Masked Mycotoxins of Deoxynivalenol and Zearalenone – Unpredicted Toxicity

Inji Shikhaliyeva[1], Tuğba Teker[2] and Gülruh Albayrak[3]

[1]Institute of Graduate Studies in Sciences, Programme of Molecular Biology and Genetics, Istanbul University, Turkey

[2]Institute of Graduate Studies in Sciences, Programme of Molecular Biotechnology and Genetics, Istanbul University, Turkey

[3]Department of Molecular Biology and Genetics, Faculty of Sciences, Istanbul University, Turkey

*Corresponding author: Tuğba Teker, Institute of Graduate Studies in Sciences, Programme of Molecular Biotechnology and Genetics, Istanbul University, Turkey

ABSTRACT

Mycotoxins are secondary metabolites produced by fungal species. Detoxification processes of plants which are infected with the toxigenic fungi are responsible for the conversion of them to mycotoxin derivatives, called masked mycotoxins. Masked mycotoxins are less toxic metabolites for plants according to their free forms. Both of these metabolites have toxic effects on animals and humans. Masked mycotoxins are hydrolyzed into their free forms by human and animal intestinal microbiomes. Here, we reviewed the unforeseen toxicity of masked trichothecenes, especially focused on deoxynivalenol (DON) and zearalenone (ZEN), which are classified as major mycotoxins of *Fusarium* species.

Keywords: Masked Mycotoxins; Toxicity; Fusarium; Zearalenone (ZEN); Deoxynivalenol (DON)

Introduction

Since ancient times the importance of food in human health has been known and their relationship was highlighted by Hippocrates in the 5th Century BC with the statement "Let thy food be thy medicine and medicine be thy food" [1]. Every year approximately a million people experience a foodborne illness. Food contaminated with microorganisms and/or their chemicals, leads to these illnesses and becomes a burden on public health [2]. Among the main food toxicants, mycotoxins are secondary metabolites, produced by various fungal organisms. Aflatoxin, ochratoxin A, citrinin, patulin, trichothecenes, fumonisins, and zearalenone (ZEN) are the most common mycotoxins synthesized by *Aspergillus, Fusarium, Penicillium, Alternaria* species [3-5]. Mycotoxin contamination can occur at all stages from the cultivation of plants in the field to various production steps - such as processing, distribution, storage, preparation - of foods and agricultural products [2,6,7]. Cereals are the basic source of the human and animal diet. *Fusarium graminearum* and *F. culmorum* are the most prevalent phytopathogenic species that cause epidemics such as Fusarium Head Blight (FHB), crown and root rot diseases in small-grain cereals, especially wheat, barley, and maize. Mycotoxin contamination in the cereals lead to reduction in crop quality and quantity and resulted in economic losses around the World [8-10]. Class B-trichothecenes and ZEN are included in the major groups of Fusarium mycotoxins [11,12]. Class B-trichothecenes comprise deoxynivalenol (DON), nivalenol (NIV) and their acetylated derivatives (15-acetylated deoxynivalenol (15-ADON) and 3-acetylated deoxynivalenol (3-ADON), 4-acetylated nivalenol (4-ANIV)). However, DON is the most accumulated class-B trichothecene by cereals [6,13-18].

Masked forms of DON and ZEN, and their Toxicity

Masked mycotoxins are generated as a result of the transformation of the main type of mycotoxins by living plants in order to protect themselves from xenobiotic compounds [19]. They were detected in early 1990 and termed as masked due to the inability to be screened in food and feed through conventional analytical methods [20]. The most frequently detected masked forms of *Fusarium* toxins are deoxynivalenol-3-glucoside (DON-3G) and zearalenone-14-D-glucopyranoside (ZEN-14G). The isolation

of DON-3G was first reported from naturally contaminated maize and wheat [21]. Then, the DON-3G also has been found in barley, oat and cereal-based food and feeds [22-25]. The toxicity of DON is provided by three free hydroxyl groups (-OH). DON is converted into DON-3G as a result of glucose transferring to its hydroxyl

