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Fungal Toxins and their Effects on Various Vital Body Parts in Human

Dr. Dilip Kumar Sharma

Director, Vardhman Mahaveer Open University, Kota, Rajasthan, India

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ABSTRACT

The secondary metabolites produced by fungi known as mycotoxins, are capable of causing mycotoxicosis (diseases and death) in human and animals. Contamination of feedstuffs as well as food commodities by fungi occurs frequently in a natural manner and is accompanied by the presence of mycotoxins. The occurrence of mycotoxins' contamination is further stimulated by the on-going global warming as reflected in some findings. This review comprehensively discussed the role of mycotoxins (trichothecenes, zearalenone, fumonisins, ochratoxins, and aflatoxins) toward gut health and gut microbiota. Certainly, mycotoxins cause perturbation in the gut, particularly in the intestinal epithelial. Recent insights have generated an entirely new perspective where there is a bi-directional relationship exists between mycotoxins and gut microbiota, thus suggesting that our gut microbiota might be involved in the development of mycotoxicosis. The bacteria–xenobiotic interplay for the host is highlighted in this review article. It is now well established that a healthy gut microbiota is largely responsible for the overall health of the host. Findings revealed that the gut microbiota is capable of eliminating mycotoxin from the host naturally, provided that the host is healthy with a balance gut microbiota. Moreover, mycotoxins have been demonstrated for modulation of gut microbiota composition, and such alteration in gut microbiota can be observed up to species level in some of the studies. Most, if not all, of the reported effects of mycotoxins, are negative in terms of intestinal health, where beneficial bacteria are eliminated accompanied by an increase of the gut pathogen. The interactions between gut microbiota and mycotoxins have a significant role in the development of mycotoxicosis, particularly hepatocellular carcinoma. Such knowledge potentially drives the development of novel and innovative strategies for the prevention and therapy of mycotoxin contamination and mycotoxicosis.

KEYWORDS: fungal toxins, vital, body, human, effect, mycotoxins, carcinoma, pathogen, toxicosis

INTRODUCTION

The momentum of scientific paper publication toward mycotoxin is an increasing trend where 16,821 papers were recorded in Scopus since the first mycotoxin, aflatoxin (AF) was identified in the year 1965. Data clearly showed the significance of mycotoxin research which will be further discussed later in this review paper. Nevertheless, the global health issue arose from mycotoxin is still frequently ignored in many low-income countries, where mycotoxins affect staple foods (Wild and Gong, 2010). The exposure is long-term and often at high doses, regretfully these particular regions are the least regulated in terms of agricultural practices and human exposure. The attention only has

been paid in the richer nations of the world, to meet stringent import regulations on mycotoxin contamination (Battilani et al., 2016). To date, the world still desires for a more accurate evidence-based on mycotoxins and human health, as well as a better biomarker of exposure and data from studies of disease distribution. Current data are valid to justify and respond to reduce exposure in vulnerable populations (Freire and da Rocha, 2017). The implementation of more practical and affordable mycotoxin removal techniques at the household level to effectively reduce exposure are becoming increasingly important. When mycotoxins are introduced into the organism from food, they first come to interact with the gastrointestinal (GI) tract (Assunção et al., 2016). The GI tract is where the gut microbiota resides: it is known for its role in modulating the immune system and digestive processes. Gut microbiota work in concert with the GI tract protects the host from the toxicity of mycotoxins. Accordingly, integration of microbial-based approaches through maintaining a healthy gut microbiota is highly demanded.

Mycotoxins, the low molecular mass (MW ~700 Da) secondary metabolites mainly produced by Aspergillus, Penicillium, and Fusarium are highly noxious substances on animals and humans. However, not all mycotoxin are classified as such, for example, Penicillin, is widely used an antibiotic (Speight, 2012). The structural form of mycotoxins varies from simple four C compounds, e.g., moniliformin, to complex substances such as the phomopsins (Zain, 2011). Fungal proliferation and production of mycotoxins rise naturally due to environmental factors, especially during tropical conditions (Mohd-Redzwan et al., 2013). Besides, the downstream processing such as poor harvesting practices, improper storage and less than optimal conditions during transportation, processing, and marketing can also contribute to the growth of fungi and increase the risk of the major food spoilage agent caused by mycotoxin production (Khazaeli et al., 2014). Due to their ubiquitous nature of fungi, mycotoxins have been increasingly attracting the concern of health organizations where their occurrence in foods cannot be ignored and already poses risk to consumers (Jahanian, 2016).

