Review

Nation-Based Occurrence and Endogenous Biological Reduction of Mycotoxins in Medicinal Herbs and Spices

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Abstract: Medicinal herbs have been increasingly used for therapeutic purposes against a diverse range of human diseases worldwide. Moreover, the health benefits of spices have been extensively recognized in recent studies. However, inevitable contaminants, including mycotoxins, in medicinal herbs and spices can cause serious problems for humans in spite of their health benefits. Along with the different nation-based occurrences of mycotoxins, the ultimate exposure and toxicities can be diversely influenced by the endogenous food components in different commodities of the medicinal herbs and spices. The phytochemicals in these food stuffs can influence mold growth, mycotoxin production and biological action of the mycotoxins in exposed crops, as well as in animal and human bodies. The present review focuses on the occurrence of mycotoxins in medicinal herbs and spices and the biological interaction between mold, mycotoxin and herbal components. These networks will provide insights into the methods of mycotoxin reduction and toxicological risk assessment of mycotoxin-contaminated medicinal food components in the environment and biological organisms.
Keywords: mycotoxins; herbal medicine; spice; aflatoxin; ochratoxin A; fumonisin

1. Introduction

Herbal medicine has been increasingly used for therapeutic purposes against a diverse range of human diseases worldwide. However, contaminated chemicals in herbal medicines produce severe problems [1,2] that have seriously affected the value of herbal products and damaged human health. As one of the major contaminants, mycotoxins are the secondary metabolites produced by various species of fungi, such as Aspergillus, Alternaria, Penicillium and Fusarium [3], and trigger several ailments of the kidneys, liver, digestive tract, skin, respiratory organs, genital organs and nervous system [4,5]. More than 400 types of mycotoxins have been identified in the world to date. Among mycotoxins, aflatoxins (AFs), ochratoxin A (OTA), fumonisins (FBs), zearalenone (ZEA) and deoxynivalenol (DON) are the most frequently detected mycotoxins in herbal medicines. Generally, contamination can occur either in the pre-harvest or in the post-harvest and storage stages. Climate change, poor storage and damage from insects or harvest processing make them more susceptible to mycotoxin contamination [6]. The present review addresses the occurrence of mycotoxins in medicinal herbs and spices and the biological interaction between mold, mycotoxin and herbal components to get better exposure and toxicity assessments of the mycotoxin mixed with the health-promoting natural components.

2. The Global Occurrence of Mycotoxins in Medicinal Herbs and Spices

Information on mycotoxin occurrence in medicinal herbs and spices from different areas was compared based on the literature (Table 1). Different environmental conditions, agronomic practices and post-harvest processes, including storage and drying, resulted in a wide spectrum of mycotoxin contamination levels in medicinal herbs and spices.

Among Indian herbal samples, black pepper and long pepper are the most highly contaminated with AFB1. Out of the 150 samples, 43% were contaminated with AFB1, 6% with OTA, 6% with citrinin and 4% with ZEA. Crude samples of all 12 medicinal plants and spices [7] were randomly collected from gunny bags, metal containers, glass containers, wooden boxes and the bare ground in different store houses in India. Especially, samples collected from bags and the bare ground showed a significantly higher occurrence of mycotoxins than those from metal containers, glass containers and wooden boxes, suggesting an association of the storage conditions with mycotoxin production. In another report, 17 out of 84 samples [8] of medicinal herbs and spices from India were found to be contaminated with AFB1 and OTA. No mycotoxins were found in herbal samples of cinnamon, saffron, curcuma, rose or lesser galangal. All of the 84 medicinal herbs obtained from India were free of penicillic acid, ZEA and T-2 toxin [8]. Since mycotoxin quantitation in both reports was based on relatively old methods, such as thin layer chromatography and its subsequent UV or fluorescence spectrometric detection, more sensitive analytical methods to detect lower levels of mycotoxin contamination are also required to get the international recognition using the official methods of analysis from Association of Official Analytical Chemists (AOAC) international.
Mycotoxin occurrence in traditional Chinese herbal medicines has been extensively investigated. Different from the Indian surveys, the total of 51 dried samples of traditional Chinese medicinal herbs were examined for the mycotoxin contamination in 2010 using ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) [9]. The more accurate and sensitive analyses demonstrated that only four samples were found to have low levels of OTA and OTB contamination. Liu et al., found that 27 out of 174 total samples of Chinese herbs were contaminated with aflatoxins, which indicates a 15.5% incidence rate of aflatoxin contamination. Products from Guangxi province showed the highest levels of contamination, with aflatoxins at up to 290.8 μg/kg in 27 contaminated samples. The mycotoxin analysis in Chinese herbal products was also performed using the immunoaffinity pre-column and HPLC-MS/MS [10]. Despite the relatively low incidence rate of aflatoxin contamination in Chinese herbs, the high levels of AFs in some medicinal herbs were high enough to cause serious health problems [10].

In Africa, 16 samples of traditional medicinal herbs from South Africa revealed the presence of Fb\textsubscript{1} in 13 samples at up to 139 μg/kg. However, all of the 16 samples from South Africa using HPLC and MS analysis were free of AFB\textsubscript{1} contamination [11]. In Morocco, spices, such as pepper, paprika, cumin, ginger and saffron, are extensively used in flavoring foods and medications. Spices are usually dried on the ground in an open space. These are unsuitable conditions in regions with a tropical climate, which poses a high risk of fungal contamination and is favorable for mycotoxin production. Among the total of 55 samples of four types of spices, 14 samples of red paprika contained higher levels of aflatoxins (9.68 μg/kg), a 100% incidence rate [12].