group at carbon 3 [6,26]. ZEN-14G is another common masked mycotoxin that has occurred in naturally infected cereals such as wheat, barley and maize. ZEN is reduced to phase I metabolites named α-zearalenol (α-ZEL) and β-zearalenol (β-ZEL). The glucose conjugates of these compounds are also produced (Figure 1).
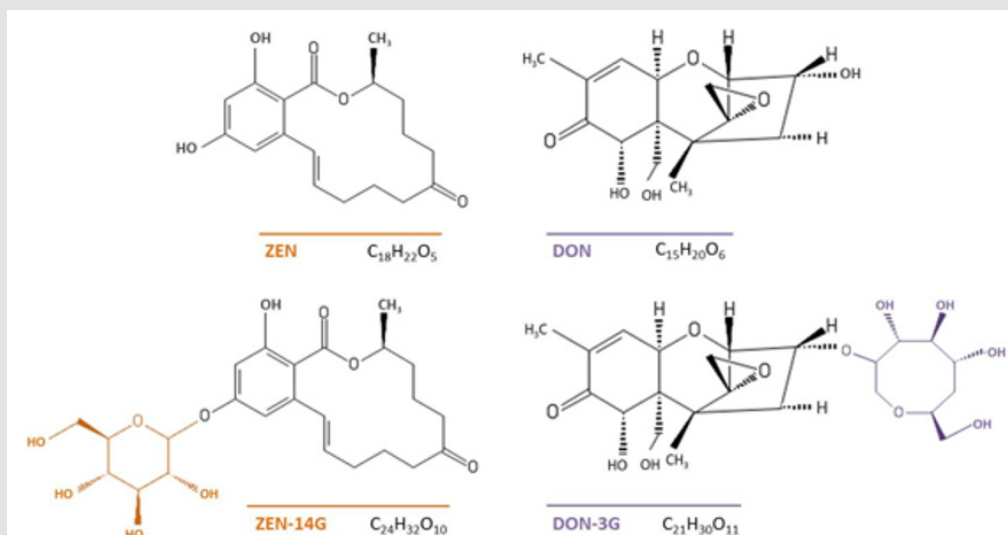
Figure 1: Structures and molecular formulas of ZEN, DON, and their masked forms, ZEN-14G and DON-3G.

Transformation of DON, ZEN and their metabolites with glucose, glutathione, and sulfate groups were listed in Table 1. In addition to masked forms, the modified forms of mycotoxins could occur by transformation or degradation of mycotoxins during food processing and the production of industrial goods. Due to their stable structure and features, mycotoxins tend to remain in the ultimate products [5]. While all these forms can be called as hidden, conjugated, and bound, the term masked is used only for plant metabolites [3,12,27-34].

Mycotoxins have various effects like mutagenic, teratogenic, carcinogenic on eukaryotic organisms [5,35,36]. Epidemiological cases were reported in different regions of Asia (Japan, Korea, China, India) related to the consumption of contaminated cereals and cereal-based foods. The population affected by DON caused outbreaks to trigger especially gastrointestinal disorders in the population [37-39]. DON can cause anorexia, growth retardation, immune dysregulation, altering neuroendocrine signaling, proinflammatory gene induction, and disruption of the growth hormone axis. At the cellular level, DON can inhibit protein synthesis; can disrupt cell signaling, differentiation and proliferation; and even can cause death [40-42]. ZEN, on the other hand, has a toxic effect on the endocrine and reproductive system and also shows developmental toxicity. Due to its estrogenic activity, it most affects the reproductive organs and their functions [43,44]. The natural and artificial DON and ZEN intakes are resulted in accumulation of these mycotoxins in organs, tissues and biofluids of animals and humans. DON is detected in urine, ZEN in the endometrium, ZEN and α-ZEL in the blood of humans, whereas DON, ZEN, and their metabolites can be found in almost all animals' tissues and organs.

Interestingly, these mycotoxins also appear in hen eggs, cow and sheep milks, chicken meat, fish [45,46], which are consumed as a food. Therefore, people are exposed to mycotoxins not only through plants but also through animals.