Notably, it has been estimated that 25% of the world's crops such as nuts, cereals, and rice are contaminated by mold and fungal growth, as reviewed by the United Nations Food and Agriculture Organization and the World Health Organization (Pandya and Arade, 2016). The toxic effect of mycotoxins on animal and human health is referred to as mycotoxicosis. Exposure to mycotoxins is mostly by ingestion but also occurs by the dermal and inhalation routes. The extent of adverse effects of mycotoxins on human or animals health mainly depends on the extent of exposure (dosage and period), type of mycotoxins, physiological and nutritional status as well as possible synergistic effects of other chemicals to which the animals or humans are exposed (Gajecka et al., 2013). In 1960, interest on mycotoxins was initiated by the occurrence of Turkey X disease caused by AF, which killed more than 100,000 turkeys. Subsequently, it was found that AFs are carcinogenic and cause hepatocellular carcinoma (HCC) in animals and humans, and this has stimulated research on mycotoxins (Peraica et al., 1999). Since then, around 400 mycotoxins are known, but AFs, ochratoxins, zearalenone (ZEA), fumonisins (FBs) and trichothecenes are mostly focused on public health issues (Ates et al., 2013). Mycotoxin exposure is not only limited to pure mycotoxins but also masked mycotoxin which formed when plants protect themselves by conjugating mycotoxins to biopolymers. In addition, some people are more susceptible to getting mycotoxicosis than others, and this is due to the pharmacogenetic variability where specific gene mutations such as cytochrome p450 (CYP 450) genes could either increase or decrease the metabolic activity (cytotoxicity) of the challenging mycotoxins (Sun et al., 2016). For instance, in both in vivo (Muhammad et al., 2017) and in vitro (Lewis et al., 2000) studies, CYPs' 1A2 and 3A4 appear as the most important enzymes that increased metabolism of AFB1 to its active form, AFB1-8,9-epoxide and subsequently to AFB1-DNA adduct formation, in which the biomarker has been linked to the development of liver cancer (Ceccaroli et al., 2015).

Chronic mycotoxicosis causes a greater impact on human health. Mycotoxin can induce diverse and powerful toxic effects in test systems: some are carcinogenic, mutagenic, teratogenic, estrogenic, hemorrhagic, immunotoxic, nephrotoxic, hepatotoxic, dermatoxic and neurotoxic (Milićević et al., 2010). Frequently, mycotoxicosis remains unrecognized by medical professionals. Mycotoxicosis can be weighed when a disease appears in several persons, with no obvious connection to a known

etiological agent, such as microorganisms (Viegas et al., 2015).

By the year 2030, the world's population is estimated to reach 8.2 billion people, and with 842 million people estimated as having been undernourished in the period of the year 2011–2013, food supply will definitely present a growing challenge in the next decades (FAO, 2014). This scenario will, in turn, have a tremendous negative impact on food supply (FAO, 2014). It is worth to note that the presence of hazardous substances (e.g., mycotoxins) also limits or reduces the marketability of food products in international markets (Anater et al., 2016).There is now widespread consensus that the earth is warming at an unprecedented rate (Medina et al., 2015). The geographic distribution and production of the crop, as well as the phyllosphere microflora of crops, are expected to be strongly affected by climate change. For instance, mycotoxigenic Aspergillus flavus are able to grow under high temperatures and drought conditions. The resilient growth of A. flavus under extreme heat and dry condition is an expected and emerging dilemma mainly in the Mediterranean and other temperate regions (Logrieco et al., 2003). For example, the impacts of climate change have been observed in Serbia, where no contamination occurred previously, but prolonged hot and dry weather in the year 2012 resulted in 69% of maizes contaminated with AFs (Medina et al., 2015). A similar case also found in Hungary, where the increase in AFs contamination may be due to climate change conditions (Dobolyi et al., 2013).The world's largest agri-food exporters include countries such as Brazil and Argentina and parts of Asia including China and India are identified as hot spots for impacts of climate change (Ray et al., 2012). Thus, from a food security perspective, a more accurate prediction of impacts of climate change on mycotoxins need to be addressed to prevent compromised food sustainability which possibly resulting in negative social consequences.

