Detoxification of Fumonisins with Biological Antioxidants

Subjects: Toxicology

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Food safety is related to the national economy and people's livelihood. Fumonisins are widely found in animal feed, feed raw materials, and human food. This can not only cause economic losses in animal husbandry but can also have carcinogenicity or teratogenicity and can be left in animal meat, eggs, and milk which may enter the human body and pose a serious threat to human health. Although there are many strategies to prevent fumonisins from entering the food chain, the traditional physical and chemical methods of mycotoxin removal have some disadvantages, such as an unstable effect, large nutrient loss, impact on the palatability of feed, and difficulty in mass production. As a safe, efficient, and environmentally friendly detoxification technology, biological detoxification attracts more and more attention from researchers and is gradually becoming an accepted technique.

Mycotoxins Fumonisins biological detoxification

1. Introduction

Mycotoxins are toxic secondary metabolites produced by many filamentous fungi of ascomycetes [1]. Mycotoxin pollution is a persistent global problem which is inevitable and unpredictable. The production of mycotoxins is affected by the surrounding environment; even a good growth and storage environment cannot completely prevent the production of mycotoxins [2]. Fumonisins are a group of toxins that pose a significant threat to food and animal health after aflatoxins. Fumonisins have high toxicity and often appear together with aflatoxin toxicity. They cause huge economic losses to the livestock and poultry breeding industry and threaten human health [3][4]. Therefore, several studies have been exploring methods to control and alleviate fumonisin toxicity. Fumonisins easily contaminate corn, rice, and other grains, causing damage to the liver and kidneys of several animals that feed on these grains and even causing tumor problems [5][6]. In addition, fumonisin toxicity is implicated in causing human esophageal cancer and neural tube defect disease [7][8], thus fumonisins have gradually become a research hotspot after aflatoxin.

Fumonisins are a water-soluble secondary metabolite mainly produced by *Fusarium verticillioides*, *Fusarium proliferatum,* and other *Fusarium* species [9]. It exists on a variety of substrates, mainly on grains such as corn, and can also be found in products manufactured using grains as raw materials [5]. Fumonisins can be divided into four categories: A, B, C and P, including 28 structural analogues: FA_1, FA_2, FA_3, $PHFA_{3a}$, $PHFA_{3b}$, HFA_3, FAK_1, FBK_1, FB_1, Iso-FB_1, $PHFB_{1a}$, $PHFB_{1b}$, HFB_1, FB_2, FB_3, FB_4, FB_5, FC_1, N-acetyl-FC_1, Iso-FC_1, N-acetyl-iso-FC_1, OH-FC_1, N-acetyl-OH-FC_1, FC_3, FC_4, FP_1, FP_2, and FP_3 (Table 1). Notably, the fumonisin B family is the main and most toxic

family. Fumonisin B_1 (FB_1) and fumonisin B_2 (FB_2) are the most abundant and most toxic variants that naturally contaminate maize, accounting for 70–80% and 15–25% of the total number of fumonisins [10][11].

WHO (2001) established a provisional maximum daily tolerable level of fumonisins at 2 µg/kg-BW (body weight), owing to its high levels and high toxicity [12]. The European Commission (2006 and 2007) set the maximum levels of fumonisins for unprocessed maize at 4000 µg/kg, FB at 1000 µg/kg for human corn-based foods, 800 µg/kg for corn breakfast cereals and snacks, and 200 µg/kg for corn-based baby foods [13][14]. The International Agency for Research on Cancer (IARC) classifies fumonisins into group 2B, which is a possible human carcinogen owing to their harmful effects [15]. Therefore, it is particularly significant to reduce the content and detoxify fumonisins in food.

Fumonisins are highly soluble in water and have strong thermal stability, thus they are chemically stable under various conditions. It is therefore challenging to remove them from ordinary grain processing to meet normal edible standards [16]. Physical and chemical methods cannot effectively remove fumonisins and other toxic substances from grains. Studies report that biological methods can effectively remove fumonisins in crops. Therefore, studies have widely explored the inhibition of fumonisin-producing strain growth and degradation of fumonisins through biological control and biodegradation [17][18].

