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ALLEVIATION OF AFLATOXIN B1-INDUCED GUT TOXICITY VIA PROBIOTIC INTERVENTION THROUGH MODULATION OF GUT PROTEOMES AND MICROBIOTA

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Aflatoxin (AF) is a pervasive, extremely toxic contaminant produced by *Aspergillus* sp. that demands further research to explain the mechanisms of toxicity. A better understanding of AF's patterns of toxicity and food contamination helps to address the harmful impacts on nation's health and economy. Among AFs, aflatoxin B1 (AFB1) is the most toxic and has been studied extensively. *Lactobacillus casei* Shirota (Lcs) is a probiotic with potential AFB1-binding ability. There is limited study available on the binding efficiency and interactions between Lcs and AFB1. The toxicity of AFB1, particularly towards the gut is not well studied. Besides, the pathways involved in the alleviation of AFB1-induced toxicity by probiotics remained undiscovered. Therefore, this research investigated the mechanism of Lcs in alleviating toxicity induced by AFB1 in both *in vitro* and *in vivo* experiments.

Three distinct Lcs cellular components: live cell, cell wall, and heat-treated cell were incubated with different levels (2, 4, 6, 8, and 10 µg/mL) of AFB1. The AFB1-binding efficiencies of the bacterial cell fractions were estimated using an adsorption isotherm. The interactions between Lcs and AFB1 were investigated using scanning electron microscopy (SEM). The AFB1-removal ability of Lcs was further evaluated using the rat model. Sprague Dawley rats (Male; n=40) were separated into five treatment groups (Control, AFB1 exposure, Charcoal+AFB1, Lcs+AFB1, and Lcs). The rats were subjected to 25 µg/kg body weight (b.w.) daily. Upon the end of the animal study (four weeks), the biological samples (blood serum, urine, feces, intestine, spleen, liver, and kidney) were collected. Serum AFB1 and urinary AFM1 were evaluated using enzyme-linked immunosorbent assay (ELISA). Meanwhile, histological examination was performed on the tissues via hematoxylin and eosin (H&E) staining. The feces samples were subjected to gut microbiota analysis using metagenomic sequencing. Besides, the AFB1 most affected site was subjected to proteomic analysis via liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS).

The Langmuir model demonstrated that live bacterial cell and cell wall fraction possessed the highest binding efficiencies at $14.32x10^{10}$ and $16.34x10^{10}$ respectively. Lcs cells incubated with AFB1 appeared in curve-shaped with irregular and rough surface under SEM. Meanwhile, the AFB1 biomarkers' level in both blood serum and urine samples, has been significantly ($p<0.05$) decreased by Lcs to 42% and 6%, respectively. Inflammation and abnormal cell growth were observed in AFB1-exposed rats, mainly in the jejunal tissue. Such adverse effects were greatly alleviated by Lcs supplementation.

Moreover, AFB1 significantly induced the overgrowth of potentially pathogenic bacteria (*Prevotellaceae* NK3831 group and *Prevotella* 9) and reduction of normal/ beneficial microbiota (*Lactobacillus*, *Eubacterium coprostanoligenes* group, and *Ruminiclostridium* 6). This research showed that Lcs intervention successfully normalized the gut microbiota altered by AFB1 significantly ($p<0.05$). Based on the gut proteomes analysis, several pathways related to cancer, inflammation, and ROS generation were induced by AFB1. The altered gut proteome were reduced upon Lcs intervention. This may explain the alleviation of gut damage such as abnormal cell growth and inflammation observed in the intestine tissues. A total of 24 pathways involved in the alleviation of AFB1-induced toxicity by probiotic were identified.