DISCUSSION

The GI tract is an organ within humans and other animals which responsible for food ingestion, digestion, energy and nutrients absorption, immune response, as well as elimination of waste products (feces) (Celi et al., 2017). The architecture of the GI tract is intended to facilitate these functions. The basic feature of GI tract is a muscular tube lined by a mucous membrane and comprised four layers forming a continuous passage. All segments of the GI tract are divided into four layers: mucosa, submucosa, muscularis propria, and serosa (Jaladanki and Wang, 2016). The mucosa is made up of three layers (epithelium, lamina propria, and muscular mucosae). The entire mucosa rests on the submucosa, beneath which is the muscularis propria. The outermost layer is named as the serosa. The complex infolding at mucosa layer forms an immense surface area for the most efficient nutrient absorption. The submucosa contains arteries, veins, inflammatory cells, lymphatics, and autonomic nerves. The muscularis mucosa is a thin layer of smooth muscle that forms the basis of peristalsis. While, the serosa is made of connective tissue that contains blood vessels, nerves, and fat (Jaladanki and Wang, 2016).

The epithelium layer at the innermost of mucosa is of vital importance for intestinal barrier function. The intestinal epithelium is one layer of thin cells lining the gut lumen. The epithelial contains enterocytes, enteroendocrine, and goblet cells at villi, whereas the Paneth cells, located under the crypts (Fink and Koo, 2016). It acts as a barrier to block the entry of harmful agents such as pathogens, toxins, and foreign antigens. Besides, it is also an important site for nutrient absorption including electrolytes, dietary nutrients, and water via its selective permeable membrane (Constantinescu and Chou, 2016). Each intestinal epithelial cell is connected by desmosomes, tight junctions (TJs), and adherens junctions (AJs). The AJs and desmosomes are responsible for the mechanical linkage of adjacent cells. Whereas, the TJs control the intercellular space and regulate selective paracellular ionic solute transport (Capaldo et al., 2014). Above the epithelium lies a complex microflora which is recognized as gut microbiota and the role of gut microbiota will be discussed later in this review article. The selective permeable barrier of mucosal epithelium establishes the interplay between the intestinal immune system and the luminal contents. Upon ingestion of contaminated food or feed, the GI tract is particularly affected by mycotoxin. Generally, intestinal barrier in the GI tract functions as a filter against harmful mycotoxins. However, some mycotoxins have been found to exert their detrimental effects in the GI tract. For example, mycotoxins can alter the normal intestinal functions such as barrier function

and nutrient absorption. Some mycotoxins also affect the histomorphology of intestine. The impacts of mycotoxins include trichothecenes, zearalenone, fumonisins, ochratoxins, and AFs on general and gut health will be comprehensively reviewed. Fusarium graminearum is the main fungi species that produces tricothecenes. All tricothecenes contain an epoxide at the C12, C13 positions, which is responsible for their toxicological activity (Nathanail et al., 2015). T-2 toxin (Type A) and DON (Type B) are the major mycotoxins that cause toxicity to humans and animals via oral ingestion (Nathanail et al., 2015).During World War II, a biological weapon caused an acute syndrome consists of cough, sore throat, dyspnea, bloody nasal discharge, and fever was reported by Soviet scientists (Pitt and Miller, 2016). Twenty years later, T-2 mycotoxin was discovered when civilians consumed wheat that was unintentionally contaminated with Fusarium fungi (Pitt and Miller, 2016). A human toxicosis due to ingestion of moldy rice contaminated with T-2 toxin has been reported in China. According to Wang Z. et al. (1993), 65% of patients developed food poisoning symptoms such as chills, nausea, abdominal distension, dizziness, vomiting, thoracic stuffiness, abdominal pain, and diarrhea. Similar to T-2 toxicity, victims of DON outbreak suffered from vomiting syndromes (Etzel, 2014). Several outbreaks of acute DON toxicity in human have been reported in India, China, and the USA (Etzel, 2014).Trichothecenes toxic effects in animals (dairy cattle, swines, broilers, and rats) include decreased plasma glucose, reduced blood cell and leukocyte count, weight loss, alimentary toxic aleukia, as well as pathological changes in the liver and stomach (Adhikari et al., 2017). The mechanism involved in T-2 and DON toxicity is generally via oxidative stress-mediated deoxyribonucleic acid (DNA) damage and apoptosis (Wu et al., 2014). Furthermore, T-2 and DON are well-known inhibitors of protein synthesis resulting from the binding of peptidyl-transferase, which is located in the 60s ribosomal subunit (Yang et al., 2017).In the GI tract, a decreased absorption of glucose was observed following T-2 and DON intoxication resulted from suppressed SGLT1 (glucose transporter) mRNA expression. Apart from the glucose absorption, SGLT1 also responsible for water reabsorption, thus reduction of SGLT1 transporter induces diarrhea as well (Grenier and Applegate, 2013). The weight loss effect of trichothecenes involved neuroendocrine factors and cytokines. DON and T-2 elevated concentrations of the indoleamines, serotonin and 5-hydroxy-3-indoleacetic acid (HIAA) in all brain regions (Wang J. et al., 1993). These neuroendocrine factors can affect the secretion of both anorexigenic and/or orexigenic hormones (Maresca, 2013). Through increasing gene expression of anorexia-inducing proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), trichothecenes exacerbate the condition of anorexia (Wu et al., 2015). In addition, DON and T-2 also induced the release of the satiety hormones, peptide YY (PYY) and cholecystokinin (CCK), which are critical mediators of anorexia (Wu et al., 2015).Using animal models, trichothecenes was found to induce necrotic lesions in the GI tract (Kolf-Clauw et al., 2013). A shortening of villi height was also observed in trichothecenes-treated animals (swine, poultry, and rat model). The changes on villi were due to activation of the apoptotic pathway by trichothecenes, which in turn leads to nutrition malabsorption (Alizadeh et al., 2015). Furthermore, results obtained from in vivo and in vitro studies showed that trichothecenes increased intestinal permeability. Using porcine epithelial cell, trichothecenes increased the intestinal permeability by lowering tight junction proteins expression (Osselaere et al., 2013). In addition, previous studies revealed a significant ($P < 0.05$) decreased in the number of goblet cells that secrete mucin in trichothecenes-treated animals. Mucin is primarily involved in the gut barrier function (Pinton and Oswald, 2014). The disruption in the integrity of intestinal epithelium allows the entry of the pathogen into the gut lumen (Lessard et al., 2015). Besides, trichothecenes have been linked with a decreased level of IL-8 in the intestine, which is responsible for pathogen removal (Kadota et al., 2013). Overall, trichothecenes exert negative impacts on GI tracts specifically on the gut absorption, integrity, and immunity.