2. Polyphenols

Curcumin is a natural polyphenolic compound extracted from the rhizome of Zingiberaceae and other plants.[19]. Notably, curcumin increases ceramide concentration by stimulating de novo synthesis of ceramide, activating neutral sphingomyelinase and inhibiting the activity of sphingomyelin synthase [20]. Lloyd-Evans et al. observed that curcumin reduces the intracellular accumulation of So, sphingomyelin, glycosphingolipids, and cholesterol by restoring the intracellular calcium content. These characteristics are the main features of Niemann-PicktypeC1 disease [21], as well as features for fumonisin poisoning. Feeding chicks with curcumin nanocapsules supplemented with 600 mg/kg fumonisin and 10 mg/kg curcumin, showed protecting protective effects to the liver and an antioxidant effect, as well as reducing the level of thiobarbituric acid active substance in ROS and improving the weight gain of chicks compared with the control group [22]. Moreover, curcumin reduces PK-15 death in vitro. Administration of curcumin PK-15 cells pretreated with 50 µM FB_1 showed an increase in the cell survival rate from 53.7% to 77% and a decrease in the intracellular ROS content from 97.4% to 75.5% [23]. Silymarin (SIL) is also a polyphenol with a similar effect to that of curcumin. Sozmen et al. reported that SIL significantly reduced hepatocyte apoptosis ($p < 0.0001$) and upregulated the expression of Caspase-8 and TNF-α ($p < 0.0001$) in BALB/c mice treated with 100 mg/kg FB_1 as well as 1.5 mg/kg SIL in vivo [24]. Furthermore, Ledur et al. observed that the administration of 50 µM FB_1 to PK-15 cells pretreated with 2.5 µM SIL increased the cell survival rate from 53.7% to 89.2% and decreased the intracellular ROS content from 97.4% to 34.2% [23]. Moreover, Marnewick et al. reported that tea polyphenols alleviate hepatotoxicity induced by FB_1. For instance, the administration in male Fischer rats of 250 mg/kg FB_1 and aqueous extracts of rooibos (*Aspalathus linearis*), honeybush (*Cyclopia intermedia*), herbal, and green and black (*Camellia sinensis*) teas before and after fermentation showed a significant increase in the scavenging ability of mouse liver cells to free radicals. In addition, fermented herbal teas

and unfermented honeybush significantly reduced liver lipid peroxidation induced by FB_1. Moreover, the three tea extracts improved the activities of CAT, GPx, and GR at varying degrees [25]. Chlorogenic acid also has an inhibitory effect on fumonisin-producing strains. Chlorogenic acid is a common dietary polyphenol with significant bioactivity. The inhibition rate of fumonisin-producing strains after administration of chlorogenic acid was up to 70% [26].

3. Sterols

Hassan et al. explored the protective effect of ginseng extract (PGE) on mice exposed to FB_1, as PGE contains a lot of sterols such as ginsenosides. The findings indicated that PGE reduced fragmentation of DNA in the liver and kidney after the administration of 20 mg/kg-BW of PGE and 100 μg/kg-BW FB_1 to male mice at the same time. Moreover, PGE alleviated LP changes in the liver and kidney, increased GSH level, and upregulated GPx, SOD1, and CAT mRNA expression. In addition, the GPx, SOD1, and CAT mRNA expression levels of mice in the PGE group treated with 20 mg/kg-BW of FB_1 were significantly higher relative to the expression levels of mice in the blank control group [27]. Additionally, Abdel-Wahhab et al. explored the effect of red ginseng on FB_1 toxicity in Sprague-Dawley rats and reported consistent findings [28]. The root extract of *Panax notoginseng* has an inhibitory effect on the carcinogenicity of FB_1. Takao et al. administered FB_1 and acetone to female SENCAR mice through a skin smear to stimulate papilloma formation. The treatment group was administered with *Panax notoginseng* acetone extract 1 h before each administration of FB_1. The findings showed that 100% of the mice in the control group developed papilloma after 12 weeks of FB_1 and acetone skin smearing, whereas only about 20% and 50% of the mice in the treatment group developed papilloma after 12 and 15 weeks, respectively [29]. Moreover, daily consumption of ginseng may have a preventive or detoxifying effect on fumonisin toxicity.

