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Aflatoxins biosynthesis, toxicity and intervention strategies: A review

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ABSTRACT

Aflatoxins (AFTs) are toxic products of fungal metabolism, associated with serious health consequences and substantial economic losses to agriculture, livestock and poultry sectors, particularly in the developing countries. This review outlines the current information on AFTs in terms of historical background, classification, relative occurrence and co-existence with other mycotoxins in various food commodities. The phenomenon of aflatoxin (AFT) biosynthesis has been elucidated with reference to molecular basis, genetic regulation and factors affecting the AFT production. Moreover, the *in vivo* disposition kinetics, toxicological action and toxico-pathological consequences of AFTs have also been highlighted. Currently employed strategies for the detection and detoxification of AFTs, biomarkers of exposure assessment, potential economic impact and regulatory considerations regarding the AFTs have been emphasized.

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Capsule Summary: Aflatoxins biosynthesis, toxicity and intervention strategies along with *in vivo* disposition kinetics, toxicological action and toxico-pathological consequences are discussed in this article.

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INTRODUCTION

Molecular basis of AFT biosynthesis pathway

The conversion of acetyl-CoA and malonyl-CoA catalyzed by fatty acid synthase-1 (Fas-1) and fatty acid synthase-2 (Fas-2) provides the starter unit for AFT biosynthesis known as hexanoate (Minto and Townsend, 1997). Hexanoate is further acted upon by the iterative type I polyketide synthase to generate an intermediate compound called norsolorinic acid anthrone which on oxidation by the HypC enzyme forms the first stable intermediate, anthraquinone norsolorinic acid (Ehrlich et al., 2010). The sequential action of multiple enzymes including oxidoreductase, monooxygenase,

dehydrogenase, flavin adenine dinucleotide-containing monooxygenase, esterase and versicolorin-B synthase leads to the production of versicolorin B. Versicolorin B desaturase catalyzes the conversion of versicolorin B into versicolorin A. The 2, 3 double bond present in the dihydrobisfuran ring of versicolorin A can be oxidized by the host enzyme to yield a reactive epoxide with carcinogenic, mutagenic and cytotoxic potential. Versicolorin A is converted to demethylsterigmatocystin followed by sterigmatocystin and then O-methylsterigmatocystin through multiple enzymatic reactions and finally, AFB₁ from O-methylsterigmatocystin is produced cytochrome P-450 monooxygenase OrdA action.

Genetic regulation of AFT biosynthesis

Table 1: Reported LD₅₀/LC₅₀ values of AFTs for different species of animals, birds and aquaculture

Animal	LD ₅₀ (mg/kg)	References
Rabbit	0.3	Newberne and Butler (1969)
Duckling	0.3-0.6	Howard (1983)
Rainbow trout	0.5	Lovell (1989)
Cat	0.55	Newberne and Butler (1969)
Pig	0.62	Newberne and Butler (1969)
Mosquitofish	0.68	McKean et al. (2006b)
Cattle calf	0.5-1.0	Wogen (1969)
Turkey	0.5-1.0	Wogen (1969)
Dog	1.0	Newberne and Butler (1969)
Copepod	1.0 (LC ₅₀)	Reiss (1972b)
Guinea pig	1.4-2.0	Howard (1983)
Horse	2.0	Wogen (1969)
Sheep	2.0	Armbrecht et al. (1970)
Monkey	2.2	Howard (1983)
Rat	5.5-17.9	Howard (1983)
Chicken	6.3	Howard (1983)
Mouse	9.0	Newberne and Butler (1969)
Salmon	10	Schoental (1967)
Hamster	10.2	Robins and Richard (1992)
Catfish	10-15	Jantrarotai et al. (1990)
Rohu	12-13.3	Sahoo et al. (2003)
Brine shrimp	14.0 (LC ₅₀)	Reiss (1972a)
Nile tilapia	100	Tuan et al. (2002)
Pacific blue shrimp	100.5	Wiseman et al. (1982)
Pacific white shrimp	50-300	Wiseman et al. (1982)

The biosynthesis of AFTs encompasses at least 25 genes for encoding the enzymes to catalyze 18 enzymatic reactions and associated regulatory pathways (Yu et al., 2004). The AFT pathway genes regulated by the regulatory gene, *aflR*, consist of 70 kb of fungal genome located in the cluster of genome (Yabe and Nakajima, 2004; Price et al., 2006). Flaherty and Payne, 1997 recorded up-regulated transcription of AFT pathway genes due to overexpression of *aflR* in *A. flavus*. The expression of other AFT pathway genes abolished following the deletion of *aflR* in *A. parasiticus* (Cary et al., 2000). AFT synthesis also requires the *aflS* (*aflJ*) gene and knockout of *aflS* deprived the mutant fungi of AFT synthesizing capacity (Meyers et al., 1998). Other genes like *laeA* and *veA* have been reported to exert a global regulatory function on AF biosynthesis (Bok and Keller, 2004; Calvo et al., 2004). The *laeA* gene encodes a nuclear protein called LaeA which triggers the transcription of gene clusters associated with AFT synthesis and secondary metabolism (Yu, 2012). Deletion of *veA* gene in *A. flavus* (*A. flavus*) and *A. parasiticus* (*A. parasiticus*) abolished the AFT formation (Yu, 2012).

Factors affecting the AFT biosynthesis

The AFT biosynthesis is affected by various biotic and abiotic factors. For the sake of convenience, these elements are categorized into biological, physiological, nutritional, environmental and agricultural factors.

A) Biological factors

Several biological factors including cultivar, soil type, viable fungal species in the soil and plant metabolites have been documented to influence the AFT formation.

B) Cultivars

Given that, the local varieties of maize and peanuts were relatively more susceptible to AFT contamination (Hell et al., 2003; Mutege et al., 2009), the development of transgenic, AFT-resistant cultivars represented a promising strategy to reduce AFT contamination of crops. Contrary to typical peanuts, the transgenic variety exhibiting Bt (*Bacillus thuringiensis*) gene displayed considerably lower level of AFTs (Ozias-Akins et al., 2002). Thakare et al. (2017) employed the host-induced gene silencing and transformed

maize by targeting the *aflC* gene, encoding an enzyme involved in AFT biosynthetic pathway.

C) Soil type

The survival of AFTs is greatly affected by the type of soil. Sandy loam soil led to rapid decomposition and shorter persistence of AFTs than silt loam and silty clay loam soils (Angle, 1986). Heavier soil with a high water-holding potential declined the level of AFT contamination. While light and sandy soil promoted the growth of *A. flavus* and thereby increased the likelihood of AF contamination (Torres et al., 2014).

D) Viable fungal species inhabiting the soil

Strain-specific variations in terms of AFT production have been documented for soil isolates of *A. flavus*. Horn and Dorner, (1999) reported relatively high levels of AFTs produced by the isolates of S-strain than the L-strain of *A. flavus*. The occurrence of S-strain of *A. flavus* was associated with the level of AFTs in peanuts while such correlation was not recorded for L-strain (Mutege et al., 2012).

