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Aflatoxins and their effects on fish health

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ABSTRACT

Aflatoxins are secondary metabolites produced mainly by two molds *A. Flavus* and *A. parasiticus*. The molds grow on a variety of improperly stored foods such as Aflatoxin B_1 is the most potent of all known aflatoxins and causes severe toxicity known as aflatoxicosis in a variety of animals including human beings who consume contaminated foods. Aflatoxicosis is found in fish also and is a matter of great concern for aquaculture industry worldwide. Aflatoxicosis in fish depends upon the species, dose of the toxin as well as the time of exposure. Aflatoxin B_1 produces various effect on fish such as retarded growth, increased mortality, liver and kidney disfunction, immunesuppression. Long exposure to aflatoxin B1 causes hepatocellular sarcoma and hepatocellular carcinoma in fish. This review focuses on resources, production, and control measures of aflatoxins to ensure fish safety. The review is informative for research experts in the fields

Keywords: Aflatoxins, Aflatoxicosis, immunosuppressive effects, Growth, Survival, Vital organs.

INTRODUCTION

Aflatoxins are compounds predominantly produced by two molds *Aspergillus flavus* and *Aspergillus parasiticus* (Oliviera *et al*., 2013). The molds can grow in improperly stored feeds and in feed with inferior quality of ingredients (Cheeke and Shull 1985; Ellis *et.al.,* 2000; Rodrigues *et al*., 2012). Aflatoxin was isolated from peanut meal and suggested as the cause of turkey "X" desease (Blount, 1961). Aflatoxins are common contaminant of oil seed crop and cereals such as cotton seed, peanut meal and corn. Sunflower, soybean crops including wheat, walnut, corn, cotton, peanuts and tree nuts (Serverns *et al*., 2003). *A.flavus* mainly grows on corn, cotton seeds and tree nuts whereas *A. paraticus* is dominant in peanuts (Hedayati *et.al.,*2007). Aflatoxin represents a serious source of contamination in many parts of the world. It is the cause of high mortality in livestocks, poultry and

in some cases of human beings (Read and Kasali, 1987; Mclean and Dutton, 1995, Montesano *et al*., 1995, Verma and Mehta, 1998). Among 14 different types of naturally produced aflatoxins (Wagachah and Muthomi, 2008), the major members are B_1, B_2, G_1 and G_2 (Pitt, 2000). Toxigenic *A. flavus* produces aflatoxin B_1 and B_2 whereas toxigenic*. A. parasiticus* produces aflatoxin G_1 and G_2 (Cotty *et al.,* 1994, Pitt 2000, Kosalec and Pipeljnjak, 2005. Among them aflatoxin B_1 is the most fatal and is regarded as the most potent toxin because of its strong carcinogenic, mutagenic and terratogenic effects (ICAR, 1993; Santacroce *et al.*, 2008; Han *et al*., 2008) and present in maximum quantity in culture (Kang 1970; Yu, 2012). It is classified as group I carcinogen by international agency for research on cancer (Anon, 1993) It shows resistance to both heating and freezing which enable it to remain in food chain for indefinite period of time and also reach human beings Zaki *et al*., 2011). The limiting temperature for the production of aflatoxin by *A*. *flavus* and *A*. *parasiticus* are reported as 12 ^{o} C to 41^{o} C with optimum production occurring between 25 ^{o}C and 32 ^{o} C (Lillehoj, 1983). Synthesis of aflatoxins in feeds increase at temperature above 27^{o} C, humidity level greater than 62% and moisture level in the feed above 14% (Royes and Yanong, 2002).

Two other metabolites called AFM_1 and AFM_2 are the hydroxylated metabolites of AFB_1 and AFB_2 respectively (Kang, 1970; Giray *et al.,* 2007; Hussain and Anwar, 2008) and appear in milk, urine, faeces and metabolic products. (Enomoto and Saito 1972; Weidenborner, 2001). Aflatoxins are normally refers to the group of difuranocumarins and classified in two broad groups according to their chemical compositions, the difurocoumarin cyclopentane series and the difurocoumarolactone series. Difurocoumarin cyclopentane series comprises AFB_1, AFB_2 in which a bifuran group is attached to one side of the coumarine nucleus and a pentanone ring is attached to another side. The difurocoumarolactone series including AFG_1, AFG_2, in which a lactone ring is attche to coumarine nucleus in place of pentanone ring(Bennett and Klich,2003).

