UNIVERSITI PUTRA MALAYSIA

RISK ASSESSMENT OF AFLATOXIN B1 IN HERBAL MEDICINES AND PLANT FOOD SUPPLEMENTS MARKETED IN MALAYSIA THROUGH MARGIN OF EXPOSURE APPROACH

SITI SOLEHA BINTI AB DULLAH

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By

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Aflatoxin B1 (AFB1) is a mycotoxin produced by several species of *Aspergillus* fungi that can induce liver cancer in animals and humans upon ingestion of AFB1-contaminated food. This study aims to perform the risk assessment of AFB1 in herbal medicines and plant food supplements (PFS) marketed in Malaysia through the margin of exposure (MOE) approach. A total of 31 herbal medicines and PFS samples were purchased through online platforms and over-the-counter using targeted sampling method. Samples extracted with 70% methanol were subjected to immunoaffinity column filtration and quantified using ELISA assay. Next, the MOE was calculated using the benchmark dose lower level of 10 ($BMDL_{10}$) of 63.46 ng/kg bw/day derived from the animal carcinogenicity data, and the estimated daily intake (EDI) among Malaysian adults ranged from 0.006 to 10.456 ng/kg bw/day. MOE below 10, 000 indicate the urgency for risk management actions. The estimated percentage of liver cancer attributable to AFB1 exposure was calculated by dividing the target population risk per year per 100,000 population by the age-standardised incidence rate for liver cancer. AFB1 was detected in 80.6% of samples analysed at a level ranging from 0.275 to 13.941 µg/kg. The calculated MOE ranged from 6.07 to 10227.35. In total, 24 (96%) out of 25 positive samples had MOE below 10,000. The risk of liver cancer ranged from 0 to 0.261 cancers per 100,000 population per year and the estimated percentage of liver cancer incidence ranged from 0.002% to 4.149%. This study found a moderate risk of liver cancer in Malaysian populations due to AFB1 from herbal medication and PFS, emphasising the need for risk management measures.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENILAIAN RISIKO TERHADAP AFLATOKSIN B1 DI DALAM UBATAN HERBA DAN MAKANAN TAMBAHAN BERASASKAN TUMBUHAN DIPASARAN MALAYSIA MELALUI KAEDAH MARGIN PENDEDAHAN

Oleh

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Aflatoksin B1 (AFB1) adalah mikotoksin yang dihasilkan oleh beberapa spesis kulat Aspergilus yang boleh menyebabkan barah hati pada haiwan dan manusia akibat daripada pengambilan makanan yang dicemari oleh AFB1. Kajian ini bertujuan untuk melakukan penilaian risiko terhadap AFB1 di dalam ubatan herba dan makanan tambahan berasaskan tumbuhan dipasaran Malaysia melalui kaedah margin pendedahan. Sebanyak 31 sampel ubatan herba dan makanan tambahan berasaskan tumbuhan dibeli secara atas talian dan runcit menggunakan kaedah persampelan yang bersasar. Sampel diekstrak menggunakan metanol 70% dan menjalani penapisan lajur imunoafiniti dan dikuantifikasi menggunakan ujian imunosorben berkaitan dengan enzim. Seterusnya, margin pendedahan dikira berdasarkan penanda aras rendah tahap 10 ($BMDL_{10}$) yang diperoleh daripada data ujian karsinogenisiti haiwan iaitu 63.46 ng/kg berat badan/hari dan anggaran pengambilan harian ubatan herba atau makanan tambahan berasaskan tumbuhan oleh golongan dewasa di Malaysia dari 0.006 hingga 10.456 ng/kg berat badan/hari. MOE dibawah 10, 000 menunjukkan keperluan untuk tindakan pengurusan risiko yang segera. Anggaran peratusan barah hati yang disebabkan oleh pendedahan terhadap AFB1 dihitung dengan membahagi risiko populasi sasaran per tahun per 100,000 populasi dengan kadar kejadian mengikut usia untuk barah hati. AFB1 dikesan pada 80.6% sampel yang telah dianalisis pada tahap 0.275 hingga 13.941 µg/kg. Margin pendedahan yang dikira adalah di antara 6.07 hingga 10227.35. Secara keseluruhan, 24 (96%) daripada 25 sampel mempunyai margin pendedahan di bawah 10,000. Risiko barah hati berkisar antara 0 hingga 0.261 barah per 100,000 populasi per tahun dan anggaran peratusan kejadian barah hati antara 0.002% hingga 4.149%. Kajian ini menunjukkan risiko barah hati yang sederhana dalam kalangan penduduk Malaysia disebabkan oleh AFB1 di dalam ubatan herba dan makanan tambahan berasaskan tumbuhan, dan menekankan perlunya langkah-langkah pengurusan risiko.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
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LIST OF ABBREVIATIONS

AFB1	Aflatoxin B1
ADR	Adverse drug reaction
AFB1-FAPy	AFB1-Formamidopyrimidine
AFB2	Aflatoxin B2
AFBO	AFB1-*exo*-8,9 epoxide
AFG1	Aflatoxin G1
AFG2	Aflatoxin G2
AFM1	Aflatoxin M1
AFM2	Aflatoxin M2
AP	Apurinic
BMD	Benchmark dose
$BMDL_{10}$	Benchmark dose lower level of 10
BMDS	Benchmark dose software
BMR	Benchmark response
CYP450	Cytochrome P450
DCA	Drug Control Authority
DILI	Drug-induced liver injury
EDI	Estimated daily intake
ELISA	Enzyme-linked immunosorbent assay
EPA	Environment Protection Agency
FHF	Fulminant hepatic failure
HBV	Hepatitis B virus

HCC	Hepatocellular carcinoma
HDRM	Herbal drug raw material
HDS	Herbal dietary supplements
HILI	Herb-induced liver injury
IAC	Immunoaffinity column
LOAEL	Lowest observable adverse effect level
LOD	Limit of detection
LOQ	Limit of quantitation
MOE	Margin of exposure
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NTP	National Toxicology Program
PFS	Plant food supplement
POD	Point of departure
TCM	Traditional and complementary medicine
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Background

Aflatoxin is a secondary metabolite produced by several species of *Aspergillus* fungi known as *A. flavus, A. parasiticus*, and *A. nomius.* The most common types of aflatoxin produced by these fungi are aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), and aflatoxin G2 (AFG2), with International Agency for Research on Cancer (IARC) classifying AFB1 as a class 1 carcinogen (IARC, 2002). *A. flavus* and *A. parasiticus* are predominantly found in food and feed due to poor storage and improper handling techniques (Mahato et al., 2019). The discovery of aflatoxins began in 1960, and it has been shown to cause aflatoxicosis and cancer in animals and humans (Pickova et al., 2021). The epoxidation mechanism by cytochrome p450 (CYP450) enzymes in the liver is responsible for the toxic, genotoxic, and carcinogenic effects of AFB1 through the formation of reactive AFB1-*exo*-8,9-epoxides metabolites (Marchese et al., 2018). These metabolites are highly unstable and can react with cellular macromolecules such as DNA, RNA, and protein albumin to form adducts that can affect gene expression and disrupt essential cellular functions (Marchese et al., 2018).