Probiotic Lcs was capable of maintaining the composition of gut microbiota and offers protection towards the gut health status. Lcs has become a popular probiotic supplement and its health-promoting effect coupled with its AF-removal ability is remarkable as a novel dietary approach for management of aflatoxicosis and AFs exposure. Nevertheless, further studies to elucidate the efficiency of Lcs at different dosages of AFB1 are warranted.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENGURANGAN KETOKSIKAN USUS TERARUH AFLATOKSIN B1 DENGAN INTERVENSI PROBIOTIK MELALUI MODULASI PROTEOM DAN MIKROBIOTA USUS

Oleh

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Aflatoksin (AF) merupakan bahan cemar yang luas merebak dan sangat toksik. AF dihasilkan oleh *Aspergillus* sp. dan memerlukan penyelidikan lanjut untuk menjelaskan mekanisme ketoksikan. Pemahaman yang lebih baik tentang ketoksikan AF dan kemunculannya dalam bahan makanan manusia dan haiwan boleh membantu dalam menangani kesan berbahaya AF terhadap kesihatan awam dan ekonomi negara. Antara AF, aflatoksin B1 (AFB1) adalah yang paling toksik dan telah dikaji secara meluas. *Lactobacillus casei* Shirota (Lcs) adalah probiotik yang berpotensi untuk mengikat AFB1. Hasil kajian berkaitan dengan keberkesanan pengikatan dan interaksi antara Lcs dan AFB1 adalah terhad. Tapak jalan yang melibatkan ketoksikan AFB1, terutamanya dalam usus masih belum difahami sepenuhnya. Selain itu, tapak jalan yang melibatkan pengurangan ketoksikan AFB1 oleh probiotik masih belum ditemui. Maka, penyelidikan ini menyiasat mekanisme Lcs dalam mengurangkan ketoksikan yang diaruh oleh AFB1 dalam eksperimen *in vitro* dan *in vivo*.

Tiga fraksi sel Lcs yang berlainan: sel hidup, sel dengan rawatan-haba, dan dinding sel diinkubasi dengan kepekatan AFB1 yang berbeza (2, 4, 6, 8, dan 10 µg/mL). Keberkesanan pengikatan AFB1 bagi fraksi sel bakteria diperolehi menggunakan isoterma penjerap. Interaksi antara Lcs dan AFB1 telah dikaji menggunakan mikroskop elektron pengimbasan (SEM). Keberkesanan Lcs dalam penyingkiran AFB1 telah dikaji secara selanjutnya menggunakan model tikus. Tikus Sprague Dawley jantan (n=40) dibahagikan kepada lima kumpulan rawatan (Kawalan, pendedahan AFB1, Arang+AFB1, Lcs+AFB1 dan Lcs).

Dos AFB1 sebanyak 25 µg/kg berat badan diberikan kepada tikus setiap hari. Sampel biologi (serum darah, air kencing, najis, usus, limpa, hati, dan buah pinggang) telah dikumpulkan setelah tamat kajian haiwan (empat minggu). AFB1 dalam serum darah

dan AFM1 dalam air kencing disukat menggunakan asai imunoserapan terangkai enzim (ELISA). Sementara itu, analisis histologi dijalankan ke atas tisu-tisu melalui pewarnaan hematoxylin dan eosin (H&E). Sampel najis telah tertakluk kepada analisis mikrobiota usus menggunakan penjujukan metagenomik. Selain itu, tisu yang terjejas tertakluk kepada analisis proteomik melalui kromatografi cecair ditambah dengan spektrometri jisim tandem (LC/MS/MS).

Model Langmuir menunjukkan bahawa sel bakteria hidup dan fraksi dinding sel mempunyai keberkesanan pengikatan yang tertinggi masing-masing pada $14.32x10^{10}$ dan $16.34x10^{10}$. Sel Lcs yang diembas dengan AFB1 berbentuk lengkung dan mempunyai permukaan yang tidak teratur dan kasar di bawah SEM. Sementara itu, Lcs juga dengan ketara ($p<0.05$) mengurangkan aras biopenanda AFB1 dalam kedua-dua serum darah dan sampel air kencing, sehingga 42% dan 6% masing-masing. AFB1 menyebabkan keradangan dan pertumbuhan sel yang tidak normal, terutamanya pada jejunum. Kesan buruk sedemikian telah banyak dikurangkan dengan suplemen Lcs.

