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Original article

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Evaluation of cytochromes and arylhydrocarbon receptor ligands effect on aflatoxin G_1 genotoxic markers

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ABSTRACT

Introduction. Aflatoxins are highly toxic metabolites produced by *Aspergillus* fungi, with strong carcinogenic and immunosuppressive properties. Their genotoxicity arises from the formation of reactive epoxides during metabolic activation by CYP1A2 and CYP3A4 cytochrome enzymes. The aryl hydrocarbon receptor (AhR) plays a critical role in regulating aflatoxin metabolism and cellular response to toxicity.
This study investigates the genotoxic effects of aflatoxin G_1 (AFG_1) with a focus on its interaction with CYP450 enzymes and AhR, and its impact on DNA repair and apoptosis in human hepatoma HepaRG cells.

Material and methods. Cellular toxicity of AFG_1 was assessed using xCELLigence RTCA impedance analysis, which revealed an LC_{50} value of 9.79 μM. DNA repair activity was analyzed using the Luminex xMAP multiplex technology. The study also evaluated the effects of AhR agonists (FICZ, ITE), an antagonist (CH223191), and CYP inhibitors (α-naphthoflavone for CYP1A2, ketoconazole for CYP3A4) on AFG_1-induced genotoxicity.

Results. AhR ligands exhibited moderate cytoprotective effects, increasing cell viability under AFG_1 exposure. In contrast, CYP inhibitors more effectively reduced activation of DNA repair proteins. The protective role of AhR ligands may involve competitive binding with AFG_1 and modulation of downstream signaling.

Limitations. The study was conducted using a cell culture model; extrapolation of the findings to the whole organism requires consideration of toxicodynamic and toxicokinetic data.

Conclusion. These findings highlight the pivotal role of CYP enzymes and AhR in shaping the genotoxic profile of AFG_1.

Keywords: *aflatoxin G_1; polyaromatic hydrocarbon, arylhydrocarbon receptor; cytochromes; HepaRG; genotoxicity*

Compliance with ethical standards. The study does not require approval from a biomedical ethics committee or any other related documentation.

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Introduction

Aflatoxins are among the principal groups of mycotoxins and are polyketide secondary metabolites produced by several fungal species, including *Aspergillus* (A.) *flavus*, *A. nomius*, and *A. Parasiticus* [1, 2]. Consumption of foods contaminated with aflatoxins can lead to numerous adverse outcomes, including immunosuppression, infertility, endocrine disruption, teratogenesis associated with congenital malformations, and carcinogenesis [3, 4]. It has been reported that 4.6–28.2% of hepatocellular carcinoma cases are attributable to aflatoxin exposure [5].

Aflatoxins exert pronounced genotoxic effects linked to their metabolic activation in the liver. During biotransformation by cytochrome P450 enzymes (primarily CYP1A2 and CYP3A4), highly reactive epoxide metabolites are formed, notably the aflatoxin exo-8,9-epoxide. These compounds covalently bind to DNA, inducing mutations, oxidative stress, mitochondrial damage, apoptosis,

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and lipid peroxidation. Concomitantly, tyrosine kinase signaling cascades are activated, promoting cell proliferation and neoplastic transformation [6–8].

Expression of the cytochrome CYP1A2 is regulated by the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor activated by numerous xenobiotics, including aflatoxins. Owing to their planar configuration, aflatoxins can interact with AhR by binding its PAS-domain and triggering receptor translocation to the nucleus, where it activates transcription of genes encoding xenobiotic-metabolizing enzymes [9]. Beyond cytochrome induction, AhR activation disrupts cellular homeostasis. In particular, it is associated with accumulation of the cell-cycle inhibitor $p27^{Kip1}$ and modulation of the expression of key DNA damage–response proteins, including p53 [10–12].

It is therefore presumed that inhibiting expression of the aforementioned cytochromes and modulating AhR activity should reduce the formation of genotoxic metabolites and minimize DNA damage. The extent to which putative protective compounds influence the genotoxic action of aflatoxins can be assessed by measuring the levels of active forms of DNA repair–system proteins. These include the serine-threonine protein kinases ATR, Chk1, and Chk2; histone H2A.X; the E3 ubiquitin-protein ligase Mdm2; tumor protein p53; and cyclin-dependent kinase inhibitor 1 (p21) [8, 13].