In 1960, aflatoxins were found to be the causative agent of the unknown disease called Turkey X disease, which caused thousands of poultry died and it was linked to the contamination of Brazilian peanuts used as a major ingredient in animal feed in the Cheshire region in London (Blount, 1961). In 1961, study had shown the association between toxic peanut meals containing AFB1 and the induction of primary liver tumor in rats, which was followed by sufficient studies supporting the evidence of carcinogenicity of aflatoxin in animals and humans (Awuchi et al., 2021; Hamid et al., 2013; Li et al., 2018). Globally, over 4 billion humans are exposed to dietary aflatoxins, which can result in hepatocellular carcinoma (HCC) (Liu et al., 2012). Considering there are approximately 520,000 new HCC cases reported each year in China, Southeast Asia, and sub-Saharan Africa, reducing aflatoxin in human diets to levels below detectable levels could prevent 72,800 to 98,800 cases of HCC every year in these regions (Liu et al., 2012).

Malaysia is a tropical country with a "jungle of pharmacy", which refers to the tropical rainforest with great diversity of flora, fauna, and herbaceous plants with therapeutic properties (Abu Bakar et al., 2018). According to the World Health Organisation, herbal medicines have been defined as "herbs and/or herbal materials and/or herbal preparations and/or finished herbal products in a form suitable for administration to patients" (WHO, 2018b). Malaysians' demand for natural products has grown rapidly in recent years due to various factors, including the easy availability of herbs and the enjoyment of their "natural" taste

at a reasonable price (Tengku Mohamad et al., 2019). In addition, people's reliance on drug therapy has shifted to herbal medicines and herbal supplements, as they believe that these natural products are safer and more effective than conventional medicine and have fewer adverse effects (Ekor, 2014; Tengku Mohamad et al., 2019). In Malaysia, herbal products with therapeutic claims must undergo a similar rigorous process as other therapeutic drugs in terms of standardisation of the active compound within the extract and relevant supporting data from pre-clinical and clinical studies (Ahmad et al., 2015).

Despite many regulations to be followed by manufacturers, the lack of quality control to regulate herbal products can be seen in the number of cases involving adverse reactions to herbal products (Ekor, 2014). The interchangeable terms between herbal medicines and PFS causes many local manufacturers to register their products under the food category to avoid compliance with quality standards and adhere to less stringent legislation, the Food Act 1983 and Food Regulations 1985 under the Department of Food Safety & Quality, Ministry of Health Malaysia (Ismail et al., 2020). Hence, consuming herbal medicines or PFS without prior approval from a doctor or pharmacist could lead to many health problems as raw herbs and their finished products may contain contaminants such as AFB1, which has been linked to human hepatotoxicity and liver cancer (Amadi & Orisakwe, 2018; Bunchorntavakul & Reddy, 2013; Maddukuri & Bonkovsky, 2014). Herbal medicines and PFS have been reported in Lee et al. (2020) as one of the most common causative agents for hepatic adverse drug reactions and most of the products involved were not registered with the Ministry of Health (Lee et al., 2020).

The uncontrolled use of herbal medicines is becoming a growing concern as some of in Malaysia, including imported products from Indonesia, have been found to contain AFB1, AFB2, and AFG1 at concentrations of 0.02 to 1.00 µg/kg, 0.01 to 0.40 µg/kg and 0.02 to 0.22 µg/kg, respectively (Ali et al., 2005). AFB1 was present in the majority of the 23 commercial "jamu" and "makjun" samples, followed by AFB2 and AFG1 (Ali et al., 2005). Although aflatoxin contamination in the herbal medicines discovered so far was relatively low, continuous intake of contaminated herbal medicines and supplements may increase the risk of HCC. Hence, the present study aims to evaluate the risk of AFB1, one of the most potent genotoxic carcinogens found in herbal medicines and plant food supplements (PFS) sold in Malaysia through the margin of exposure (MOE) approach.

1.2 Problem statement

The International Food and Agriculture Organization (FAO) estimates that about 25% of the world's food is contaminated with mycotoxins, making aflatoxin contamination a global problem (Eskola et al., 2020). Therefore, some countries such as Korea, Germany, Italy, and European Pharmacopoeia have issued

regulations on the maximum allowable levels of aflatoxin in medicinal plants, which are 10 µg/kg and µg/kg, 2 µg/kg, 4 µg/kg, and 2 µg/kg for AFB1 in the respective countries (Lee et al., 2014). Unfortunately, Malaysia has not yet set a specific limit for AFB1 in herbal medicines and PFS. AFB1 contamination of herbal medicines and PFS products has been studied worldwide, including Brazil (Prado et al., 2012), Korea (Shim et al., 2012), and China (Zhang et al., 2020). The presence of AFB1 herbal medicines and PFS should be regarded as an important issue in food safety since they could lead to aflatoxicosis and liver cancer. In Malaysia, very few studies have been conducted, most of which do not include risk assessments. Considering that low levels of AFB1 were found in most of the “jamu” and “makjun” products available in Malaysia analysed by Ali et al. (2005), continuous exposure to low levels of aflatoxins could pose a serious health risk to consumers. Therefore, risk assessment is important in Malaysia to ensure the safe use of herbal medicine and PFS.

1.3 Objective

1.3.1 General objective

To perform the risk assessment of AFB1 in herbal medicines and PFS marketed in Malaysia through margin of exposure (MOE) approach.

1.3.2 Specific objectives

1. To quantify the AFB1 contamination level in herbal medicines and PFS samples using ELISA assay.

2. To characterise risk of AFB1 exposure to human based on qualitative margin of exposure (MOE) approach and quantitative liver cancer risk estimation.

1.4 Hypothesis

1. AFB1 contamination level is below than the European regulatory limit of 5 µg/kg for all herbal medicines and PFS samples.

2. The MOE value of AFB1 exposure is more than 10,000 indicating low priority for risk management.

3. There is a low percentage of risk attributable to AFB1 exposure through consumption of herbal medicines and PFS samples.

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REFERENCES

Abdullah, N., Borhanuddin, B., Patah, A. E. A., Abdullah, M. S., Dauni, A., Kamaruddin, M. A., Shah, S. A., & Jamal, R. (2018). Utilization of Complementary and Alternative Medicine in Multiethnic Population: The Malaysian Cohort Study. *J Evid Based Integr Med*, *23*, 2515690x18765945. https://doi.org/10.1177/2515690x18765945

Abdullah, R., Diaz, L. N., Wesseling, S., & Rietjens, I. M. C. M. (2017). Risk assessment of plant food supplements and other herbal products containing aristolochic acids using the margin of exposure (MOE) approach. *Food Additives & Contaminants: Part A*, *34*(2), 135-144.

Abu Bakar, F. I., Abu Bakar, M. F., Abdullah, N., Endrini, S., & Rahmat, A. (2018). A review of Malaysian medicinal plants with potential anti-inflammatory activity. *Advances in Pharmacological Sciences*, *2018*, 8603602. https://doi.org/10.1155/2018/8603602

Ahmad, F., Zaidi, M. S., Sulaiman, N., & Majid, F. A. A. (2015). Issues and challenges in the development of the herbal industry in Malaysia. *Proceedings of The Malaysian National Economic Conference (PERKEM)*, *10*, 227-238.