These names have been given on the basis of the characteristic fluorescence produced by the toxin on Thin Layer Chromatography (TLC) plate when viewed under 363 nm of U.V. light. AFB_1 and AFB_2 produce blue fluorescence whereas AFG_1 and AFG_2 produce green fluorescence. AFM_1 and AFM_2 also produce blue -violet - fluorescence (Enomoto and Saito 1972). Microsomal enzymes specifically cytochrom P-450 dependant mixed function oxidase (MFO) of liver have been suggested responsible for AFM_1 production by the oxidation of AFB_1 (Portman, 1963). Aflatoxin M_1 (AFM_I) was the first metabolite which has been identified and was so named because of its presence in milk where it occurs principally in the protein fraction (Allecroft and Carnaghan, 1963).

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AFLATOXICOSIS

Aflatoxicosis is poisoning which results from ingestion of aflatoxin in contaminated food and feed. The name aflatoxicosis is coined by a group of scientists in the early 1960's for the famous Turkey 'X' disease which resulted in the death of nearly one lakh Turkey birds in United Kingdom in 1960 (Blount, 1961).

Aflatoxicosis is reported from all parts of the world in almost all domesticated and non-domesticated animals. Since aflatoxin is transferred at low rates into edible tissue, and the melting point of aflatoxin ranges from 237 ^{0}C to 299 ^{0}C (Castegnaro *et al.,* 1980), these toxins are not readily degraded under normal cooking condition (Goldblatt, 1969). Thus it is not only of concern for animal health but also for human health who consumes food of animal origin.Aflatoxin produces various effect on animals system such as teratogenicity (Di Paolo *et al.,* 1967), mutagenicity (Ong, 1975), carcinogenicity (New berne and Roger, 1981) and immunosuppression (Pier, 1973, Thaxon *et al*., 1974). The toxic effects depend upon the species, dose of the toxin as well as the time of exposure (Columbe *et al.* 1984, Ngethe *et al.*1993, Centoducati 1993). Due to the growth requirement of the fungi, aflatoxin poses a particular risk in warmer climates. Clinical and experimental studies revealed that exposure to large doses of aflatoxin may cause acute toxicity with lethal effects whereas exposure to small doses for prolonged period is carcinogenic.

Toxic effect triggers when ingested aflatoxin B1 is metabolized into a highly toxic unstable form called aflatoxin-8,9 epoxide (AFBO) in liver by microsomal cytochrome P450 enzymes which then reacts with DNA and protein causing genotoxicity and cytotoxicity (Doi *et al.,* 2002; Diaz *et al.,* 2010). In birds CYP2A6 and CYP1A1are responsible for conversion of AFB1 into AFBO (Diaz *et al*., 2010) but in mammal CYP1A1 and CYP3A4 are the main enzymes for this conversion and also for AFB1 metabolism to AFM1, aflatoxin Q1

and other metabolites (Gallaghar *et al.*, 1996; Guengerich *et al.*, 1996). Alternatively, AFBO is detoxified through conjugation with Glutathione (GSH) by the enzyme glutathione s- transferase. This is supposed to be main pathway for detoxification (Diaz *et al.*, 2010). AFBO causes both genotoxicity and cytotoxicity. Damage to DNA occurs when AFBO binds to N7 atom of guanine residue particularly at 3rd guanine residue of 249 codon on P53/PT 53 tumor suppresser gene (31-32) forming a stereospecific aflatoxin- DNA adduct. The adduct is highly unstable, dissociates itself leading to formation of apurinic DNA which results in hepatocarcinoma in human, primates, birds and fishes (Caguan *et al.,* 2004; Verma, 2004; Do and Choi,2007; Ferguson and Philpott, 2008). Cytotoxicity occurs when AFBO is hydrolysed by an epoxide hydrolase to AFBI-8,9 dihydrodiol which binds with protein and alters its activities(Eaton and Gallagher, 1994). Metabolites of aflatoxin are present in milk, muscle, liver and kidney of animals and produce their toxic effects on human.