4. Phenylpropionic Acids

Ferulic acid is a phenyl propionic acid compound derived from Ferula feruloides (Steudel) Korovin and other plants. Ferulic acid at 10–25 mM significantly decreased the growth rate of *Fusarium oxysporum* compared with the control group ($p < 0.001$). In addition, fumonisin production was inhibited to a certain extent [30]. Ferulic acid can be extracted from cheap agricultural by-products, therefore, the extraction of ferulic acid from low-cost agricultural by-products can be an important source in controlling the production of fumonisins in plants [31][32].

5. Vitamins

Vitamin E is an important antioxidant. Pretreatment of mice with 25 μM vitamin E (tocopherol) for 24 h before 18 μM FB_1 treatment significantly reduces FB_1-induced DNA damage and apoptosis [33][34]. In addition, vitamin E can be combined with selenium, CoQ10, and L-carnitine to prepare a compound with synergistic effects. In a study, mice were pretreated with vitamin E (30 IU/kg), selenium (1 mg/kg), CoQ10 (30 mg/kg), and L-L-carnitine (2.8 mg/kg), then intravenously administered with 1.55 mg/kg-BW FB_1. The results indicated that a combination of these antioxidants alleviated DNA damage and increased the activities of aspartate aminotransferase and alanine

aminotransferase by 18% and 18%, respectively, compared with the level of mice not exposed to FB_1 [35]. Oginni et al. administered juvenile catfish with vitamin E and vitamin C at the same time and observed that the decrease in nutrient content in juvenile catfish induced by FB_1 was improved. Notably, the crude protein content in juvenile catfish was higher compared with that of the FB_1 group ($p < 0.05$) [36]. Furthermore, folic acid has a protective effect on cytotoxicity induced by fumonisins. Sadler et al. reported that folic acid reduced the toxic effect of FB_1 on mouse embryos and improved the growth of mouse embryos after culturing embryos with a mixture of 10 mM folic acid and 2 μM FB_1, indicating that folic acid improves the toxic effect of fumonisins, however, the change was not significant [37].

6. Essential Oil

Essential oils are unique aromatic substances extracted from plants, mainly containing alcohols, aldehydes, phenols, acetones, terpenes, and other volatile secondary metabolites synthesized by plants [38][39]. Several types of essential oils such as *Litsea cubeba*, cinnamon, and ginger have been reported, and most have an inhibitory effect on bacterial growth. Pante et al. conducted an in vitro experiment and reported that *Litsea cubeba* essential oil inhibited mycelial development of *Furium verticillioides* and synthesis of FB_1 and FB_2. The minimum inhibitory concentration of *Fusarium verticillioides* was 125 μg/mL and the inhibitory effect was dose dependent. The antioxidant effect of *Litsea cubeba* essential oil was evaluated by DPPH and ABTS methods, showing excellent antioxidant activity [40]. Bomfim et al. reported that *Rosmarinus officinalis* L. essential oil (REO) had a similar effect. Administration of 300 μg/mL REO caused significant morphological changes such as bacterial cell wall rupture and cell content flow out in a dose-dependent manner [41]. In addition, *Zingiber officinale* essential oil (GEO) inhibits the growth of fumonisin-producing bacteria and fumonisin production. Notably, administration of 2000 μg/mL GEO and 4000 μg/mL GEO significantly inhibits the production of FB_1 and FB_2. The inhibition rates of ergosterol biosynthesis after administration of 4000 μg/mL and 5000 μg/mL GEO were 57% and 100%, respectively [42]. Ergosterol modulates the activity of several membrane binding enzymes [43], and the reduction of ergosterol activity could result in membrane synthesis disorders, thus exhibiting a bacteriostatic effect. Castro et al. reported similar results with minimum inhibitory concentrations of *Cinnamomum zeylanicum* and *Cymbopogon martinii* essential oils to *Fusarium verticillioides* at 250, 250, and 500 μg/mL, respectively [44]. Plant essential oils inhibit the growth of fumonisin-producing bacteria and fumonisin production, as well as reduce or prevent toxicity caused by fumonisins. Essential oils have a strong smell and react with some drugs, thus, embedding technology is commonly used to embed essential oils. Cinnamon essential oil embedded with whey protein effectively improved the serum levels of ALT, AST, ALP, Urea, and Uric acid, and restored the normal levels in male Sprague-Dawley male rats treated with 100 mg/kg-BW FB_1. Furthermore, testosterone levels in rats were restored to normal values thus reducing reproductive toxicity. Lipid peroxidation and tumor marker TNF-α in liver and kidney tissues were improved to some extent but were not restored to normal levels [38]. Studies report that the cinnamon extract glycerol monolaurate (GML) has similar effects. The levels of serum triglyceride, globulin, cholesterol, liver lipid peroxidation, SOD, and serum reactive oxygen species were restored to normal or below normal levels after chicks were fed with 400 μg/kg fumonisins and GML coated with 8 mg/kg nanomaterials. However, the body weight of chicks was not improved indicating that GML does not reduce the oxidative stress caused by fumonisins to a minimum. However,

