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Mini-review

Dietary mycotoxins, co-exposure, and carcinogenesis in humans: Short review

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ABSTRACT

Mycotoxins, toxic secondary metabolites of fungi, affect global agriculture so prolifically that they are virtually ubiquitous at some concentration in the average human diet. Studies of *in vitro* and *in vivo* toxicity are discussed, leading to investigations of co-exposed mycotoxins, as well as carcinogenic effects. Some of the most common and toxicologically significant mycotoxins, such as the aflatoxins, ochratoxins, fumonisins, deoxynivalenol, T-2 toxin, HT-2 toxin, patulin, zearalenone, and some ergot alkaloids are outlined. The wide variety of pathogenic mechanisms these compounds employ are shown capable of inducing a complex set of interactions. Of particular note are potential synergisms between mycotoxins with regard to carcinogenic attributable risk, indicating an important field for future study.

Contents

1. Introduction

Fungi have been observed for millennia, and are found to be relatively ubiquitous in nature, with spores able to travel vast distances across the surface of the planet [43]. Many important agricultural products, especially those rich in carbohydrates, are

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attractive colonization sites for fungi. Some toxic secondary metabolites of fungal growth are identified as mycotoxins, and may be found to contaminate agricultural products [23].

Many species from the *Alternaria*, *Aspergillus*, *Claviceps*, and *Fusarium* genera, as well as some *Penicillium* species, and several others are known to produce mycotoxins [110]. Mycotoxins are small organic molecules produced as secondary metabolites of fungal growth, observed as toxic to animals and humans. Mycotoxicosis is the term used for poisoning associated with exposures to mycotoxins. The symptoms of mycotoxicosis depend on the type of mycotoxin, the concentration and duration of exposure, as well as age, health, and sex of the exposed individual [11].

Like all toxicological syndromes, mycotoxicoses can be categorized as acute or chronic. Acute toxicity generally has a rapid onset and an obvious toxic response, while chronic toxicity is characterized by low-dose exposure over a long time-period, resulting in cancers and other generally irreversible effects [106]. Although the main human and veterinary health burdens of mycotoxin exposure are related to chronic exposure (*e.g.*, cancer, kidney damage, immune suppression), the best-known mycotoxin episodes are manifestations of acute effects (*e.g.*, Turkey X-syndrome, human ergotism, stachybotryotoxicosis in livestock) [11].

Some of the most frequently encountered mycotoxins, ochratoxin A (OTA) and deoxynivalenol (DON), are reported to interfere with mammalian cellular processes including DNA replication and protein synthesis [13,79]. Other mycotoxins, particularly aflatoxin B_1 (AFB_1) and its metabolic precursor sterigmatocystin, have been identified as carcinogenic by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) Monographs Program [47]. The IARC Monographs identify environmental factors associated by scientific literature with increased risk of carcinogenesis in humans.

Because of crops affected by fungal infection being eaten, either directly by humans or as feed for livestock, mycotoxins are introduced to the food chain. Mycotoxins are able to resist decomposition or being broken down by mammalian digestion, even by ruminant livestock, allowing these compounds to persist in meat and even dairy products [51]. This gives rise to certain partially metabolized mycotoxins, such as aflatoxin M_1 (AFM_1), present in milk from cows or humans that consumed feed or food contaminated by aflatoxins. Even temperature treatments, such as cooking and freezing, do not inactivate some mycotoxins.

Due to the broad, overlapping habitats of fungal species, it is observed that multiple species may affect a given region [3,49]. Furthermore, one fungal species may produce many different mycotoxins, and the same mycotoxin may also be produced by several different species. Since many species are each capable of producing multiple mycotoxin compounds, and agricultural products from many sources may be aggregated prior to processing *en masse*, there is a very high likelihood of multiple mycotoxins co-occurring in food and feed products [71]. Consequently, in the richly varied modern Western diet, individuals undergo dietary exposure to a very wide variety of mycotoxins [1,88]. Unfortunately, third-world nations with relatively consistent diets are no safer, being reliant on cereal crops grown and processed under laxer regulation and prone to significantly higher levels of contamination [52].

Various mycotoxins were investigated since early last century for individual toxicity, usually in regard to acute pathologies [84]. However, recent research is indicating complex interactions between chronic co-exposure to multiple mycotoxins possibly having synergistic, or even mitigating effects [12,41]. Some of the most common and toxicologically significant mycotoxins, such as the aflatoxins, ochratoxins, fumonisins, three prominent trichothecenes, patulin, zearalenone, and some ergot alkaloids, are outlined below, followed by a description of possible health burdens caused by co-occurrence and co-exposure of multiple mycotoxins, as well as their carcinogenic effects.

2. Mycotoxins

2.1. Aflatoxins

The aflatoxins were isolated and characterized after the death of more than 100,000 turkey poults ("turkey X disease"), and was traced to the consumption of an *Aspergillus*-contaminated peanut meal [17]. Developing nations, including most of Africa, Latin and South Americas, and Asia are identified as high risk areas for aflatoxin exposure, leading to aflatoxicosis [105]. There are six predominant aflatoxins, named AFB_1, aflatoxin B_2 (AFB_2), aflatoxin G_1 (AFG_1), aflatoxin G_2 (AFG_2), AFM_1, and aflatoxin M_2 (AFM_2) [38,24]. In this nomenclature, 'B' and 'G' are used to denote compounds that fluoresce blue or green, respectively, under ultraviolet light. The 'M_1' and 'M_2' compounds are not found on cereal products themselves, but are metabolites expressed in milk of mammals whose diet was contaminated by aflatoxins B_1 and B_2, respectively. Finally, the '$_2$' numbered aflatoxins are structural isomers missing one double bond, as compared to the respective '$_1$' numbered molecule, illustrated in Fig. 1. Among the *Aspergillus* genus, species in the section *Flavi* are most frequently reported producers of AFB_1, while *Aspergillus flavus* and *Aspergillus*

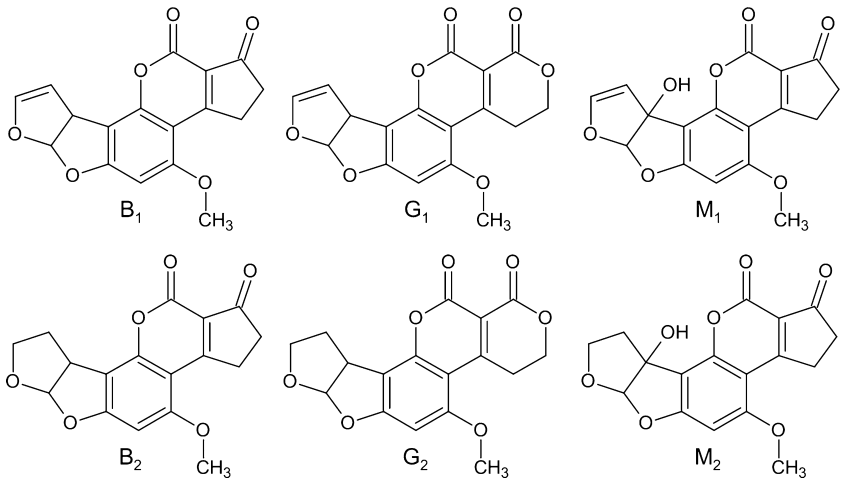

Fig. 1. Chemical structures of six different aflatoxins: aflatoxin B_1, aflatoxin B_2, aflatoxin G_1, aflatoxin G_2, aflatoxin M_1, and aflatoxin M_2.