IMPLICATIONS

Zearalenone (ZEA) is a mycotoxin that primarily produced by Fusarium graminearum and Fusarium culmorum in foods and feeds. The high rate of co-occurrence of ZEA with FBs and DON indicates that these mycotoxins might be involved in a wide range of synergistic and additive interactions. ZEA has been linked to scabby grain toxicosis occurred in Japan, China,

Australia, and the USA, with symptoms including nausea, vomiting, and diarrhea (Liao et al., 2009).It is well recognized that ZEA is a non-steroidal estrogenic mycotoxin that is implicated in the reproductive disorders of farm animals (swines, cattle, and sheep) and hyperoestrogenic syndromes in humans (Kotowicz et al., 2014). Toxicological studies of ZEA revealed its effects on the reproductive system, including enlarged uterus, altered reproductive tract, decreased fertility, as well as abnormal level of progesterone and estradiol. Besides, the ingestion of ZEA during pregnancy reduced fetal weight and survival rate of embryo (Zhang et al., 2014). This phenomenon can be explained through the structure of ZEA. ZEA has a structure which allows it to bind to the mammalian estrogen receptor, although with lower affinity compared to the natural-occurring estrogens (Hueza et al., 2014). Besides, ZEA has also been shown to be hepatotoxic, haematotoxic, immunotoxic and genotoxic (Zhou et al., 2017).

