses of nitrofuran derivatives include CNS involvement (excitement, tremors, convulsions, peripheral neuritis), GI disturbances, poor weight gain, and depression of spermatogenesis. Various hypersensitivity reactions can also be seen. Some nitrofurans are carcinogenic, and their future use is in doubt (20-22).

CONCLUSION

Studies have shown that the use of growth promoting antibiotics contributes to contamination of flocks and food products by antibiotic resistant pathogens, including *Campylobacter*, *Salmonella*, *Enterococcus* and *Escherichia coli* and thereby increase risk of human infections and other resistant pathogens. There is increasing public health concern, however, over use of antibiotics for growth promotion in food and animal production contributes for increasing rates of antibiotic resistance.

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