Biocatalytic transformation of various mycotoxins: modern problems and existing potential

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Abstract. A number of microorganisms and some plants have biochemical mechanisms of protection against the toxic effects of mycotoxins. The transformation of mycotoxins in the cells of these organisms is catalyzed by a number of enzymes, including oxidases, peroxidases, lactone hydrolases, laccases, lipases, amidases, aminotransferases, etc. recombinant variants of enzymes obtained by cloning the genes encoding these enzymes. The enzymes are basis for the development of new effective materials with decontamination activity against different micotoxins. The investigation and knowledge about the properties of the enzymes, sources of their isolation and specificity of their action as well as products of reactions catalyzed by them compose the modern scientific base for creation of new effective protective means (sorbents, fabrics etc.).

1. Introduction

Mycotoxins compose a large group of secondary metabolites of filamentous fungi, affecting agricultural products. (Table 1). As a rule, mycotoxins are highly stable compounds that are not degradable even at high temperatures, so they can be detected in heat-treated foods. These compounds pose a serious danger to humans and animals, have carcinogenic, immunosuppressive and teratogenic effects, causing various kinds of acute and chronic serious diseases (Table 1) [1-4].

The most toxic among the known mycotoxins are aflatoxins (AF), ochratoxin A (OTA), fumonisins (F), deoxynivalenol (DON) and other trichocytes, zearalenone (ZEA), patulin (PAT) and ergot alkaloids [5].

The toxicity of mycotoxins is determined by the combination of chemical groups present in their molecular structures (Table 2), capable of participating in chemical reactions. So, the common toxic link in the molecules of P and AF is the coumarin fragment, and the similarity of the structure of AF, ZEA P is determined by the presence of a lactone ring. Carboxyl derivatives, making a significant contribution to the overall toxicity of mycotoxins, are also often present both in the lactone part and in other fragments of the structure of these compounds.

A number of microorganisms, including pro- and eukaryotes, capable of carrying out biological modification or transformation of mycotoxins, have been isolated and studied [6-8]. Despite the large number of studies on the biological detoxification of mycotoxins, there is no much information about the selected individual enzymes that are capable of catalyzing this process.

Enzymatic catalysis holds a special place among approaches that can be used to detoxify mycotoxins [9]. A distinctive feature of the enzymatic detoxification is its specificity. Enzymes that specifically act on various functional groups of mycotoxins and belong to different classes are presented in Table 2.
Owing to economic point of view, most of the scientific investigations are devoted to enzymatic
destruction of most significant mycotoxins: AF, OT, ZEA, DON, F and PAT [10].

It is interesting the use different functional materials that are based on the use of enzymatic
nanobiocatalysts that catalyze the detoxification of mycotoxins. They can have functioning under
physiological conditions with high efficiency and specificity of action, and, like all catalysts, can be
introduced into the reaction medium in much smaller amounts as compared to the substrates
transformed by them. The stability of such enzymes can be realized via creation of polyelectrolytic
complexes with various polyanions or polycations [11-15]. The activity of enzymatic preparations is
usually high enough in such complexes, but noncovalent variants are preferable, since it is not
necessary to additionally use different toxic coupling agents.