Al-Malahmeh, A. J., Alajlouni, A. M., Ning, J., Wesseling, S., Vervoort, J., & Rietjens, I. M. C. M. (2017). Determination and risk assessment of naturally occurring genotoxic and carcinogenic alkenylbenzenes in nutmeg-based plant food supplements. *Journal of Applied Toxicology*, *37*(10), 1254-1264. https://doi.org/https://doi.org/10.1002/jat.3491

Alajlouni, A. M., Al-Malahmeh, A. J., Wesseling, S., Kalli, M., Vervoort, J., & Rietjens, I. M. C. M. (2017). Risk assessment of combined exposure to alkenylbenzenes through consumption of plant food supplements containing parsley and dill. *Food Additives & Contaminants: Part A*, *34*(12), 2201-2211. https://doi.org/10.1080/19440049.2017.1338837

Algammal, A. M., Elsayed, M. E., Hashem, H. R., Ramadan, H., Sheraba, N. S., El-Diasty, E. M., Abbas, S. M., & Hetta, H. F. (2021). Molecular and HPLC-based approaches for detection of aflatoxin B1 and ochratoxin A released from toxigenic Aspergillus species in processed meat. *BMC Microbiology*, *21*(1), 82. https://doi.org/10.1186/s12866-021-02144-y

Ali, N., Hashim, N. H., Saad, B., Safan, K., Nakajima, M., & Yoshizawa, T. (2005). Evaluation of a method to determine the natural occurrence of aflatoxins in commercial traditional herbal medicines from Malaysia and Indonesia. *Food and Chemical Toxicology*, *43*(12), 1763-1772.

Ali, N., & Watt, J. (2019). Risk assessment of dietary exposure to Aflatoxin contamination in spices. *Advances in Clinical Toxicology*, *4*(1), 1-16.

Amadi, C. N., & Orisakwe, O. E. (2018). Herb-induced liver injuries in developing nations: An update. *Toxics*, *6*(2), 24. https://doi.org/10.3390/toxics6020024

Arzandeh, S., Selamat, J., & Lioe, H. (2010). Aflatoxin in raw peanut kernels marketed in Malaysia. *Journal of Food and Drug Analysis*, *18*(1).

Awuchi, C. G., Ondari, E. N., Ogbonna, C. U., Upadhyay, A. K., Baran, K., Okpala, C. O. R., Korzeniowska, M., & Guiné, R. P. F. (2021). Mycotoxins Affecting Animals, Foods, Humans, and Plants: Types, Occurrence, Toxicities, Action Mechanisms, Prevention, and Detoxification Strategies—A Revisit. *Foods*, *10*(6). https://doi.org/10.3390/foods10061279

Azmi, M., Junidah, R., Mariam, A., Safiah, M., Fatimah, S., Norimah, A., Poh, B., Kandiah, M., Mohd Shariff, Z., Manan, W., Mohd Din, S. H., & Aris, T. (2009). Body mass index (BMI) of adults: Findings of the Malaysian Adult Nutrition Survey (MANS). *Malaysian journal of nutrition*, *15*, 97-119.

Azziz-Baumgartner, E., Lindblade, K., Gieseker, K., Rogers, H. S., Kieszak, S., Njapau, H., Schleicher, R., McCoy, L. F., Misore, A., DeCock, K., Rubin, C., Slutsker, L., & Aflatoxin Investigative, G. (2005). Case-control study of an acute aflatoxicosis outbreak, Kenya, 2004. *Environmental health perspectives*, *113*(12), 1779-1783. https://doi.org/10.1289/ehp.8384

Barnes, J. M., & Butler, W. H. (1964). Carcinogenicactivity of aflatoxin to rats. *Nature*, *202*(4936), 1016-1016. https://doi.org/10.1038/2021016a0

Basu, A. (2018). DNA Damage, Mutagenesis and Cancer. *International Journal of Molecular Sciences*, *19*. https://doi.org/10.3390/ijms19040970

Bbosa, G. (2013). Aflatoxins metabolism, effects on epigenetic mechanisms and their role in carcinogenesis. *Health*, *5*, 14-34. https://doi.org/10.4236/health.2013.510A1003

Benford, D., Leblanc, J.-C., & Setzer, R. W. (2010). Application of the margin of exposure (MOE) approach to substances in food that are genotoxic and carcinogenic: Example: Aflatoxin B1 (AFB1). *Food and Chemical Toxicology*, *48*, S34-S41.

Benford, D. J. (2015). The use of dose-response data in a margin of exposure approach to carcinogenic risk assessment for genotoxic chemicals in food. *Mutagenesis*, *31*(3), 329-331.

Benkerroum, N. (2020). Chronic and acute toxicities of aflatoxins: Mechanisms of action. *International Journal of Environmental Research and Public Health*, *17*(2), 423.

Björnsson, E. S., Bergmann, O. M., Björnsson, H. K., Kvaran, R. B., & Olafsson, S. (2013). Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland.

Gastroenterology, *144*(7), 1419-1425.e1413. https://doi.org/10.1053/j.gastro.2013.02.006

Blount, W. (1961). Tukey “X” disease. *Turkeys*, *9*, 52-78.

Bryda, E. C. (2013). The Mighty Mouse: the impact of rodents on advances in biomedical research. *Missouri medicine*, *110*(3), 207-211. https://pubmed.ncbi.nlm.nih.gov/23829104

Bunchorntavakul, C., & Reddy, K. R. (2013). Review article: herbal and dietary supplement hepatotoxicity. *Alimentary Pharmacology & Therapeutics*, *37*(1), 3-17. https://doi.org/https://doi.org/10.1111/apt.12109

Butler, W. H., & Barnes, J. M. (1968). Carcinogenic action of groundnut meal containing aflatoxin in rats. *Food and Cosmetics Toxicology*, *6*(2), 135-141.

Cambaza, E., Koseki, S., & Kawamura, S. (2018). Aflatoxins in Mozambique: Impact and Potential for Intervention. *Agriculture*, *8*(7). https://doi.org/10.3390/agriculture8070100

Carvajal-Moreno, M. (2015). Metabolic Changes of Aflatoxin B1 to become an Active Carcinogen and the Control of this Toxin. *Immunome Research*, *11*. https://doi.org/10.4172/1745-7580.10000104

Chen, L., Mulder, P. P. J., Peijnenburg, A., & Rietjens, I. M. C. M. (2019). Risk assessment of intake of pyrrolizidine alkaloids from herbal teas and medicines following realistic exposure scenarios. *Food and Chemical Toxicology*, *130*, 142-153. https://doi.org/https://doi.org/10.1016/j.fct.2019.05.024

Cheng, C. T. (1992). Perak, Malaysia, mass poisoning. Tale of the Nine Emperor Gods and rat tail noodles. *The American journal of forensic medicine and pathology*, *13*(3), 261-263.

Chien, M.-Y., Yang, C.-M., Huang, C.-M., & Chen, C.-H. (2018). Investigation of aflatoxins contamination in herbal materia medica in a Taiwan pharmaceutical factory. *Journal of Food and Drug Analysis*, *26*(3), 1154-1159. https://doi.org/https://doi.org/10.1016/j.jfda.2018.01.016

Chin, C. K., Abdullah, A., & Sugita-Konishi, Y. (2012). Dietary intake of aflatoxins in the adult Malaysian population-an assessment of risk. *Food Additives & Contaminants: Part B*, *5*(4), 286-294.

