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Original Article

Investigation of aflatoxins contamination in herbal materia medica in a Taiwan pharmaceutical factory

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ABSTRACT

During the years 2005–2016, a total of 1067 samples for 24 types of herbal materia medica were investigated for the presence of aflatoxins (AFs) using immunoaffinity column cleanup and HPLC-coupled to a fluorescence detector after post-column derivatization. AFs were detected in 373 (35%) out of the total samples. Among them, Platycladi Semen (65% for total AFs and 79% for AFB1), Corydalis Rhizoma (53% for total AFs and 32% for AFB1), Corni Fructus (3% for total AFs), Coicis Semen (3% for total AFs and AFB1), Nelumbinis Semen (6% for total AFs and 9% for AFB1), Arecae Semen (18% for AFB1), Polygalae Radix (5% for total AFs and AFB1), and Cassiae Semen (25% for total AFs and 38% for AFB1) exceeded the official limits of 5 and 10 µg/kg, for AFB1 and total AFs (the sum of AFB1, AFB2, AFG1, and AFG2), respectively, set by the Taiwan government. We concluded that Platycladi Semen, Corydalis Rhizoma, and Cassiae Semen are the most commonly contaminated by AFs.

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1. Introduction

During the process of harvest, store, and transport, herbal materia medica could be contaminated by fungi leading to production of mycotoxins. Aflatoxins (AFs), a class of mycotoxins, are toxic secondary metabolites produced by *Aspergillus parasiticus* and *Aspergillus flavus*. Four AFs (AFB1, AFB2, AFG1, and AFG2) can be produced by *A. parasiticus* while two of them, AFB1 and AFB2, can be produced by *A. flavus* [1]. The

official limits for the tolerance of AFs for certain herbal materia medica was established in some countries, including Korea [2] (15 µg/kg for total AFs and 10 µg/kg for AFB1), Italy [3] (10 µg/kg for total AFs and 5 µg/kg for AFB1), and Germany [3] and European Pharmacopeia [4] (4 µg/kg for total AFs and 2 µg/kg for AFB1). In Taiwan, the official limit for total AFs, no more than 15 µg/kg for 14 items, was set in 2006. Moreover, this limit was reset to 10 µg/kg for total AFs and 5 µg/kg for AFB1 for 37 items in 2016. In this study, we surveyed AFs' contamination in a total of 1067 samples for 24 monographs of herbal materia

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medica in our pharmaceutical factory using immunoaffinity column cleanup and HPLC-coupled to a fluorescence detector after post-column derivatization.

2. Materials and methods

2.1. Sample collection and preparation

All dried herbal materia medica were imported from different provinces of China. Herbal samples were prepared based on the research from Trucksess et al. [5] with minor modification. Briefly, 50 g of sample powder was placed into blender, added with 5 g of sodium chloride and 100 mL of 80% (v/v) methanol. After blended for 1 min, the mixture was filtrated by filter paper to obtain primary filtrate, and then 10 mL of primary filtrate was added with 40 mL of pure water followed by filtration using glass fiber filter paper to obtain secondary filtrate. 10 mL of the secondary filtrate was slowly passed through an Aflatest-P® immunoaffinity column (Vicam, MA, USA) at flow rate of 1 drop per sec. The column was washed twice with 10 mL of pure water and eluted with 1 mL of methanol. The 1 mL of eluent was collected and added with 1 mL of pure water to obtain sample solution.

2.2. Preparation of AFs standard solution

1 mL of AFs K-mix-M (Sigma–Aldrich, St. Louis MO, USA) containing 1 ppm of B1 and G1 as well as 0.3 ppm of B2 and G2 was added with 1 mL of 50% (v/v) methanol to obtain stock solution. 0.16 mL of stock solution was mixed with 50% (v/v) methanol to the final volume of 2 mL to obtain working solution. The different concentrations of standard solution were prepared by mixing working solution with 50% (v/v) methanol through serial dilution.