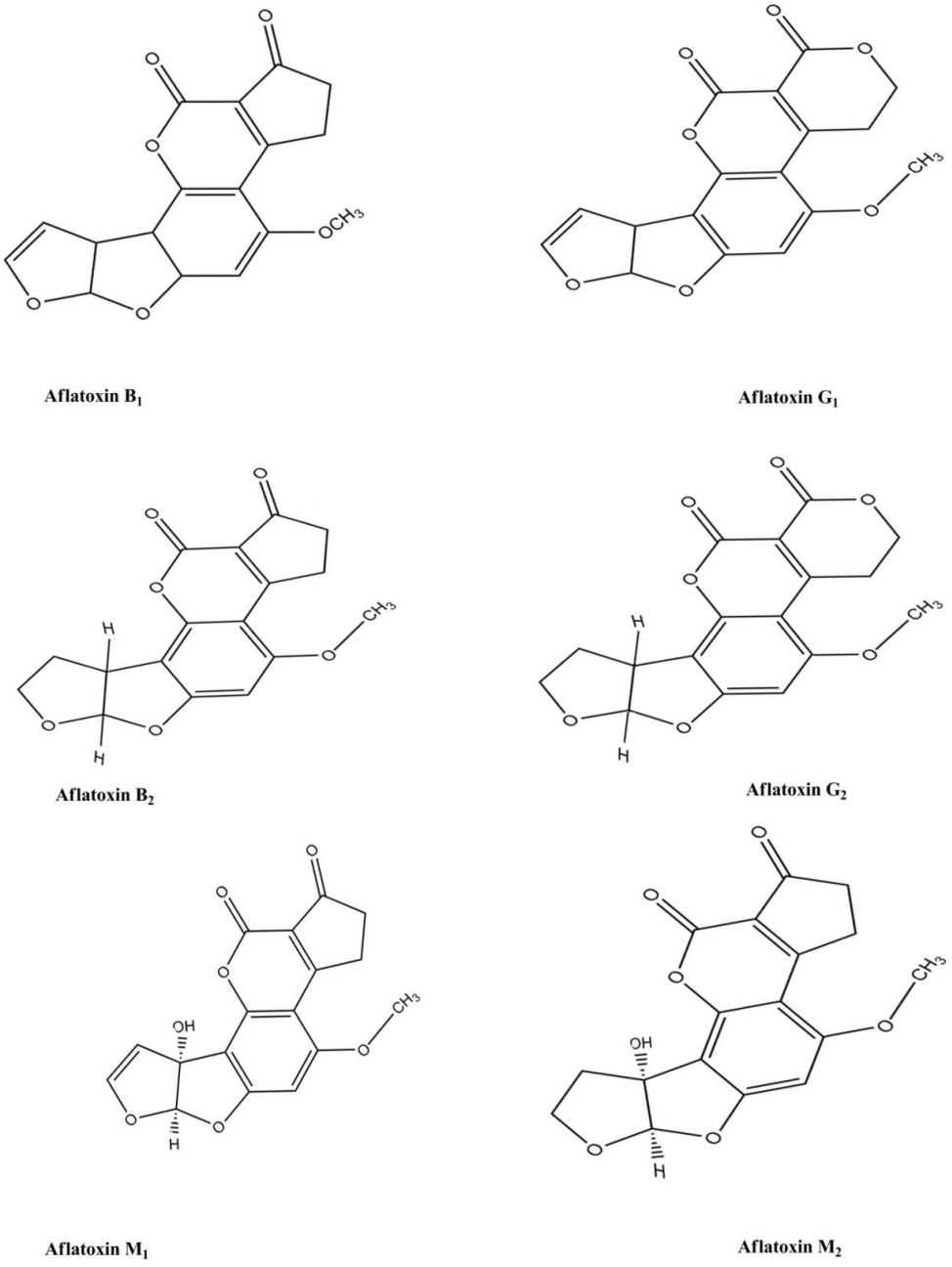

Figure 1: Chemical structure of different types of aflatoxins

EFFECTS ON FISH HEALTH

The aquaculture has shown a rapid rise in the past years (Jana, 2016, subasinghe *et al.,* 2009). However extensive fish farming is also associated with risk of spread of infectious diseases, decrease in water quality, increase of contamination and decrease of food quality which can effects the fish health (Nomoto. K.2005). One of the risks which are associated with aquaculture and fish farming is aflatoxicosis in fish as a result of exposure to aflatoxin (Santacroce *et al.*,2008). Exposure is mainly associated with contaminate feed used for fish farming..The aflatoxin producing molds grow on improperly stored food thus have access to fish feed also (Evalyn *et al.,* 2018). The principal target organ is liver and time of exposure to aflatoxin adversely effects Fish health and growth, Caguan *et al.*, 2004, Sepahdari *et al.*,2010, Zaki *et al.*, 2012, Selim *et al.*, 2013, Mehfouz *et al.*, 2015, Nunez *et al*.,2019). AFB_1 susceptibility in fish depends upon species, their liver detoxification system, genetic, age and nutritional factors (Hons *et al.*,1989; Wild *et al.*,2000). Trouts (Oncorhyncus mykiss) are the most sensitive fish to aflatoxin B1(Horn *et al.*, 1989) and the toxin at amount as low as 1ppb in the diet of trout can cause malignant hepatocellular carcinoma (Cheeke and Shull, 1985). other species such as channel cat fish (*Ictalurus punctatus*), coho salmon (*Oncorhyncus kisutch*) and zebra fish (*Danio rerio*) are less sensitive (Plakas *et al.*,1991; Hendricksand Bailey, 1989; Tsai,1996).