Chitapanarux, T., & Phornphutkul, K. (2015). Risk Factors for the Development of Hepatocellular Carcinoma in Thailand. *Journal of clinical and translational hepatology*, *3*(3), 182-188. https://doi.org/10.14218/JCTH.2015.00025

Choudhuri, S., Chanderbhan, R., & Mattia, A. (2018). Chapter 20 - Carcinogenesis: Mechanisms and Models*. In R. C. Gupta (Ed.),

Veterinary Toxicology (Third Edition) (pp. 339-354). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-811410-0.00020-9

Cova, L., Wild, C. P., Mehrotra, R., Turusov, V., Shirai, T., Lambert, V., Jacquet, C., Tomatis, L., Trépo, C., & Montesano, R. (1990). Contribution of aflatoxin B1 and hepatitis B virus infection in the induction of liver tumors in ducks. *Cancer research*, *50*(7), 2156-2163.

Daou, R., Joubrane, K., Maroun, R. G., Khabbaz, L. R., Ismail, A., & Khoury, A. E. (2021). Mycotoxins: Factors influencing production and control strategies. *AIMS Agriculture and Food*, *6*(1), 416-447. https://doi.org/10.3934/agrfood.2021025

DCA. (1984). Control of Drugs and Cosmetics Regulations 1984. *Sale of Drugs Act 1952,*. https://www.npra.gov.my/index.php/my/general-conditions-for-registration-of-drug-products-under-the-control-of-drugs-and-cosmetics-regulations-1984.html

Demissie, N. (2018). A Review of Aflatoxin: Occurrence, Prevention, and Gaps in Both Food and Feed Safety. *Novel Techniques in Nutrition & Food Science*, *1*. https://doi.org/10.31031/NTNF.2018.01.000511

Diori Karidio, I., & Sanlier, S. H. (2021). Reviewing cancer's biology: an eclectic approach. *Journal of the Egyptian National Cancer Institute*, *33*(1), 32. https://doi.org/10.1186/s43046-021-00088-y

Dirican, S. (2015). A review of effects of aflatoxins in aquaculture. *Appl. Res. J*, *1*, 1191-1196. ECHA. (2012). *Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health*. Retrieved May, 23 from http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation

EDQM. (2018). *Questions and answers on quality of herbal medicinal products/traditional herbal medicinal products* Retrieved May,12 from https://www.ema.europa.eu/en/documents/other/questions-answers-quality-herbal-medicinal-products/traditional-herbal-medicinal-products-revision-6_en.pdf

EFSA. (2005). Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. *EFSA Journal*, *3*(10), 282. https://doi.org/https://doi.org/10.2903/j.efsa.2005.282

EFSA. (2007). Opinion of the scientific panel on contaminants in the food chain [CONTAM] related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products. *EFSA Journal*, *5*(3), 446. https://doi.org/https://doi.org/10.2903/j.efsa.2007.446

EFSA. (2017). Update: use of the benchmark dose approach in risk assessment. *EFSA Journal*, *15*(1), 4658. https://doi.org/https://doi.org/10.2903/j.efsa.2017.4658

EFSA. (2019). Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment [https://doi.org/10.2903/j.efsa.2019.5708]. *EFSA Journal*, *17*(6), e05708. https://doi.org/https://doi.org/10.2903/j.efsa.2019.5708

EFSA. (2020). Risk assessment of aflatoxins in food. *EFSA Journal*, *18*(3), 6040. https://doi.org/https://doi.org/10.2903/j.efsa.2020.6040

EFSA/WHO. (2016). Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree [https://doi.org/10.2903/sp.efsa.2016.EN-1006]. *EFSA Supporting Publications*, *13*(3), 1006E. https://doi.org/https://doi.org/10.2903/sp.efsa.2016.EN-1006

Ekor, M. (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in pharmacology*, *4*, 177. https://doi.org/10.3389/fphar.2013.00177

Elashoff, R. M., Fears, T. R., & Schneiderman, M. A. (1987). Statistical analysis of a carcinogen mixture experiment. I. Liver carcinogens. *Journal of the National Cancer Institute*, *79*(3), 509-526.

Eskola, M., Kos, G., Elliott, C. T., Hajšlová, J., Mayar, S., & Krska, R. (2020). Worldwide contamination of food-crops with mycotoxins: Validity of the widely cited 'FAO estimate' of 25%. *Critical Reviews in Food Science and Nutrition*, *60*(16), 2773-2789. https://doi.org/10.1080/10408398.2019.1658570

European Commission. (2006). Commission Regulation (EC) No. 1881/2006 setting maximum levels for certain contaminants in foodstuffs. *Journal of the European Union*, *364*, 5-24.

European Commission. (2014). Commission Regulation (EU) No 519/2014 of 16 May 2014 amending Regulation (EC) No 401/2006 as regards methods of sampling of large lots, spices and food supplements, performance criteria for T-2, HT-2 toxin and citrinin and screening methods of analysis. *The Official Journal of the European Union 147*, 29-43.

European Food Safety, A. (2005). Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic [https://doi.org/10.2903/j.efsa.2005.282]. *EFSA Journal*, *3*(10), 282. https://doi.org/https://doi.org/10.2903/j.efsa.2005.282

Felter, S. P., Conolly, R. B., Bercu, J. P., Bolger, P. M., Boobis, A. R., Bos, P. M. J., Carthew, P., Doerrer, N. G., Goodman, J. I., Harrouk, W. A., Kirkland, D. J., Lau, S. S., Llewellyn, G. C., Preston, R. J., Schoeny, R., Schnatter,

A. R., Tritscher, A., van Velsen, F., & Williams, G. M. (2011). A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. *Critical Reviews in Toxicology*, *41*(6), 507-544.

Frisvad, J. C., Hubka, V., Ezekiel, C. N., Hong, S. B., Nováková, A., Chen, A. J., Arzanlou, M., Larsen, T. O., Sklenář, F., Mahakarnchanakul, W., Samson, R. A., & Houbraken, J. (2019). Taxonomy of Aspergillus section Flavi and their production of aflatoxins, ochratoxins and other mycotoxins. *Studies in Mycology*, *93*, 1-63. https://doi.org/https://doi.org/10.1016/j.simyco.2018.06.001

FSSAI. (2011). Food safety and standard (Contaminants, toxins and residues) regulation. *Ministry of Health and Family Welfare. Food Safety and Standards Authority of India*, 1-19.

Garcia-Alvarez, A., Egan, B., de Klein, S., Dima, L., Maggi, F. M., Isoniemi, M., Ribas-Barba, L., Raats, M. M., Meissner, E. M., Badea, M., Bruno, F., Salmenhaara, M., Milà-Villarroel, R., Knaze, V., Hodgkins, C., Marculescu, A., Uusitalo, L., Restani, P., & Serra-Majem, L. (2014). Usage of plant food supplements across six European countries: Findings from the PlantLIBRA consumer survey. *PloS one*, *9*(3), e92265-e92265. https://doi.org/10.1371/journal.pone.0092265

Gelband, H., Chen, C.-J., Chen, W., Franceschi, S., Hall, A., London, W. T., McGlynn, K. A., & Wild, C. P. (2015). Liver cancer. *Cancer: Disease Control Priorities, Third Edition (Volume 3)*.