2.3. HPLC analysis

Analytical HPLC was performed on Hitachi D-7000 interface equipped with L-7485 fluorescence detector, L-7100 pump, L-7200 autosampler, L-7300 column oven, and post-column photochemical reaction system (Tokyo, Japan). Chromatographic separation was carried out on a Mightysil RP-18 column (250 × 4.6 mm, 5 μm). HPLC conditions were established according to the research from Trucksess et al. [5] with minor modification. Briefly, the wavelengths for excitation and emission were 360 nm and 440 nm, respectively. The mobile phase, flow rate, injection volume, column temperature, and stop time were set at 45% (v/v) methanol, 1.0 mL/min, 20 μL, 40 °C, and 20 min, respectively.

2.4. Method validation

The linearity of the standard curve was established using different concentrations of the four AFs and three replications were conducted for each concentration. AFs-free sample, Astragali Radix, was used in recovery tests and in limit of quantification (LOQ) determination. Recovery tests and LOQ determination were determined using spike samples. For LOQ determination, AFB1, AFB2, AFG1, and AFG2 to a final

concentration of 0.1547, 0.0956, 0.5438, and 0.1875 μg/kg, respectively, were added to Astragali Radix and conducted in triplicate. The LOQ for each AF were obtained using interpolation method according to a signal-to noise (S/N) ratio of 10:1. For recovery tests, low, medium, and high concentration of each AF were added to Astragali Radix and carried out in triplicate. The recovery rate was calculated as follows: (detection of value ÷ spike concentration) × 100%.

3. Results and discussion

3.1. Method validation

Each AF peak in the chromatogram was well identified by comparing the retention times with those of corresponding standard solution (Fig. 1). The levels of AFs in sample solution were determined by comparison to the respective standard curve. The coefficient of determination for each standard curve was higher than 0.995 (Table 1), indicating that the linearity is fine. As also shown in Table 1, the LOQ for AFB1, AFB2, AFG1, and AFG2 were 0.20, 0.10, 0.40, and 0.15 μg/kg, respectively. The ranges of recovery rate for four AFs are 87.47%–103.21% (Table 1), indicating this analytical method is valid. Herein, each value is the average from three replicated samples. It should be noted that several factors may affect the recovery rate, including the type of substrate [6,7], purification method [6], and derivatization device [6].

3.2. Survey of AFs contamination in herbal materia medica

Several studies have conducted the survey of AFs contamination in herbal materia medica. The frequency of AF contamination was report by Rizzo et al. [8] to occur in 27 of 152 samples (17.8%) with the detected range of AFB1 from 10 to 2000 μg/kg; by Roy and Chourasia [9] to occur in 26 of 50 samples (52%) with the detected range of AFB1 from 170 to 670 μg/kg; by Chourasia [10] to occur in 65 of 150 samples (43%) with the detected range of AFB1 from 50 to 910 μg/kg; by Lee et al. [2] to occur 124 of 729 samples (17%) with the detected range of AFB1 from 0.1 to 404.7 μg/kg; by Santos et al. [11] to occur 81 of 84 samples (96%) with the detected range of total AF from 1.4 to 855 μg/kg; and by Romagnoli et al. [12] to occur 0 of 27 samples. There are many differences in the amount and incidence rate of AFs contamination in herbal materia medica.

We summarized the survey of AFs contamination in herbal materia medica by Taiwan Food and Drug Administration (TFDA) from 2002 to 2013 [13–16]. A total of 1230 samples, belonging to 43 species, were collected from Chinese medicinal manufactory plants and drug stores and 107 (8.7%) AFs-contaminated samples were detected (Table 2). Among these AF-contaminated samples, 35 samples (2.8%) and 41 samples (3.3%) were above the current legislative level permissible in Taiwan (10 μg/kg for total AFs and 5 μg/kg for AFB1) (Table 2). Nelumbinis Semen (11.4% for total AFs and AFB1), Platycladi Semen (50% for total AFs and 60% for AFB1), and Corydalis Rhizoma (11.4% for total AFs and 14.3% for AFB1) are the most commonly contaminated by AFs and above the official limits (Table 2).