In the present study, we analyzed the genotoxic effects of aflatoxin G_1 (AFG_1). Produced by *A. parasiticus*, AFG_1 is recognized as the second most toxic aflatoxin after aflatoxin B_1 (AFB_1) [7]. The choice of AFG_1 was driven not only by its prevalence in food products [14] but also by the insufficient characterization of its interactions with AhR and P450, especially in the context of their contribution to the initiation of programmed cell death.

The aim of the study was to evaluate the effect of cytochrome CYP3A4 and CYP1A2 inhibitors, aryl hydrocarboxylic receptor agonist and antagonist on intracellular markers of the genotoxic effect of aflatoxin G_1 in HepaRG cells.

Material and methods

Substances used. The following substances were used: aflatoxin G_1 (Sigma, USA); ketoconazole (CYP3A4 inhibitor); α-naphthoflavone (CYP1A2 inhibitor) (Sigma, USA); methyl ester of 2-(1H-indol-3-ylcarbonyl)-4-thiazolecarboxylic acid (ITE) (AhR agonist); 5,11-dihydroindolo[3,2-b]carbazole-6-carboxaldehyde (FICZ) (AhR agonist) (Tocris Bioscience, UK); 2-methyl-2H-pyrazole-3-carboxylic acid (CH223191) (AhR antagonist) (Sigma, USA).

Cell cultivation. Experiments were performed using human hepatoma HepaRG cells (HepaRG™ 5F Control Cells, Sigma-Aldrich, MTOX1010, USA). Cells were cultured in complete growth medium consisting of Williams' E medium (Gibco, USA) supplemented with 10% fetal bovine serum (HyClone, USA), 5 μg/mL insulin (Gibco, USA), 50 μM hydrocortisone hemisuccinate (Sigma, USA), 100 U/mL streptomycin, and 100 μg/mL penicillin (Gibco, USA) at 37 °C in an atmosphere of 5 % CO_2 and 100% relative humidity.

The contents of a cryoprobe with HepaRG cells were rapidly thawed by incubating in a water bath at 37 °C. Cryopreservant was removed by washing the cells in complete medium followed by centrifugation at 200 g (RCF) for 3 min at room temperature. The supernatant was removed by vacuum aspiration, the pellet was resuspended, and the suspension transferred to a culture flask. Upon reaching 70–80% confluence, cells were subcultured into new flasks at $2 \cdot 10^6$ cells per 5 mL of medium. Cells were detached using a trypsin–Versene solution (Biolot, Russia). Cell counts were obtained with a Countess automated cell counter (Invitrogen, USA). Visual assessment of the cell condition was performed using a Zeiss AxioVert inverted microscope (Zeiss, Germany). All procedures were performed under sterile conditions in a Class II laminar-flow biological safety cabinet (Faster, Italy).

Assessment of genotoxicity markers. For genotoxicity assessment of aflatoxin G1, HepaRG cells were seeded in 24-well plates ($0{,}5 \cdot 10^6$ cells per well). After 24 h, the medium was replaced with medium containing additives, and cells were incubated for 48 h at 37 °C in 5% CO_2. The medium was supplemented with 10 μM aflatoxin G_1 and one of the following: (1) 2 μM ketoconazole; (2) 0.5 μM α-naphthoflavone; (3) 10 nM ITE; (4) 100 nM CH223191. In parallel, control cells were cultured without these additions. After incubation, cells were lysed with Cell Signaling Lysis Buffer (Millipore, USA) supplemented with cOmplete™ Roche protease inhibitor (Sigma, USA) and enzyme benzonase (Sigma, USA). Protein concentration was determined by the Lowry method. Genotoxicity markers were analyzed in cell lysates using Luminex xMAP immunofluorescence technology and a set of MILLIPLEXMAP 7-plex DNA Damage / Genotoxicity Magnetic Bead Kit reagents (Millipore, USA). Changes in the content of phosphorylated proteins Chk1 (Ser345), Chk2 (Thr68), H2A.X (Ser139), p53 (Ser15), as well as proteins ATR, MDM2, and p21 were determined.