In Saudi Arabia, 50 different samples of 10 types of spices were analyzed for naturally-occurring mycotoxins using the thin layer chromatographic technique. A total of 10 different samples of five types of spices, such as anise, black cumin, black pepper, peppermint and marjoram, were found to be contaminated with aflatoxins at up to 40 μg/kg. Cardamom, cloves and ginger were free from aflatoxins and sterigmatocystin, whereas some spice samples of red pepper, cumin and marjoram were contaminated with sterigmatocystin at up to 25 μg/kg. This indicates that mycotoxin contamination of the spices from Saudi Arabia is of low incidence and occurs at only low concentrations. However, chronic exposure to even low levels of mycotoxins can be problematic, depending on the exposure population, because anise and cumin are commonly used as a carminative and expectorant for colic and flatulence in children.

In Turkey, aflatoxin contamination of dried figs has been reported [13–15]. As a result of reverse phase HPLC analysis, a total of 219 samples of dried figs demonstrated high incidence rates (47.5%) of aflatoxin at up to 278.04 μg/kg, whereas 2461 samples for export had a relatively lower incidence of aflatoxin contamination (23.6%) [15]. In addition, 75% of the 115 dried fig samples were found to be contaminated with extremely high levels of FB\textsubscript{1}, up to 3649 μg/kg [14].
### Table 1. Occurrence of mycotoxins in medicinal herbs and spices.

| Country of Origin | Sample Name          | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|-------------------|----------------------|-------------------|--------------------------------------------|-----------|
| India             | Asparagus racemosus  | AFB₁              | 220                                        | [7]       |
|                   |                      | AFB₂              | 50                                         |           |
|                   |                      | ZEA               | 100                                        |           |
|                   | Celery               | AFB₁              | 200                                        |           |
|                   |                      | ZEA               | 70                                         |           |
|                   | Cinnamomum zeylanicum| AFB₁              | 140                                        |           |
|                   | Cuminum cyminum      | AFB₁              | 310                                        |           |
|                   |                      | ZEA               | 100                                        |           |
|                   | Elettaria cardamomum | AFB₁              | 400                                        |           |
|                   |                      | AFB₂              | 210                                        |           |
|                   |                      | OTA               | 50                                         |           |
|                   |                      | ZEA               | 20                                         |           |
|                   | Emblica officinalis  | AFB₁              | 380                                        |           |
|                   |                      | AFB₂              | 80                                         |           |
|                   |                      | AFG₁              | 170                                        |           |
|                   |                      | OTA               | 120                                        |           |
|                   |                      | ZEA               | 190                                        |           |
|                   | Mesua ferrea         | AFB₁              | 270                                        |           |
|                   |                      | AFB₂              | 100                                        |           |
|                   | Long pepper          | AFB₁              | 570                                        |           |
|                   |                      | AFB₂              | 160                                        |           |
|                   |                      | AFG₁              | 190                                        |           |
|                   |                      | OTA               | 80                                         |           |
|                   |                      | ZEA               | 50                                         |           |
|                   | Black pepper         | AFB₁              | 510                                        |           |
|                   |                      | AFB₂              | 150                                        |           |
|                   |                      | OTA               | 200                                        |           |
|                   |                      | ZEA               | 100                                        |           |
|                   | Indica               | AFB₁              | 310                                        |           |
|                   | Baccala              | AFB₁              | 190                                        |           |
|                   | Ginger               | AFB₁              | 370                                        |           |
|                   |                      | AFB₂              | 220                                        |           |
|                   |                      | AFG₁              | 100                                        |           |
|                   |                      | ZEA               | 70                                         |           |
|                   | Black cumin          | AFB₁              | 30                                         |           |
|                   |                      | OTA               | 35                                         |           |
|                   | Fennel               | AFB₁              | 160                                        |           |
|                   |                      | OTA               | 80                                         |           |
|                   | Lime tree            | AFB₁              | 75                                         |           |
|                   | Wormwood             | AFB₁              | 25                                         |           |
|                   |                      | OTA               | 20                                         |           |
|                   | Cinnamon             | -                 | -                                          |           |
Table 1. Cont.