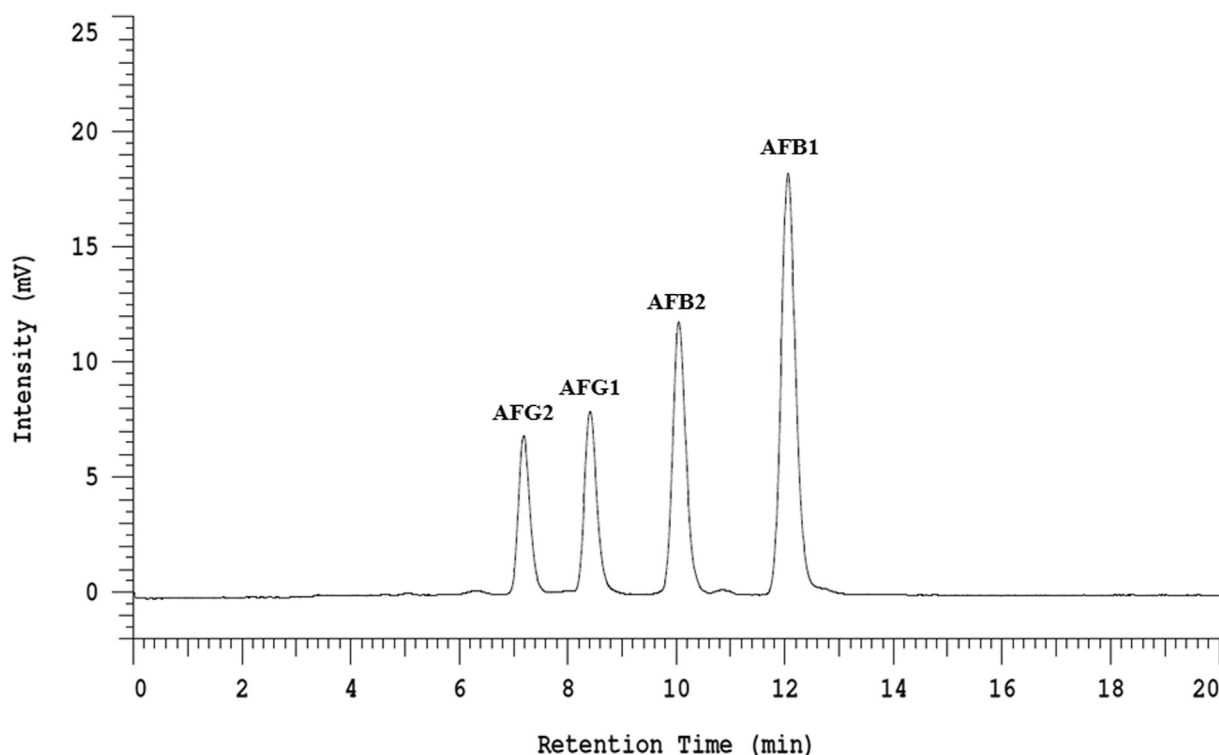


Fig. 1 – HPLC chromatogram of four aflatoxins (B1, B2, G1, and G2).

Table 1 – Linearity, LOQ, and recovery rate of four aflatoxins in *Astragali Radix* by HPLC.