Gilbert Sandoval, I., Wesseling, S., & Rietjens, I. M. C. M. (2019). Aflatoxin B1 in nixtamalized maize in Mexico; occurrence and accompanying risk assessment. *Toxicology reports*, *6*, 1135-1142.

Gold, L. S., Sawyer, C. B., Magaw, R., Backman, G. M., de Veciana, M., Levinson, R., Hooper, N. K., Havender, W. R., Bernstein, L., Peto, R., & et al. (1984). A carcinogenic potency database of the standardized results of animal bioassays. *Environmental health perspectives*, *58*, 9-319. https://doi.org/10.1289/ehp.84589

Goodarzi, E., Ghorat, F., Jarrahi, A. M., Adineh, H., Sohrabivafa, M., & Khazaei, Z. (2019). Global incidence and mortality of liver cancers and its relationship with the human development index (HDI): An ecology study in 2018. *World Cancer Research Journal*, *6*, 12.

Gurav, N., & Medhe, S. (2018). Analysis of Aflatoxins B1, B2, G1 and G2 in peanuts: validation study. *Analytical Chemistry: An Indian Journal 17*, 126.

Haber, L. T., Dourson, M. L., Allen, B. C., Hertzberg, R. C., Parker, A., Vincent, M. J., Maier, A., & Boobis, A. R. (2018). Benchmark dose (BMD) modeling: current practice, issues, and challenges. *Critical Reviews in Toxicology*, *48*(5), 387-415. https://doi.org/10.1080/10408444.2018.1430121

Hamid, A. B. (1997). Present status and future prospects of research on the groundnuts aflatoxin problem in Malaysia. Aflatoxin Contamination Problems in Groundnut in Asia: Proceeding of the First Asia Working Group Meeting.

Hamid, A. S., Tesfamariam, I. G., Zhang, Y., & Zhang, Z. G. (2013). Aflatoxin B1-induced hepatocellular carcinoma in developing countries: Geographical distribution, mechanism of action and prevention. *Oncology letters*, *5*(4), 1087-1092. https://doi.org/10.3892/ol.2013.1169

Hariprasad, P., Durivadivel, P., Snigdha, M., & Venkateswaran, G. (2013). Natural occurrence of aflatoxin in green leafy vegetables. *Food Chemistry*, *138*(2), 1908-1913. https://doi.org/https://doi.org/10.1016/j.foodchem.2012.11.093

Hariprasad, P., Vipin, A. V., Karuna, S., Raksha, R. K., & Venkateswaran, G. (2015). Natural aflatoxin uptake by sugarcane (Saccharum officinaurum L.) and its persistence in jaggery. *Environmental Science and Pollution Research*, *22*(8), 6246-6253. https://doi.org/10.1007/s11356-014-3851-2

Hlobsile, K., Bwembya, G. C., Mamba, S., & Thwala, J. (2015). Assessment of aflatoxins B1 , B2 , G1 and G2 status of home grown maize in Swaziland. *African Journal of Food, Agriculture, Nutrition and Development*, *15*, 10522-10541.

IARC. (2002). IARC monographs on the evaluation of carcinogenic risks to humans: Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, *82*.

Ingenbleek, L., Lautz, L., Dervilly, G., Darney, K., Astuto, M., Tarazona, J., Liem, A., Kass, G., Leblanc, J., & Verger, P. (2020). Risk assessment of chemicals in food and feed: principles, applications and future perspectives.

Ismail, N. A., Sabran, S. F., Mohamed, M., & Abu Bakar, M. F. (2018). Ethnomedicinal knowledge of plants used for healthcare by the Javanese-Malay community in Parit Jelutong, Batu Pahat, Johor, Malaysia. AIP conference proceedings.

Ismail, S. F., Azmi, I. M. A. G., Daud, M., Abd Jalil, J., & Safuan, S. (2020). Regulatory control of herbal and traditional medicines in Malaysia: Issues and concerns. *International Journal of Business and Society*, *21*(S1), 192-204.

Ithnain, N., Panting, A. J., Kassim, R., Amirudin, N., & Krishnan, M. (2020). Perception of conventional medicine and herbal medicine usage amongst diabetic patients: A qualitative study in Negeri Sembilan, Malaysia. *Global Journal of Health Science*, *12*(10), 122-132.

Javed, A., Naeem, I., Benkerroum, N., Riaz, M., Akhtar, S., Ismail, A., Sajid, M., Tayyab Khan, M., & Ismail, Z. (2021). Occurrence and health risk assessment of aflatoxins through intake of Eastern herbal medicines collected from four districts of Southern Punjab, Pakistan. *International Journal of Environmental Research and Public Health*, *18*(18), 9531.

Johny, A. K., Cheah, W. L., & Razitasham, S. (2017). Disclosure of Traditional and Complementary Medicine Use and Its Associated Factors to Medical Doctor in Primary Care Clinics in Kuching Division, Sarawak, Malaysia. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 5146478. https://doi.org/10.1155/2017/5146478

Kemp, C. J. (2015). Animal Models of Chemical Carcinogenesis: Driving Breakthroughs in Cancer Research for 100 Years. *Cold Spring Harbor protocols*, *2015*(10), 865-874. https://doi.org/10.1101/pdb.top069906

Kew, M. C. (2013). Aflatoxins as a cause of hepatocellular carcinoma. *Journal of Gastrointestinal and Liver Diseases*, *22*(3), 305-310.

KFDA. (2021). *Ministry of Food and Drug Safety: Food Code (No.2021-54, 2021.6.29.)*. Retrieved August, 26 from http://www.mfds.go.kr/

Kimura, M., Fujii, Y., Yamamoto, R., Yafune, A., Hayashi, S.-m., Suzuki, K., & Shibutani, M. (2013). Involvement of multiple cell cycle aberrations in early preneoplastic liver cell lesions by tumor promotion with thioacetamide in a two-stage rat hepatocarcinogenesis model. *Experimental and Toxicologic Pathology*, *65*(7), 979-988. https://doi.org/https://doi.org/10.1016/j.etp.2013.01.012

Kobets, T., Iatropoulos, M. J., & Williams, G. M. (2018). Mechanisms of DNA-reactive and epigenetic chemical carcinogens: applications to carcinogenicity testing and risk assessment. *Toxicology research*, *8*(2), 123-145. https://doi.org/10.1039/c8tx00250a

Kostik, V. (2015). Occurrence of aflatoxins in some medicinal plants stored under different conditions. *IOSR Journal Of Pharmacy*, *5*(2), 38-44.

Krishnamachari, K. A., Bhat, R. V., Nagarajan, V., & Tilak, T. B. (1975). Hepatitis due to aflatoxicosis. An outbreak in Western India. *Lancet*, *1*(7915), 1061-1063. https://doi.org/10.1016/s0140-6736(75)91829-2

Kumar, A., Pathak, H., Bhadauria, S., & Sudan, J. (2021). Aflatoxin contamination in food crops: Causes, detection, and management: a review. *Food Production, Processing and Nutrition*, *3*(1), 17. https://doi.org/10.1186/s43014-021-00064-y

Lasfar, A. (2018). *Liver Cancer*. BoD–Books on Demand.

