Pro-proliferative and Pro-migratory Effects of Deoxynivalenol and Zearalenone on Cancer Cells: Postprint

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Date: 2018-12-24T00:00:00+00:00

Abstract

This study aimed to investigate the proliferation-promoting and migration-promoting effects of deoxynivalenol (DON) and zearalenone (ZEN) on human colorectal adenocarcinoma cells (HCT116 cells), human lung cancer cells (A549 cells), and human hepatocellular carcinoma cells (HepG2 cells). A blank control group was established, with ochratoxin A (OTA) used as a positive control. Cell viability and cell migration ability were detected using the thiazolyl blue (MTT) colorimetric assay and cell scratch wound healing assay, respectively. The results showed that: compared with the blank control group, 0.080, 0.400 mol/L OTA could significantly or extremely significantly enhance the viability of HCT116, A549, and HepG2 cells ($P<0.05$ or $P<0.01$), while 50.000 mol/L OTA could extremely significantly reduce the viability of HCT116, A549, and HepG2 cells ($P<0.01$); DON at low concentrations (0.016, 0.080 mol/L) had no significant effect on the viability of HCT116 and A549 cells ($P>0.05$), but could extremely significantly enhance the viability of HepG2 cells ($P<0.01$), while at medium and high concentrations (2.000, 10.000, 50.000 mol/L), DON could extremely significantly reduce the viability of HCT116, A549, and HepG2 cells ($P<0.01$); ZEN at concentrations of 0.016~50.000 mol/L could significantly or extremely significantly enhance the viability of HepG2 cells ($P<0.05$ or $P<0.01$), and ZEN at high concentration (50.000 mol/L) could extremely significantly reduce the viability of HCT116 and A549 cells ($P<0.01$). The results of the cell scratch wound healing assay showed that, compared with the blank control group, treatment with 1, 10 nmol/L OTA, DON, and ZEN for 24, 48 h could extremely significantly promote the migration of HepG2 cells ($P<0.01$). Thus, within the concentration range of 0.016~50.000 mol/L, DON and ZEN exhibited significant proliferation-promoting and migration-promoting effects on HepG2 cells, indicating that DON and ZEN possess potential carcinogenicity in the HepG2 cell line.

Full Text

Effects of Deoxynivalenol and Zearalenone on Promoting Proliferation and Migration of Cancer Cells

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Abstract

This study investigated the effects of deoxynivalenol (DON) and zearalenone (ZEN) on promoting proliferation and migration in human colorectal adenocarcinoma cells (HCT116), human lung cancer cells (A549), and human hepatocellular carcinoma cells (HepG2). A blank control group was established, with ochratoxin A (OTA) serving as the positive control. Cell viability and migration capacity were assessed using methyl thiazolyl tetrazolium (MTT) colorimetric assay and cell scratch wound healing test, respectively. The results demonstrated that compared with the blank control group, 0.080 and 0.400 mol/L OTA significantly or extremely significantly enhanced the viability of HCT116, A549, and HepG2 cells ($P<0.05$ or $P<0.01$), while 50.000 mol/L OTA extremely significantly decreased the viability of all three cell lines ($P<0.01$). At low concentrations (0.016 and 0.080 mol/L), DON had no significant effect on HCT116 and A549 cell viability ($P>0.05$) but extremely significantly enhanced HepG2 cell viability ($P<0.01$). At middle and high concentrations (2.000, 10.000, and 50.000 mol/L), DON extremely significantly decreased the viability of HCT116, A549, and HepG2 cells ($P<0.01$). ZEN at concentrations ranging from 0.016 to 50.000 mol/L significantly or extremely significantly enhanced HepG2 cell viability ($P<0.05$ or $P<0.01$), while at high concentration (50.000 mol/L) it extremely significantly decreased HCT116 and A549 cell viability ($P<0.01$). The cell scratch wound healing test revealed that compared with the blank control group, 1 and 10 nmol/L OTA, DON, and ZEN extremely significantly promoted HepG2 cell migration after 24 and 48 hours of treatment ($P<0.01$). These findings indicate that within the concentration range of 0.016–50.000 mol/L, DON and ZEN significantly promote proliferation and migration in HepG2 cells, suggesting potential carcinogenic-like properties of these mycotoxins in the HepG2 cell line.