### Table 1. The most commonly detected mycotoxins in various agricultural products [1-4]

| Type of toxin | Producer | Pollution objects | Tolerable daily intake | Toxic effect |
|---------------|----------|------------------|-----------------------|-------------|
| AF | Aspergillus flavus, A. niger, A. parasiticus, A. pseudotamarii A. alliaceus, A. auricomus, A. carbonarius, A. glaucus, A. melleus, A. niger, A. ochraceus, Penicillium cyclopium, P. verrucosum, P. viridicatum Fusarium culmorum, F. crookwellense, F. equiseti, F. graminearum, F. pteronii, F. poverticillioide | Grains, tobacco, peanuts, pistachios, cassava, cottonseeds and oilseeds, milk | 0.15 g/kg | Liver damage, genotoxicity, oncogenic immunosuppression |
| OT | A. alliaceus, A. auricomus, A. carbonarius, A. glaucus, A. melleus, A. niger, A. ochraceus, Penicillium cyclopium, P. verrucosum, P. viridicatum Fusarium culmorum, F. crookwellense, F. equiseti, F. graminearum, F. pteronii, F. poverticillioide | Grains, grapes, currants, nuts, dried fruits, coffee, cocoa, spices, red wine | 14 ng/kg | Kidney damage, genotoxicity, carcinogenicity, immunosuppression |
| ZEA | F. culmorum, F. graminearum | Grains, walnuts | 0.25 µg/kg | Estrogenic, reduced reproductive function |
| DON | F. culmorum, F. graminearum F. anthophilum, F. dlamini, F. oniliforme, F. napiformel, F. nygama, F. proliferatum, F. verticillioide | Cereals, hops | 5 µg/kg | Gastrointestinal disorders, reduction of reproductive function, immunosuppressive effect, neurochemical disorders in the brain |
| FB1 | Cereals, beans, asparagus | 2 µg/kg | Central nervous system damage, liver damage, genotoxicity, immunotoxicity |
| PAT | Apples, pears, grapes, cherries, blueberries, cereals, greens | 0.43 µg/kg | Central nervous system damage |
2. Aflatoxins (AF)
AF are produced by fungi of the genus *Aspergillus*, belong to the class of furanocoumarins (Table 2) [6]. The toxicity of AF is associated with the presence of a lactone ring, the splitting of which produces a series of non-fluorescent products with low biological activity. The groups of enzymes that can detoxify aflatoxins include laccases, peroxidases, oxidases, etc.

Several studies have described the possibilities of modifying the difuran ring *in vitro* under the action of individual enzymes. Manganese-containing peroxidase (Mn-peroxidase) (EC 1.11.1.13) was isolated from the white rot fungus *Phanerochaete sordida* YK-624 [16]. The maximum reached detoxification efficiency of AFB1 was 69.2% in 48 h in the presence of this enzyme. AFB1 is firstly oxidized to AFB1-8,9-epoxide and then is hydrolyzed to AFB1-8,9-dihydrodiol, a compound that is significantly less mutagenic than the original mycotoxin. A similar transformation pathway for AFB1 was observed under the action of enzymes isolated from the fungus *Armillariella tabescens* [17].

| Type of toxin | Structure | Enzyme for detoxification | References |
|--------------|-----------|---------------------------|------------|
| AFB1         | ![AFB1 Structure](image) | Mn-peroxidase, Aflatoxide oxidase, Laccase, F$_{420}$H$_2$-dependent reductase | [16-28] |
| OTA          | ![OTA Structure](image) | Carboxypeptidase A, Lacton hydrolase, Lipase | [34-38] |
| ZEA          | ![ZEA Structure](image) | Lacton hydrolase, Unspecified a/b-hydrolase, Peroxiredoxin, Cytochrome, Fimbrial protein precursor | [41-47] |
| DON          | ![DON Structure](image) | 3-O-acetyltransferase, UDP glycosyl transferase, Cytochrome P-450, FAD-dependent ferredoxin reductase, ferredoxin [2Fe-2S] | [54-57] |
| F            | ![F Structure](image) | Carboxyl esterasise, Aminooxidase, Aminotransferase | [63-67] |
As a result of incubation in the presence of aflatoxin-detoxifying enzyme (ADTZ), produced by tabescens (E20), toxicity and mutagenicity of AFB1 were completely eliminated [18]. The enzyme "opened" the furan ring AFB1, which led to the subsequent hydrolysis of this mycotoxin [19]. This enzyme is assumed to be a new kind of aflatoxoxidase (AFO), which has more similarity to hydrolases, such as dipeptidyl peptidase III (EC 3.4.14.4), than oxidases that can destroy APV1 such as fungal laccase or horseradish root peroxidase [19]. AFO from the fungus A. tabescens can hydrolyze a furan ring of the molecule AFB1 [20]. It is believed that this enzyme acts on the 8,9-unsaturated carbon-carbon bond in the AFB1 molecule. AFO is an oxygen-dependent enzyme, as a result of which hydrogen peroxide is formed, which, apparently, also plays a significant role in detoxifying AFB1. The extremely low Km value (0.33 μM) determined for this enzyme indicates the high specificity of this oxidase in relation to this mycotoxin. Some attempts are known to produce a recombinant AFO enzyme from A. tabescens [21]. Such recombinant protein with specific activity of 234 units/mg detoxified AFB1 under optimal conditions (pH 6.0 and 30 °C). Km for this reaction was 39.3 μM. Mn-peroxidase with a specific activity of 78 units/mg isolated from the culture filtrate of the fungus Pleurotus ostreatus could effectively detoxifying AFB1. The maximum efficiency of degradation of AFB1 (1 mM) was observed with enzyme activity of 1.5 units/ml and was 90% after 48 h [22].