Lee, F. Y., Wong, H. S., Chan, H. K., Mohamed Ali, N., Abu Hassan, M. R., Omar, H., & Abdul Mutalib, N. A. (2020). Hepatic adverse drug reactions

in Malaysia: An 18-year review of the national centralized reporting system. *Pharmacoepidemiology and drug safety*, *29*(12), 1669-1679.

Lee, S. D., Yu, I. S., Jung, K., & Kim, Y. S. (2014). Incidence and level of aflatoxins contamination in medicinal plants in Korea. *Mycobiology*, *42*(4), 339-345. https://doi.org/10.5941/MYCO.2014.42.4.339

Leong, Y.-H., Rosma, A., Latiff, A. A., & Ahmad, N. I. (2011). Exposure assessment and risk characterization of aflatoxin B1 in Malaysia. *Mycotoxin research*, *27*(3), 207-214. https://doi.org/10.1007/s12550-011-0097-4

Li, H., Xing, L., Zhang, M., Wang, J., & Zheng, N. (2018). The Toxic Effects of Aflatoxin B1 and Aflatoxin M1 on Kidney through Regulating L-Proline and Downstream Apoptosis. *BioMed Research International*, *2018*, 9074861. https://doi.org/10.1155/2018/9074861

Lin, N.-H., Yang, H.-W., Su, Y.-J., & Chang, C.-W. (2019). Herb induced liver injury after using herbal medicine: A systemic review and case-control study. *Medicine*, *98*(13).

Liu, Y., Chang, C.-C. H., Marsh, G. M., & Wu, F. (2012). Population attributable risk of aflatoxin-related liver cancer: Systematic review and meta-analysis. *European Journal of Cancer*, *48*(14), 2125-2136. https://doi.org/https://doi.org/10.1016/j.ejca.2012.02.009

Lopez-Valdes, S., & Mario, M. (2017). The Relationship of Aflatoxin B1 and Hepatocellular Carcinoma: A Mini Review. *J. Liver Res. Disord. Ther*, *3*, 5-6.

Lye, M. S., Ghazali, A. A., Mohan, J., Alwin, N., & Nair, R. C. (1995). An outbreak of acute hepatic encephalopathy due to severe aflatoxicosis in Malaysia. *The American journal of tropical medicine and hygiene*, *53*(1), 68-72.

Maddukuri, V. C., & Bonkovsky, H. L. (2014). Herbal and dietary supplement hepatotoxicity. *Clinical Liver Disease*, *4*(1), 1-3. https://doi.org/https://doi.org/10.1002/cld.364

Mahato, D. K., Lee, K. E., Kamle, M., Devi, S., Dewangan, K. N., Kumar, P., & Kang, S. G. (2019). Aflatoxins in Food and Feed: An Overview on Prevalence, Detection and Control Strategies. *Frontiers in Microbiology*, *10*, 2266-2266. https://doi.org/10.3389/fmicb.2019.02266

Malik, A., Ali, S., Shahid, M., & Bhargava, R. (2014). Occupational exposure to Aspergillus and aflatoxins among food-grain workers in India. *International Journal of Occupational and Environmental Health*, *20*(3), 189-193. https://doi.org/10.1179/2049396714Y.0000000055

Marchese, S., Polo, A., Ariano, A., Velotto, S., Costantini, S., & Severino, L. (2018). Aflatoxin B1 and M1: Biological properties and their involvement

in cancer development. *Toxins*, *10*(6), 214. https://doi.org/10.3390/toxins10060214

Masood, M., Iqbal, S. Z., Asi, M. R., & Malik, N. (2015). Natural occurrence of aflatoxins in dry fruits and edible nuts. *Food Control*, *55*, 62-65.

McCullough, A. K., & Lloyd, R. S. (2019). Mechanisms underlying aflatoxin-associated mutagenesis - Implications in carcinogenesis. *DNA repair*, *77*, 76-86. https://doi.org/10.1016/j.dnarep.2019.03.004

Merican, I., Guan, R., Amarapuka, D., Alexander, M., Chutaputti, A., Chien, R., Hasnian, S., Leung, N., Lesmana, L., Phiet, P., Sjalfoellah Noer, H., Sollano, J., Sun, H., & Xu, D. (2000). Chronic hepatitis B virus infection in Asian countries. *Journal of Gastroenterology and Hepatology*, *15*(12), 1356-1361. https://doi.org/https://doi.org/10.1046/j.1440-1746.2000.0150121356.x

MOH. (2013). National coordinating committee on food and nutrition; Malaysian dietary guidelines for children and adolescents-Summary. *Ministry of Health*.

MOH. (2014). *Food Act 1983*. Retrieved May from https://www.fmm.org.my/images/articles/Draf-pindaan-PPM1985-Bil3-2014_draft%20food%20(amendment)%20reg%20(No%203)%202014.pdf

Mohd-Redzwan, S., Jamaluddin, R., Abd-Mutalib, M. S., & Ahmad, Z. (2013). A mini review on aflatoxin exposure in Malaysia: Past, present and future. *Frontiers in Microbiology*, *4*, 334-334. https://doi.org/10.3389/fmicb.2013.00334

Navarro, V. J., Barnhart, H., Bonkovsky, H. L., Davern, T., Fontana, R. J., Grant, L., Reddy, K. R., Seeff, L. B., Serrano, J., Sherker, A. H., Stolz, A., Talwalkar, J., Vega, M., & Vuppalanchi, R. (2014). Liver injury from herbals and dietary supplements in the U.S. drug-induced liver injury network. *Journal of Hepatology* *60*(4), 1399-1408. https://doi.org/10.1002/hep.27317

Navarro, V. J., & Lucena, M. I. (2014). Hepatotoxicity induced by herbal and dietary supplements. Seminars in liver disease.

Ning, J., Cui, X., Kong, X., Tang, Y., Wulandari, R., Chen, L., Wesseling, S., & Rietjens, I. M. C. M. (2018). Risk assessment of genotoxic and carcinogenic alkenylbenzenes in botanical containing products present on the Chinese market. *Food and Chemical Toxicology*, *115*, 344-357. https://doi.org/https://doi.org/10.1016/j.fct.2018.03.020

Nixon, J. E., Sinnhuber, R. O., Lee, D. J., Landers, M. K., & Harr, J. R. (1974). Effect of cyclopropenoid compounds on the carcinogenic activity of diethylnitrosamine and aflatoxin B in rats. *Journal of the National Cancer Institute*, *53*(2), 453-458. https://doi.org/10.1093/jnci/53.2.453

Njoroge, S. M. C. (2018). A Critical Review of Aflatoxin Contamination of Peanuts in Malawi and Zambia: The Past, Present, and Future. *Plant Disease*, *102*(12), 2394-2406. https://doi.org/10.1094/PDIS-02-18-0266-FE

Nohmi, T. (2018). Thresholds of Genotoxic and Non-Genotoxic Carcinogens. *Toxicological Research*, *34*(4), 281-290. https://doi.org/10.5487/TR.2018.34.4.281

NPRA. (2019). Drug Registration Guidance Document (DRGD) Second Edition – September 2016, revised January 2019. https://www.npra.gov.my/

NPRA. (2021a). *Food-drug interphase products*. Retrieved August, 31 from https://www.npra.gov.my/index.php/en/classification-guideline/product-classification-guideline.html

NPRA. (2021b). *Natural products*. Retrieved August, 28 from https://www.npra.gov.my/index.php/en/component/content/article/142-guidelines-central/guidelines-traditional/1678-natural-products

NPRA. (2022). Guideline on Registration of Natural Products. *Drug Registration Guidance Document (DRGD) Third Edition, Second Revision January 2022*.