Selain itu, AFB1 dengan ketaranya ($p<0.05$) mendorong pertumbuhan berlebihan bakteria berpotensi patogen (kumpulan *Prevotellaceae* NK3831 dan *Prevotella* 9) dan pengurangan mikrobiota normal/ bermanfaat (kumpulan *Eubacterium coprostanoligenes*, *Lactobacillus*, dan *Ruminiclostridium* 6). Kajian ini mendapati bahawa intervensi Lcs secara ketara ($p<0.05$) menormalkan mikrobiota usus yang terjejas oleh AFB1. Analisis proteom usus menunjukkan bahawa AFB1 meningkatkan kejadian keradangan, kanser, dan penghasilan ROS melalui beberapa tapak jalan. Perubahan sedemikian dalam proteom usus mampu dikurangkan oleh Lcs. Hal ini dapat menjelaskan pengurangan kerosakan usus seperti keradangan dan pertumbuhan sel yang tidak normal yang diperhatikan di jejunum. Sebanyak 24 tapak jalan yang terlibat dalam pengurangan ketoksikan yang disebabkan oleh AFB1 oleh probiotik telah dikenalpasti.

Probiotik Lcs berkeupayaan untuk mengekalkan komposisi mikrobiota usus dan menawarkan perlindungan terhadap status kesihatan usus. Lcs telah menjadi suplemen probiotik yang popular dan kesannya terhadap kesihatan ditambah dengan keupayaan penyingkiran AFnya membolehkan Lcs menjadi salah satu pendekatan pemakanan untuk mencegah pendedahan AF dan kesan berbahaya terhadap kesihatannya. Walaubagaimanapun, kajian lanjutan atas keberkesanan Lcs ke atas dos AFB1 yang berbeza adalah wajar.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

8-oxo-dG	7,8-dihydro-8-oxo-20-deoxyguanosine
Acet	Acetaldehyde
AF	Aflatoxin
AFB1	Aflatoxin B1
AFB2	Aflatoxin B2
AFG1	Aflatoxin G1
AFG1	Aflatoxin G2
AFM1	Aflatoxin M1
AFP1	Aflatoxin P1
AFQ1	Aflatoxin Q1
AP	Apurinic/apyrimidinic
Bcl-2	B-cell lymphoma 2
BER	Base excision repair
BW	Body weight
Cdc	Cell division cycle
CDK	Cyclin-dependent kinases
CDKN1A	Cyclin-dependent kinase inhibitor 1A
CFU	Colony forming unit
CHR	Cell cycle gene homology region
Cro	Crotonaldehyde
CYP	Cytochrome C-P450
CYP1A	Cytochrome P450 Family 1 Subfamily A
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1

CYP1A2	Cytochrome P450 Family 1 Subfamily A Member 2
CYP2A5	Cytochrome P450 Family 2 Subfamily A Member 5
CYP2A6	Cytochrome P450 Family 2 Subfamily A Member 6
CYP321A1	Cytochrome P450 Family 321 Subfamily A Member 1
CYP3A	Cytochrome P450 Family 3 Subfamily A
CYP3A13	Cytochrome P450 Family 3 Subfamily A Member 13
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
DNA	Deoxyribonucleic acid
DREAM	Dimerization partner, RB-like, E2F and multivulval class B
ELISA	Enzyme-linked immunosorbent assay
FAO	United Nations Food and Agriculture Organization
FAPy	Formamidopyrimidine
G0	Gap 0
G1	Gap 1
G2	Gap 2
GF	Germ free
GI	Gastrointestinal
GST	Glutathione S-transferase
GSTM1	Glutathione S-transferase Mu 1
HCC	Hepatocellular carcinoma
IAC	Immunoaffinity column
IBS	Irritable bowel syndrome
Ig	Immunoglobulin
Ig A	Immunoglobulin A
IL	Interleukin

IL-1	Interleukin 1
IL-6	Interleukin 6
IL-12	Interleukin 12
IL-17	Interleukin 17
IL-23	Interleukin 23
LC/MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
Lcs	*Lactobacillus casei* Shirota
LFQ	Label-free quantification
LPO	Lipid oxidation
M	Mitosis
MDA	Malondialdehyde
Mdm2	Mouse double minute 2 homolog
meth-OH-PdG	Cyclic α-methyl-γ-hydroxy-1,N2-propano-dG
MRS	Man Rogosa Sharpe
Nanoflow-ESI-LC/MS/MS	Nanoflow liquid chromatography electrospray-ionization coupled with tandem mass spectrometry
NEIL1	Nei Like 1
NER	Nucleotide excision repair
NMDS	Nonmetric multidimensional scaling
Nrf2	Nuclear erythroid-2 related factor-2
O.D.	Optical density
OTU	Operational Taxonomic Unit
PBS	Phosphate buffered saline
PCA	Principal component analysis
PCR	Polymerase chain reaction

