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Co-exposure of *Fusarium* mycotoxins: *In vitro* myelotoxicity assessment on human hematopoietic progenitors

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ABSTRACT

Mycotoxins such as beauvericin (BEA), deoxynivalenol (DON), enniatin B (ENB), fumonisin B1 (FB1), T-2 toxin and zearalenone (ZEA) can co-occur in food commodities.

This aim of this study was to assess the myelotoxicity of these mycotoxins in couple using *in vitro* human granulo-monocytic (Colony Forming Unit-Granulocyte and Macrophage, CFU-GM) hematopoietic progenitors. Clonogenic assays have been performed in the presence of the following couples of fusariotoxins: DON + BEA, DON + FB1, DON + T-2, DON + ZEA, T-2 + ZEA and BEA + ENB.

Co-exposure of human CFU-GM to DON + BEA resulted in synergic myelotoxic effects. The combination of DON + T-2 presented additive or synergic myelotoxic effects. The couples DON + ZEA, T-2 + ZEA and BEA + ENB had additive myelotoxic effects, while the combination of DON + FB1 showed antagonist myelotoxic effects.

These *in vitro* results suggested that the simultaneous presence of mycotoxins in food commodities and diet may be more myelotoxic than the presence of one mycotoxin alone. Diminution of hematopoietic progenitors could give rise to a decrease number of mature blood cells, inducing agranulocytosis and/or thrombocytopenia and in severe cases aplastic anemia.

1. Introduction

Mycotoxins are secondary metabolites produced under suitable environmental conditions by strains of filamentous fungi in various commodities. *Fusarium* fungi are important pathogens of cereals, and are the most prevalent mycotoxin producing fungi in the temperate regions (Placinta et al., 1999; Jestoi, 2008; Kokkonen et al., 2010). *Fusarium* species can produce several toxins (called fusariotoxins) such as the trichothecenes deoxynivalenol (DON), nivalenol (NIV) and T-2 toxin, zearalenone (ZEA), fumonisin B1 (FB1), beauvericin (BEA) and enniatins (ENs) which have been identified as important contaminants in foodstuffs all around the world (Fig. 1).

Mycotoxins are known to co-occur in commodities, in particular in cereal grains. A worldwide survey has evaluated the occurrence of major mycotoxins aflatoxins, zearalenone, deoxynivalenol, fumonisins and ochratoxin A in maize, soybean, wheat, barley and rice. Among more than 3.300 samples tested during 2010, 36% of tested samples were positive for one tested mycotoxin and 42% were contaminated with two or more mycotoxins (Rodrigues and Naeher, 2010). In the same way, a multi-mycotoxin