| Country of Origin | Sample Name          | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|-------------------|----------------------|-------------------|-------------------------------------------|-----------|
| India             | Peppermint           | AFB<sub>1</sub>   | 25                                        |           |
|                   | Carob tree           | AFB<sub>1</sub>   | 10                                        |           |
|                   | Chamomile            | AFB<sub>1</sub>   | 145                                       | [8]       |
|                   | Saffron              | -                 | -                                         |           |
|                   | Curcuma longa        | -                 | -                                         |           |
|                   | Worm wood            | AFB<sub>1</sub>   | 90                                        |           |
| India             | Rhizoma coptidis-1   | OTA               | 0.4                                       |           |
|                   | Rhubarb              | OTA               | 0.2                                       |           |
|                   | Ephedra              | OTA               | 0.3                                       | [9]       |
|                   |                      | OTB               | 0.4                                       |           |
|                   | Fructus mume         | OTA               | 1.5                                       |           |
|                   |                      | OTB               | 0.8                                       |           |
| China             | Baohe pills          | DON               | 50.5                                      | [16]      |
|                   | Sping Jujuba seed    | AFB<sub>1</sub>   | 4.67                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.89                                      |           |
|                   |                      | AFG<sub>1</sub>   | 2.14                                      |           |
|                   | Barley               | AFB<sub>1</sub>   | 1.72                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.95                                      |           |
|                   | Areca seeds          | AFB<sub>1</sub>   | 32.03                                     |           |
|                   |                      | AFB<sub>2</sub>   | 2.73                                      |           |
|                   |                      | AFG<sub>1</sub>   | 15.89                                     |           |
| China             | Biota seed           | AFB<sub>1</sub>   | 25.33                                     |           |
|                   |                      | AFB<sub>2</sub>   | 7.71                                      |           |
|                   |                      | AFG<sub>1</sub>   | 0.59                                      |           |
|                   |                      | AFG<sub>2</sub>   | 0.21                                      |           |
|                   | Cassia seed          | AFB<sub>1</sub>   | 5.69                                      |           |
|                   |                      | AFB<sub>2</sub>   | 1.81                                      |           |
|                   | Nutmeg               | AFB<sub>1</sub>   | 239.62                                    | [10]      |
|                   |                      | AFB<sub>2</sub>   | 13.5                                      |           |
|                   |                      | AFG<sub>1</sub>   | 34.21                                     |           |
|                   |                      | AFG<sub>2</sub>   | 3.5                                       |           |
|                   | Bitter orange        | AFB<sub>1</sub>   | 0.15                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.77                                      |           |
|                   | Pharbitis seed       | AFB<sub>1</sub>   | 0.47                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.14                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.07                                      |           |
|                   |                      | AFG<sub>1</sub>   | 0.08                                      |           |
|                   |                      | AFG<sub>2</sub>   | 0.09                                      |           |
|                   | Bitter apricot seed  | AFB<sub>1</sub>   | 0.47                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.06                                      |           |
|                   | White Aractylodes rhizome | AFB<sub>1</sub>   | 0.47                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.06                                      |           |
|                   | Groomwell root       | AFB<sub>1</sub>   | 1.03                                      |           |
|                   |                      | AFB<sub>2</sub>   | 0.48                                      |           |
Table 1. Cont.

| Country of Origin | Sample Name       | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|-------------------|-------------------|-------------------|--------------------------------------------|-----------|
| China             | Japanese knotweed rhizome | AFB₁             | 0.77                                       | [10]      |
|                   |                   | AFB₂             | 0.32                                       |           |
|                   | Aractylodes rhizome | AFB₁             | 0.58                                       |           |
|                   |                   | AFB₂             | 0.93                                       |           |
|                   | Corydalis rhizome  | AFB₁             | 68.4                                       |           |
|                   |                   | AFB₂             | 1.71                                       |           |
|                   |                   | AFG₁             | 0.95                                       |           |
|                   | Coix seeds        | AFB₁             | 0.09                                       |           |
|                   |                   | AFB₂             | 0.05                                       |           |
|                   |                   | ZEA              | 211.4                                      | [17]      |
| South Africa      | Uthuvana          | FB₁              | 40                                         |           |
|                   | Isica Katha       | FB₁              | 87                                         |           |
|                   | Umsila Wengwe     | FB₁              | 117                                        |           |
|                   | Sibindi           | FB₁              | 30                                         |           |
|                   | Mudhora           | FB₁              | 25                                         |           |
|                   | Matunga           | FB₁              | 139                                        | [11]      |
|                   | Mredeni           | FB₁              | 21                                         |           |
|                   | Red carrot        | FB₁              | 30                                         |           |
|                   | Roselina          | FB₁              | 126                                        |           |
|                   | Seloka            | FB₁              | 67                                         |           |
|                   | Thepe             | FB₁              | 26                                         |           |
|                   | Anise             | AFB₁, AFB₂       | 38                                         |           |
|                   | Black cumin       | AFB₁, AFB₂       | 35                                         |           |
|                   | Black pepper      | ST               | 40                                         |           |
|                   | Red pepper        | AFB₁, AFB₂       | 25                                         | [18]      |
| Saudi Arabia      | Peppermint        | AFB₁, AFB₂       | 17                                         |           |
|                   | Cumin             | ST               | 20                                         |           |
|                   | Marjoram          | AFB₁, AFB₂       | 12                                         |           |
|                   | Cinnamon          | AFs              | 4.67                                       | [19]      |
| Morocco           | Pepper            | AFs              | 0.55                                       |           |
|                   | Cumin             | AFs              | 0.18                                       | [20]      |
|                   | Ginger            | AFs              | 9.10                                       |           |
|                   | Red paprika       | AFs              | 9.68                                       |           |
| USA               | Ginger            | AFs              | 31                                         |           |
|                   | Ginseng products  | AFs              | 0.1                                        | [21]      |
|                   | Ginseng root      | AFs              | 16                                         | [22]      |
|                   | Kava-kava         | AFB₁             | 0.5                                        | [23]      |
|                   | Milk thistle      | AFs              | 2.0                                        | [24]      |
| Country of Origin | Sample Name       | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|------------------|------------------|-------------------|-------------------------------------------|-----------|
| Spain            | Sage leaves      | AFs               | 25.2                                      | [25]      |
|                  |                  | OTA               | 17.3                                      |           |
|                  |                  | FBs               | 133.3                                     |           |
|                  |                  | DON               | 102.2                                     |           |
|                  |                  | Citrinin          | 273.2                                     |           |
|                  | Chamomile flower | AFs               | 161                                       |           |
|                  |                  | FBs               | 90.0                                      |           |
|                  | Valerian root    | T2                | 13.3                                      |           |
|                  |                  | DON               | 64.7                                      |           |
|                  |                  | Citrinin          | 20.5                                      |           |
| Spain            | Senna leaves     | AFs               | 434.3                                     |           |
|                  |                  | FBs               | 86.7                                      |           |
|                  |                  | DON               | 35.2                                      |           |
|                  | Rhubarb          | AFs               | 71.2                                      |           |
|                  |                  | OTA               | 13.9                                      |           |
|                  |                  | ZEA               | 24.4                                      |           |
|                  |                  | T2                | 23.0                                      |           |
|                  |                  | DON               | 58.4                                      |           |
|                  |                  | Citrinin          | 42.9                                      |           |
| Spain            | Artichoke        | AFs               | 12.1                                      |           |
|                  |                  | T2                | 29.8                                      |           |
|                  |                  | DON               | 200.2                                     |           |
|                  |                  | Citrinin          | 29.8                                      |           |
| Spain            | Boldus           | AFs               | 86.6                                      |           |
|                  |                  | ZEA               | 10.3                                      |           |
|                  |                  | T2                | 26.7                                      |           |
|                  |                  | DON               | 343.5                                     |           |
|                  |                  | Citrinin          | 25.8                                      |           |
| Spain            | Burdock root     | AFs               | 10.3                                      |           |
|                  |                  | ZEA               | 10.9                                      |           |
|                  |                  | Citrinin          | 25.8                                      |           |
| Spain            | Dandelion        | AFs               | 21.7                                      |           |
|                  |                  | OTA               | 10.6                                      |           |
|                  |                  | ZEA               | 17.0                                      |           |
|                  |                  | DON               | 66.5                                      |           |
|                  |                  | Citrinin          | 96.0                                      |           |
Table 1. Cont.