it alleviates oxidative stress caused by fumonisins and enhances the activity of glutathione S-transferase which is the enzyme responsible for liver detoxification [45].

7. Other Antioxidants

In addition to the above-mentioned antioxidants, several other types of antioxidants have been reported in previous studies. Domijan et al. reported that sodium copper chlorophyllin (CHL) had a protective effect on FB_1-induced cell and DNA damage after administration of 100 µg/mL (CHL) in combination with 20 µg/mL of FB_1. Oxidative stress is the main cause of DNA damage caused by FB_1, thus CHL indirectly prevented FB_1-induced cell death, DNA damage, and possible carcinogenesis by preventing oxidative stress [46]. Zhao et al. conducted a study whereby indole glucosinolates (IGS) were infiltrated into wild-type Col-0 plants followed by a 10 µM FB_1 solution into the wild-type IGS plants and compared the results with the administration of only the FB_1 solution. The findings showed that IGS inhibited FB_1-induced apoptosis. IGS decomposition products produced through the action of β-glucosinolase effectively reduce the accumulation of ROS, increase the activity of antioxidant enzymes, and improve ROS scavenging ability, thus reducing FB_1-induced oxidative stress and apoptosis [47]. CHL and IGS are widely distributed in green leafy vegetables, thus eating more green leafy vegetables may have a preventive effect on fumonisins toxicity.

In addition to single-component antioxidants, several compound antioxidants have been reported. Hassan et al. observed that all biochemical and cytogenetic test parameters and histological images of liver tissue were significantly improved after feeding mice with an ethanol extract of *Aquilegia vulgaris* L. at 10 mg/kg-BW and 200 mg/kg voronisin [48]. Gbore et al. reported that the food intake of female rabbits approached the normal level after administration of Moringa leaf meal (MLM) in combination with FB_1 and the effect of MLM was dose dependent. The antioxidant effect of MLM improved the adverse effects of FB_1 on nutrient utilization and growth performance of female rabbits. Notably, MLM is a cheaper alternative compared with commercial antioxidants. MLM can be used as an antidote in traditional feed to reduce the harmful effects of FB_1 on domestic animal production [49].

Moreover, insect products have antioxidant effects. Several honeybee products are potential sources of natural antioxidants and can counteract the effects of oxidative stress caused by various diseases [50]. Royal jelly (RJ) contains several bioactive substances and phenolic compounds, mainly comprising flavonoids and fenac, and has antioxidant activities. Liver and kidney indexes were significantly improved when male Sprague-Dawley rats were administered with a combination of 200 mg/kg fumonisins and 150 mg/kg-BW RJ compared with the levels in mice fed with FB_1 alone. Liver and kidney indexes were also restored to normal levels, indicating that RJ has a protective effect on fumonisin toxicity. Notably, the protective effect was dose dependent [51].

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