Effect on growth and survival

Reduction in growth and survival are one of the effects of aflatoxin B1 in fish. Significant reduction in growth and appetite was reported in tilapia when fed with 1800 ppb of aflatoxin for 75 days (Royes *et al*., 2002). 33% survival and significant decrease in average length gain and average body weight gain was reported in the same fish when fed with aflatoxin B_1 contaminated feed for 90 days (Caguan *et al.,* 2004). Similer effects of AFB1 in tilapia have been reported by several other investigators(Mahfouz and Sherif, *2015*; Ayyat *et al.,* 2018). Channel cat fish (*Ictalurus punctataus*) showed significant reduction in growth after prolonged exposure to 10 ppm/kg aflatoxin B_1 (Janrarotai and Lovel,1990).

Effect on vital organs

The principal target organ of aflatoxin B1 is liver. When aflatoxin is ingested by animals, it is readily absorbed via gastrointestinal tract into portal blood and is carried to liver. In the liver cells aflatoxin is converted into various classes of metabolites that may be transmitted to edible animal products (Hsieh, 1983). HSR is the ratio of liver weight to body weight.The decrease in HSR is an indicator of liver degeneration(Deng *et al.,* 2010;Zycowskey *et al.,* 2013).Decrease in HSR was reported in tilapia when exposed to more than 100µg AFB1/kg(Mahfouz and Sherif *et al.,* 2015;Hussain *et al.,* 2017)Rainbow trout fed a diet containing 0.02 mg. AFB_1 per kg feed (20 ppb) for eight months resulted in 58% occurrence of liver tumor and continued feeding for twelve months resulted in 83% incidence of tumor (Jantrarotai and Lovell 1990). Hepatocellular adenoma (HCA) and hepatocellular carcinoma (HCC)were reported in rainbow trout when the fish was exposed to aflatoxin B_1 (Cheeke and Shull,1985; Neunez *et al*.,1991). Moreover exposure to aflatoxin B_1 causes lysosomal stability leading to a disorder of hepatocyte permeability and a subsequent increased in serum AST and ALT level in *Oreochromis niloticus* and *Oreochromis mossambicus*(Varior and Philip,2012; Selim *et al.,* 2014).

Aflatoxin B_1 adversely effects s kidney and gill lamellae also which is indicated by a high level of creatinine and urea in fish such as tilapia and Labeo (El-Boshy *et al*., 2008; Selim *et al.,* 2014; Ruby *et al.,* 2014). Urea in fish is excreted primarily by the gills (Stoskoph,1993) and aflatoxin B_1 causes hyperplasia of gills in *O. niloticus* (Hussein *et al.,* 2000). Degenerated urinary tracts and necrosis of urinary tract epithelial cells are reported in aflatoxin-treated rohu (*Labeo rohita*) (Sahoo *et al*., 2001; 2003). Blood clots, necrosis and atrophy of glomeruli, as well as melanosis coli are other alterations found in *Oreochromis niloticus* fed aflatoxin-contaminated diet (Chávez-Sánchez *et al.,* 1994).

Immunosuppressive effects

Immunosuppressive effects of flatoxin in fish is well documented (Almeida *et al.,* 2011). Flatoxin B_1 adversely effects both nonspecific and specific immunity. nonspecific immunity reduction includes decrease in serum bactericidal activity, reduced lysozyme activity, decreased Superoxide anion production by blood phagocytes, decreased macrophage phagocytic activities and reduction in population of glass-adherent NBT-positive cells in Aflatoxin treated fish *L. rohita* and *O. niloticus* (Sahoo and Mukherjee, 2001,2003; El-Boshy *et al.,* 2008). Suppression of adaptive immunity by aflatoxin includes altered

activity of hemopoitic tissue, lymphopenia and decreased IgM production in trouts, *O.niloticus* and *Clarias lazera* (Ottinger and Kaatari, 1998; El-Boshy *et al.,* 2008; Zaki and Fawzy,2012).