PCNA	Proliferating cell nuclear antigen
PPI	Protein-Protein Interaction
PUMA	p53-up-regulated modulator of apoptosis
QIIME	Quantitative Insight Into Microbial Ecology
RNA	Ribonucleic acid
ROS	Reactive oxygen species
r.t.	Room temperature
S	Synthesis phase
SCFA	Short-chain fatty acids
SD	Standard deviation
SEM	Scanning electron microscopy
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
TLR	Toll-like receptors
TNF	Tumor necrosis factor
UPM	Universiti Putra Malaysia
UPGMA	Unweighted pair group method with arithmetic mean
USA	United States of America
WHO	World Health Organization
XPC	Xeroderma pigmentosum complementation group C
XPD	Xeroderma pigmentosum complementation group D
XRCC1	X-ray repair cross-complementing protein 1
XRCC3	X-ray repair cross-complementing protein 3
XRCC4	X-ray repair cross-complementing protein 4
XRCC7	X-ray repair cross-complementing protein 7

CHAPTER 1

INTRODUCTION

1.1 Background of the study

AFB1 is one of the predominant natural toxins produced by the fungi, *Aspergillus flavus* and *A. parasiticus*. The Joint United Nations Food and Agriculture Organization (FAO) and World Health Organization (WHO) Expert Committee on Food Additives described AFB1 as the most toxic mycotoxin and has been categorized as a Group 1 carcinogen (Coppock, Christian, and Jacobsen, 2018). Moreover, AFB1 also induces various health issues such as gastrointestinal (GI) pain, diarrhea, disturbs the growth of livestock and human being, and others as reported in several findings as reviewed by Rushing and Selim (2019).

According to FAO and WHO, fungal growth led to the spoilage of 25% food crops globally (Moretti et al., 2019). The contaminated food serves as the entry point of AFs in the food supply of animals and humans. Food contaminated with AFB1 is regarded as one of the top priorities in food safety globally (Sheng et al., 2014). The European Union regulations only allow AFB1 not exceeding 2mg/kg in nuts, groundnuts, cereals, and dried fruits (Kemboi et al., 2020), and Malaysia has set up its regulation in the Food Act 1983 and Food Regulations 1985 to limit its occurrence in the foods (Regulation, 1986).

Various approaches such as chemoprotectant and enterosorption have been developed to reduce the effects of aflatoxin exposure. Phenolic extracts from plants offer chemoprotection against carcinogenesis induced by AF (Costa et al., 2007). However, this strategy has been deemed cost-ineffective and unfeasible for poor communities, which are mostly exposed to a high level of AF. On the other hand, enterosorption involves the use of clay to bind to AF selectively in the GI tract. This AF enterosorbent reduces the bioavailability and toxicities of AFB1 (Zychowski et al., 2013). Nonetheless, clay may pose a potential health threat to humans and animals as it is made of chemicals. Lately, there has been an increasing interest on biology approach for its cost-effectiveness and simplicity. The vital phase in the development of biological method is choosing the ideal microorganisms to reduce AF levels in contaminated feed and food sources.

Upon intake of food or feed containing AFB1, the health of the GI tract is undoubtedly disturbed by the toxin. Indeed, mycotoxins exert negative effects on the gut, particularly in the intestinal epithelial (Gao et al., 2020). A complex gut microbiota resides in the GI tracts (Dhar & Mohanty, 2020). Gut microbiota is responsible for health maintenance (Dhar & Mohanty, 2020). An entirely new perspective has been generated based on the findings of recent studies where a bi-directional interaction was shared between gut microbiota and mycotoxins as reviewed by Jin et al. (2021). Such findings suggest that

gut microbiota of different compositions may promote or alleviate the mycotoxicosis process.