Although the reproductive organ is the main target for ZEA to induce toxicity, the adverse effects of ZEA on GI tracts have been reported. The effects of ZEA ingestion on the GI tract are not as detrimental compared to the other mycotoxins. Studies using intestinal epithelial cells showed that ZEA induced cell death without altering the cell integrity as indicated by transepithelial electrical resistance (Marin et al., 2015). In contrast, it was discovered that the metabolites of ZEA (α- and β-zearalenol) significantly ($P < 0.05$) decreased the cell integrity. The study showed that ZEA and its metabolites acted differently in the gut (Marin et al., 2015). Abassi et al. (2016) demonstrated that ZEA enhanced cell proliferation, increased colony formation and fastened cell migration of colon carcinoma cell line HCT116. Another study also showed that ZEA down-regulated the expression of tumor-suppressor genes (PCDH11X, DKK1, and TC5313860) in intestinal cells (Taranu et al., 2015). In fact, the modulation of gene expression was responsible for the carcinogenic effects of ZEA. Nevertheless, swines ingested ZEA did not showed changes in the height of villi, the thickness of the mucosa, and number of goblet cells (Gajecka et al., 2016a,b; Lewczuk et al., 2016). In brief, ZEA plays a negative role in gut health although no apparent histological changes have been observed. Fusarium verticillioides is the major producer of fumonisins, where fumonisin B1 (FB1) is the most abundant in nature (Lerda, 2017). In contrast to most mycotoxins, which are hydrophobic in nature, fumonisins are hydrophilic compounds, which hinders its discovery until 1988 (Gelderblom et al., 1988). Human epidemiological studies in South Africa, Italy, and China revealed that the esophageal cancer is related to the intake of corn grains containing fumonisins (Chilaka et al., 2017). Another epidemic of neural tube defects (birth defects of the brain, spine, or spinal cord) occurred along the Texas-Mexico border, China and South Africa were also found to be associated with fumonisins-contaminated corn consumption (Ortiz et al., 2015). In animals, fumonisins have been found to cause pulmonary edema and hydrothorax in swines; leukoencephalomalacia in equine; and HCC in rats (da Rocha et al., 2014).FB1 shares the same structure as cellular sphingolipids (Masching et al., 2016). Sphingolipids are responsible for neurological and immunological diseases, as well as cancer. Normal degradation of sphingolipids to ceramide requires sphingomyelinase and ceramidase (Boini et al., 2017). However, FB1 disturbs sphingolipids metabolism via ceramide synthase inhibition which leads to sphingosine accumulation in cells (Masching et al., 2016). FB1 elevates sphingosine levels in urine, serum, kidney, liver, and small intestine. The abnormal turnover of sphingosine induced cytotoxicity, oxidative stress, apoptosis in cells (Hahn et al., 2015).Using intestinal cell lines (IPEC-1, Caco-2, and HT29), Minervini et al. (2014) found FB1 decreased the cell viability and proliferation in a concentration-dependent manner. A possible mechanism has been suggested through the accumulation of sphinganine by FB1. In the intestinal epithelial cells, sphinganine accumulation blocked G0/G1 phase in cell and resulted in growth inhibition and apoptosis (Angius et al., 2015). The accumulation of sphinganine also altered glycoprotein distribution in the jejunum and caused an increase in transepithelial passage of FB1 (Yamazoe et al., 2017). In addition, FB1 altered the integrity of intestinal barrier by suppressing tight junction (TJ) protein expression level (Romero et al., 2016). The increase in intestinal permeability, in turn, promotes translocation of bacteria (Kelly et al., 2015).

Besides, high levels of FB1 also induced an overgrowth in intestinal goblet cell of broiler and swine (Alassane-Kpembi and Oswald, 2015). Goblet-cell hyperplasia is associated with increased mucin secretion. However, continuous hypersecretion of mucins might

deplete the number of goblet cells, resulting in devastation of mucus barrier (Johansson and Hansson, 2016). Previous studies conducted using intestinal cell lines (IPEC-1, Caco-2, and HT29) showed that FB1 was able to regulate immune responses. Upon LPS exposure to the FB1-treated cell line, a reduction in IL-8 synthesis was detected (Minervini et al., 2014). Such reduction could be responsible for a low number of polymorphonuclear leukocytes (PMNs) recruited to infection sites, thus leading to the ineffective elimination of pathogen from the gut (Brazil et al., 2013). Generally, in the gut, FB1 increased intestinal cell apoptosis, reduced intestinal barrier and caused immune dysfunction. Ochratoxin is mainly produced by Aspergillus species and Penicillium species. Ochratoxin A (OTA) is the most prevalent and relevant fungal toxin of this group (Liuzzi et al., 2017). The main target site of OTA is kidney. Previous findings from animals showed OTA is a potent renal carcinogen (Russo et al., 2016). The International Agency for Research on Cancer (IARC) categorized OTA as possibly carcinogenic to humans under Group 2B carcinogen. Apart from that, OTA is an immunosuppressive, teratogenic, and nephrotoxic compound (Ladeira et al., 2017).