| Country of Origin | Sample Name  | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|-------------------|--------------|-------------------|-------------------------------------------|-----------|
| Spain             | Frangula     | AFs               | 64.7                                      |           |
|                   |              | ZEA               | 44.1                                      |           |
|                   |              | T2                | 12.6                                      |           |
|                   |              | DON               | 60.9                                      |           |
|                   |              | Citrinin          | 38.4                                      |           |
|                   | Ginkgo       | AFs               | 23.3                                      |           |
|                   |              | T2                | 29.4                                      |           |
|                   |              | DON               | 134                                       |           |
|                   |              | Citrinin          | 354.8                                     |           |
|                   | Lemon verbena| AFs               | 37.7                                      |           |
|                   |              | ZEA               | 14.0                                      |           |
|                   |              | T2                | 28.6                                      |           |
|                   |              | DON               | 143.7                                     |           |
|                   |              | Citrinin          | 79.1                                      |           |
|                   | Olive leaves | AFs               | 77.6                                      |           |
|                   |              | ZEA               | 42.7                                      |           |
|                   |              | DON               | 149.9                                     |           |
|                   |              | Citrinin          | 14.9                                      |           |
|                   | Red tea      | AFs               | 853.4                                     | [25]      |
|                   |              | ZEA               | 11.2                                      |           |
|                   |              | T2                | 42.8                                      |           |
|                   |              | DON               | 179.9                                     |           |
|                   |              | Citrinin          | 22.3                                      |           |
|                   | Ribgrass     | AFs               | 16.1                                      |           |
|                   |              | T2                | 256.9                                     |           |
|                   | Spearmint    | AFs               | 29.7                                      |           |
|                   |              | DON               | 91.1                                      |           |
|                   |              | Citrinin          | 43.3                                      |           |
|                   | St Mary’s thistle | AFs           | 11.5                                      |           |
|                   |              | FBs               | 236.7                                     |           |
|                   |              | T2                | 35.6                                      |           |
|                   | Star anise   | AFs               | 104.2                                     |           |
|                   |              | FBs               | 146.7                                     |           |
|                   |              | ZEA               | 10.1                                      |           |
|                   |              | T2                | 60.5                                      |           |
|                   |              | DON               | 321.2                                     |           |
|                   | Vervain      | AFs               | 104.5                                     |           |
|                   |              | T2                | 20.4                                      |           |
|                   |              | DON               | 60.0                                      |           |
|                   |              | Citrinin          | 31.2                                      |           |


| Country of Origin | Sample Name   | Type of Mycotoxin | Maximum Concentration of Mycotoxin (μg/kg) | Reference |
|-------------------|---------------|-------------------|--------------------------------------------|-----------|
| Spain             | White tea     | AFs               | 254.0                                      | [25]      |
|                   |               | ZEA               | 11.2                                       |           |
|                   |               | T2                | 42.8                                       |           |
|                   |               | DON               | 259.1                                      |           |
|                   |               | Citrinin          | 19.7                                       |           |
|                   | Red paprika   | OTA               | 73.8                                       | [26]      |
|                   | Licorice      | OTA               | 252.8                                      | [27]      |
| Turkey            | Chamomile     | AFB₁              | 38.9                                       | [15]      |
|                   | Rose hip      | AFB₁              | 52.5                                       |           |
|                   | Dried figs    | AFs               | 278.04                                     | [28]      |
|                   |               | OTA               | 15.31                                      | [29]      |
|                   |               | FB₁               | 3649                                       | [14]      |

AF, aflatoxin; DON, deoxynivalenol; OTA, ochratoxin; T2, T2 toxin; FB, fumonisin; ZEA, zearalenone.