Cytotoxicity assay. Overall cytotoxicity was assessed using an xCELLigence RTCA system (ACEA, USA). HepaRG cells ($1 \cdot 10^4$ per well) were inserted into the well of a specialized tablet and cultured in a complete Williams medium. On the day after seeding, the

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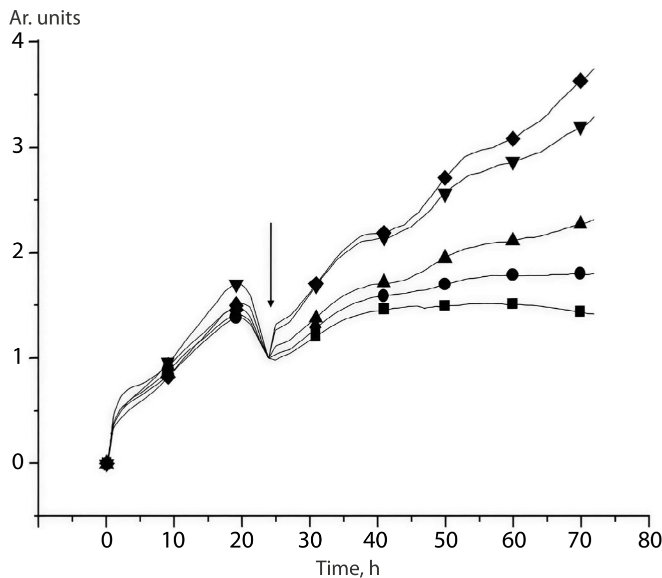


Fig. 1. Time-dependent changes in the normalized cell index (arbitrary units) of HepaRG cells incubated with aflatoxin G_1 (AFG_1) at concentrations of 1 μM, 5 μM, 10 μM, 25 μM, and 50 μM. The arrow indicates the time point at which the compounds were added.

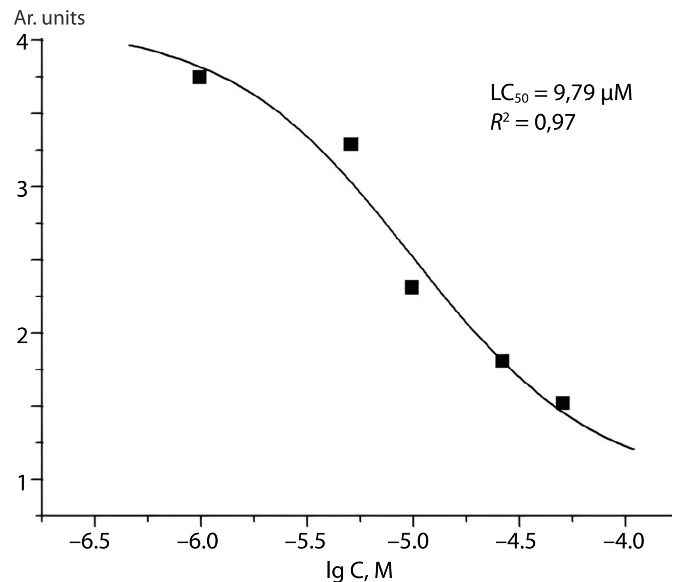
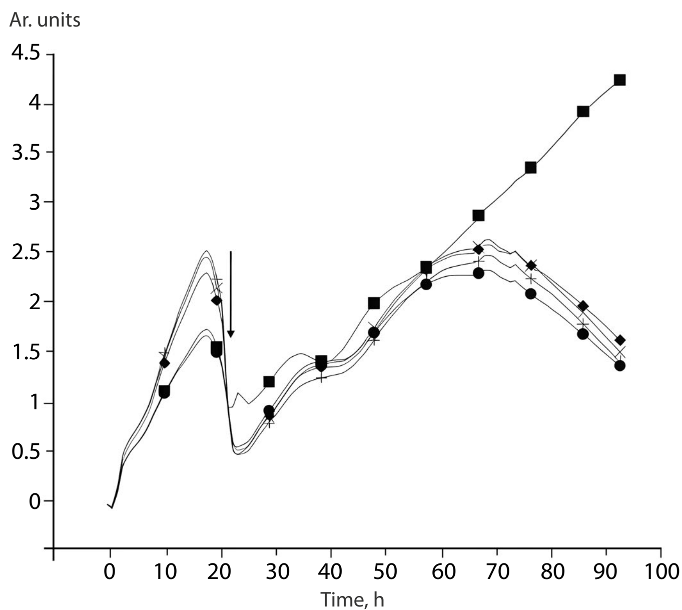


Fig. 2. Normalized cell index (arbitrary units) of HepaRG cells as a function of the logarithmic concentration (M) of aflatoxin G_1 (AFG_1).