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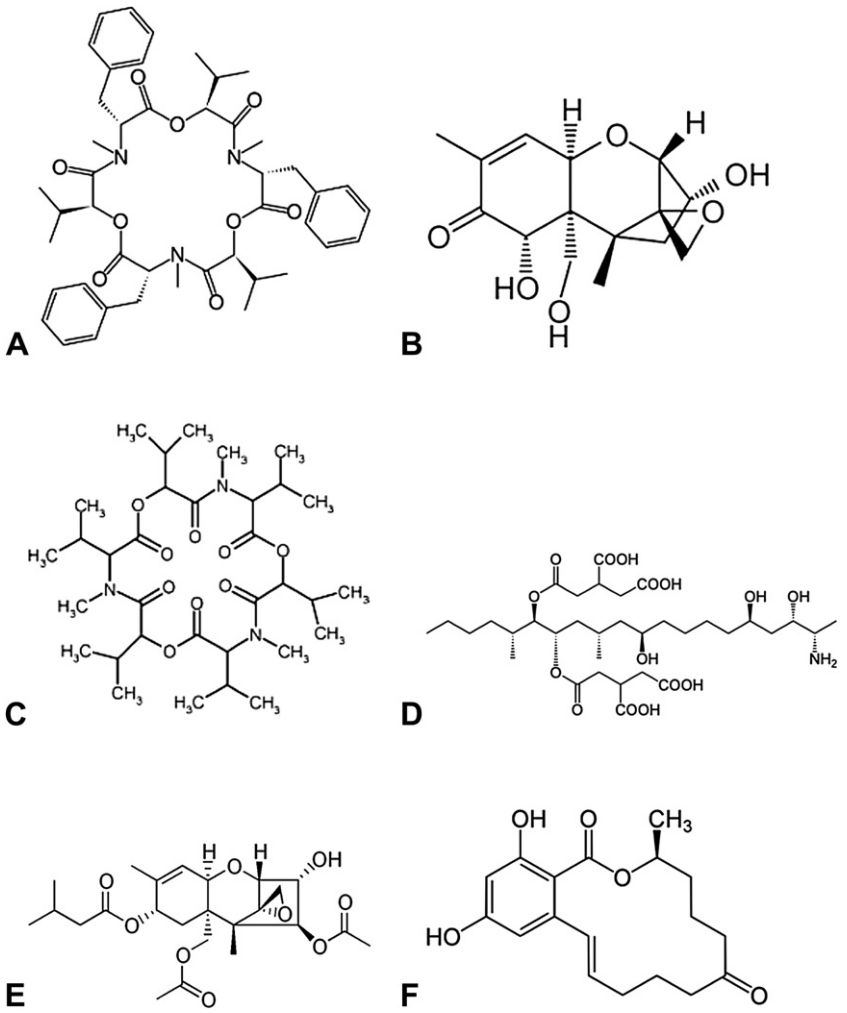

Fig. 1. The chemical structures of beauvericin (A), deoxynivalénol (B), enniatin B (C), fumonisin B1 (D), T-2 (E) and zearalenone (F).

LC-MS/MS method for simultaneous detection of 23 mycotoxins has shown that on wheat or maize samples obtained from Czech Republic, Hungary, Spain and Portugal, 7% were contaminated by one mycotoxin, and 75% were contaminated with more than one mycotoxin (Monbaliu et al., 2010).

The natural co-occurrence of fusariotoxins has been reported. Deoxynivalenol, nivalenol, fumonisins and zearalenone have been found together on wheat, maize, barley and oat in various countries (Placinta et al., 1999). Monbaliu et al. (2010) have demonstrated that the main co-occurring mycotoxins detected in wheat or maize samples from various countries were type B-trichothecenes and fumonisins. Other fusariotoxins such as zearalenone or type A-trichothecenes co-contaminated these cereals. Furthermore, beauvericin has been found on wheat and barley samples co-infected by other mycotoxins such as nivalenol, T-2 toxin, HT-2 toxin, deoxynivalenol, fumonisins, zearalenone, enniatins or moniliformin (Jestoi et al., 2004; Jestoi, 2008).

As a consequence, consumer may probably be exposed to several fusariotoxins after consumption of either one sort of commodity contaminated by several mycotoxins, or several contaminated foodstuffs. Human may also be exposed to multiple fusariotoxins *via* products of animals having eaten contaminated food (Cavret and Lecoeur, 2006). Multi-exposure may lead to additive, synergic or antagonist toxic effects. Additive effect occurs when the combined effects of multiple toxins are equal to the sum of individual effects of each toxin alone. Synergism occurs when the combined effects of multiple toxins are greater than the sum of individual effects of each toxin alone. Antagonism occurs when the combined effects of multiple toxins are lower than the sum of individual effects of each toxin alone. Few data are available on the interaction between concomitantly occurring fusariotoxins, especially on hematopoiesis. Thus their co-occurrence is an increasing concern due to the potential risk of oral chronical exposure to combined mycotoxins to humans, which could be expected to exert greater toxicity than exposure to single mycotoxins.

Until now, most of the *in vivo* published studies concern the interactions between aflatoxins and other mycotoxins or between ochratoxin A and citrinin (For review, see Grenier