An enzyme was isolated rom the cultural medium of the fungus Pleurotus ostreatus, and it destroyed AFV1 in the presence of H₂O₂ [23]. During the incubation of AFB1 with this enzyme, the intensity of fluorescence decreases, which was due to the rupture of the lactone ring. It is known that laccases (EC 1.10.3.2) are able to detoxify AFB1. Pure laccase preparations: the enzyme isolated from the saprophytic fungus Trametes versicolor, as well as the recombinant enzyme produced by A. niger D15-Lcc2 # 3, provided 87.34% and 55% degradation of AFB1 during 72 h, respectively [24].

The effectiveness of the degradation of mycotoxin AFB1 under the action of a commercial laccase from the fungus T. versicolor was 67% for 2 days, while the prooxidant properties and mutagenicity of the products of degradation were significantly less pronounced than the initial toxin [25].

The efficiency of degradation of AFB1 (1 mg / ml) under the action of the isoenzyme (Lac2) of laccase, produced by the fungus Pleurotus pulmonarius, was 23%. In the presence of acetosyringing redox mediator (10 mM), the efficiency of degradation of AFB1 during 72 h of incubation at 250°C reached 90%, and AFM1 (0.05 mg/ml) under same conditions was completely destroyed. The authors of the study suggested that in this case there is oxidative demetoxylation [26].

Aflatoxin-detoxifying enzymes of bacterial origin are also known, for example, F420-dependent oxidoreductase from Mycobacteria smegmatis cells, reducing AF and other furanocoumarins, which is followed by the subsequent spontaneous hydrolysis of lactones. The efficiency of degradation of aflatoxins AFG1 and AFM1 after 48 h of incubation in the presence of this enzyme (100 units/ml) was 96.6 and 95.8%, respectively. This mechanism and products of AF degradation have not been established in this case [27].

F₄₂₀H₂-dependent reductases from Mycobacteria smegmatis have been identified and characterized. The most active against AFB1 was the recombinant protein FDR-A MSMEG_5998, the catalytic characteristics of which Km and Kcat were 47 mM and 63 min⁻¹, respectively. As compared to AFO [20] this enzyme was less specific to AFB1, but had a higher catalytic activity [28].

Contrary to AFO [16] or Mn–peroxidase [16], catalyzing the destruction of the difuran site of the AFB1 molecule, F₄₂₀H₂-dependent reductases catalyze α,β-unsaturated double bond between C-2 and C-6, which leads to destabilization of the lactone ring of this structure [28].
3. Ochratoxins (OT)

OT are a group of mycotoxins, which are coumarin derivatives, produced by some types of microscopic mold fungi of the genus *Aspergillus* and *Penicillium*, which infect grain crops, grapes, coffee, and cocoa, are found in the products of their processing due to the high thermal stability of these compounds [29]. The most common and toxic is OTA, which is a phenylalanyl derivative of isocoumarin. In the OTA molecule, the isocoumarin site - охратоксин α - is linked to an L-β-phenylalanine amide bond (Table 2) [30].

OTA toxicity is mainly associated with the isocoumarin fragment of the molecule. The carboxyl group of the phenylalanine part, as well as the group containing Cl, also contributes to the toxicity of OTA [31]. Biological destruction of OTA can be carried out by hydrolysis of the amide bond under the action of non-specific peptidases, for example, carboxypeptidase A, with the formation of L-β-phenylalanine and OT α, a compound that is much less toxic than OTA [32].