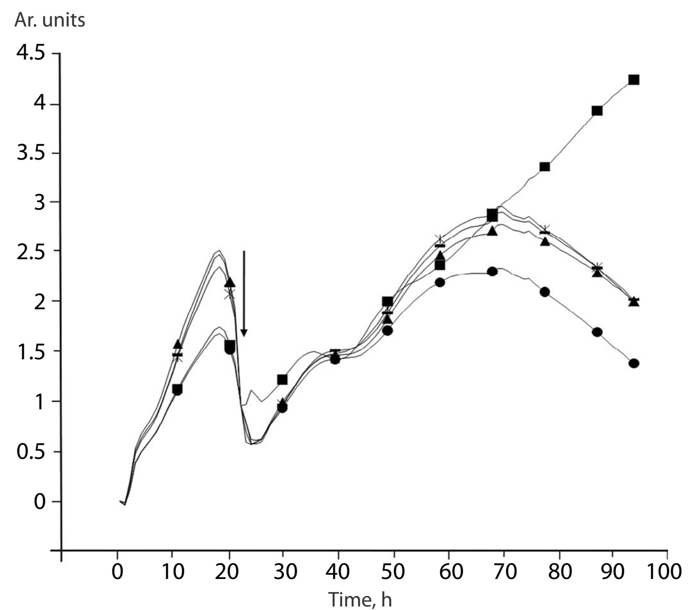


Fig. 3. Time-dependent changes in the normalized cell index (arbitrary units) of HepaRG cells exposed to AFG_1 and its combinations with the following compounds: *a* – Ketoconazole (AFG_1+Ket), α-naphthoflavone (AFG_1 + aN), and a combination of both (AFG_1 + Ket + aN); *b* – CH223191 (AFG_1 + CH223191), ITE (AFG_1 + ITE), FICZ (AFG_1 + FICZ). Untreated cells served as control. The arrow indicates the time point of compound addition.

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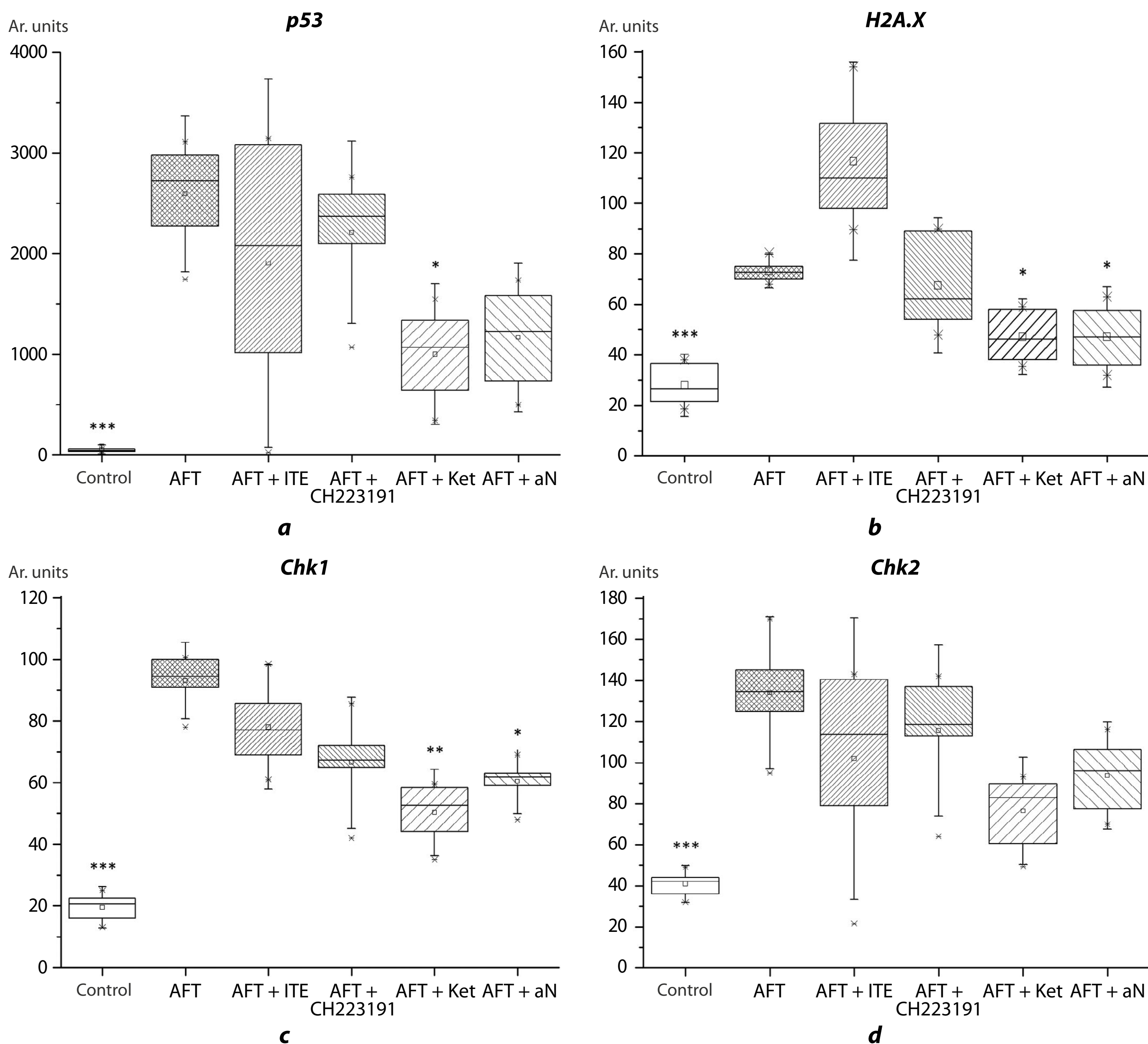