Table 1: Masked forms of DON and ZEN in cereals.

Toxin	Product
deoxynivalenol-di-hexoside (DON-di-hexoside)	wheat [28]
deoxynivalenol-malonyl-glucoside (DON-MalGlc)	wheat [28]
deoxynivalenol-S-glutathione (DON-S-glutathione)	wheat [28]
deoxynivalenol-2H''-S-glutathione (DON-2H"-S-glutathione)	wheat [28]
15-acetyl-deoxynivalenol-3-glucoside (15-ADON-3G)	wheat [28]
deoxynivalenol-S-cysteinyl-glycine (DON-S-cys-gly)	wheat [28]
deoxynivalenol-S-cysteine (DON-S-cys)	Wheat [28]
deoxynivalenol-3-sulfate (DON-3S)	wheat [29]
deoxynivalenol-15-sulfate (DON-15S)	wheat [29]
zearalenone-4-glucoside (ZEN-4G)	wheat, maize, oats, cereals [30-32]
α-zearalenol-4-glucoside (α-ZEL-4G)	wheat, maize, oats [32]
β-zearalenol-4-glucoside (β-ZEL-4G)	wheat, maize, oats [32]
zearalenone-16-glucoside (ZEN-16G)	barley, wheat, oats [33,34]
zearalenone-4-sulfate (ZEN-4S)	wheat, maize, oats [32]
zearalenone-14-sulfate (ZEN-14S)	barley, wheat, oats, maize [32,34]

In addition to main forms, masked endotoxins co-occur as contamination agents of foods and feeds. Masked mycotoxins exhibit lower toxicity than their free forms. This attenuated toxicity of masked forms was demonstrated *in vitro* in mammalian cell lines. Distinct intestinal epithelial (the piglet IPEC-J2, the human Caco-2) cell lines were treated with DON and DON-3G, it was detected that DON reduced cell viability, whereas DON-3G showed no cytotoxic effect on these cell lines. Moreover, non-cytotoxic concentration of DON induced a significant decrease in trans-epithelial electrical resistance (TEER), by contrast DON-3G did not decrease TEER. In addition, differentiated cells were more resistant to DON and DON-3G than the proliferative cells [47,48]. It was also confirmed that DON-3G displayed no cytotoxic effect on human gastric epithelium (GES-1) cells [49]. Likewise, the viability of Caco-2 cells, exposed to ZEN and to its masked forms, was not significantly affected. Intestinal transfer of two glucosylated masked forms of ZEN (ZEN-14G and ZEN-16G) revealed that intestinal cells took these masked forms up, and then ZEN was released by enzymatic cleavage [50,51]. ZEN-14G showed no effect on human breast cancer (MCF-7) cells. Also, these cells converted of ZEN-14G to several common aglycones with xenoestrogen activity and all of these metabolites ultimately occasioned the toxic impact [1].

Besides, *in vitro* toxicity studies were conducted through imitating organism's fluids [52]. Artificial digestive juices (saliva, gastric juice, duodenal juice, bile) exhibited no capacity to hydrolyze masked forms (DON-3G, ZEN-14G, and ZEN-14S) of *Fusarium* mycotoxins. Acidic hydrolysis and enzymatic simulations of lower gastrointestinal (GI) tract also showed no ability to regenerate main forms [53-57]. It was demonstrated that DON-3G was not hydrolyzed in the stomach of mammals and also by human cytosolic glucosidases. Fungal cellulase and cellobiose preparations carry out the partial cleavage, while several lactic acid bacteria such as *Lactobacillus plantarum, Enterococcus durians, Enterococcus Mundie* have significant capacity to hydrolyze of DON-3G (*in vitro*) [53]. Thus, specific intestinal microbiomes consisting of various bacterial species are able to transform masked mycotoxins to their parent forms [58]. The investigation of ZEN-14G metabolism in liver microsomes (*in vitro*) of several animals (rats, chickens, swine, goats, cows) and humans indicated that the hydrolysis of the masked form occurred via the main metabolic pathway, which include reduction, hydroxylation and glucuronic acid (GlcA) conjugation [59]. Human's fecal microbiota (*in vitro*) are able to deconjugate masked mycotoxins DON-3G, ZEN-14G, ZEN-14S, and thereby to release toxic aglycones and generate unspecified catabolites. The released main mycotoxins, as a result of masked forms transformation, lead to an increase in the toxic effects in exposed individuals. For this reason, masked mycotoxins should be also included in the consideration during the evaluation of the population exposed to mycotoxin [55,60].