Keywords: mycotoxins; cell; proliferation; migration

Mycotoxins are secondary metabolites produced by fungi such as *Fusarium*,

Aspergillus, and *Penicillium* species. Common mycotoxins that pose significant threats to animal husbandry include aflatoxins (AFs), trichothecenes (such as T-2 toxin and deoxynivalenol, DON), zearalenone (ZEN), ochratoxin A (OTA), and fumonisins. These toxins are widely present in food and feed, representing a major global challenge for livestock production, product quality safety, and food security. Iqbal et al. detected AFs, OTA, and ZEN in 35%, 41%, and 52% of chicken meat samples, respectively, and in 28%, 35%, and 32% of egg samples. Gong et al. analyzed 65 corn samples from the Chinese market in 2015, finding that over 90% of samples from southern regions were contaminated with AFB1, ZEN, and DON. Du reported that co-contamination with multiple mycotoxins is common in feed and raw materials, with up to 96.48% of feed and raw materials contaminated by two or more mycotoxins. Long-term exposure to mycotoxins causes severe health effects in humans and animals, including cancer induction, nephrotoxicity, and immunosuppression. Numerous studies using cell models have demonstrated that mycotoxins inhibit cell proliferation, exhibit cytotoxicity, and even induce apoptosis.

According to the International Agency for Research on Cancer (IARC) classification, AFB1 is classified as a Group 1 carcinogen, AFM1 and OTA as Group 2B, while ZEN and DON are classified as Group 3, indicating that their carcinogenic effects remain unclear. China' s current National Food Safety Standard GB 2761−2011 sets maximum residue limits for six toxins in food, including AFB1, AFM1, DON, patulin (PAT), OTA, and ZEN. The limit for ZEN in cereals and cereal products is 60 g/kg, higher than four other toxins except DON (with a limit of 1,000 g/kg). Recent studies have reported that low doses of mycotoxins can promote cancer cell proliferation. For example, T-2 toxin (<0.0096 nmol/L) and OTA (<0.0032 nmol/L) significantly promoted proliferation of Myc gene-transfected human embryonic lung fibroblasts (MRC-5 Myc). The carcinogenic characteristics of certain mycotoxins, particularly ZEN and DON, remain unclear and require further investigation.

Cancer cell proliferation, migration, and invasion are critical indicators for studying tumor malignancy, with epithelial-to-mesenchymal transition (EMT) being a key event enabling cancer cells to acquire metastatic capacity. He et al. investigated IBP' s role in EMT in colon cancer cells by examining proliferation and migration. Abassi et al. found that ZEN promoted proliferation and migration in colon cancer cells, suggesting potential carcinogenicity. Therefore, this study utilized three cancer cell models—HCT116, A549, and HepG2 cells—with OTA as the positive control to investigate the proliferation- and migration-promoting effects of ZEN and DON.

1.1 Test Materials

The HCT116, A549, and HepG2 cell lines were purchased from the National Experimental Cell Resource Sharing Platform, Basic Medical Cell Center, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. OTA, ZEN, DON, methyl thiazolyl tetrazolium (MTT), and dimethyl sulfoxide (DMSO)

were purchased from Sigma-Aldrich (USA). OTA, ZEN, and DON were dissolved in methanol to prepare stock solutions (20 mmol/L) and stored at -20 °C, then diluted to working concentrations with culture medium before use. IMDM medium, McCoy' s 5A medium, DMEM medium, fetal bovine serum (FBS), L-glutamine (200 mmol/L), and penicillin (100 IU/mL)-streptomycin (100 g/mL) were purchased from Gibco (USA).