In Spain, 84 different samples of 42 types of medicinal and aromatic herbs were analyzed for multiple mycotoxins, including AF, OTA, ZEA, FBs, DON, T-2 toxin and citrinin, by using liquid chromatography with fluorescence detection (HPLC-FD) and HPLC-MS analysis. One hundred percent of the herbal samples were multi-contaminated with several mycotoxins, and 87% of samples were contaminated with four or more types of mycotoxins. Furthermore, 99% of the 84 samples were contaminated with T2, 98% with ZEA, 96% with AFs, 63% with OTA, 62% with DON, 61% with citrinin and 13% with FB₁. Hierro et al. [26] analyzed five mycotoxins in 21 different samples of red paprika. Although 90% of the samples were contaminated with AFB₁, the maximum levels of AFs were relatively low (AFB₁: 3.8 μg/kg, AFB₂: 0.7 μg/kg, AFG₁: 1.1 μg/kg, AFG₂: 0.8 μg/kg). However, OTA contamination was found in 15 samples, and the maximum levels of OTA were relatively high (73.8 μg/kg).

Finally, in the USA, botanicals used for medicinal and health-promoting purposes, including ginseng, ginger and kava-kava, were assessed for aflatoxin contamination by using HPLC-based AOAC methods. In a recent study, relatively high levels of aflatoxins, over the national regulatory limits, were found in ginger products (31 μg/kg) [21]. In particular, ginger and ginseng root samples possessed more aflatoxins than other herbal products. In another report, 19% of 83 milk thistle samples were also found to be contaminated with aflatoxins ranging from 0.04 to 2.0 μg/kg [24].

Since most of the cited assessments were dependent on market-based sampling, other exogenous factors, such as the field environment, agronomic and the postharvest procedures, were not critically considered. Therefore, it is very hard to make direct comparisons of mycotoxin levels among countries. The procedure-based sampling and mycotoxin measurement would provide critical control points for the preventive reduction of fungal growth and mycotoxin production in the agricultural commodities. A recent study on the mycotoxin reduction in the medicinal plant adlay (Job’s Tears) demonstrated that the critical control point-based assessment was efficient to reduce the fungal growth and trichothecene production in the final product of the herbal medicine [30]. In addition to the diversities in the exogenous compounding factors affecting mycotoxin production in the medicinal herbs and spices, the quantitation...
methods should be the internationally recognized official methods of analysis, such as those by AOAC international.

3. Regulation of Fungal Growth and Mycotoxin Production by Components from Medicinal Herbs and Spices

Although the occurrence and exposure of mycotoxins in most medicinal herbs and spices in various countries are inevitable, many of the bioactive components in the medicinal herbs and spices are capable of regulating the fungal growth, mycotoxin production and their toxic actions in the exposed individuals. Therefore, the ultimate effects of mycotoxins on the exposure and toxicity can be potently influenced by the presence of endogenous antagonistic components in the edible matrix of the medicinal herbs and spices. Despite the efficiency of synthetic chemical compounds in eliminating mycotoxin-producing fungi and mycotoxin reduction, the residues of many chemicals pose health risks to humans and animals. Due to the toxicity of these exogenous xenobiotics used to reduce mycotoxin production and fungal growth, numerous studies have been conducted to identify effective natural product alternatives, such as herbs and spices [31,32]. Hussain et al. [33] studied the effect of herbal compounds and spices on toxin-producing Aspergillus flavus and Aspergillus parasiticus. Among nine samples of different herbal compound and spices, clove and clove oil showed complete growth-inhibitory activities against A. flavus and A. parasiticus, while ajwain, kalonji oil and turmeric produced only partial inhibition. Similarly, Azzouz et al. [34] examined the effects of spices on several toxigenic species of Aspergillus and Penicillium. Certain concentrations of cloves and cinnamon (more than 8%) completely inhibited fungal growth and their mycotoxin production. Mostafa et al. [35] assessed the inhibitory effects of 24 commercial spices and found that Chinese cassia, cinnamon, clove and thyme completely inhibited toxin production of four toxigenic Aspergillus (A. flavus and A. versicolor) and Penicillium (P. citrinum and P. corylophilum) species. Several reports have shown that powdered black and white pepper and cardamom inhibit aflatoxin production of different strains of A. flavus and A. parasiticus [36–38]. Atanda et al. reported that sweet basil leaves have a fungistatic effect on A. parasiticus CFR 223 and subsequent aflatoxin production, which suggests the possibility of their use against Aspergillus contamination of agricultural products [39]. In addition, essential oil extracted from medicinal herbs including cinnamon, marigold, spearmint, basil and quysum, sufficiently inhibits the growth of fungi, such as Aspergillus flavus, A. parasiticus, A. ochraceus and F. moniliforme [40]. Moreover, Montes-Belmont and Carvajall et al. [41] and Basilico and Basilico et al. [42] demonstrated the antifungal activity of thyme, spearmint and basil on the toxigenic fungi A. flavus, A. parasiticus, A. ochraceus, A. fumigatus and Fusarium spp. These antifungal effects could be linked to common components known to have biological functions, such as α-pinene and β-pinene in basil, thyme and spearmint. Furthermore, basil oil contains ocimene and methyl chavicol as the most prevalent components. The major substances found in thyme oil are thymol and p-cymene. Many previous reports had demonstrated that cinnamon extract has effective antifungal activities against diverse toxigenic fungi. The three major components of cinnamon extracts (cinnamic aldehyde [43], o-methoxycinnamaldehyde [44] and carfone [45]) have proven anti-fungal activity. These anti-fungal plant-derived compounds have protective effects on the crop health by reducing detrimental fungal growth and mycotoxin actions, all of which are also beneficial for plant consumers, including human beings and domestic animals.
4. Regulation of Mammalian Toxicity of Mycotoxins by Components from Medicinal Herbs and Spices