The intrinsic toxicity study revealed that oral uptake of DON-3G in rats was hardly hydrolyzed in the stomach, whereas ZEN-14G was rather unstable in the stomach and formed the main form ZEN. The intense hydrolysis of DON-3G, ZEA-14G to their main forms was detected in the intestine [61]. Studies on pigs (*in vivo*) related to conversion of masked mycotoxins (DON-3G) to their main forms indicated the hydrolyzing of DON-3G in the distal small and large intestine [62]. Likewise, it was exhibited that this masked form was cleaved during digestion in rats and pigs (*in vivo*), and recovered as DON, which subsequently excreted in feces and urine [63,64]. Additionally, oral uptake of ZEN-14G and ZEN-16G in piglets showed that these masked forms were converted in the digestive tract to the ZEN, which then was detected in feces and urine [65]. After intravenous and oral administration of α-ZEL and α-ZEL-14G on rats' plasma, a large extent of ZEN, α-ZEL and GlcA conjugates detected as a result of transformation. Despite the fact that the oral bioavailability was exceedingly low, ZEN, α-ZEL, ZEN-14G are able to instigate toxicity after hydrolysis. Consequently, low oral bioavailability of masked mycotoxins does not have a correlation with limited toxicity [59,66]. Although earlier findings showed the lower toxicological relevance of masked forms compared to main mycotoxins, recent studies with intravenous and oral administration highlighted the systemic exposure of organisms depending on the releasing considerable level of main forms [67]. As can be understood from these examples, the intestinal microbiome plays a major role in the chemical modification of masked mycotoxins also in humans. In conclusion, masked forms of *Fusarium* mycotoxins can be reconstructed to free forms during digestion and thus potentially increase the risk of these forms for humans and animals. Considering all of these risks, the Panel on Contaminants in the Food Chain of the European Food Safety Authority concluded that the modified forms of mycotoxin must be valued with the similar toxicity of its main form [58,68,69].

Conclusion

Food safety has great importance in the maintenance of human health and wellbeing. For this reason, it is essential to prevent the contamination with DON and ZEN, the foodborne *Fusarium* endotoxins, which is a major concern all over the world. Originating from this point, we tried to highlight the different toxic effects of these two major toxins and their masked forms by comparing the *in vitro* and *in vivo* studies. Although *in vitro* studies show that masked forms have a lower toxic effect on animal and human cells than main mycotoxins, *in vivo* studies have demonstrated that masked forms have significant toxicity due to their conversion to the free form by enzymatic reactions. Since these toxins cause losses in agricultural production and various human health problems, unexpected toxicity of masked forms should be considered. Therefore, identification of toxin types and its masked forms in agricultural products and then measurement of the exposure to them by using validated biomarker analysis or PCR-based approaches have great importance for the risk management. The *Fusarium* outbreaks which strongly correlated to climate change lead to inevitably spreading of its mycotoxin in food and feed. Moreover, transporting

agricultural goods causes the spreading of *Fusarium* species, and the increase in contaminated human and animal numbers by these secondary metabolites, which previously influence in definite regions. In agricultural areas, levels of mycotoxins and their masked forms should be screened routinely and continuously with rapid diagnostic kits. However, the most important approach for controlling mycotoxins and their harmful effects is fighting against *Fusarium* species in agricultural areas. In this context, various strategies, such as breeding of *Fusarium* resistant plant species, crop rotation and using synthetic or natural fungicides, have been used for the management of *Fusarium* outbreaks.

Conflict of Interest

The authors have declared no conflict of interest.

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