Fig. 4. Fluorescence intensity (FI) (arbitrary units.) (box plot, median, mean, standard deviation (SD)) of the active forms of proteins: *a* – p53 (Ser15); *b* – H2A.X (Ser139); *c* – Chk1 (Ser345); *d* – Chk2 (Thr68). FI was measured in lysates of intact HepaRG cells (control), as well as 48 h after exposure to: AFG_1, a mixture of AFG_1 and ITE (AFG_1 + ITE), a mixture of AFG_1 and CH223191 (AFG_1 + CH223191), (a mixture of AFG_1 and ketoconazole (AFG_1 + Ket), a mixture of AFG_1 and α-naphthoflavone (AFG_1 + aN). * $p < 0.05$ compared with aflatoxin G_1.

medium was supplemented with 10 μM aflatoxin G_1 and one of the following: (1) 2 μM ketoconazole; (2) 0.5 μM α-naphthoflavone; (3) 2 μM ketoconazole plus 0.5 μM α-naphthoflavone; (4) 10 nM ITE; (5) 100 nM CH223191; (6) 1 nM FICZ. In parallel, the cells were cultured under control conditions. After that, the cellular index was monitored for 3 days.

Statistical analysis. Statistical processing of fluorescence intensity data of phosphorylated forms of proteins of the DNA repair system was carried out in the Bio-Plex Data Pro program. Cytotoxicity data were processed in the RTCA SP program. Statistical significance of differences between groups was evaluated using Microsoft Excel and Origin 2021 by one-way analysis of variance (ANOVA). Differences were considered significant at $p < 0.05$.

Results

When aflatoxin G_1 was exposed to HepaRG cells at various concentrations, a direct dependence of the rate of cell death on the concentration of the toxin was observed (Fig. 1).

Next, we determined the half-lethal concentration (LC_{50}) for aflatoxin G_1, which was 9.79 μM (Fig. 2). In this regard, in further experiments, we used an

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aflatoxin G_1 concentration of 10 μM, which is close to a half- lethal concentration.

Aflatoxin G_1 slowed the growth of HepaRG cultures, with the onset of cell death occurring ~50 h after mycotoxin addition, consistent with the time required for metabolic activation. Ketoconazole, α-naphthoflavone, CH223191, ITE, and FICZ reduced cell death in the presence of aflatoxin G_1; among the cytochrome inhibitors, ketoconazole exerted the more pronounced cytoprotective effect (Fig. 3, *a*). AhR agonists and antagonists (CH223191, ITE, and FICZ) generally exhibited stronger protective effects than the cytochrome inhibitors, while not differing from one another (Fig. 3, *b*).

Aflatoxin G_1 significantly increased the levels of phosphorylated forms of proteins of Chk1, Chk2, H2A.X, and p53 in HepaRG cell lysates at 48 h compared with control. Levels of the active forms of p53 and Chk1 were significantly reduced 48 h after incubation with aflatoxin G_1 in combination with α-naphthoflavone or ketoconazole (Fig. 4, *a*, *c*). The level of histone H2A.X phosphorylated at Ser^{139} in cell lysates decreased slightly on the second day of action of AFG_1 mixtures with alpha-naphthoflavone or ketoconazole (Fig. 4, *b*).