E) Plant metabolites

Plants synthesize the antimicrobial substances known as phytoalexins that affect the process of AFT synthesis (Greene-McDowelle et al., 1999). The resistance of immature peanut pods against fungal infection was attributed to phytoalexins (Vidhyasekaran et al., 1972) and peanuts challenged with certain species of fungi, including *A. flavus* synthesized the phytoalexins (Wotton and Strange, 1985; Dorner et al., 1989). Under specific conditions, *n*-decyl aldehyde diminished the growth of *A. parasiticus* and subsequent AFT formation by more than 95% (Wright et al., 2000). Yu, (2012) documented that octanal and hexanal reduced the fungal growth by 60% and 50% respectively. However, octanal augmented the AFT formation by 500%, while hexanal had no effect on AFT synthesis.

Physiological factors

AFT biosynthesis is also affected by certain physiological attributes including the culture pH, developmental stage of crop and oxidative stress.

A) Culture pH

AFT production differs with variation in acid-base equilibrium ratio of the culture medium. Fungal AFT production increased by almost 5-10 times at the pH levels of 4 or 5 than pH 8 (Keller et al., 1997). Low pH led to activation of AFT-producing genes therefore acidic medium favored the AFT biosynthesis by *A. flavus* (Cotty, 1988; Marroquín-Cardona et al., 2014).

B) Developmental stage of crop

Lack of fungal sporulation and serial subculturing resulted in the loss of AFT-producing capacity (Bennett and Papa, 1988) and AFT synthesis was blocked by some compounds capable to inhibit the sporulation in *Aspergillus nidulans* (*A. nidulans*) and *A. parasiticus* (Reib, 1982). Likewise, smaller and immature kernels being deficient in phytoalexins were highly susceptible to *A. flavus*-induced invasion and AFT formation (Hill et al., 1983; Sanders et al., 1985).

F) Oxidative stress

Oxidative stress has been proposed to trigger AFT synthesis as an essential element of the fungal cellular response through the production of reactive oxygen species (Narasaiah et al., 2006; Reverberi et al., 2006; Roze et al., 2011). Jayashree and Subramanyam, (2000) regarded the oxidative stress as a prerequisite for AFT synthesis. Consequently, antioxidants including ascorbic acid, caffeic acid and hydrolysable tannins efficiently inhibited the pathway of AFT biosynthesis (Mahoney and Molyneux, 2004; Kim et al., 2008; Yu, 2012).

Nutritional factors

Nutritional sources including amino acids, carbon, nitrogen, lipids and trace elements have been documented to affect the AFT biosynthesis (Luchese and Harrigan, 1993; Cuero et al., 2003).

A) Amino acids

Current studies have demonstrated the variable effects of some amino acids on AFT biosynthesis. Media containing alanine, aspartate, asparagine, proline and glutamine favored the process of AF synthesis (Reddy et al., 1979). Payne et al., (1983) examined the effects of asparagine, ammonium sulphate, casein and proline on AFT production by *A. flavus* and *A. Parasiticus*. Proline triggered the AFT production per gram of mycelium than the other amino acids being investigated. Wilkinson et al., (2007) reported that tyrosine improved while tryptophan inhibited the AFT formation by *A. flavus*.

B) Carbon

Although lactose, sorbose and peptone did not influence the AFT synthesis, simple sugars such as glucose, fructose, maltose and sucrose promoted the AFT formation (Buchanan and Lewis, 1984). Woloshuk et al., (1997) documented the correlation between AFT synthesis and α -amylase activity in *A. flavus*. Nevertheless, the molecular mechanism underlying the regulation of AFT gene pathway expression by carbon sources needs further research (Yu, 2012).

C) Nitrogen

Table 2: Reported LD₅₀/LC₅₀ values of AFTs for different species of animals, birds and aquaculture

Exposed species	Dose of AFTs	Clinico-pathological effects	References
Hereford cattle calves	2230 ppb	Anorexia, depression, photosensitization, diarrhoea, jaundice, elevated serum levels of bilirubin and hepatic enzymes, hepatocyte damage and death	McKenzie et al. (1981)
Male Holstein cattle calves	1130 ppb	General unthriftiness, diarrhea, hydrothorax, lymphopenia, monocytosis, megalocytosis, hepatic congestion with necrosis and 17% mortality	Kaleibar and Helan (2013)
Adult Cattle	33500 ppb	Anorexia, depression, diarrhea, photosensitization, visceral hemorrhages, blood exudation from natural orifices, prolapse, anasarca and death	Umar et al. (2015)
Nili-Ravi buffaloes	500 ppb per animal per day	Reduction of average daily feed intake and hematological parameters, while elevation of serum biochemical parameters	Akhtar et al. (2014)
Nili-Ravi buffalo heifers	554 ppm, 953 ppm, 2022 ppm, 3202 ppm	Concentrations of serum glucose, total protein and cholesterol remain unaltered while concentration of serum urea was significantly elevated	Aslam et al. (2014)
Camels	2.5-6.2 ppm	Anorexia, dullness, lethargy, submandibular oedema, enlargement and congestion of liver with centrilobular necrosis, cellular vacuolation, cirrhosis and bile duct hyperplasia	Osman et al. (2004)
	0.1-1.0 ppb and 0.05-0.1 ppb	Fatty degeneration, congestion and fibrosis of liver with petechial hemorrhages, vacuolar degenerations, cholangitis, cirrhosis, bile duct carcinoma and hepatocellular carcinoma	Al-Hizab et al. (2015)
Mature Arabian horses	58.4 ppb	Anorexia, icterus, rapid weight loss immediately before death, black colored liver with marked centrilobular hepatic necrosis and bile duct hyperplasia, congestion of adrenal cortex	Greene and Oehme (1976)
Adult male Shetland ponies	0.075 ppm (over 36 or 39 days), 0.15 ppm (over 25 or 32 days) and 0.3 ppm (over 12 or 16 days)	Anorexia, depression, generalized icterus, Prothrombin time, total plasma bilirubin and the icteric index increased markedly before death, hemorrhages, brown to tan livers and dark colored kidneys, centrilobular fatty change with hepatic-cell necrosis and periportal fibrosis	Cysewski et al. (1982)
Sheep	4 ppm	Anorexia, diarrhea, excessive salivation, ruminal atony, scour, rectal prolapse, fever and death	Wylie and Morehouse (1978)
	0.75 ppm	Anorexia, apathy, hepatic lesions, neurological signs and death	Suliman et al. (1987)
Crossbreed goats	0.1ppm for 34 days; 0.2 ppm for 18 days; and 0.4 ppm for 10 days	Anorexia, loss of body weight, mucopurulent nasal discharge, dyspnea, coughing, lethargy, icterus, diarrhea, elevated hematological and serum biochemical parameters and subnormal body temperature 24 to 48 hours before death	Clark et al. (1984)
Male goats	0.1ppm for 34 days; 0.2 ppm for 18 days; and 0.4 ppm for 10 days	Pneumonia, rhinitis, nasal discharge, ascites, paleness of liver, petechial hemorrhages, icterus, bile duct proliferation, hepatocytic karyomegaly and hepatocellular degeneration	Miller et al. (1984)
White tailed deer fawns	800 ppb for 8 weeks	Diminished feed intake, body weight gain and liver functions	Quist et al. (1997)
Bullfrogs	667.0, 11.65, 141.74, and 3.53 ppm for 120 days	Absence of liver tumors, increased hepatocyte and biliary duct cell proliferation and appearance of basophilic hepatocytes	Grassi et al. (2007)

Table 2: Continue...