Linearity				
Items	Concentration range ($\mu\text{g}/\text{kg}$)	Linear regression equation	R^2	
AFB1	0.309375–19.8	$Y = 83270X + 2748$	0.99999	
AFB2	0.095625–6.12	$Y = 181589X + 1490$	0.99999	
AFG1	0.54375–17.4	$Y = 34305X + 385$	0.99994	
AFG2	0.1875–6	$Y = 72147X + 3185$	0.99871	
LOQ				
Items	Spike value ($\mu\text{g}/\text{kg}$)	Detection value ($\mu\text{g}/\text{kg}$)	S/N ratio	S/N = 10 ($\mu\text{g}/\text{kg}$)
AFB1	0.1547	0.1869	9.08	0.20
AFB2	0.0956	0.1060	12.35	0.10
AFG1	0.5438	0.5738	14.73	0.40
AFG2	0.1875	0.1857	12.58	0.15
Recovery rate				
Items	Spike value ($\mu\text{g}/\text{kg}$)	Detection value ($\mu\text{g}/\text{kg}$)	Recovery rate (%) ^a	
AFB1	0.309375	0.2922 ± 0.02	94.45%	
	2.475	2.5072 ± 0.05	101.30%	
	19.8	20.2128 ± 0.30	102.08%	
AFB2	0.095625	0.0953 ± 0.01	99.66%	
	0.765	0.7853 ± 0.03	102.65%	
	6.12	6.2072 ± 0.40	101.42%	
AFG1	0.54375	0.5612 ± 0.03	103.21%	
	2.175	2.1856 ± 0.07	100.49%	
	17.4	17.2867 ± 0.48	99.35%	
AFG2	0.1875	0.1640 ± 0.02	87.47%	
	0.75	0.7519 ± 0.01	100.25%	
	6	5.8828 ± 0.18	98.05%	

^a The recovery rate was calculated as follows: (detection of value \div spike concentration) \times 100%.

During 2005 to 2016, the amount and incidence rate in a total of 1067, belonging to 24 species, herbal materia medica were examined for the presence of AFs. 373 (35%) AFs-contaminated samples were detected and the amount of AFB1 in AFs-contaminated samples was in the range of 0.2052–693.38 $\mu\text{g}/\text{kg}$ (Table 3). Eight herbal samples, including *Platycladi Semen*, *Corydalis Rhizoma*, *Polygalae Radix*, *Nelumbinis Semen*, *Coicis Semen*, *Arecae Semen*, *Cassiae Semen*, and *Corni Fructus*, exceeded the official limits of 5 and 10 $\mu\text{g}/\text{kg}$ established by the Taiwan government for AFB1 and total AFs, respectively, accounted for 214 (20%) for total AFs and 259 (24%) for AFB1 (Table 3). Among them, *Platycladi Semen* (65% for total AFs and 79% for AFB1), *Corydalis Rhizoma* (53% for total AFs and 32% for AFB1), and *Cassiae Semen* (25% for total AFs and 38% for AFB1) are the most commonly contaminated by AFs and are above the official limits (Table 3).

Based on the different parts, AF-contaminated samples were detected in semen of 237 samples (69%), in rhizome of 98 samples (47%), in fructus of 23 samples (8%), in radix of 6 samples (4%), and in others of 9 samples (10%). The samples exceeded the official limits of Taiwan regulations in semen of 156 samples (46%) for total AFs and 193 samples (56%) for AFB1, in rhizome of 53 samples (25%) for total AFs and 63 samples (30%) for AFB1, in fructus of 2 samples (0.7%) for total AFs, in radix of 3 samples (2%) for total AFs and 3 samples (2%) for AFB1. These results were similar with the finding that semen is the most commonly contaminated by AFs, as indicated by previous studies [2,13–16].

It should be noted that several differences exist between TFDA surveys and our study. One is that Taiwan government establish the official limits for AFs in herbal materia medica (15 $\mu\text{g}/\text{kg}$ for total AFs for 14 items was set in 2006 and 10 $\mu\text{g}/\text{kg}$ for total AFs and 5 $\mu\text{g}/\text{kg}$ for AFB1 for 37 items in 2016) based on

Table 2 – Survey of aflatoxins contamination in herbal materia medica by Taiwan Food and Drug Administration from 2002 to 2013 [13–16].