Other effects

Aflatoxin B1 causes several other effects. It decreases Prorein Synthesis (Buhler *et al*., 2000, Joner *et al.,* 2000). Decreases serum level of total protein, albumin and albumin (Shehata *et. al.* 2009; Ayyat *et al.,* 2013). Aflatoxin B_1 also causes anaemia, decreased haematological indices such as PCV, MCV, MCH in fish (Nurcan *et al.,* 2012; Selim *et al.,* 2014)

Control of afltoxin

Aflatoxin B_1 exposure is best managed by measures aimed at preventing contamination of crops in the field, post-harvest handling, and storage, or via measures aimed at detecting and decontaminating contaminated commodities or materials used in animal feed. Aflatoxins limits are regulated in food commodities in most of the countries. Currently the worldwide range of limits for aflatoxin B1 and total aflatoxin is 1-20ng and 1-30ng respectively but European regulation is much more strigent and the maximum limit is set at 8 ng in sample (Wesolek and Roudot, 2014; FAO, 2004)

Various physical, chemical and biological techniques are applied effective degradation, mitigation and management of aflatoxin (Shcherbakova *et al.,* 2015). The aflatoxins AFB1and AFG1are completely removed by ozone treatment at 8.5–40 ppm at different temperatures, but AFB2 andAFG2 are not affected by this method (Agriopoulou *et al.,* 2016). However, biological methods of degradation are more favoured at both pre harvested and post harvested level due to its eco-friendly nature. Over the past decades several bacterial and fungi including non-toxicogenic strains of *Aspergillus flavus* (Chang *et al.,* 2007) have been used to limit aflatoxin contamination (xian *et al.,* 2018). The bacterium *Flavobacterium aurantiacum* reportedly removes AFM1 from milk and *Nocardia asteroides* transforms AFB1 to fluorescent product (Wu etal., 2009). *Rhodococcus* species are able to degrade aflatoxins (Teniola *et al.,* 2005) Bacillus licheniformis CFR1 can reduce AFBI by 94 % (Raksha *et al.,* 2017). The edition of mycotoxin binder has been considered as the the most effective approach to reduced the effect of mycotoxin present in contaminated feed. The binders probably bind with the myxotoxin and prevent its absorption through the digestive tract and prevent its adverse effects on the body (Galvano *et al.,* 2001). Supplementation of coumarine, ozone and natural clay in the contaminated feed significantly reduced the effect of aflatoxin B1 in *O.niloticus* (Ayyat *et al.,* 2013. Addition of fix in toxin (sodium calcium alumino silicate), Esterified Glucomannan and β 1,3 Glucan significantly improved the haematological, biochemical parameters and reduced the immunosuppressive effect in *Clarias lazera* and *Oreochromis niloticus* exposed to dietary aflatoxin (Zaki and Fawzy ,2012; El-Boshy *et al.,* 2008; Selim *et al.,* 2014).

Several investigations have showed positive results of vitamins in reducing aflatoxicosis, Vitamin A can reduce the rate of production of aflatoxin in *A. Parasiticus* (Verma *et al.,* 1996). Vitamin C is a strong reducing agent and by donating electrons to free radicals released as a result of aflatoxin B1, negates their reactivity which subsequently reduces their damaging effects on cells. (Alpsoy *et al.,* 2007, EL-Gendy *et al.,* 2010, Ahmad Al Jewary 2012, Sohair 2017). Maryam *et al.,* 2018 reported that vitamin c prevents *Aspergillus parasiticus* growth in the culture and negate the production of aflatoxin by inhibiting aflatoxin gene expression. Vitamin C supplementation reduces adverse effects of aflatoxib B1 on biochemical parameters such as ALT, AST, serum protein and also improves Growth performance in fish (Nayek *et al.,* 2007; Shehata *et al*. 2009).

CONCLUSIONS

Aflatoxins are widespread, highly toxic contaminants that require further research to clarify many essential aspects for better knowledge of their toxicity in fish. However, the advent of new and sensitive techniques to reduce the effect of aflatoxins and growth of their producer are the steps in the right direction to unfold the gray areas.

Conflicts of Interest: The authors declare no conflict of interest.

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