In human studies, OTA is associated with kidney diseases, such as Balkan endemic nephropathy (BEN). BEN is a chronic tubulointerstitial disease which slowly progressed into terminal renal failure. Indeed, a 15 years study confirmed that BEN is correlated with upper urothelial tract cancer (Rouprêt et al., 2015). Furthermore, OTA has been associated with the occurrence of upper urothelial tract cancer (Fahmy et al., 2014). However, a systemic review by Bui-Klimke and Wu (2015) revealed that there is no significant evidence for human health risks associated with OTA exposure based on the epidemiological data. The modes of toxic action of OTA are identified through the blockage of protein synthesis and energy production, the formation of DNA adduct formation, apoptosis, as well as the induction of oxidative stress (Kőszegi and Poór, 2016). Moreover, recent studies showed OTA triggered autism via epigenetic mechanism (Mezzelani et al., 2016).Other than its adverse effects on the kidney, previous studies also revealed the gut changes induced by OTA. OTA altered nutrition absorption in the intestine. In vitro studies demonstrated that OTA decreased glucose absorption via SGLT1 transporter (Peraica et al., 2011). In addition, OTA-treated animals experienced faster and more harmful parasite infections (provoked by Eimeria acervulina and E. adenoeides) in chicks and turkey compared to control. The results showed that animals fed with OTA had higher lesion and oocyst indexes in the intestine and more damage at mucosa (Manafi et al., 2011). This can be explained by the increased intestinal permeability in the presence of OTA. In addition, results from immunoblotting and immunofluorescence showed that the expression of TJ proteins responsible for intestinal integrity was significantly ($P < 0.05$) suppressed by OTA (McLaughlin et al., 2004). Besides, OTA-induced oxidative stress also can alter intestinal permeability (Anderson et al., 2016). The oxidative stress induced by OTA has been found to be associated with the apoptosis in the intestinal IPEC-J2 cells (Wang et al., 2017). A study by Solcan et al. (2015) on OTA-fed broilers revealed there is a decrease in villi height and increase in apoptosis of intestinal epithelial cells. Similar results were obtained from another study using broiler model (Qu et al., 2017). Inflammation pathway in the intestine was also affected by OTA. The expression of inflammation-related cytokines (IL-8, IL-6, IL-17A, IL-12, and IL-18) was significantly ($P < 0.05$) decreased in the intestine of the piglets exposed to the toxin (Marin et al., 2017). The alteration of immune system renders the gut vulnerability to infection. OTA exerted its effect on gut via the reduction of nutrient absorption, disruption of intestinal permeability, cell apoptosis, and modulation of immune system. AF is a mycotoxin produced by Aspergillus flavus and Aspergillus parasiticus. The most common mycotoxin found in human food and animal feed is AFB1. In fact, AFB1 is the most potent hepatocarcinogen recognized in mammals and listed as Group I carcinogen by IARC (Muhammad et al., 2017). Liver is the main target site of AFB1. Cumulative evidences from human and animals revealed a strong linkage occurs between AFB1 and HCC. While, acute aflatoxicosis induced abdominal pain, vomiting, edema, and death (Mohd-Redzwan et al., 2013).

Aflatoxicosis outbreak has been recorded four times in Kenya from 2004 to 2014, with near to 600 individuals were affected and 211 deaths were reported from the tragic outbreak (Awuor et al., 2017). As discussed earlier, p450 enzymes in the liver metabolize AFB1 into AFB1-8,9-exo-epoxide. The highly reactive exo-epoxides

form derivatives with DNA, RNA and proteins which subsequently react with the p53 tumor suppressor gene. The reaction generates AFB1-N7-Gua which is then converted to its stabilized form, AFB1-formamidopyrimidine (AFB1-FABY) adduct. AFB1-FABY causes transversion of guanine (G) to thymine (T), which leads to mutation and malignant transformation (Kew, 2013). In addition to the hepatotoxicity of AFB1 mentioned above, other adverse effects include growth retardation, immunosuppression, and genotoxicity have been reported (Kumar et al., 2017).Like most of the mycotoxins, AFB1 compromised the health of GI tracts. Colon cell line (Caco-2) was used in in vitro experiment to determine the AFB1 toxicity in the intestine. AFB1 significantly ($P < 0.05$) inhibited cell growth, increased lactate dehydrogenase activity and caused genetic damage. It is found that the mechanism of AFB1 cytotoxicity are associated with reactive oxygen species (ROS) generation, which leads to the damage of cell membrane and DNA (Zhang et al., 2015). Besides, transepithelial electrical resistance assay showed a reduction in intestinal Caco-2 cells' integrity after AFB1 treatment (Romero et al., 2016).Similar result has been observed in in vivo study where AFB1 affects intestinal barrier function in broiler model as indicated by an increased ratio of lactulose to rhamnose ratio in the plasma (Chen et al., 2016). Several studies on broiler exposed to AFB1 showed that the density (weight/length) of intestine was reduced (Hossein and Gurbuz, 2015). An increase of apoptotic events was found in the jejunum, accompanied with elevated apoptotic markers (Bax and caspase-3) mRNA expression level. Moreover, the increased apoptosis was corresponded to a lower jejunal villi height as found in the other studies (Peng et al., 2014; Zheng et al., 2017). Another study by Akinrinmade et al. (2016) demonstrated intestinal injuries induced by AFB1 in rats. In the AFB1-fed rat, leucocyte and lymphocyte infiltration were observed at lamina propria of the intestinal mucosa. In the duodenum and ileum, AFB1 exposure caused intestinal lesions such as the development of sub-epithelial space and villi degeneration. The adverse effects on the gut from AFB1 exposure include the disruption of intestinal barrier, cell proliferation, cell apoptosis, and immune system. Although AFB1 is the most life-threatening mycotoxin, yet its toxicity on the gut is comparable to the other mycotoxins.