Pigs	3400 ppb and 1460 ppb	Tachycardia, weight loss, tachypnea, lethargy, muscle tremors, diarrhea, jaundice, ascites, petechial hemorrhages, mesocolon, hydropericardium, subcutaneous oedema, diffuse hepatocellular fatty degeneration, proliferation of bile ducts, hepatocellular necrosis, cholestasis and 65.8% mortality	Olinda et al. (2016)
Dogs	<5 ppm to 4946 ppm	Icterus, hepatosis, haematemesis, gastro-enterorrhagia, depression, haematochezia, melaena, bile duct proliferation and fatty hepatosis	Arnot et al. (2012)
Beagle dogs	1, 5, and 20 μ g/kg body weight for 5 days per week for a period of 10 weeks	Icterus, anorexia, yellow-orange colored urine, increased prothrombin time, bile duct proliferation and bile pigment accumulation in the portal areas	Armbrecht et al. (1971)
Rhesus monkeys	500 ppb for 18 days followed by doses of 1ppm	Biliary fibrosis with fatty infiltration, enlarged kidneys and fat deposition in the tubular epithelial cells	Madhavan et al. (1965)
Baladi rabbits	100 ppb for 21 days	Reduction in daily consumption of feed and water, poor weight gain, increased relative weights of liver, heart, kidneys and adrenal glands	Abd El-Hamid (1990)
New Zealand White rabbits	15 and 30 ppb	Reduction in body weights and serum testosterone concentration, relative weight of testis decreased, while those of brain, liver, spleen and kidneys remain unaffected	Ibrahim (2000)
Male White Swiss mice	1 ppm for 16 months	Appearance of liver tumors in 15% of mice with widespread pleomorphism of the nontumorous liver cell nuclei and globular, eosinophilic structures in the cytoplasm	Newberne (1965)
Rats	4-5 ppm	Marked biliary proliferation with rare cholangiofibrosis and hepatic carcinoma	Salmon and Newberne (1963)
Guinea pigs	1.4 ppm	Centrilobular hepatic necrosis, periportal fatty changes, biliary proliferation and parenchymal cell necrosis	Butler (1966)
Chinchillas	212 ppb	Hepatic enlargement with pale-yellowish coloration, diffuse cytoplasmic vacuolation, appearance of cytoplasmic vacuoles in the hepatocytes	Pereyra et al. (2008)

The causal relationship between nitrogen and AFT synthesis has been validated by nitrate-induced suppression of AFT production (Kachholz and Demain, 1983; Payne and Brown, 1998). Moreover, the addition of ammonium nitrite, ammonium nitrate and ammonium sulfate supported AFT production; whereas sodium nitrite and sodium nitrate had no impact on AFT synthesis (Reddy et al., 1979).

D) Lipids

Lipid substrate constitutes an excellent carbon source for AFT synthesis (Fanelli et al., 1995) and 0.5% soybean oil induced the lipase gene expression followed by AFT formation (Yu et al., 2003). Saturated fatty acids (stearic acid, palmitic acid and myristic acid) stimulated while unsaturated fatty acids (linoleic acid and oleic acid) inhibited the AFT

synthesis (Priyadarshini and Tulpule, 1980). However, Chulze et al., (1991) reported the stimulation of AFT production attributed to unsaturated fatty acids.

Environmental factors

The impact of environmental attributes like topography, climate and weather on AFT production has been markedly established.

A) Topography

A. flavus has been isolated from the soil of all climatic zones, but it is quite common in warm regions (latitudes 26-35°) and relatively rare in areas with latitudes above 45° (Klich, 2002). *Aspergillus nomius* (*A. nomius*) and *A. parasiticus*

responsible to produce both B and G AFTs, are seldom found in some areas (Cotty and Cardwell, 1999). Consequently, the areas with latitudes below 35° are more likely to come across the AFT contamination (Logrieco and Visconti, 2004).

B) Climate

Climatic conditions represent the main determinant of fungal invasion followed by AFT production (Magan et al., 2003) and acute aflatoxicosis with mortality has been attributed to climate change (Lewis et al., 2005). AFT producing fungi usually inhabit the tropical, warm arid and semi-arid regions and irrigated hot deserts with characteristic changes in climate (Bock et al., 2004). Hot and dry climate enhanced the susceptibility of maize to AFT contamination by facilitating the development, conidiation and dispersion of *A. flavus* and thereby attenuating the growth of affected maize (Scheidegger and Payne, 2003; Cotty and Jaime-Garcia, 2007; Chauhan et al., 2008; Magan et al., 2011).

C) Weather

Weather conditions reflected as short-term changes in temperature, rainfall pattern and relative humidity are recognized to affect the fungal AFT production (Miraglia et al., 2009; Marroquín-Cardona et al., 2014).

D) Temperature

Temperature is a major determinant that alters fungal growth and subsequent mycotoxin production (Marroquín-Cardona et al., 2014). Both low and high temperatures diminished the fungal viability and resultant AFT production (Miraglia et al., 2009; Paterson and Lima, 2011). Chilies produced during summer season in Pakistan, exhibited considerably high AFT content than those produced in winter (Iqbal et al., 2011). Generally, the optimal temperature for AFT synthesis ranged from 24°C to 30°C (Klich, 2007). However, OBrian et al., (2007) suggested a favorable temperature range of 28°C to 35°C while AFT production ceased as soon as temperature exceeded 36 °C (Yu, 2012).

E) Drought

Drought represents another modulating factor of AFT contamination. The xerophyte fungi, *A. flavus* and *A. parasiticus* are capable to grow and proliferate under drought condition. Drought stress deteriorated the natural immunity of crops against fungi through the reduction of phytoalexins synthesis (Dorner et al., 1989) and facilitated the AFT production by raising the proline content of exposed crops (Payne and Hagler, 1983).

F) Rainfall

Although adequate rainfall has been documented to impede or lessen the AFT contamination of peanuts, rain-fed conditions led to extensive AFT formation (Reddy et al., 2003). Besides, sorghum grown during monsoon season in India manifested comparatively high level of AFTs (Ratnavathi et al., 2012). Exposure to heavy rainfall has been implicated in AFT contamination of cottonseed and maize crops (Jaime-Garcia and Cotty, 2003; Lewis et al., 2005).

G) Water activity

Water activity (aw) also affects the fungal growth and AFT production (Marroquín-Cardona et al., 2014). Mousa et al., (2013) found the highest AFT production by *A. flavus* in polished rice at 21°C with aw range of 0.9–0.92 following an incubation period of 21 days. Peanuts synthesized adequate amount of phytoalexins at high aw (>0.97), which was ultimately ceased at aw < 0.95 (Dorner et al., 1989).

H) Interactive effect of multiple weather elements on AFT synthesis

In addition to the impact of individual weather elements, studies have also revealed the combined effect of various weather determinants on AFT biosynthesis. Drought and high temperature, promoted the AFT production (Bankole et al., 2006) and predisposed the peanuts (Craufud et al., 2006), transgenic Bt cottonseed (Bock and Cotty, 1999; Magan et al., 2011) and European maize (Paterson and Lima, 2011) to aflatoxicosis. Likewise, low rainfall with high ambient temperature enhanced the susceptibility of peanuts to aflatoxicosis (Chauhan et al., 2010; Paterson and Lima, 2010). Variations in environmental temperature and its interactive effect with water activity affected the expression pattern of AFT pathway regulatory genes (*aflR* and *aflS*) in *A. parasiticus* and *A. flavus* (Magan and Aldred, 2007; OBrian et al., 2007; Schmidt-Heydt et al., 2010). Gallo et al., (2016) recorded maximum fungal growth, AFB₁ synthesis and upregulated expression levels of *aflR* and *aflS* genes at 0.96 aw and 28°C, while 20°C and 37°C led to downregulation of AFT gene pathway.