1.2.1 Cell Culture

HCT116, A549, and HepG2 cells were cultured in IMDM, McCoy' s 5A, and DMEM media, respectively, at 37 °C in a 5% CO incubator with saturated humidity (Nuaire, USA). All media were supplemented with 10% FBS, 1% L-glutamine, and 1% penicillin-streptomycin.

1.2.2 Cell Viability Assay

Logarithmic-phase HCT116, A549, and HepG2 cells were digested with 0.05% trypsin-EDTA solution, after which complete medium was added to terminate digestion. Cells were centrifuged at 1,000 r/min for 5 min, the supernatant was discarded, and cell concentration was adjusted to 1×10 cells/mL with medium. Cells were seeded in 96-well plates at 100 L/well and incubated for 24 h at 37 °C in a 5% CO incubator with saturated humidity. Based on reference studies, treatment groups received 100 L of complete medium containing various concentrations of mycotoxins (OTA, ZEN, DON) at 0.016, 0.080, 0.400, 2.000, 10.000, and 50.000 mol/L, while the blank control group received mycotoxin-free medium (0 mol/L). Each group had six replicate wells, and the experiment was repeated three times. After 24 h of incubation, the medium was removed, and 100 L of 0.5 mg/mL MTT solution was added to each well. Following 4 h of incubation at 37 °C, the supernatant was removed, 100 L of DMSO was added to each well, and the plates were shaken for 10 min. Absorbance at 492 nm (A) was measured using a Sunrise microplate reader (Tecan, Austria). Cell viability was calculated using the formula: Cell viability (%) = (A of treatment group / A of blank control group) × 100.

1.2.3 Cell Migration Assay

Logarithmic-phase HepG2 cells were digested with 0.05% trypsin-EDTA solution, after which complete medium was added to terminate digestion. Cells were centrifuged at 1,000 r/min for 5 min, the supernatant was discarded, and cell concentration was adjusted to 3×10 cells/mL with medium. Cells were seeded in 35 mm diameter culture dishes with markings on the bottom at 2 mL/well and incubated for 24 h at 37 °C in a 5% CO incubator with saturated humidity. A scratch was made perpendicular to the bottom surface using a 10 L pipette tip. The supernatant was aspirated, and cells were washed three times with 1 mL phosphate-buffered saline to remove cell debris. Treatment groups received OTA, DON, and ZEN at 1, 10, and 100 nmol/L, while the blank control group received medium only. Each group had three replicate wells, and the experiment

was repeated three times. Images were captured under a microscope. Based on the collected images, cell scratch healing rate was calculated using the formula: Cell scratch healing rate (%) = [(scratch width at T - scratch width at T) / scratch width at T] × 100.

1.2.4 Statistical Analysis

Data are expressed as mean ± standard deviation. One-way ANOVA was performed using GraphPad Prism 6.0 software, followed by LSD multiple comparisons between groups when significant differences were detected. $P<0.05$ was considered statistically significant, and $P<0.01$ was considered extremely significant.

2.1 Effects of Mycotoxin Type and Concentration on Cell Viability

2.1.1 Effects of Three Mycotoxins on HCT116 Cell Viability

The effects of three mycotoxins on HCT116 cell viability are shown in [Figure 1: see original paper]. Different concentrations of OTA exhibited differential effects on HCT116 cell viability. Compared with the blank control group, low concentrations of OTA (0.080 and 0.400 mol/L) significantly or extremely significantly enhanced HCT116 cell viability ($P<0.05$ or $P<0.01$), demonstrating clear proliferation-promoting effects. In contrast, high concentrations of OTA (10.000 and 50.000 mol/L) extremely significantly decreased HCT116 cell viability ($P<0.01$), showing obvious cytotoxicity. Treatment with 10.000 mol/L OTA reduced HCT116 cell viability to 83.78% of the blank control, while 50.000 mol/L reduced it to 75.06%. Compared with the blank control group, DON at middle and high concentrations (0.400 mol/L) extremely significantly decreased HCT116 cell viability ($P<0.01$). ZEN only extremely significantly decreased HCT116 cell viability at concentrations of 0.400 and 50.000 mol/L ($P<0.01$). Specifically, 0.400 mol/L DON and ZEN reduced HCT116 cell viability to 80.56% and 85.22% of the blank control, respectively. These results indicate that low concentrations (0.016 and 0.080 mol/L) of DON and ZEN do not exhibit proliferation-promoting effects similar to OTA in HCT116 cells.