RESULTS

The gut microbiota represents an ensemble of microorganisms including bacteria, viruses, and fungi that harbor within the GI tracts of living organisms. In the past, gut microbiota studies have been focused on the association of single pathogenic organisms with human health. Non-pathogenic microbes were previously thought to be benign as compared to the pathogens (Holmes et al., 2011). Nevertheless, the gut microbiota has recently become a blooming research area (Hoffmann et al., 2013).The rapid rise of remarkable and cost-effective next-generation DNA sequencing methods provide an effective approach to study the composition of the host microbiota. Metagenomic sequencing and amplicon sequencing using specific genes markers are established to replace culture-independent methods for host microbiota analysis (Kuczynski et al., 2012). The amplified sequences resulting read abundance, which reflects the microbial diversity. The advances in molecular biology have provided innovative ways to entangle the complex microbial communities. Using the methods, it has been revealed that majority of microorganisms resides in the gut cannot be cultured outside the host. In the human, for instance, approximately 80% of the total bacterial species in the gut failed to be cultured under laboratory conditions (Guarner and Malagelada, 2003). Besides, these methods also revealed differences in gut bacterial community between anatomical sites, between individuals, and between healthy and diseased states. The findings have completely transformed the view of mammals biology (Weinstock, 2012). As such, growing interest has led to an increasing research into the communities of non-pathogenic microbes that inhabit the human body, and the need to describe the genomes of these organisms to understand the human microbiota has been recognized.The composition of the gut microbiota varies significantly at the relative ratios of dominant phyla, genera, and species. In particular, stable and healthy gut microbiota is generally indicated by the rich diversity of gut bacteria (Mosca et al., 2016). The rapid development of gut microbiota study has revealed its significant role in maintaining human health. The involvement of gut microbiota in nutrition, metabolism, and immune

function has been well established. The gut microbiota allows the host to metabolize a vast range of dietary substrates. For example, the metabolism of carbohydrate is a major catalytic function of the microbiota. The gut microbiota (specifically Bacteroides, Bifidobacterium, Enterobacterium, Fecalibacterium, and Roseburia) assist in the fermentation of complex polysaccharides that escaped proximal digestion (Jandhyala et al., 2015). The fermentation process produces monosaccharides and short chain fatty acids (SCFAs) which include acetate, butyrate, and propionate that are rich energy sources for the host (Jandhyala et al., 2015). Similarly, metabolism pathways of proteins, bile, and phytochemicals, as well as vitamins synthesis by the microbiota, has been also elucidated (Rowland et al., 2017).Apart from that, the gut microbiota protects the host against infections via several mechanisms. The microbes reside in the gut modulate the population of pathogenic microorganisms via competitive exclusion for attachment sites and nutrient (Donaldson et al., 2016). The significance of gut microbiota in the development of immunity can be readily appreciated from the study of germ-free (GF) mice. By comparison to normal mice, GF mice which have a lack of microbiota have been shown to exhibit irregularities in cytokines profile, contain poorly formed local and systemic lymphoid structures as well as the abnormal level of immune cells (Sekirov et al., 2010). Furthermore, accumulating recent data demonstrated that the functions of gut microbiota further extend beyond the gut. Mechanisms studies suggesting that microbial metabolites have taken the role by sending signals to peripheral organs, including the liver, adipose tissue, pancreas, cardiovascular system, lung, and even to the brain (Lv et al., 2017).

It is widely recognized that the composition of gut microbiota in newborns is obtained from mothers during delivery (Dominguez-Bello et al., 2010). While the alteration in the composition of the gut microbiota is mediated by numerous factors including dietary changes (Cani and Everard, 2016), development of disorders and diseases (Hand et al., 2016), genetics as well as stressful experiences (Karl et al., 2017). Sufficient evidence has revealed the inter-relationship between dietary habit and the intestinal microbiota composition (Cani and Everard, 2016). For example, high fat diet renders the host to harbor a gut microbiota enriched in the phylum Firmicutes and depleted in Bacteriodetes. Besides, high fat diet has been also identified to promote proliferation of specific bacterial strains such as Enterobacteriaceae, which may increase intestinal lipopolysaccharide and subsequently increase gut permeability as well as triggering inflammation (Bibbò et al., 2016). On the other hand, a diet rich in fiber has been observed to modulate gut microbiota by altering fermentative metabolites and intestinal pH. Fermentation of fiber by the colonic microbiota produces SCFAs, wherein the metabolites play a significant role in regulating pH in the intestine. It has been demonstrated that a decrease in pH is able to significantly ($P < 0.05$) decrease the population of Bacteriodetes spp. and members of Enterobacteriaceae while promoting the growth of beneficial butyrate-producing microorganisms (Duncan et al., 2009).