Agricultural factors

Inappropriate agricultural systems, such as sowing time, tillage, crop rotation, irrigation, and application of fertilizers also contributed to *A. flavus* infestation followed by AFT production (Torres et al., 2014). Crop rotation, particularly comprising of fungi-resistant crops reduced the likelihood of between-season fungal viability (Mutegi et al., 2012). For instance, the rate of fungal infection and AFT synthesis enhanced when peanuts were continuously grown on the same land (Ortiz et al., 2011). Kebede et al., (2012) demonstrated the effectiveness of irrigation for diminishing plant stress to counteract the AFT problem. Insect damage triggered the fungal penetration and AFT contamination in affected cereals, nuts, crops and other food commodities.

Table 3: Reported clinico-pathological effects associated with aflatoxicosis in different avian species

Exposed species	Dose of AFTs	Clinico-pathological effects	References
Broiler breeders	5 and 10 ppm for 4 weeks	Reduction in egg production and hatchability of fertile eggs declined, enlargement of liver and spleen	Howarth and Wyatt (1976)
	3.5 ppm for 4 weeks	Decreased feed intake and weight gain, 10% mortality, increased relative weights of all internal organs	Kubena et al. (1990)
	0.3 ppm for 5 weeks	Diminished body weight, Reduced feed intake, 3.33% mortality and increased weights of liver and kidneys	Raju and Devegowda (2000)
Broilers	0.16 ppm for 5 weeks	Decreased feed intake, poor growth rate, increased relative weight of liver and gizzard	Arvind et al. (2003)
	1 ppm for 3 weeks	Reduced feed consumption, poor weight gain and increased relative weight of liver and gizzard	Gowda et al. (2008)
	5 ppm for 3 periods each consisting of 28 days	Reduced egg production, Congestion and hemorrhage of liver and immature ova, enlargement of spleen	Iqbal et al. (1983)
White Leghorn laying hens	2.50, 3.19 and 3.91 ppm for 39 weeks	Diminished feed consumption, egg production and egg weights, paleness of breast muscles, discoloration of liver, enlargement of heart, lungs and kidneys lymphoid depletion and hyperplasia of spleen	Pandey and Chauhan (2007)
Japanese quail	0.00-0.75 ppm for 100 days	Reduction in feed intake, weight gain, egg production, hatchability of fertile eggs and serum total protein, increased serum glutamic pyruvic transaminase level	Johri et al. (1990)
Turkeys	0, 100, 200 or 400 ppb for 2 weeks	Decreased feed intake, weight gain, liver to body weight ratio, mild liver damage with enzymatic perturbations and slightly altered blood coagulation pattern	Quist et al. (2000)
Mallard ducks	10-250 ng/g (on dry weight basis)	Anorexia, depression, enlarged, pale, hemorrhagic and swollen liver, and acute hepatocellular degeneration	Robinson et al. (1982)
Geese	500 ng/g (on dry weight basis)	Apparent blindness, weakness, inability to fly, subcutaneous and visceral fat deposition and acute hepatic necrosis with biliary proliferation	Robinson et al. (1982)

Waliyar et al., (2008) observed high AFT concentration in peanuts exposed to insect damage. Fungicides and insecticides have been successfully employed in the field to avert fungal growth and insect damage thereby preventing the AFT biosynthesis (D'Mello et al., 1998; Dorner et al., 2003). Application of insecticide during the cultivation of peanuts led to remarkable reduction in *A. flavus* infestation and AFT production (Bowen and Mack, 1993).

Even though, harvesting should be preferably done at a proper time, following the maturation of crops. However, earlier harvesting is recommended for some nuts to evade potential hull splitting and insect damage which reinvigorate the fungal infection. Timely harvesting of fruits with subsequent cooling is critical to minimize the risk of fungal invasion (Marroquín-Cardona et al., 2014). Inappropriate threshing and digging practices enhanced the vulnerability of peanuts to fungal infection and ensuing AFT contamination because of mechanical damage to kernels (Heathcote and Hibbert, 1978). Post-harvest AFT contamination of peanuts could be effectively controlled through proper drying with the maintenance of a safe humidity level (Torres et al., 2014)

and segregation followed by the exclusion of contaminated peanuts (Dorner, 2008).

Mechanism of action of AFTs

The cytotoxic and carcinogenic potential of AFT metabolite, AFB₁ has been clearly established. Studies have reported the induction of lipid peroxidation followed by oxidative injury to hepatic tissue of rats and inhibition of cyclic nucleotide phosphodiesterase activity in liver, heart, brain and kidney tissues by AFB₁ (Shen et al., 1995; Bonsi et al., 1999). The reactive metabolite of AFB₁ (AFB₁-8, 9-epoxide) binds with N₇ of guanine through covalent linkage (Lillehoj, 1991) to yield AFB₁-N₇-guanine adducts in exposed cells (Bailey, 1994). These AFB₁-N₇-guanine adducts have been implicated to instigate G to T transversions, mutations and tumor formation (Foster et al., 1983). The G to T transversion occurring at codon 249 of p53 tumor suppressor gene has been linked with human hepatocellular carcinomas (Wang and Groopman, 1999).