2.1.2 Effects of Three Mycotoxins on A549 Cell Viability

The effects of three mycotoxins on A549 cell viability are shown in [Figure 2: see original paper]. Compared with the blank control group, OTA at low and middle concentrations (2.000 mol/L) significantly or extremely significantly enhanced A549 cell viability ($P<0.05$ or $P<0.01$), demonstrating clear proliferation-promoting effects. At high concentrations (10.000 and 50.000 mol/L), OTA extremely significantly decreased A549 cell viability ($P<0.01$), with 10.000 mol/L reducing A549 cell viability to 79.81% of the blank control, showing obvious cytotoxicity. Compared with the blank control group, DON at middle and high concentrations (2.000, 10.000, and 50.000 mol/L) extremely

significantly decreased A549 cell viability (P<0.01), with 2.000 mol/L DON reducing A549 cell viability to 69.59% of the blank control. ZEN only extremely significantly decreased A549 cell viability at 50.000 mol/L (P<0.01), reducing it to 73.25% of the blank control. These findings indicate that the minimum concentrations showing cytotoxicity in A549 cells were 10.000 mol/L for OTA, 2.000 mol/L for DON, and 50.000 mol/L for ZEN, resulting in a toxicity ranking of DON > OTA > ZEN. In A549 cells, low-concentration OTA exhibited proliferation-promoting effects, whereas DON and ZEN at these concentrations showed no such effects.

2.1.3 Effects of Three Mycotoxins on HepG2 Cell Viability

The effects of three mycotoxins on HepG2 cell viability are shown in [Figure 3: see original paper]. Compared with the blank control group, OTA, DON, and ZEN at low concentrations (0.016 and 0.080 mol/L) all extremely significantly enhanced HepG2 cell viability (P<0.01), demonstrating clear proliferation-promoting effects. Compared with the blank control group, DON at middle and high concentrations (2.000 mol/L) extremely significantly decreased HepG2 cell viability (P<0.01), showing obvious cytotoxicity. OTA only extremely significantly decreased HepG2 cell viability at 50.000 mol/L (P<0.01), also showing cytotoxicity, indicating that DON is more toxic than OTA. ZEN at concentrations ranging from 0.016 to 50.000 mol/L significantly or extremely significantly enhanced HepG2 cell viability (P<0.05 or P<0.01), demonstrating clear proliferation-promoting effects. These results indicate that the cytotoxicity ranking of the three mycotoxins in HepG2 cells is DON > OTA > ZEN, while low concentrations of DON and ZEN exhibit proliferation-promoting effects similar to OTA.

2.2 Effects of Mycotoxins on HepG2 Cell Migration Capacity

Cell scratch wound healing assays were used to evaluate the effects of 1–100 nmol/L OTA, DON, and ZEN on HepG2 cell migration capacity, with results shown in [Figure 4: see original paper] and [Figure 5: see original paper]. The results demonstrated that compared with the blank control group, 1 and 10 nmol/L OTA extremely significantly promoted HepG2 cell migration after 13, 24, and 48 h of treatment (P<0.01), while 100 nmol/L OTA extremely significantly promoted migration after 24 and 48 h (P<0.01). Both 1 and 10 nmol/L DON and ZEN extremely significantly promoted HepG2 cell migration after 24 and 48 h (P<0.01), with the most pronounced effect observed at 1 nmol/L after 48 h of treatment.