Parts	Items	No. of samples	AF-contaminated samples	AFB1 detected value (µg/kg)	No. of out of specifications		
					Total AF > 10 ppb	AFB1 > 5 ppb	
Semen	Coicis Semen	120	24 (20%)	0.2–45.3	3 (3%)	2 (2%)	
	Nelumbinis Semen	70	8 (11%)	22.4–394.4	8 (11%)	8 (11%)	
	Platycladi Semen	20	20 (100%)	1.3–25.4	10 (50%)	12 (60%)	
Rhizoma	Corydalis Rhizoma	70	14 (20%)	2.3–256.5	8 (11%)	10 (14%)	
	Alismatis Rhizoma	20	1 (5%)	3.6	–	–	
	Batatae Rhizoma	50	–	–	–	–	
	Curcumae Longae Rhizoma	20	–	–	–	–	
	Cimicifugae Rhizoma	20	–	–	–	–	
	Atractylodis Rhizoma	20	–	–	–	–	
	Acori Graminei Rhizoma	20	–	–	–	–	
	Zingiberis Rhizoma	20	–	–	–	–	
	Pinelliae Rhizoma	20	–	–	–	–	
	Fructus	Setariae Germinatus Fructus	20	11 (55%)	0.2–8.6	1 (5%)	1 (5%)
		Piperis Fructus	20	1 (5%)	–	–	–
Ligustri Fructus		20	–	–	–	–	
Foeniculi Fructus		20	–	–	–	–	
Crataegi Fructus		20	–	–	–	–	
Jujubae Fructus		20	–	–	–	–	
Lycii Fructus		20	–	–	–	–	
Corni Fructus		20	–	–	–	–	
Anisi Stellati Fructus		20	–	–	–	–	
Citri Immaturus Fructus		20	–	–	–	–	
Gardeniae Fructus		20	–	–	–	–	
Schisandrae Fructus		20	–	–	–	–	
Radix		Astragali Radix	140	9 (6%)	4.3–64.3	3 (2%)	7 (5%)
		Polygalae Radix	20	11 (55%)	0.7–8.1	1 (5%)	–
		Puerariae Radix	20	1 (5%)	–	–	–
		Glycyrrhizae Radix	20	–	–	–	–
		Scutellariae Radix	20	–	–	–	–
	Paeoniae Alba Radix	20	–	–	–	–	
	Gentianae Macrophyllae Radix	20	–	–	–	–	
	Gentianae Rhizoma et Radix	20	–	–	–	–	
	Ginseng Radix	20	–	–	–	–	
	Others	Citri Reticulatae Pericarpium	40	6 (15%)	–	–	–
		Massa Medicata Fermentata	20	1 (5%)	6.7	1 (5%)	1 (5%)
Arecae Pericarpium		20	–	–	–	–	
Farfae Flos		20	–	–	–	–	
Polyporus		20	–	–	–	–	
Fritillariae Cirrhosae Bulbus		20	–	–	–	–	
Poria		20	–	–	–	–	
Clematidis Caulis		20	–	–	–	–	
Cinnamomi Ramulus		20	–	–	–	–	
Moutan Radicis Cortex		20	–	–	–	–	
Total			1230	107 (9%)	–	35 (3%)	41 (3%)

Table 3 – Investigation of aflatoxin contamination in herbal materia medica in our factory from 2005 to 2016.