Table 4: AFTs detection methods in food and feed items

AFB1, AFB2, AFG1, AFG2	Cereals, Baby food	Acetonitril:water (80:20)	BEH C18 Analytical (1.7µm, 2.1×50mm), (Waters) MS-TQD™, R _t -	H ₂ O+NH ₄ Ac+HCO OH 300µL/min	0.1/- µg/Kg (cereals) 0.025/- µg/Kg (infant)	Beltran et al. (2011)
AFB1, AFB2, AFG1, AFG2	Dried fruit and Beans	Methanol: water (80:20)+ 1g	Intercell ODS-3 (5µm, 4.6×250mm) GL Science, Tokyo, Japan. FD(365-450nm), R _t -	acetonitril :methanol:Water (8:27:65), 0.8mL/min	0.5/- 1.0/- µg/Kg 0.5/- 1.0/-	Lutfullah and Hussain (2011)
AFB1, AFB2, AFG1, AFG2	Herbs, Plants, Tea	Methanol: water (8:2)	RP C-18 (5µm, 4.6×250mm) FD (360-435nm), R _t -	Water: acetonitril:methanol (6:2:3), 1mL/min	0.5/1.5 0.2/0.6 µg/Kg 0.5/1.5 0.2/0.6	Romagnoli and others (2007)
AFB1, AFB2, AFG1, AFG2	Maize, Rice	Acetonitril:water (99:1)	RP C-18 (10µm, 4.6×250mm) FD(360-450nm), R _t -	methanol:acetonitril :Water (20:20:60), 1mL/min,	0.05/- 0.0074/- µg/Kg 0.1/- 0.0074/-	Liu et al. (2006)
AFB1, AFB2, AFG1, AFG2	Dried fruits, Nuts	Methanol: water (80:20)+ 1g	Intercell ODS-3 (5µm, 4.6×250mm) GL Science, Tokyo, Japan. FD(365-450nm), R _t -	acetonitril :methanol:Water (8:27:65), 0.8mL/min	0.5/- 1.0/- 0.5/- µg/Kg 1.0/-	Lutfullah and Hussain (2011)
AFB1, AFB2, AFG1, AFG2	Sorghum, Pistachio	Methanol: water (80:20)	ODS2-Spherisorb (5µm, 4.6×250mm)(capital HPLC Ltd) FD(365-435nm), R _t =(8.8,7.6,6.5,5.8)min	methanol:acetonitril:Water (20:20:60), 1mL/min	0.03/0.16 0.03/0.08 0.03/0.08 µg/Kg 0.03/0.08	Ghali et al. (2009)
AFB1, AFB2, AFG1, AFG2 AFM1 AFM2	Egg, Milk, Meat	Acetone:water (100:100), Chloroform	Thermo LC-Si (4.6×250mm), FD(365-435nm),	Toluene:ethylacetate:formic acid:methanol (90:5:2.2:2.5), 2mL/min	0.05/- 0.05/- 0.05/- µg/Kg 0.05/- 0.05/-	Herzallah (2009)
AFB1, AFB2	Pistachio	Methanol: water (80:20)+5g NaCl	ODS-(4.6×250mm), FD(362-450nm),	Water:methanol:acetonitril (60:20:20)+350µL 4M HNO ₃ 1mL/min		Sheibani and Ghaziaskar (2009)
AFB1, AFB2, AFG1, AFG2	Peanuts	Methanol: water (80:20)	HPLC Cat (5µm, 4.6×250mm) FD(365-435nm), AR _t (9.09,10.41,11.46,13.38) min BR _t (12.03,14.05,15.82,18.58) min CR _t (28.34,03,33.08,38.74,46.39) min	acetonitril:Water: methanol A(23:54:23),0.4mL/min>LOD B(17:54:29),1mL/min<R _t C(8:54:38),1mL/min=<<R _t	0.03/0.1 0.01/0.04 (ng/L) 0.09/0.3 0.06/0.2	Afsah-Hejri et al. (2011)
AFB1, AFB2, AFG1, AFG2	Peprika	Methanol: water (60:40)	RP-LiChrosorb C18(5µm, 4.6×250mm), Merck, Germany FD(365-435nm) R _t	methanol:acetonitril:Water (20:20:60), 1mL/min	0.09/0.23 0.09/0.23 µg/Kg 0.14/0.45 0.14/0.45	Shundo et al. (2009)

Table 4: Continue...

AFTs	Food	Extraction	Colum, detector, retention time	Solvent, Flow rate	LOD/LOQ	References
AFB1	Cereal Breakfast	Methanol: water (80:20)	C ₁₈ Nova-Pak 60 A,(4µm, 46×250mm), FD(335,465nm), R _t =5.85min	Water:acetonitril: methanol (20:4:3), 1mL/min	0.05/4.33 ngg ⁻¹	Villa and Markaki (2009)
AFB1, AFM1	Breast milk	Nacl+Chloroform (0.4mL+2.4mL)	ODS2-Spherisorb (5µm, 4.6×25mm)(capital HPLC Ltd), FD(365-418nm), R _t =3.46min, R _t =2.83min	methanol:acetonitril :Water (25:50:25), 1mL/min	5/- (ng/L)	Gurbay et al. (2006)
AFB1	Wheat	Methanol	Capcell-Pak C ₁₈ UG 80 (5µm, 4.6×250mm), (Shiseido, Japan), FD(474-484nm), R _t =8.9min	acetonitril :Water (25:75), 1mL/min	0.14/.74 (µg/L)	Giray et al. (2007)
AFB1, AFB2, AFG1, AFG2	Cocoa	Methanol:water (8:2)	Shimpack (4.6×250mm), FD(362-455nm), 425nm,	Water:acetonitril: methanol (6:2:3), 1mL/min	0.001/- (µg/L)	Copetti et al. (2011)
AFB1, AFB2, AFG1, AFG2	Red Pepper	Methanol:water (8:2)	Ascentic C ₁₈ (4.6×250mm),(supelco) FD(360-440,465nm), R _t =(12.4,10.5,9.2,7.9)min	methanol:acetonitril :Water (5:2:3),1mL/min,	0.05/- (mg/Kg) 0.02/- 0.06/- 0.06/-	Cheraghali et al. (2007)
AFB1, AFB2, AFG1, AFG2	Pistachio Nuts	Methanol:water (3:2)+5g Nacl/250mL Extract	Ascentic C ₁₈ (4.6×250mm),(supelco) FD(360-440,465nm), R _t =(12.4,10.5,9.2,7.9)min	methanol:acetonitril :Water (5:2:3),1mL/min,	0.06/- (mg/Kg) 0.03/- 0.08/- 0.07/-	Cheraghali et al. (2007)
AFB1, AFB2, AFG1, AFG2	Chilli powder	Methanol: water (80:20)	Hichrome Hipersil H5ODS C ₁₈ (4.6×250mm) FD(365-450nm), R _t -	acetonitril :methanol :Water (250:125:600),1.5 mL/min,	0.1/- (µg/Kg) 0.1/- 0.1/- 0.1/-	O' Riordan and Wilkinson (2009)
AFB1, AFB2, AFG1, AFG2	Cassava, Yam Chips	Methanol: water (85:15)	Supelcosil LC-C ₁₈ (4.6×150mm, 3µm) Supelco, USA. FD(335-440nm), R _t -	methanol :Water:acetic acid (45:55:2),1mL/min,	0.1/- (µg/Kg) 0.1/- 0.1/- 0.1/-	Basaran and Akhan (2008)
AFB1, AFB2, AFG1, AFG2	Spices	Methanol: water (70:30)	Capcell-Pak C-18 UG 80 (5µm, 4.6×250mm), (Shiseido, Japan) FD(360-460nm), R _t -	Water:acetonitril (90:10), 1mL/min	0.01/0.03 0.01/0.03 (µg/Kg) 0.15/0.45 0.02/0.06	Cho et al. (2008)
AFB1, AFB2, AFG1, AFG2	Figs, Apricot	Methanol:water (100:150)+4g NaCl	C-18 (5µm, 4.6×250mm) FD(362-425nm), R _t -	Water:acetonitril: methanol (6:2:3), 1mL/min	0.02/- 0.02/- (µg/Kg) 0.02/- 0.02/-	Bircan (2009)
AFB1, AFB2, AFG1, AFG2	Noodles	methanol:acetonitril :Water (51:9:40)	ODS2-Spherisorb (5µm, 4.6×250mm)(capital HPLC Ltd) FD-, R _t -	Water:methanol:acetonitril (65:25:10), 1mL/min	0.01-1/0.05-1.8 0.01-1/0.05-1.8 (µg/Kg) 0.01-1/0.05-1.8 0.01-1/0.05-1.8	Sirhan et al. (2011)
AFB1, AFB2, AFG1, AFG2	Air in poultry forms	Water (25ml)+.04g/mL NaCl	Nova-Pak C-18 and Symmetry shield TM RP-18 FD-, R _t -	Methanol+Acetonitril+ 1%phosphoric acid, 1mL/min	0.25/- 0.25/- ng/L 0.25/- 0.25/-	Wang et al. (2008)

Table 4: continue...