3 Discussion

Mycotoxins exhibit nephrotoxicity, hepatotoxicity, and immunotoxicity, and can cause teratogenic, mutagenic, and carcinogenic effects. Many studies have investigated mycotoxin toxicity and mechanisms using cell models. Mycotoxin

concentration plays a critical role in studies of cellular toxicity and mechanisms. Most research indicates that relatively high concentrations of mycotoxins exhibit obvious cytotoxicity. OTA at 15 mol/L can induce apoptosis in HeLa cells, and concentrations above 15 mol/L show significant cytotoxicity in human lymphocytes. In Abassi' s study, high-concentration OTA showed obvious cytotoxicity in wild-type human colon cancer cells (HCT116 WT), FLIP-overexpressing HCT116 cells (HCT116 FLIP), and MRC-5 Myc cells, with IC values of 170, 120, and 20 mol/L, respectively. Dai et al. reported that DON toxicity to mouse intestinal epithelial cells (ESCs) increased with dose or exposure time within the range of 100–1,600 ng/mL. ZEN at concentrations exceeding 5 mol/L significantly reduced the viability of mouse Leydig tumor cells (MLTC-1). While 50 mol/L ZEN showed no obvious toxicity to Chang liver cells (CCL-13), 100 mol/L ZEN significantly reduced CCL-13 cell viability. In this study, MTT assays revealed that OTA (>10.000 mol/L) and ZEN (50.000 mol/L) both extremely significantly reduced HCT116 and A549 cell viability, showing obvious cytotoxicity. Additionally, DON (>2.000 mol/L) exhibited strong, dose-dependent cytotoxicity in all three cell types.

Furthermore, when investigating mycotoxin cytotoxicity, low concentrations generally show no cytotoxic effects. For example, Kang et al. reported that high-concentration ZEN (100 mol/L) significantly reduced CCL-13 cell viability, while low-concentration ZEN (50 mol/L) showed no obvious toxicity. However, other reports indicate that low-concentration ZEN (1–1,000 nmol/L) promotes proliferation of human colon cancer HCT116 cells, potentially indicating carcinogenicity. This study investigated the proliferation-promoting effects of low-concentration mycotoxins, revealing that OTA, classified by IARC as a Group 2B carcinogen, promoted proliferation in all three cancer cell types at low concentrations (<0.400 mol/L). In contrast, DON (2.000 mol/L) and ZEN (50.000 mol/L) showed no proliferation-promoting effects in HCT116 and A549 cells but significantly promoted proliferation in HepG2 cells. At 0.016 mol/L, DON and ZEN increased HepG2 cell viability by 26.2% and 33.8% compared with the blank control, respectively, both exceeding OTA' s 21.3% increase.

Cell migration participates in various physiological activities including embryonic development, wound healing, and tissue regeneration, while also representing a fundamental process in disease development such as tumor formation. During tumorigenesis, cell migration plays a central role as the key step enabling cell diffusion and tissue invasion. Abassi et al. reported that ZEN promotes migration of human colon cancer HCT116 cells, suggesting potential carcinogenicity. This study further investigated the effects of DON and ZEN on migration capacity in HCT116, A549, and HepG2 cells using the cell scratch wound healing assay with OTA as the positive control. The results showed that 1 nmol/L DON treatment for 48 h produced migration-promoting effects in HepG2 cells similar to those of 10 nmol/L OTA, while ZEN' s migration-promoting effect was slightly weaker.

Future studies should further refine experimental models and employ multiple

toxicological approaches to comprehensively evaluate the potential carcinogenicity of DON and ZEN at low concentrations, providing cellular-level experimental support for toxicological research on relevant mycotoxins. Further investigation into the toxicological mechanisms of these two mycotoxins, particularly their carcinogenicity, is crucial for predicting and preventing harmful effects on human and animal health.

4 Conclusion

Under the experimental conditions of this study, the positive control OTA exhibited proliferation-promoting effects in all three cell systems, whereas DON and ZEN only showed significant proliferation-promoting effects in HepG2 cells. Additionally, DON and ZEN demonstrated migration-promoting effects in HepG2 cells similar to those of OTA, indicating that DON and ZEN exhibit potential carcinogenic-like properties in the HepG2 cell line.

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Note: Figure translations are in progress. See original paper for figures.