Parts	Items	No. of samples	AF-contaminated samples	AFB1 detected value ($\mu\text{g}/\text{kg}$)	Out of specifications	
					Total AFs > 10 ppb	AFB1 > 5 ppb
Semen	Platycladi Semen	233	216 (93%)	0.25–592.0	151 (65%)	183 (79%)
	Coicis Semen	37	7 (19%)	0.40–12.0	1 (3%)	1 (3%)
	Nelumbinis Semen	32	4 (13%)	0.31–163.3	2 (6%)	3 (9%)
	Arecae Semen	17	5 (29%)	1.54–38.5	–	3 (18%)
	Cassiae Semen	8	4 (50%)	2.67–12.9	2 (25%)	3 (38%)
	Ziziphi Spinosae Semen	8	1 (13%)	1.03	–	–
	Persicae Semen	7	–	–	–	–
Rhizoma	Corydalis Rhizoma	200	98 (49%)	0.21–693.4	53 (27%)	63 (32%)
	Belamacanae Rhizoma	10	–	–	–	–
Fructus	Jujubae Fructus	99	–	–	–	–
	Corni Fructus	66	23 (35%)	0.25–0.73	2 (3%)	–
	Crataegi Fructus	35	–	–	–	–
	Lycii Fructus	34	–	–	–	–
	Ligustri Fructus	27	–	–	–	–
	Foeniculi Fructus	25	–	–	–	–
	Radix	Astragali Radix	75	–	–	–
Hedysari Radix		28	–	–	–	–
Polygalae Radix		16	6 (38%)	2.26–118.1	3 (19%)	3 (19%)
Saposhnikoviae Radix		6	–	–	–	–
Scrophulariae Radix		5	–	–	–	–
Glycyrrhizae Radix		5	–	–	–	–
Others	Citri Reticulatae Pericarpium	65	2 (3%)	0.30–0.53	–	–
	Massa Medicata Fermentata	15	7 (5%)	0.38–2.03	–	–
	Arecae Pericarpium	14	–	–	–	–
Total		1067	373 (35%)	–	214 (20%)	259 (24%)

the TFDA surveys from 2002 to 2013. Our study applied the current regulations to summary and to compare the results between TFDA surveys and our findings. Another is that the incidence of AF-contaminated samples and maximum quantity of AFB1 in Platycladi Semen and Corydalis Rhizoma were quite different. The possible explanation for this difference may attribute the source and origin of herbal materia medica. In TFDA surveys, herbal samples were collected from Chinese medicinal manufactory plants and drug stores in Taiwan which have been pre-tested for AFs contamination, by contrast, our herbal samples were collected from different provinces of China.

Notably, AFB1 is well known carcinogen and exhibited the strongest toxicity among these four AFs [5] and the LD50 of AFB1 in mouse is 9 mg/kg [17]. A formula is available for converting animal dose to human equivalent dose (HED) in mg/kg, i.e., multiply the mouse dose in mg/kg/day by 0.08 [18]. By calculation, the LD50 of AFB1 for the 60-kg healthy person consumption is around 44 mg/day. In spite of the ingested level, the cumulative effect of AFB1 is to increase cancer risk. Therefore, how to reduce AFs contamination in herbal materia medica is an important issue. The treatments of AFs-contaminated herbal materia medica in our factory can be divided into two ways. One is that AFs-detected value is higher than 5 $\mu\text{g}/\text{kg}$ for AFB1 and 10 $\mu\text{g}/\text{kg}$ for total AFs, we must reject or destroy. Another is that AFs-detected value is under current official limits, we will store herbal materia medica at $-20\text{ }^{\circ}\text{C}$ freezer to avoid the growth of *A. parasiticus* and *A. flavus*. In addition, several innovative technologies, such as biological control, sorting technology, electromagnetic radiation, ozone fumigation, chemical agents, and

improved packaging materials, have been used to minimize AFs contamination in agricultural products [19].

4. Conclusion

This survey provides useful information about the AFs-contaminated herbal materia medica and hopes to boost the awareness of crisis among farmers, manufacturer, and consumers. To ensure the quality of final products, the most important task is to control each herbal materia medica before manufacturing. We concluded that Platycladi Semen, Corydalis Rhizoma, and Cassiae Semen are the most commonly contaminated by AFs.

Conflicts of interest

We declare no conflict of interest involved in this study.

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