AFB ₁	Grapes	n-hexane chloroform: water (40:20)	Uptisphere C18-ODB(5µm, 4.6×250mm) FD(364-440nm)	A(1%Phosphoric acid) B(Methanol:water =50:50) A:B(56:44), 1mL/min Water:acetonitril: methanol (20:4:3), 1mL/min	0.01/- µg/Kg	El Khoury et al. (2008)
AFB ₁	Black and Green olive	Methanol: water (80:20)	C ₁₈ Nova-Pak (4µm, 4.6×250 mm) (Waters, Millipore; Milford, MA) FD(335-465nm)		0.15/- ng/g	Ghitakou et al. (2006)

AFB₁ epoxide also led to coagulopathy in animals by disrupting the formation of vitamin K and related clotting factors (Bababunmi et al., 1997).

Toxicokinetics of AFTs

The *in vivo* toxicokinetics of AFTs comprise of absorption into the bloodstream, distribution in body tissues and fluids, biotransformation (predominantly through hepatic metabolism) and elimination from the body (mainly via biliary or renal excretion). Dietary exposure to AFTs is followed by the ingestion, intestinal absorption and distribution to various body organs particularly the liver (Dhama et al., 2007). Generally, the hepatic metabolism of AFB₁ occurs through demethylation, epoxidation, hydration and hydroxylation catalyzed by microsomal cytochrome P450 (CYP) monooxygenases. The major human CYP enzymes responsible for the metabolism of AFTs are CYP1A₂ which catalyzes the synthesis of AFB₁-endo-8, 9-epoxide and AFM₁, and CYP3A₄ which results in the formation of AFB₁-exo-8, 9-epoxide and AFQ₁ (Ueng et al., 1995; Gallagher et al., 1996). The o-demethylation and epoxidation (at 2, 3 double bond) of AFB₁ yields AFP₁ (relatively non-toxic) and AFB₁-8, 9-epoxide (acutely toxic, mutagenic, and carcinogenic) respectively. AFB₁-8, 9-epoxide and AFM₁ undergo detoxification via glutathione conjugation catalyzed by glutathione-S-transferase enzyme in mammalian tissues (Massey et al., 1995). The hydrolysis of AFB₁-8, 9-epoxide to dihydrodiol constitutes another way of its detoxification (Longouet et al., 1998). Certain avian species carry out the metabolism of AFB₁ through hydration at C₂-C₃ double bond to form a relatively non-toxic metabolite referred to as AFB_{2a} (Patterson and Roberts, 1970). When subjected to hydroxylation at C₄ or C₂₂, the AFB₁ is converted to AFM₁ (acutely toxic) and AFQ₁ (relatively non-toxic) respectively. Alternatively, the ketoreduction of AFB₁ and AFB₂ leads to aflatoxicol and dihydroaflatoxicol respectively in birds (Verma, 2005). Factors like age, breed, gender, species and physiological status have been reported to influence the *in vivo* disposition pattern of xenobiotics (Adil et al., 2013). For instance, ducklings, guinea-pigs and rabbits rapidly

metabolize an LD₅₀ dose of AFTs within 12 minutes. Whereas mice, sheep, pigs and chicken have moderate biotransformation capacity (an LD₅₀ dose is metabolized in a few hours), while rats exhibit slow metabolizing potential and hence require several days to carry out the metabolism of an LD₅₀ dose of AFTs (Patterson, 1973). The excretion of unchanged AFB₁ or its metabolites occurs in urine, feces, and milk (Allcroft et al., 1968). Wong and Hsieh (1980) recorded the elimination of 54%, 47% and 32% of administered dose of AFB₁ by mouse, rat and monkey respectively.

Toxicological effects of AFTs

A) Human aflatoxicosis

Human exposure to AFTs occurs either from the direct ingestion of contaminated nuts and maize or the carry-over of AFM₁ from AFT-infected feed to milk and milk products. The clinical manifestations of human AFT poisoning vary with age, gender, nutritional status and concomitant exposure to viral or parasitic infections. Human aflatoxicosis is clinically characterized by abdominal pain, vomiting, pulmonary edema and hepatic necrosis with fatty infiltration. Various cases of acute human aflatoxicosis have been documented in developing countries (Shank et al., 1971). Outbreaks of acute toxic hepatitis have been reported in humans in Africa and China with mortality rates ranging from 10-60% (Bhat and Krishnamachari, 1977). The consumption of molded corn by households resulted in aflatoxin poisoning with at least 97 fatalities in India (Krishnamachari et al., 1975; Bhat and Krishnamachari 1977). AFT-contaminated maize had been associated with incidents of human aflatoxicosis in Kenya in 1980s and 2004 with 20% and 125 deaths respectively (Ngindu et al., 1982). Lye et al., (1995) reported acute hepatic encephalopathy in Malaysian children following the utilization of AFT-infected noodles. Likewise, chronic dietary exposure to AFTs has been implicated to cause about 250000 annual deaths resulting from hepatocellular carcinomas in exposed population of Sub-Saharan Africa and China (Groopman et al., 1992; Wild et al., 1992). Several studies have revealed a causal association

between dietary AFT exposure and human hepatocellular carcinomas (Peers and Linsell, 1977; Van Rensburg et al., 1985; Lunn et al., 1997), Reye's syndrome and Kwashiorkor disease (Becroft and Webster, 1972), and childhood growth impairment (Gong et al., 2002; Okoth and Ohingo 2004; Turner et al., 2007; Sadeghi et al., 2009; Mahdavi et al., 2010; Shuaib et al., 2010).

B) Aflatoxicosis in animals, birds and aquaculture species

All animal species are predisposed to aflatoxicosis but the vulnerability of individual animals depends upon the species, gender, age and nutritional status of exposed animal together with the dose of AFT and duration of exposure (Bbosa et al., 2013). Aflatoxicosis has been reported in domestic animals including cattle (McKenzie et al., 1981; Kaleibar and Helan, 2013; Umar et al., 2015), buffaloes (Akhtar et al., 2014; Aslam et al., 2014), camels (Osman et al., 2004; Al-Hizab et al., 2015), horses (Greene and Oehme 1976; Cysewski et al., 1982), sheep (Wylie and Morehouse, 1978; Suliman et al., 1987), goats (Clark et al., 1984; Miller et al., 1984), dogs (Armbrecht et al., 1971; Arnot et al., 2012) and pigs (Yalagod Shivasharanappa et al., 2013; Olinda et al., 2016). Cattle calves, piglets and pregnant sows are highly sensitive to acute aflatoxicosis whereas sheep, goats and adult cattle are relatively resistant to acute AFT poisoning but chronic dietary exposure results in detrimental health effects and production deficits (Dhama et al., 2007). Suckling animals may be exposed to AFM₁ released in the milk (Jones et al., 1994). The carry-over of AFM₁ from AFT-contaminated feed poses a serious public health hazard via the consumption of contaminated milk and dairy products (Veldman et al., 1992). The reported values of median lethal dose/concentration (LD₅₀/LC₅₀ values) of AFTs for different species of animals, birds and aquaculture have been enlisted in table-1.