O'Brien, J., Renwick, A. G., Constable, A., Dybing, E., Müller, D. J. G., Schlatter, J., Slob, W., Tueting, W., van Benthem, J., Williams, G. M., & Wolfreys, A. (2006). Approaches to the risk assessment of genotoxic carcinogens in food: A critical appraisal. *Food and Chemical Toxicology*, *44*(10), 1613-1635. https://doi.org/https://doi.org/10.1016/j.fct.2006.07.004

Ozakyol, A. (2017). Global Epidemiology of Hepatocellular Carcinoma (HCC Epidemiology). *Journal of Gastrointestinal Cancer*, *48*(3), 238-240. https://doi.org/10.1007/s12029-017-9959-0

Panrapee, I., Phakpoom, K., Thanapoom, M., Nampeung, A., & Warapa, M. (2016). Exposure to aflatoxin B1 in Thailand by consumption of brown and color rice. *Mycotoxin research*, *32*(1), 19-25. https://doi.org/10.1007/s12550-015-0236-4

Peers, F. G., & Linsell, C. A. (1973). Dietary aflatoxins and liver cancer-A population based study in Kenya. *British journal of cancer*, *27*(6), 473-484. https://doi.org/10.1038/bjc.1973.60

Pfliegler, W. P., Pócsi, I., Győri, Z., & Pusztahelyi, T. (2020). The aspergilli and their mycotoxins: metabolic interactions with plants and the soil biota [Review]. *Frontiers in Microbiology*, *10*(2921). https://doi.org/10.3389/fmicb.2019.02921

Pickova, D., Ostry, V., Toman, J., & Malir, F. (2021). Aflatoxins: History, Significant Milestones, Recent Data on Their Toxicity and Ways to Mitigation. *Toxins*, *13*(6). https://doi.org/10.3390/toxins13060399

Prado, G., Altoé, A. F., Gomes, T. C., Leal, A. S., Morais, V. A., Oliveira, M. S., Ferreira, M. B., Gomes, M. B., Paschoal, F. N., von, S. S. R., Silva, D. A., & Cruz Madeira, J. E. (2012). Occurrence of aflatoxin B1 in natural products. *Brazilian Journal of Microbiology*, *43*(4), 1428-1436. https://doi.org/10.1590/s1517-838220120004000026

Probst, C., Njapau, H., & Cotty, P. J. (2007). Outbreak of an acute aflatoxicosis in Kenya in 2004: Identification of the causal agent. *Applied and Environmental Microbiology Journal*, *73*(8), 2762-2764. https://doi.org/10.1128/aem.02370-06

Qi, L. N., Bai, T., Chen, Z. S., Wu, F. X., Chen, Y. Y., De Xiang, B., Peng, T., Han, Z. G., & Li, L. Q. (2015). The p53 mutation spectrum in hepatocellular carcinoma from Guangxi, China: role of chronic hepatitis B virus infection and aflatoxin B1 exposure. *Liver International*, *35*(3), 999-1009.

Rajeshwari, P., & Raveesha, K. (2016). Mycological analysis and aflatoxin B1 contaminant estimation of herbal drug raw materials. *African Journal of Traditional, Complementary, and Alternative Medicines*, *13*(5), 123-131. https://doi.org/10.21010/ajtcam.v13i5.16

Raschi, E., & De Ponti, F. (2015). Drug- and herb-induced liver injury: Progress, current challenges and emerging signals of post-marketing risk. *World journal of hepatology*, *7*(13), 1761-1771. https://doi.org/10.4254/wjh.v7.i13.1761

Richard, J. L. (2008). Discovery of aflatoxins and significant historical features. *Toxin Reviews*, *27*(3-4), 171-201. https://doi.org/10.1080/15569540802462040

Sargeant, K., Sheridan, A., O'kelly, J., & Carnaghan, R. (1961). Toxicity associated with certain samples of groundnuts. *Nature*, *192*(4807), 1096-1097.

Sarkar, S., Horn, G., Moulton, K., Oza, A., Byler, S., Kokolus, S., & Longacre, M. (2013). Cancer Development, Progression, and Therapy: An Epigenetic Overview. *International Journal of Molecular Sciences*, *14*(10). https://doi.org/10.3390/ijms141021087

Savić, Z., Dudaš, T., Loc, M., Grahovac, M., Budakov, D., Jajić, I., Krstović, S., Barošević, T., Krska, R., Sulyok, M., Stojšin, V., Petreš, M., Stankov, A., Vukotić, J., & Bagi, F. (2020). Biological control of aflatoxin in maize grown in Serbia. *Toxins*, *12*(3), 162.

Scaglioni, P. T., Becker-Algeri, T., Drunkler, D., & Badiale-Furlong, E. (2014). Aflatoxin B1 and M1 in milk. *Analytica Chimica Acta*, *829*, 68-74. https://doi.org/https://doi.org/10.1016/j.aca.2014.04.036

Schoental, R. (1961). Liver changes and primary liver tumours in rats given toxic guinea pig diet (MRC diet 18). *British journal of cancer*, *15*(4), 812.

Selim, M. I., Popendorf, W., Ibrahim, M. S., Sharkawy, S. E., & Kashory, E. S. E. (2020). Anatoxin B1 in common Egyptian foods. *Journal of AOAC INTERNATIONAL*, *79*(5), 1124-1129. https://doi.org/10.1093/jaoac/79.5.1124

Serafimova, R., Coja, T., & Kass, G. E. N. (2021). Application of the Threshold of Toxicological Concern (TTC) in Food Safety: Challenges and Opportunities [Review]. *Frontiers in Toxicology*, *3*. https://doi.org/10.3389/ftox.2021.655951

Shan, Y. (2019). The toxic effects of aflatoxin B1: An Uupdate. In *Aflatoxin B1 occurrence, detection and toxicological effects*. IntechOpen.

Shim, W.-B., Kim, K., Ofori, J. A., Chung, Y.-C., & Chung, D.-H. (2012). Occurrence of aflatoxins in herbal medicine distributed in South Korea. *Journal of Food Protection*, *75*(11), 1991-1999. https://doi.org/10.4315/0362-028x.jfp-12-190

Shrivastava, A., & Gupta, V. B. (2011). Methods for the determination of limit of detection and limit of quantitation of the analytical methods. *Chronicles of young scientists*, *2*(1), 21-25.

Sirma, A. J., Ouko, E. O., Murithi, G., Mburugu, C., Mapenay, I., Ombui, J. N., Kang'ethe, E. K., & Korhonen, H. (2015). Prevalence of aflatoxin contamination in cereals from Nandi County, Kenya.