Exposure to AFG_1 cells in a mixture with the aryl hydrocarboxylic receptor antagonist CH223191 or with its agonist ITE reduced the level of the active form of the Chk1 protein after 48 hours (see Fig. 4, *c*). At the same time, we detected no changes in the level of phosphorylated forms of p53 and H2A.X (see Fig. 4, *a*, *b*). The content of active Chk2 did not undergo statistically significant changes in any group treated with cytochrome/ aryl hydrocarboxylic receptor ligands compared with AFG1-exposed cells (Fig. 4, *d*).

Discussion

Metabolism of aflatoxin G_1, as with other aflatoxins, involves cytochrome P450 enzymes and the aryl hydrocarbon receptor (AhR). Polycyclic aromatic hydrocarbons (PAHs), such as benzo[a] pyrene (BaP), undergo metabolic transformation via analogous pathways. We previously showed that the CYP3A4 and CYP1A2 inhibitors ketoconazole and α-naphthoflavone reduce the genotoxic effects of BaP in HepaRG cells by limiting formation of its reactive metabolites [8]. Similar findings have been reported for aflatoxin B_1 (AFB_1): incubation of bovine hepatocytes with α-naphthoflavone plus AFB_1 decreased genotoxic metabolite levels [15], and undifferentiated HepaRG cells lacking CYP1A2 and CYP3A4 expression were resistant to AFB_1 [16]. These data suggested that such protection could be implemented with the action of AFG_1.

Our results confirm that ketoconazole and α-naphthoflavone indeed mitigate the genotoxic effects of AFG_1. Their presence in the medium reduced the levels of active DNA-repair proteins, including phosphorylated p53, H2A.X, Chk1, and Chk2, which indicates a lower degree of induced DNA destabilization.

We additionally examined the impact of AhR agonists (ITE, FICZ) and AhR antagonist (CH223191) on AFG_1 toxicity. CH223191 is known to inhibit AhR-mediated signaling, attenuating PAH effects, including reducing lipid accumulation in epithelial cells exposed to benzo[a]pyrene [17]. In the present study, we show that modulation of AhR activity also influences AFG_1 genotoxicity: both agonists and the antagonist decreased expression of DNA-repair proteins, albeit less effectively than the cytochrome inhibitors.

These findings are consistent with literature data on the role of AhR in aflatoxin metabolism. In particular, it has been shown that AFB_1 directly binds to the N-terminal domain of AhR, induces its translocation into the nucleus, activates the expression of CYP1A1 and CYP1A2, promotes the formation of DNA adducts and the accumulation of long-chain fatty acids [18]. At the same time, AhR knockout increased the resistance of cells to AFB_1, which confirms the participation of AhR in the realization of the toxic effect.

It is interesting that the AhR agonists ITE and FICZ, despite the general activation of the signaling pathway, showed some protection. This may be due to competition for AhR binding binding, in which they, having a higher affinity, can partially block the access of AFG_1 to the receptor. In addition, there is evidence that ITE is able to enhance the expression of CYP450 enzymes, thereby paradoxically enhancing AFG_1 metabolism [19]. Our results suggest that the protective effect of AhR agonists is realized due to the balancing effect between the activation of metabolic pathways and blocking of the receptor binding of the toxin.

It is also important to consider the potential role of CYP2A13, previously characterized as a key activator of AFB_1. Zhang et al. [20] demonstrated that stable CYP2A13 expression increases epithelial-cell sensitivity to low doses of AFB_1 and enhances DNA-adduct formation and activation of repair proteins (ATR, Mre11, Rad50, Rad51). Although AFG_1 was the primary toxicant in our study, these data suggest that CYP2A13 may likewise participate in AFG_1 biotransformation alongside CYP1A2 and CYP3A4 [21].

Thus, our findings indicate that cytochrome P450 enzymes and AhR are key targets for reducing AFG_1 genotoxicity. Their inhibition or competitive modulation may represent promising strategies for pharmacological protection during aflatoxin exposure.

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Limitations. This study was conducted the study was conducted using a cell culture model; extrapolation of the findings to the whole organism requires consideration of toxicodynamic and toxicokinetic data.

Conclusion

In this study, we investigated the effects of aflatoxin G_1; the cytochrome inhibitors ketoconazole and alpha-naphthoflavone; the AhR agonists ITE and FICZ; and the antagonist CH223191 on the HepaRG cell line. Aflatoxin exposure increased cell death beginning ~50 h after mycotoxin addition and elevated levels of DNA-repair pathway proteins. The most noticeable cytoprotective effect in the genotoxic action of aflatoxin was demonstrated by alpha-naphthoflavone and ketoconazole. They reduced the number of dying cells and led to less activation of the DNA repair system.

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