Likewise, the AFT-induced pathological effects have been described in some wild animals such as deer (Quist et al., 1997), and Rhesus monkeys (Madhavan et al., 1965). Aflatoxicosis has been successfully induced in experimental animals including mice (Kanbur et al., 2011), rats (Salmon and Newberne, 1963; Wei et al., 2014), rabbits (Abd El-Mageed, 1987; Abd El-Hamid, 1990; Ibrahim, 2000), guinea pigs (Butler, 1966), frogs (Grassi et al., 2007) and chinchillas (Pereyra et al., 2008). Mice were comparatively resistant to aflatoxicosis while rats were highly susceptible (Ramsdell and Eaton 1990). The general toxicological effects of aflatoxicosis in animals encompass inappetance, depression, abdominal pain, vomiting, diarrhea, pulmonary edema, ascitis, poor weight gain, reduced productivity, hepato-renal dysfunctions, convulsions, circling, blindness, photosensitization, immunosuppression, carcinogenicity, teratogenicity, abortion, hepatoencephalopathy and death following hydrocephalus and fatty infiltration of heart, liver and kidneys (Pier, 1992; Agag, 2004; Fapohunda et al., 2007; Bbosa et al., 2013). The clinicopathological effects of AFTs

recorded in different animal species have been summarized in table-2.

Aflatoxicosis results in huge economic losses to poultry industry by affecting many avian species like broilers (Kubena et al., 1990; Raju and Devegowda, 2000; Aravind et al., 2003; Gowda et al., 2008), laying hens (Iqbal et al., 1983; Pandey and Chauhan, 2007), quails (Johri et al., 1990), turkeys (Quist et al., 2000), ducks (Robinson et al., 1982) and geese (Robinson et al., 1982). Ducks and turkeys were highly susceptible to AFT poisoning followed by quails while chickens were quite resistant to aflatoxicosis (Rawal et al., 2010; Monson et al., 2015). In birds, anorexia, weight loss, reduced egg production, poor pigmentation, immunosuppression, poor reproductive performance, hemato-biochemical and hormonal perturbations, hepatic necrosis with fatty infiltration and congestion, renal dysfunction, bruising and increased mortality were the most common adverse effects of AFT poisoning (Agag, 2004; Hussain et al., 2008). The clinicopathological effects of aflatoxicosis recorded in different avian species have been summarized in table-3.

Certain aquaculture species like catfish (Jantrarotai and Lovell, 1990), Indian common carp (Murjani, 2003), tilapia (Chivez-Sanchez et al., 1994; Tuan et al., 2002), trout (Lovell, 1989), sturgeon (Sepahdari et al., 2010) and shrimps (Lightner et al., 1982; Wiseman et al., 1982) are also prone to aflatoxicosis. Fry were highly sensitive than adult fish (Royes and Yanong, 2002) and Rainbow trout were more vulnerable to aflatoxicosis than channel catfish, coho salmon and zebrafish (Jantrarotai and Lovell 1990; Hendricks 1994; Dirican, 2015). Poor weight gain, retarded growth, impaired blood clotting, paleness of gills, liver tumors and increased mortality have been documented in fish affected by aflatoxicosis (Royes and Yanong, 2002). The clinicopathological effects of AFTs recorded in different aquaculture species have been summarized in table-4.

C) Co-occurrence and combined toxicity of AFTs with other mycotoxins

As humans and animals are concurrently exposed to multiple mycotoxins (Schothorst and van Egmond, 2004; Streit et al., 2013), the currently applicable single mycotoxin risk assessment strategy also requires modification. Concomitant exposure to different toxins may lead to additive, synergistic or antagonistic effects. Several techniques including the arithmetic definition of additivity, factorial design and theoretical biology-based definition of additivity have been employed to investigate the phenomenon of concurrent mycotoxicosis (Alassane-Kpembi et al., 2016).

D) Natural co-occurrence of AFTs with other mycotoxins in food and feed commodities

The natural co-existence of AFTs with other mycotoxins in food/feed commodities has been extensively studied. Rodrigues and Naehrer 2012 investigated the worldwide

occurrence of mycotoxins in feed and foodstuff for three years and documented that 48% of analyzed samples contained two or more mycotoxins (aflatoxins, deoxynivalenol, fumonisins, ochratoxin A and zearalenone). Streit et al., 2012 reported that 75-100% of examined animal feeds contained more than a single mycotoxin. Likewise, 95% samples of Spanish barley were contaminated with more than two mycotoxins (Ibanez-Vea et al., 2012).

The co-existence of AFTs and fumonisins has been widely reported in maize from several countries including Argentina (Broggi et al., 2007; Garrido et al., 2012), Brazil (Moreno et al., 2009), Burkina Faso (Warth et al., 2012), Cameroon (Njumbe Ediage et al., 2014), China (Sun et al., 2011), Cote D'Ivoire (Sangare-Tigori et al., 2006), Croatia (Klaric et al., 2009), Egypt (Madbouly et al., 2012), Ghana (Kpodo et al., 2000), India (Shetty and Bhat, 1997), Italy (Covarelli et al., 2011), Mozambique (Warth et al., 2012), Serbia (Krnjaja et al., 2013), South Africa (Chilaka et al., 2012), Tanzania (Kimanya et al., 2008), Turkey (Oruc et al., 2006), USA (Chamberlain et al., 1993) and Vietnam (Trung et al., 2008). Furthermore, AF and citrinin have also been concurrently identified in different food and feed ingredients (Garon et al., 2006; Richard et al., 2009).

E) Simultaneous natural exposure of humans to multiple fungal toxins

Concomitant human exposure to different mycotoxins has been evinced from several countries. Klaric et al., 2009 detected the co-existence of AFB₁, ochratoxin A and FB₁ in 20% of feed and cereal samples randomly collected from households in Croatia. Likewise, more than 40% of the pregnant Egyptian women exhibited the co-occurrence of AFT and deoxynivalenol (Piekkola et al., 2012). Abia et al., 2013 documented the concurrent occurrence of AFM₁, ochratoxin A and deoxynivalenol in 63% of human urine samples in Cameroon. Similarly, more than 80% of the examined children were recorded as positive for urinary FB₁ and blood AFB₁-albumin adducts in Tanzania (Shirima et al., 2013).