If humans and animals are exposed to medicinal herbs and spices contaminated with mycotoxins, the ultimate biological sequelae would result from the interaction between the mycotoxins and components of the herbs and spices. Several medicinal herbs and spices are reported to be useful detoxification or protection agents against mycotoxin absorption, metabolism, distribution, excretion or toxicity. For instance, the induction of general metabolic enzymes in the liver, such as gamma-glutamyl transferase (γGT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), in response to aflatoxin exposure was significantly normalized by thyme oil treatment. Moreover, thyme oil enhances the excretion of aflatoxins and their metabolites via urine [46]. Several protective roles of sulforaphane have been identified by previous studies. In addition, Nayak et al. [47] observed that curcumin supplements, a bioactive principle of turmeric (Curcuma longa Linn), normalized aflatoxin-altered activities of lactate dehydrogenase and alanine transaminase (ALT).

In particular, aflatoxin-triggered oxidative stresses are also modulated by other diverse natural components in the medical herbs and spices. Similarly, the weight loss of chicks due to AFB₁ was significantly restored by the supplementation with a turmeric (C. longa) powder containing curcumin [48]. In addition, turmeric powder alleviated AFB₁-suppressed antioxidant activity, such as peroxides’ and superoxide dismutase (SOD) activity, and total antioxidant concentration in liver homogenates [48]. Akcam et al. [49] demonstrated that the intraperitoneal injection of caffeic acid phenethyl ester, an active component of honeybee propolis extract, exerts a protective effect against AFB₁-induced hepatotoxicity. AFB₁-altered levels of serum γGT, ALP, glutathione S-transferase (GST) and nitric oxide were significantly decreased by caffeic acid phenethyl ester in rats. The hepatoprotective roles of chitosan, derived from chitin found in crustacean shells, including Pandalus borealis, has been documented in several reports. Mosaad et al. [50] showed that chitosan nanoparticles ameliorate hepatotoxicity in response to AFB₁ in the rat liver. Moreover, Subhapradha et al. [51] reported that β-chitosan sufficiently normalized oxidative stress-induced plasma AST and ALT levels in rats. The hepatoprotective roles of chitosan are most likely due to the elimination or prevention of free radicals by its antioxidant property. Cyanidin, a natural anthocyanidin found in diverse medicinal herbs as well as fruits and vegetables, such as grapes, bilberry, blackberry, cherry, cranberry, hawthorn, loganberry, acai berry, raspberry, red cabbage and red onion, has been reported to have a protective effect against AFB and OTA toxicity [52–54]. Guerra et al. [55] observed that cyanidin reduces AFB₁ and OTA-mediated production of reactive oxygen species, suppression of protein and DNA synthesis and apoptosis in both hepatocytes and enterocytes. Moreover, carotenoid lycopene protects against the DNA damage, hepatotoxicity and renal oxidative stress caused by mycotoxins, including OTA and AFB₁ [56–58]. Cyanidin and lycopene can be thus an efficient beneficial component to attenuate the mixture toxicity of the two genotoxic mycotoxins.

Moreover, Aboobaker et al. [59] examined the effect of various plant-derived phenolic compounds, including flavonoids, such as fisetin, kaempferol, morin, naringin and catechin, phenolic acids, such as caffeic acid and chlorogenic acid, and other phenolics, such as eugenol and vanillin, and found that they attenuate the hepatotoxicity of AFB₁. Likewise, many types of herbs with potential uses for hepatotoxicity have been identified by several studies. Singh et al. [60] presented a list of 23 types of
medicinal herbs and their active components with a hepatoprotective activity. Similar to the protective roles of chitosan or thyme on aflatoxin-mediated hepatotoxicity, these herbs also possess a hepatoprotective effect against mycotoxins accumulated in the liver (Table 2).