On the other hand, studies revealed that the host genotype contributes remarkably to the resemblances in the gut microbial taxa. The genes linked with microbial taxa are particularly responsible for diet sensing, immunity, and metabolism (Goodrich et al., 2016b). Moreover, data showed a family belongs to the Firmicutes and Christensenellaceae has the highest heritability. The presence of Christensenellaceae in the gut is frequently associated with low serum triglyceride levels observed in lean and healthy human phenotype (van Opstal and Bordenstein, 2015). In genotype factor studies, monozygotic twins which developed from one zygote are often used as the subjects. As compared to dizygotic twins, it has been shown that there is a higher carriage of Methanobrevibacter smithii in monozygotic twins. M. smithii has also found to be related with leanness (Goodrich et al., 2016a). Besides, numerous studies have linked genetic loci with population of gut bacteria in mice and humans. For instance, LCT gene which encodes for lactase-phlorizin hydrolase. Single nucleotide polymorphisms (SNPs) in LCT are directly correlated with lactose intolerance and the abundance of lactose-metabolizing bacteria, specifically Bifidobacterium (Lerner et al., 2017).Recently, the occurrence of diseases has often been linked consequentially to dysbiosis of gut microbiota. A wide range of gut microbiota-related diseases have been revealed include autism, asthma, colon cancer, Crohn's Disease, irritable bowel syndrome (IBS), food allergies, cardiovascular disease, obesity, diabetes, eczema and hepatic encephalopathy, mental disorders (Kamada et

al., 2013; Sommer and Bäckhed, 2013; Korem et al., 2015). For instance, bacterial overgrowth in the small intestine is commonly observed in patients with IBS. An investigation using 16S rRNA-based microbiota profiling approaches on IBS subjects revealed quantitative and qualitative changes in both mucosal and fecal gut microbiota (Simrén et al., 2012; Collins, 2014). The findings suggested that the gut microbiota balance was compromised in the events of gut inflammation. The dysbiosis of gut microbiota initiates mucosal innate immune responses and increases intestinal permeability. Subsequently, translocation of pathogens occurs, and harmful metabolites can enter the intestinal epithelium. Such events in the gut further exacerbate the severity of diseases (Collins, 2014). Apart from that, evidence showed that the gut microbiota-derived products (SCFA, neurotransmitters, enzymes, and toxins) can be absorbed from the gut, and subsequently affect the metabolic phenotype of the host (Lee and Hase, 2014). In addition, metabolites from the host are transported into the gut via the enterohepatic circulation and serve as substrates for the microbiota. These processes give rise to an interspecies cross-talk between the host genome and the gut microbiota (Lee and Hase, 2014).Regrettably, fewer studies have discussed on the importance of the minorities such as virus, commensal fungi, archaea, and protozoa. The gut virome comprised plant-derived viruses, giant viruses, and abundant (90%) bacteriophages. Pathogenicity of gut viruses includes gastroenteritis, pneumonitis, and diarrhea (Scarpellini et al., 2015). Whereas, fungal communities in the gut mainly consist of the Ascomycota, Basidiomycota, and Zygomycota. Candida species have been primarily associated in inflammatory bowel diseases (IBD), Crohn's disease (CD), ulcerative colitis (UC), obesity and gut inflammation (Sam et al., 2017). Undeniably, the gut microbiota influences almost all system resides in our body, which is of vital importance for survival, therefore, maintaining a balanced microbiota is essentially important.

CONCLUSIONS

Mycotoxins disrupt the gut microbiota balance, and thereby dysregulate intestinal functions and impair local immune response, which may eventually result in systemic toxicity that leads to chronic mycotoxicosis, HCC. The severity of HCC condition can be positively governed by restoration of gut microbiota balance and gut health via probiotics administration. Probiotic which generally helps restore the natural harmony of gut microbiota coupled with its mycotoxins reducing ability could increase its health-promoting value. Regardless, more studies are needed to elucidate the interaction between the gut microbiota and mycotoxin and the implication of such interaction for mycotoxicosis prevention/treatment.

Conflict of interest statement

Authors declare that they do not have any conflict of interest.

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