Snigdha, M., Hariprasad, P., & Venkateswaran, G. (2015). Transport via xylem and accumulation of aflatoxin in seeds of groundnut plant. *Chemosphere*, *119*, 524-529. https://doi.org/https://doi.org/10.1016/j.chemosphere.2014.07.033

Stournaras, E., & Tziomalos, K. (2015). Herbal medicine-related hepatotoxicity. *World journal of hepatology*, *7*(19), 2189-2193. https://doi.org/10.4254/wjh.v7.i19.2189

Suk, K. T., Kim, D. J., Kim, C. H., Park, S. H., Yoon, J. H., Kim, Y. S., Baik, G. H., Kim, J. B., Kweon, Y. O., Kim, B. I., Kim, S. H., Kim, I. H., Kim, J. H., Nam, S. W., Paik, Y. H., Suh, J. I., Sohn, J. H., Ahn, B. M., Um, S. H., Lee, H. J., Cho, M., Jang, M. K., Choi, S. K., Hwang, S. G., Sung, H. T., Choi, J. Y., & Han, K. H. (2012). A prospective nationwide study of drug-induced liver injury in Korea. *American Journal of Gastroenterology*, *107*(9), 1380-1387. https://doi.org/10.1038/ajg.2012.138

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries [https://doi.org/10.3322/caac.21660]. *CA: A Cancer Journal for Clinicians*, *71*(3), 209-249. https://doi.org/https://doi.org/10.3322/caac.21660

Suparmi, S., Mulder, P. P. J., & Rietjens, I. M. C. M. (2020). Detection of pyrrolizidine alkaloids in jamu available on the Indonesian market and accompanying safety assessment for human consumption. *Food and Chemical Toxicology*, *138*, 111230. https://doi.org/https://doi.org/10.1016/j.fct.2020.111230

Tahir, N., Hussain, S., Javed, M., Rehman, H., Shahzady, T., Parveen, B., & Ali, K. (2018). Nature of aflatoxins: Their extraction, analysis, and control. *Journal of Food Safety*, *38*. https://doi.org/10.1111/jfs.12561

Tanaka, T., Shimizu, M., Kochi, T., & Moriwaki, H. (2013). Chemical-induced Carcinogenesis. *Journal of Experimental & Clinical Medicine*, *5*(6), 203-209. https://doi.org/https://doi.org/10.1016/j.jecm.2013.10.009

Tassaneeyakul, W., Razzazi-Fazeli, E., Porasuphatana, S., & Bohm, J. (2004). Contamination of aflatoxins in herbal medicinal products in Thailand. *Mycopathologia*, *158*(2), 239-244. https://doi.org/10.1023/B:MYCO.0000041892.26907.b4

Tengku Mohamad, T. A. S., Islahudin, F., Jasamai, M., & Jamal, J. A. (2019). Preference, perception and predictors of herbal medicine use among Malay women In Malaysia. *Patient preference and adherence*, *13*, 1829-1837. https://doi.org/10.2147/PPA.S227780

Teo, D. C. H., Ng, P. S. L., Tan, S. H., Lim, A. T., Toh, D. S. L., Chan, S. Y., & Cheong, H. H. (2016). Drug-induced liver injury associated with Complementary and Alternative Medicine: a review of adverse event reports in an Asian community from 2009 to 2014. *BMC Complementary and Alternative Medicine*, *16*(1), 192. https://doi.org/10.1186/s12906-016-1168-z

Valencia-Quintana, R., Milić, M., Jakšić, D., Šegvić Klarić, M., Tenorio-Arvide, M. G., Pérez-Flores, G. A., Bonassi, S., & Sánchez-Alarcón, J. (2020). Environment Changes, Aflatoxins, and Health Issues, a Review. *International Journal of Environmental Research and Public Health*, *17*(21), 7850. https://doi.org/10.3390/ijerph17217850

Wai, C. T., Tan, B. H., Chan, C. L., Sutedja, D. S., Lee, Y. M., Khor, C., & Lim, S. G. (2007). Drug-induced liver injury at an Asian center: A prospective study. *Liver International*, *27*(4), 465-474.

Welz, A. N., Emberger-Klein, A., & Menrad, K. (2018). Why people use herbal medicine: insights from a focus-group study in Germany. *BMC Complement Altern Med*, *18*(1), 92. https://doi.org/10.1186/s12906-018-2160-6

WHO. (2017). Evaluation of certain contaminants in food. *World Health Organization technical report series*(1002), 1-166.

WHO. (2018a). *Co-exposure of fumonisins with aflatoxins*. Retrieved July,1 from https://www.who.int/foodsafety/FSDigest_Fumonisins_Aflatoxins_EN.pdf

WHO. (2018b). WHO guidelines on good herbal processing practices for herbal medicines. *WHO Technical Report Series*(1010).

WHO. (2019). *WHO global report on traditional and complementary medicine 2019*. World Health Organization. https://apps.who.int/iris/handle/10665/312342

Wogan, G. N., & Newberne, P. M. (1967). Dose-response characteristics of aflatoxin B1 carcinogenesis in the rat. *Cancer research*, *27*(12), 2370-2376.

Wogan, G. N., Paglialunga, S., & Newberne, P. M. (1974). Carcinogenic effects of low dietary levels of aflatoxin B1 in rats. *Food and Cosmetics Toxicology*, *12*(5), 681-685.

Wu, K., Liu, M., Wang, H., Rajput, S. A., Shan, Y., Qi, D., & Wang, S. (2021). The Mechanism Underlying the Extreme Sensitivity of Duck to Aflatoxin B₁. *Oxidative Medicine and Cellular Longevity*, *2021*, 9996503. https://doi.org/10.1155/2021/9996503

Yazid, N. F. M., Azli, F. S., Ghani, F. A., Ramli, N., & Yusof, N. M. (2021). Dietary supplement intake: a study on its associated factors among university students in Terengganu. *International Journal of Academic Research in Business and Social Sciences,*, *11*(13), 33–42. https://doi.org/http://dx.doi.org/10.6007/IJARBSS/v11-i13/8500

Yusoff, S., Hassan, S. A., & Othman, W. N. W. (2019). Traditional and complementary treatments among Malay, Chinese and Indian chronic diseases: A systematic review. *Journal of Molecular Biology*, *13*, 13.

Zakaria, N. F., Mohd Noor, M. T., & Abdullah, R. (2021). Traditional and complementary medicine use among chronic haemodialysis patients: a nationwide cross-sectional study. *BMC Complementary Medicine and Therapies*, *21*(1), 94. https://doi.org/10.1186/s12906-021-03268-4

Zhang, H. E., Henderson, J. M., & Gorrell, M. D. (2019). Animal models for hepatocellular carcinoma. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1865*(5), 993-1002. https://doi.org/https://doi.org/10.1016/j.bbadis.2018.08.009

Zhang, W., Liu, Y., Liang, B., Zhang, Y., Zhong, X., Luo, X., Huang, J., Wang, Y., Cheng, W., & Chen, K. (2020). Probabilistic risk assessment of dietary exposure to aflatoxin B1 in Guangzhou, China. *Scientific Reports*, *10*(1), 7973. https://doi.org/10.1038/s41598-020-64295-8