The suppressed oxidative stress was also associated with attenuated DNA damages and carcinogenesis. According to the results of Sheen (2001) [61], diallyl sulfide, an active principle of garlic, protects hepatocytes from AFB1-induced DNA damage by activating GST and glutathione peroxidase. Similarly, genistein, a phytoestrogen derived from soy beans and medicinal herbs, including Flemingia vestita and Flemingia macrophylla, showed an antigenotoxic effect against AFB1-caused mutagenesis [62]. In addition, sulforaphane derived from cruciferous plants, such as broccoli, Brussel sprouts or cabbages, confers a protective effect against AFB1-mediated genotoxicity in human hepatocytes [63]. Sulforaphane effectively induces hepatic total GST activity and attenuates hepatic AFB1-DNA adducts in AFB1-exposed rats [64,65]. In addition, the thyme and calendula extracts alone or in combination ameliorate aflatoxin-induced oxidative stress and genotoxicity mechanistically demonstrated the alterative expression of p53, bax and bcl2 gene expression [66]. Bhattacharya et al. [67] screened 26 plant phenolic flavonoids and found that the polyhydroxy flavonols, such as robinetin, quercetin, fisetin and morin, have a strong protective activity against the carcinogenic effects of AFB1.

However, the protective role of resveratrol against mycotoxicosis by other genotoxic mycotoxins is a controversial issue. Raghubeet al. [68] found that resveratrol, a polyphenol derived from red grape, blueberries, raspberries, mulberries, peanuts and itadori, ameliorates OTA-induced cellular oxidative stress in human embryonic kidneys. In addition, aflatoxin-induced AST, ALT and SOD were reduced by resveratrol supplementation in broiler birds [69]. However, Agamy et al. [70] compared the hepatoprotective effect of curcumin and resveratrol on aflatoxin-induced liver injury; curcumin, but not resveratrol, had a protective effect against AFB1-induced liver toxicity. Moreover, resveratrol has been shown to exert no protective effect against the cytotoxicity of mycotoxins, such as DON and OTA, in intestinal epithelial cells [71]. Therefore, more systematic and chronic effects of resveratrol on the mycotoxin-induced genotoxicity need to be assessed to determine the ultimate counteraction of the pharmacological components in the medicinal herbs and spices.

In addition to the effects of the medicinal natural components in herbs and spices on aflatoxin action, other mycotoxin-induced toxicities are also counteracted by these pharmacological elements. Yang et al. [72] reported that 6-gingerol, an active constituent of fresh ginger, has a strong protective property against the genotoxicity caused by patulin and that the antioxidant effect of 6-gingerol may play a critical role in reducing genotoxicity in hepatocytes. Several studies have reported the cytoprotective effect of epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea, against inflammatory responses caused by mycotoxins [73,74]. In particular, ribotoxic mycotoxins, such as DON and HT-2, exert diverse toxic effects on HT-29 cells by inducing oxidative stress, stimulating cyclooxygenase-2, enhancing caspase-3-activated apoptosis and stimulating the transcription of nuclear factor kappa B-mediated inflammatory genes. Lycopene has been considered as one of the most powerful antioxidants and is mainly found in tomatoes and other red fruits and vegetables, including red carrots, watermelons, gac and papayas. Lycopene also possesses protective activities against acute ZEA-triggered oxidative, inflammatory, endocrine and reproductive damage in mice [75,76].
Table 2. Effects of phytochemicals in medicinal herbs and spices on mycotoxicosis.