The second, hypothetical, pathway for OTA destruction involves the destruction (rupture) of the lactone ring of this mycotoxin molecule by the action of lacton hydrolase [33]. The first OTA hydrolysis enzyme described in the literature was carboxypeptidase A (EC 3.4.17.1) from the bull pancreas [34]. The kinetic characteristics of this enzyme in the hydrolysis of ochratoxins are \( K_m = 5.6 \) and \( 266 \) mM, and \( K_{cat} = 36.8 \) and \( 2717 \) min\(^{-1}\), for ochratoxins A and B, respectively.

The enzyme produced by the nonhochogenic strain *A. niger* MUM 03.58 was isolated, hydrolyzing OTA to ochratoxin α, \( V_{max} \) of which was equal to \( 0.44 \) mM /min, and \( K_m = 0.5 \) mM. The activity of this enzyme, as in the case of carboxypeptidase A, was inhibited by a chelating agent (EDTA), while the serine proteinase inhibitor did not affect the properties of the enzyme, which indicates that this enzyme is a metalloproteinase similar in properties to carboxypeptidase A [35].

The specific activity of recombinant amidase produced by *A. niger* was equal to 900 nmoles of OTA per min/mg protein at pH 7.0 and 40°C with an initial concentration of OTA equal to \( 1 \) µg/ml. The efficiency of OTA degradation (160 pg/ml) under the action of this enzyme in 0.5 h of incubation reached 83% [36].

Lipases are known to break down amide bonds [37]. Screening was made among 23 lipases and esterases from various sources for OTA degradation. A commercial lipase preparation from the *A. niger* fungus hydrolyzed OTA with the formation of phenylalanine and OT α. The activity of the purified enzyme with respect to OTA was 2.32 units/mg and the degradation efficiency was 95% for 2 h [38].

4. Zearalenone (ZEA)

ZEA is nonsteroidal estrogenic mycotoxin, secondary metabolite of anamorphic mold fungi of the genus *Fusarium*, developing on plants living in a warm and humid climate, as well as on agricultural products during storage conditions [39]. ZEA toxicity is determined by the presence of a lactone ring and C4-hydroxyl groups in its structure (Table 2) [40]. The ZEA peculiarity is that its transformation products (α-zearalenol and β-zearalenol), like other members of the ZEA family, have similar or more pronounced estrogenic properties [32].

The destruction of the lactone ring ZEA can be carried out in two ways with the formation of different end products. In the first case, under the action of lacton hydrolase produced by *Clonostachys rosea* IFO 7063 [41, 42] ZEA was transformed into a significantly less estrogenic compound 1-(3,5-dihydroxyphenyl)-10′-hydroxy-1′-undecen-6′-one. This enzyme catalyzed the hydrolysis of the ester bond in the lactone ring, followed by spontaneous decarboxylation.

From the mycelium of the fungus *C. rosea* IFO 7063, a portion of the gene encoding the amino acid sequence of this protein was isolated and cloned into *E. coli* BL21 (DE3). At 30°C, the catalytic constant for the recombinant ZHD101 enzyme was 0.51 s\(^{-1}\). When the mixture consisting of ZEA, α-zearalenol and β-zearalenol (at a concentration of \( 2 \) µg/ml) was incubated in the presence of recombinant *E. coli* cells carrying the zhd101 gene, the concentration of all mycotoxins decreased to zero as a result of 1 h of incubation [43].
The second pathway for destruction of the lactone ring was established for basidial *Trichosporon mycotoxinivorans* sp. nov. cells [44]. The product of degradation of Z cells of *T. mycotoxinivorans*, was identified and designated as ZOM-1. It is presumably in this case, the gap of the lactone ring occurs under the action of by unspecified a/b-hydrolase in the region of the C6-ketone group. At the same time, carboxyl and hydroxyl groups are formed, which is not accompanied by decarboxylation, in contrast to what occurs when ZEA degrades under the action of the fungus *Gliocladium roseum*. The degradation product of ZEA is ZOM-1 and it does not possess estrogenic activity.