Lactobacillus sp. is well known for their health-promoting effects (Zielińska et al., 2018). Besides, *Lactobacillus* spp. were also recognized for their AF-reducing ability (Apás et al., 2014). Studies suggested that the AFB1 was bound to the surface of probiotic bacteria. The role of the cellular envelope in AFB1 binding as indicated by the reduction of AFB1 binding by *Lactobacillus* sp. upon the destruction of the bacterial cell wall (Tajik & Sayadi, 2020). Nevertheless, the mechanisms involved in AFB1 binding are poorly understood and further investigation is required. Hence, this research aims to unravel the mode of actions of Lcs in AFB1 removal and aflatoxicosis.

1.2 Problem statements

Numerous studies demonstrated the effect of Lcs on AFB1 detoxification. However, there are limitations in the studies. Most of the studies highlight the binding of AFB1 occurred at the bacterial cell wall (Hashemi & Amiri, 2020). Yet, the role of other bacterial cell components in the binding process is rarely discovered. Besides, the mode of adsorption between Lcs and AFB1 is poorly understood.

AFB1 has been well-known for its high carcinogenicity based on the literature and is linked to the development of liver cancer. The food polluted with mycotoxin affects the GI tract (Chen et al., 2016). Several mycotoxins showed detrimental effects on the intestine particularly on gut barrier, nutrient absorption, and histopathology (Guo, et al., 2019). Regrettably, a great focus has been placed on aflatoxicosis studies related to liver. Although AFB1 reaches the intestine upon ingestion, however, the effect of AFB1 on the intestine was frequently overlooked by researchers (McCullough & Lloyd, 2019). Therefore, the mechanism underlying the AFB1-induced GI toxicity was studied.

Furthermore, the impact of AFB1 on host gut microbiota was also evaluated due to limited available information. Gut microbiota is a blooming research interest that gained its popularity recently due to its role in maintaining health (Thursby & Juge, 2017). Ingestion of toxins may affect the gut microbiota balance. Moreover, probiotic administration has induced positive modulation of gut microbiota in unhealthy subjects (Gubert, et al., 2020). Thus, it is crucial to discover the effect of probiotics with AFB1-binding ability towards gut microbiota upon AFB1 exposure.

1.3 Study significance

The research involved the investigation of Lcs potential in the removal of AFB1 by *in vitro* and *in vivo* studies. The binding efficiency of Lcs to AFB1 was evaluated using the adsorption isotherms experiment. Specifically, the binding components that took part in the AFB1 removal process were identified. The present study employed probiotic, Lcs for the AF detoxification purpose. Most of the studies available did not focus on the effect of AFB1 on the intestine. In this study, a deeper understanding of the impacts of AFB1 ingestion on the intestine was achieved by performing several analyses including histological, gut microbiota, and gut proteome analysis. Probiotics have been proven in maintaining healthy gut flora; thus, the gut microbiota is postulated to play a role in the AF detoxification process. Gut microbiota modulation affected by both AFB1 and Lcs can be observed in the present research. Lastly, the gut protein expression modulated by AFB1 can be evaluated via proteome profiling. The proteome profiling also helps to provide evidence on how probiotics can alleviate the toxicity of AFB1. Hence, the current findings can provide substantial data to establish the usage of probiotics as an efficient AFB1 detoxifying agent.

1.4 Hypothesis

The hypothesis of this thesis is Lcs removes AFB1 via binding on the bacterial cell wall. Lcs alters the gut microbiota sufficiently to reduce toxicity and the resulting tissue damages in AFB1-induced rats, thus offering an additional intervention to AFB1 detoxification.

1.5 Objectives

General objective

To evaluate the mechanism of Lcs in alleviating toxicity induced by AFB1 in both *in vitro* and *in vivo* experiments.

Specific objectives

1. To determine the binding efficiency of Lcs on AFB1.
2. To observe the histological changes in the intestine of AFB1-induced rats with and without Lcs intervention.
3. To determine and identify the modulation of metagenomic profile in the gut microbiota of AFB1-induced rats with and without Lcs intervention.
4. To determine and identify the differential protein expression in AFB1-induced rats with and without Lcs intervention.

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