| Types of inhibition | Herbs and Spices | Effects on mycotoxicosis | References |
|---------------------|------------------|-------------------------|------------|
| Inhibition of fungal growth | Ajowain | *A. flavus, A. parasiticus* | [33] |
| | Basil | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [40] |
| | Cloves | *Aspergillus, Penicillium* | [35,36] |
| | Clove oil | *A. flavus, A. parasiticus* | [33] |
| | Cinnamon | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [40] |
| | Chinese cassia | *Aspergillus, Penicillium* | [35] |
| | Coriander | *A. flavus, A. parasiticus* | [33] |
| | Kalonji | *A. flavus, A. parasiticus* | [33] |
| | Kalonji oil | *A. flavus, A. parasiticus* | [33] |
| | Marigold | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [31] |
| | Neem oil | *A. flavus, A. parasiticus* | [33] |
| | Quyssum | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [40] |
| | Spearmint | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [40] |
| | Thyme | *Aspergillus, Penicillium* | [35] |
| | Thyme oil | *A. flavus, A. parasiticus, A. ochraceus, F. moniliforme* | [40] |
| | Turmeric | *A. flavus, A. parasiticus* | [33] |
| Inhibition of mycotoxin production | Anise | Sterigmatocystin, citrinin | |
| | Black cumin | AFB, sterigmatocystin, citrinin | |
| | Black pepper | AF, sterigmatocystin | |
| | Peppermint | AFB<sub>1</sub>, citrinin | |
| | Cardamom | AFB<sub>1</sub>, sterigmatocystin, citrinin | [18] |
| | Clove | AF, sterigmatocystin, citrinin | |
| | Cumin | AFB<sub>1</sub>, citrinin | |
| | Ginger | Sterigmatocystin | |
| | Marjoram | AFB<sub>1</sub>, citrinin | |
| | Sweet basil leaves | AFB<sub>1</sub> | [39] |
| Types of inhibition | Herbs and Spices | Effects on mycotoxicosis | References |
|---------------------|------------------|-------------------------|------------|
| Caffeic acid        | Caffeic acid     | Normalization of γGT, ALP, GST and NO | [49,59] |
| phenethyl ester     |                  |                         |            |
| Catechin            | Catechin         | Attenuation of DNA adduct formation | [59] |
| Chitosan            | Chitosan         | Normalization of AST and ALT levels | [50] |
| Chlorogenic acid    | Chlorogenic acid | Attenuation of DNA adduct formation | [59] |
| Turmeric            | Turmeric         | Normalization of LDH and ALT | [47,48] |
| Cyanidin            | Cyanidin         | Normalization of ROS, protein and DNA synthesis, and apoptosis in HepG2 and Caco-2 cells | [52–55] |
| Diallyl sulfide     | Diallyl sulfide  | AFB<sub>1</sub> Reduction of DNA damage | [61] |
| Epigallocatechin-3-gallate | Epigallocatechin-3-gallate | Deoxynivalenol, HT-2 toxin Suppression of inflammatory responses | [73,74] |
| Eugenol             | Eugenol          | AFB<sub>1</sub> Attenuation of DNA adduct formation | [59] |
| Fisetin             | Fisetin          | AFB<sub>1</sub> Prevention of carcinogenesis Attenuation of DNA adduct formation | [59,67] |
| Genistein           | Genistein        | AFB<sub>1</sub> Reduction of mutagenesis | [62] |
| Indole-3-carbinol   | Indole-3-carbinol| AFB<sub>1</sub> Prevention of carcinogenesis in rat liver | [77] |
| Kaempferol          | Kaempferol       | AFB<sub>1</sub> Attenuation of DNA adduct formation | [59] |
| Lycopene            | Lycopene         | AFB<sub>1</sub>, OTA ZEA Protection effect on oxidative, inflammatory, endocrine and reproductive damage in mice | [56–58,75,76] |
| Morin               | Morin            | AFB<sub>1</sub> Prevention of carcinogenesis Attenuation of DNA adduct formation | [59,67] |
| Naringin            | Naringin         | AFB<sub>1</sub> Attenuation of DNA adduct formation | [59] |
| Quercetin           | Quercetin        | AFB<sub>1</sub> Prevention of carcinogenesis | [67] |
| Robinetin           | Robinetin        | AFB<sub>1</sub> Prevention of carcinogenesis | [67] |
| Sulforaphane        | Sulforaphane     | AFB<sub>1</sub> Induction of hepatic total GST activity. Attenuation of DNA adduct formation | [63–65] |
Table 2. Cont.

| Types of inhibition | Herbs and Spices | Effects on mycotoxicosis | References |
|---------------------|------------------|--------------------------|------------|
| Inhibition of mycotoxin action | Thyme oil | AF$_{B1}$ Excretion of AFs Normalization of AST, ALP and $\gamma$GT Ameliorative effect on oxidative stress and genotoxicity | [46,66] |
|                      | Vanillin        | AF$_{B1}$ Attenuation of DNA adduct formation Patulin | [59] |
|                      | Gingerol        | Reduction of DNA damage in HepG2 | [37] |

5. Conclusions

Although the occurrence and exposure of mycotoxins in most medicinal herbs and spices in various countries are inevitable, many of the bioactive components in these agricultural commodities have been known to regulate the fungal growth, mycotoxin production and their toxic actions in the plant and its herbivores, including human beings and domestic animals. These endogenous components are thus crucial attenuators by reducing the inevitable exposure and toxicities when taken in together with the contaminated mycotoxins. Since it is not easy to completely eliminate or prevent mycotoxin contamination during pre- and post-harvest stages, active strategies for reducing fungal growth and mycotoxin production are important for minimizing the exposure and toxicity to humans and animals. Although numerous methods for the elimination of mycotoxins using physical, chemical and biological strategies have been suggested, the safety of these methods and reducing agents still remain unclear. Since many components from medicinal herbs or spices affect the fungal growth or actions of mycotoxins, these antagonizing factors, considered safe and natural, have been studied to help alleviate mycotoxin exposure and toxicity. In addition to the regulatory actions of these endogenous components on fungal growth and mycotoxin production, these antagonizing components when mixed with mycotoxins would potentially reduce the risk of toxicity to exposed humans and animals. The compensatory actions of the endogenous beneficial components in terms of metabolism, distribution, excretion and final adverse actions against cells and tissues would be useful strategies to enable safe use of the medicinal herbs and spices unavoidably contaminated with mycotoxins at levels under the regulatory limits. However, since some natural endogenous components could enhance the toxicity of mycotoxins via metabolic activation or retarded secretion by complex formation with mycotoxins, extensive investigations into these interactions is warranted for the sound toxicological assessment of herbal medicines and spices for human and animal use in the future. In summary, the biological interaction between mold, mycotoxin and herbal components might be an important strategy for overcoming the worldwide occurrence of mycotoxin contamination, including that in medicinal herbs and spices. This review presented the safest, cost-efficient and most natural strategies for better risk assessment of mycotoxin-contaminated medicinal herbs and spices in the environment and in the food chain.
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Author Contributions

Kee Hun Do, Tae Jin An, and Yuseok Moon analyzed the raw data, organized the data and set up the review hypothesis. Kee Hun Do and Yuseok Moon wrote the manuscript and Sang-Keun Oh assisted the data collection. Yuseok Moon supervised the overall project.

Conflicts of Interest

The authors declare no conflict of interest.

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