From the culture filtrate *A. niger* FS10, capable of effectively detoxifying ZEA, an active fraction was isolated containing 3 proteins with a molecular weight in the range of 30–150 kDa. The effectiveness of ZEA detoxifying in the presence of the indicated fraction was about 90% of the initial concentration of ZEA in the incubation medium. One of the proteins found in the active fraction of the culture filtrate was identified as hydrolase [45]. This fraction was immobilized using rice husk as a carrier [46]. The rates of degradation of ZEA under the action of free and immobilized enzyme preparations were similar, however, the immobilized preparation significantly exceeded the free enzyme in stability at different pH and temperature values, as well as in the level of activity preservation during storage at different temperatures. The effectiveness of detoxifying ZEA with an immobilized enzyme preparation in artificial gastric juice and intestinal fluid was 75.5% and 90.4%, respectively.

The active fraction was isolated from the culture filtrate of the bacterium *Acinetobacter sp*. SM04, able to effectively degrade ZEA with the formation of a number of less estrogenic products [47]. The structure of the two detected products (ZEN-1 and ZEN-2) indicates that under the action of the enzymes of this fraction, the lactone ring of ZEA is split into products containing carboxyl groups. Three enzymes were identified in this fraction, identified as peroxiredoxin and, presumably, cytochrome and fimbrial protein precursor [47].

5. Deoxynivalenol (DON)

DON is one of main mycotoxins produced by some phytopathogenic fungi of the genus *Fusarium* [48], infecting cereals and causing fusariouise [49]. The main structure of the molecule that determines the toxicity of DON, as well as other trichocenic mycotoxins, is epoxy ([55]).

Some microorganisms destructing the DON are known, however, individual enzymes from these bacteria were not yet isolated. However, these strains are definitely of great interest as a source of enzymes and genes encoding them for use in detoxification processes of DON [50-53].

The second toxic determinant in the DON molecule is the hydroxyl group in C3-position. All modifications of C3-OH in the DON molecule, known to date, reduce the toxicity of this compound. The most studied modification of the site is acetylation, catalyzed by 3-O-acetyltransferase from *Fusarium graminearum* and related species [54], and glycosylation, a reaction catalyzed by a UDP glycosyltransferase from the *Arabidopsis thaliana* plant, which transfers glucose from UDP glucose to the hydroxyl group of the C3- in the DON molecule [55].

The structure and kinetic characteristics of two recombinant acetyltransferases FsTRI101 and FgTRI101, encoded by the TR1101 genes in the cells of the fungi *F. sporotrichioides* and *F. graminearum*, respectively, were investigated. Km, kcat, kcat / Km for FsTRI101 and FgTRI101 with respect to DON were 1.463 μM, 28 s⁻¹ and 1.7 x 10⁷ M⁻¹ s⁻¹ and 11.7 μM, 13.5 s⁻¹ and 1.2 x 10⁶ M⁻¹ s⁻¹, respectively. The in vitro enzyme specificity of the enzyme (kcat / Km) with respect to DON in TRI101 from *F. graminearum* was 70 times higher than that of this enzyme from *F. sporotrichioides*. Significant differences in catalytic properties are explained by differences in the structure of active centers of these enzymes [56].

Some enzymes (cytochrome P-450, FAD-dependent ferredoxin reductase, and ferredoxin [2Fe-2S]) were isolated from bacterial cells *Sphingomonas* sp. PC. KSM1 and involved in the DON transformation. The catalytic efficiency of such an enzyme system (kcat/Km) was 6.4 mM⁻¹ s⁻¹ in reaction with DON, and DON detoxification product was identified as 16-hydroxy-DON [57].
6. Fumonisins (F)
FB1, FB2, FB3 are secondary metabolites of fungi of the genus Fusarium that infect cereals, as well as A. niger fungi, which are often found on grapes [58]. The toxicity of FB1 is determined by the presence of two side chains in its structure, which are tricarballylic acid, and also by the presence of free amino groups (Table 2) [59].