F) Toxicological interaction of AFTs with other mycotoxins in experimental animals

Most experimental studies pertaining to toxicological interactions of AFTs with other mycotoxins have focused the simultaneous administration of AFB₁ and (fumonisin B₁) FB₁. Co-exposure to AFB₁ and FB₁ instigated synergistic toxic effects in terms of increased carcinogenic potency of FB₁ in male Fischer rats and impaired hepato-renal functions in rabbits respectively (Gelderblom et al., 2002; Orsi et al., 2007). The combination of AFB₁ and FB₁ was more effective in decreasing the mitogenic effect of mononuclear cells (Theumer et al., 2003), and lowering the oxidative stress markers in murine primary hepatocytes and spleen mononuclear cells (Ribeiro et al., 2010; Theumer et al., 2010)

than the individual mycotoxins. McKean et al., (2006a) observed synergistic and additive toxic effects following the co-administration of AFB₁ and FB₁ in male Fischer F344 rats and human bronchiolar epithelial cells respectively. Wistar rats manifested various histopathological lesions in hepatic, intestinal and pulmonary tissues following simultaneous exposure to AFB₁ and FB₁ (Theumer et al., 2008). Isolated cells from female Balb/c mice co-exposed to AFB₁ and FB₁ revealed enhanced level of reactive oxygen species (Abbes et al., 2016). Conversely, the human hepatoma cells (HepG₂) co-treated with AFB₁ and FB₁ manifested antagonistic cytotoxicity (McKean et al., 2006b). Although Friedman et al., (1997) documented the lack of toxicological interaction in rat hepatocytes culture subjected to combination of AFB₁ and AFB₂, the ovarian cancer cells and lung fibroblasts of human origin displayed additive effect while human umbilical vein endothelial cells exhibited synergistic effect upon co-exposure to AFB₁ and AFB₂ (Braicu et al., 2010). Bacterial bioassays demonstrated enhanced genotoxic (Yates et al., 1987) and mutagenic (Vilar et al., 2003) effects of AFB₁ resulting from the concomitant use of cyclopiazonic acid. Golli-Bennour et al. (2010) suggested an additive effect following the co-exposure of Vero cells to AFB₁ and ochratoxin A. Moreover, ochratoxin A, deoxynivalenol and T-2 toxin have also been reported to augment the mutagenic effect of AFB₁ (Sedmikova et al., 2001; Smerak et al., 2001). Conversely, the comet assay revealed ochratoxin A-mediated decline in DNA damage attributed to AFB₁ (Corcuera et al., 2011).

Detection and exposure assessment of AFTs

The assessment of dietary exposure to AFTs entails measuring the contamination level in the food sample along with food intake surveys (Gong et al., 2016). However, the accurate estimation of contamination level can be precluded by the uneven distribution pattern of AFTs in the food and inadequate sampling technique. Biomarkers represent the crucial indicators of exposure and determinants of bioavailable dose of AFTs (Gong et al., 2016). Several molecular bio-indicators including urinary AFB₁-N₇-guanine, serum AFB₁-albumin adducts and urinary AFM₁ have been developed for AFT exposure estimation (Wang et al., 2001). Sputum, nasal secretions and tissue biopsies from the liver, brain and lungs of AFT-exposed individuals also reflected AFTs (Hooper et al., 2009). Furthermore, unabsorbed AFB₁ or its metabolic derivatives can be detected in fecal samples collected from exposed individuals. Although, the assessment of AFTs exposure is primarily based upon the detection and quantification of AFTs or its metabolic products (e.g., AFM₁) in biological fluids like blood, urine, saliva and milk (Makarananda et al., 1995; Wild et al., 1998) (Table 4). Nevertheless, the characteristic short half-life of AFM₁ and wide daily variation in its urinary levels limit its reliability as an effective marker of chronic exposure to AFTs (Groopman et al., 1993; Makarananda et al., 1995; Wild et al., 1998). Conversely, the AFT-albumin adduct with a longer half-life of

30–60 days, relative stability and minimum variability can be estimated in peripheral blood to measure the long-term AFT exposure (Williams et al., 2004). Results revealed that various factors are responsible for AFTs production and all living organisms are vulnerable for its toxic effects (Asare Bediako et al., 2019; Blankson et al., 2019; Chen et al., 2019; Cheng et al., 2019; Díaz Nieto et al., 2019; Frisvad et al., 2019; Gummadidala et al., 2019; Hamza et al., 2019; Magzoub et al., 2019; Mwakinyali et al., 2019; Shahbazi and Shavisi, 2019; Singh and Cotty, 2019; Tsounidi et al., 2019; Wang et al., 2019a; Wang et al., 2019b; Wu et al., 2019; Xie et al., 2019a; Xie et al., 2019b; Yu et al., 2019; Zeng et al., 2019; Zhao et al., 2019; Zhou et al., 2019). So far, there is need to develop the detoxification methods to save food and feed items without harming the nutritional and sensory characteristics.

Economic impact of AFTs

AFT-contaminated food commodities offer a serious health hazard to more than 5 billion people across the world (Strosnider et al., 2006) and AFT exposures are usually more common in Asian and sub-Saharan African countries (Liu and Wu, 2010). In developed countries, the AFT-related economic losses are primarily attributed to regulatory disposal and diminished market price of contaminated foodstuffs (Wu and Guclu, 2012). Besides the aforementioned costs, huge losses have been ascribed to human and animal health problems, rejection of contaminated livestock, poultry and aquaculture products, research projects and regulatory interventions in developing countries (Zain, 2011; Udomkun et al., 2017). AFT contamination of corn occurring in eight Southeastern states of USA during 1980 and its subsequent consumption at hog farms led to economic losses of 97 million and 100 million US dollars, respectively (Shane, 1994). The market livestock and poultry losses were estimated to cost about 1 billion US dollars in three neighboring countries-the Philippines, Indonesia and Thailand (Lubulwa and Davis, 1994). In USA, the annual AFT-related costs owing to animal health effects and losses to peanuts and maize crops were around \$500 million (Vardon et al., 2003) whereas additional costs of nearly \$20-50 million per annum were required to overcome the problem of AFT contamination (Robens and Cardwell, 2003). Moreover, the US maize growers encountered an estimated loss of \$163 million per annum on account of aflatoxin issue (Wu, 2006).

Regulation of AFTs in food and feed items

Appropriate regulatory and legislative measures are requisite to overcome the aflatoxin contamination of food and feed commodities for increasing the market value of products derived from plants and animals and reducing the healthcare costs. Although, more than 100 nations have established the maximum admissible levels of AFTs in food or feed items (Wu and Guclu, 2012), improved detection facilities and optimal legislative practices are still lacking in several developing countries, predominantly the sub-Saharan

African nations (Udomkun et al., 2017). Such regulations typically reveal the strictest levels of AFTs for export and human consumption products while lowest levels are meant for items of industrial usage (Udomkun et al., 2017). Potential intervention approaches like coordination of supply chain, technical capacity building, provision of suitable incentives to control fungal infections and enhanced public awareness through extension services are vital to address the issue of aflatoxicosis (Deng et al., 2018; Fan et al., 2018; Klingelhöfer et al., 2018; Moon et al., 2018; Peng et al., 2018; Salem et al., 2018; Spanjer, 2019; Vidal et al., 2018; Xu et al., 2018).

CONCLUSION AND RECOMMENDATIONS

AFTs represent toxic fungal metabolites implicated to provoke considerable economic losses and potential deleterious effects on human as well as animal health. Food commodities such as cereals, fruits, nuts, spices, oil seeds, beans and dried peas are primarily affected by AFTs. Various effective control measures in terms of biological, chemical, physical and genetic engineering techniques have been applied for the alleviation and control of AFTs in the food. The high levels of AFTs in food items and associated ill-effects are of greater concern in developing countries with temperate and tropical climate, food scarcity and lack of proper control strategies. The accessibility of diverse foods together with the implementation of appropriate regulatory policies can help to curtail the AFT contamination at least in developed countries. Furthermore, understanding the molecular and genetic basis of AFT biosynthesis, improved management procedures, better allocation of monitoring efforts, and adjustment of agronomic practices are requisite to circumvent AFT contamination.

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