Biological detoxification of FB1 includes at least two enzymatic stages. The process begins with deesterification, as a result of which the lateral units in the PV1 molecule, which are tricarballylic acid, are cleaved from the main chain, resulting in a compound, hydrolyzed fumonisin (HFB1), also known as aminopentol 1 (AP1), in the second stage deamination occurs received HFB1 [60]. HFB1 is significantly less toxic than FB1 [61], but it is a rather dangerous substance, since the N-acylated metabolites of this compound are even more toxic than the original F [62].

The first step in the hydrolysis of FB1 in pro- and eukaryotic microorganisms is catalyzed by carboxylestrase (EC 3.1.1.1) [63-64]. In the second stage, the resulting GFB1 is deamidated. In the case of the black yeast strain Exophiala spinifera, the second stage is catalyzed by aminooxidase, the necessary condition for the functioning of which is the presence of molecular oxygen in the medium, and H2O2 is formed as a by-product [63]. Deamination occurs under the action of aminotransferase in bacterial strains [60, 65].

The fumD gene encoding carboxylesterase in the cells of the bacterium Sphingopyxis sp. MTA144 was cloned and expressed in Pichia pastoris yeast. Km for this enzyme was 0.90 μM, and catalytic constant was 900 s⁻¹ [66].

The properties and kinetic characteristics of the recombinant enzyme (aminotransferase) produced by the transgenic E. coli strain carrying the fumI gene encoding the synthesis of aminotransferase in Sphingopyxis sp. MTA144. The final product of the degradation of HFB1 under the action of the fumI-aminotransferase was 2-keto-HFB1. It was established that the preferential co-substrate and the amino group receptor in the HFB1 deamination reaction for the purified His-tagged FumI enzyme is pyruvate (Km = 490 μM at a HFB1 concentration of 10 μM). Under optimal conditions, in the presence of 5 mM pyruvate as a co-substrate, Km and kcat of this enzyme were 1.1 μM and 104 min⁻¹, respectively [67].

7. Patulin (PAT)
PAT is pyran derivative (4-hydroxyfuropyranone), triketid, water-soluble secondary metabolite of fungi genus Penicillium, Aspergillus and Byssochlamys spp. [68-69], affecting fruits, and contaminating the products of their processing. Detoxification of PAT can occur due to the rupture of the pyran ring with the formation of E-ascadiol - the biosynthetic precursor of PAT, and/or its isomer Z-Ascladiol, as well as by breaking the lactone ring with the formation of deoxypatulinic acid (Table 2).

Enzymatic transformation of PAT was detected in a number of bacterial and yeast strains. Among such microorganisms, the yeast Rhodospiridium kratochvilovae performs biodegradation of PAT with the formation of deoxypatulinic acid (DPA) a product is not toxic for various microorganisms and the cell culture of human lymphocytes [70]. Bacteria Gluconobacter oxydans [71], yeast S. cerevisiae [72] and lactobacterium Lactobacillus plantarum transforming PAT to E- or Z-ascadiol [73], as well as basidiomycetes, the yeast Sporobolomyces sp. strain IAM 13481, belonging to the Pucciniomycotina subdivision, destroying PAT to form two different products: DPA and Z-Ascladiol [74]. It is known regarding the isolation and purification of individual enzymes that detoxify PAT [75], which were isolated from the cells of the yeast Kratochvilova RS. LS11, capable of degrading PAT with the formation of DPA [70]. It is known about the recombinant enzyme His₆-organophosphorus hydrolase, which decomposing some micotoxins including patulin [76-77].

8. Conclusion
A distinctive feature of enzymes as detoxifying agents is their high specificity with respect to mycotoxins. Currently, individual enzymes capable of deep and effective degradation of mycotoxins
have not been widely used in the development of effective means for detoxification of these compounds.

It should be noted that in the case of using enzymes to create materials capable of detoxifying mycotoxins, it is necessary to create stable forms of these proteins, since the environment in which they should function can be quite aggressive. Because the contaminated product is found, as a rule, not one, but several mycotoxins, means that can help in this kind of pollution needs to be sufficiently universal and active in relation to multiple mycotoxins, similar in structure.

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