



UNIVERSITI PUTRA MALAYSIA

***SAFETY EVALUATION OF LACTOBACILLUS STRAINS AS POTENTIAL
PROBIOTICS FOR HUMAN USE***

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PROBIOTICS FOR HUMAN USE**

By

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**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in
Fulfilment of the Requirements for the Degree of Master of Science**

November 2018

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Master of Science

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By

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November 2018

Chairman: Leslie Than Thian Lung, PhD
Faculty : Medicine and Health Sciences

Lactobacillus species are generally regarded as safe (GRAS) by the United State Food and Drug Administration (FDA) due to their long history of safe consumption in traditional fermented foods. However, there have been few reported cases of *Lactobacillus* species associated with clinical conditions such as bacteremia, endocarditis and localized infections. In view of this, it is relevant to have a more thorough safety assessment of new strains before use as probiotics. Therefore, the aim of this study was to evaluate the safety of a new potentially probiotic lactobacilli strains.

In this study, safety assessment of five lactobacilli strains, previously characterized as potential probiotic bacteria was carried out to determine their suitability for human use. Antibiotic resistance patterns were determined using agar overlay disc diffusion method. Hemolytic activity, bile salt deconjugation and amino acid decarboxylase activity were determined *in vitro* on agar plates. Enzymatic activities and carbohydrate fermentation profile were determined using API systems. Bile salt hydrolase (BSH) activity and D-/L-lactic acid production were quantified spectrophotometrically. Among the five strains, *Lactobacillus reuteri* S29 PFB was evaluated for safety *in vivo* in a 28 day sub-acute oral toxicity study in 40 BALB/c mice. The mice were randomized into 4 groups and orally fed with *L. reuteri* S29 PFB (1×10^8 , 10^9 and 10^{10} CFU/day). Blood and organs collected at the end of the intervention period were analyzed for health parameters (blood biochemistry, hematology and histopathology) and incidence of translocation to blood and organs.

Results from this study demonstrated that all the strains were able to utilize glucose and lactose and the enzymatic profiles of the strains correlated with the carbohydrate fermentation. Harmful bacterial enzymes such as beta glucuronidase was not detected in all the strains. The tested lactobacilli strains were shown to be susceptible to penicillins, chloramphenicol and tetracycline. None of the strains were shown to be hemolytic or decarboxylate histidine, tyrosine, lysine or arginine to form biogenic amines. The

concentrations of D-/L- lactic acid and bile salt hydrolase activity units were comparable to that of the commercial strain, *L. reuteri* RC-14. Results from the *in vivo* study demonstrated that oral administration of different doses of *L. reuteri* 29 PFB for 28 days had no adverse toxicological effect on the mice general health status, hematological and blood biochemical parameters and intestinal histological parameters. There were no incidence of translocation to blood and DNA fingerprinting patterns of isolates recovered from tissues did not match with that of the administered strain. Overall, the result from this study suggests that *L. reuteri* 29 PFB was shown to be a better candidate for probiotic development, and would likely be safe for human use.



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

PENILAIAN KESELAMATAN STRAIN LACTOBACILLI SEBAGAI PROBIOTIK YANG BERPOTENSI UNTUK KEGUNAAN MANUSIA

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Secara umumnya, spesis *Lactobacillus* dianggap selamat (*generally regarded as safe* (GRAS) oleh *United States Food and Drug Administration (FDA)* berikutan sejarah penggunaannya dalam makanan tradisional yang ditapai. Walau bagaimanapun, terdapat sebilangan kecil kes yang mengaitkan *Lactobacillus* spp. dengan keadaan klinikal seperti bakteremia, endokarditis dan jangkitan setempat. Berikutan hal ini, adalah relevan bagi penilaian keselamatan yang menyeluruh dijalankan terhadap strain baru sebelum digunakan sebagai probiotik. Oleh itu, tujuan kajian ini dijalankan adalah untuk menilai tahap keselamatan sejenis strain lactobacilli yang mempunyai potensi probiotik.

Dalam kajian ini, penilaian tahap keselamatan bagi lima strain lactobacilli telah dijalankan bagi menentukan kesesuaian mereka untuk kegunaan manusia. Kelima-lima strain lactobacilli ini telah dicirikan mempunyai potensi sebagai bakteria probiotik sebelum ini. Corak rintangan antibiotik telah ditentukan dengan menggunakan kaedah peresapan disk di atas lapisan agar. Aktiviti hemolisis, penyusutan garam hempedu dan aktiviti asid amino *decarboxylase* telah ditentukan secara *in vitro* di atas plat agar. Aktiviti enzim dan profil penapaian karbohidrat telah ditentukan dengan menggunakan sistem API. Aktiviti hidrolase garam hempedu (BSH) dan pengeluaran asid laktik D-/L telah dihitung dgn menggunakan spektrofotometer. Di antara kelima-lima strain tersebut, *Lactobacillus reuteri* S29 PFB telah dinilai bagi menentukan keselamatan secara *in vivo* dalam kajian ketoksikan oral sub-akut selama 28 hari dalam 40 ekor tikus jenis BALB/c. Tikus-tikus tersebut telah dibahagikan secara rawak kepada empat kumpulan dan *L. reuteri* S29 PFB (1×10^8 , 10^9 dan 10^{10} CFU / hari) telah diberikan sebagai makanan secara oral. Darah dan organ yang dikumpulkan pada akhir tempoh intervensi telah dianalisis menerusi parameter kesihatan (biokimia darah, hematologi dan histopatologi) dan jua penilaian insiden translokasi ke darah dan organ.

Hasil dari kajian ini menunjukkan bahawa semua strain berupaya menggunakan glukosa dan laktosa. Profil enzim bagi kesemua strain ini menunjukkan kaitan dengan penapaian

karbohidrat. Enzim bakteria yang berbahaya seperti *beta glucoronidase* tidak dikesan di dalam semua strain. Semua strain lactobacilli yang telah diuji menunjukkan kerentanan terhadap *penicillin*, *chloramphenicol* dan *tetracycline*. Melalui pemerhatian di dalam kajian ini, tiada satu pun strain yang bersifat hemolitik atau *decarboxylate* histidine, tirosin, lisin atau arginine yang berupaya membentuk amina biogenik. Kepekatan asid laktik D-/L dan unit aktiviti hidrolase garam hempedu adalah setanding dengan strain komersil iaitu *L. reuteri* RC-14. Keputusan dari kajian *in vivo* menunjukkan bahawa kemasukan *L. reuteri* 29 PFB secara oral dengan dos yang berlainan selama 28 hari tidak mempunyai kesan toksikologi yang buruk terhadap status kesihatan tikus secara umum serta parameter hematologi, biokimia darah dan histologi usus. Tiada insiden translokasi ke darah dan corak pencapjarian DNA isolat yang pulih dari tisu adalah tidak padan dengan strain yang dimasukkan. Kesimpulannya, hasil daripada kajian ini menunjukkan bahawa *L. reuteri* 29 PFB adalah pilihan yang lebih baik bagi pembangunan probiotik, dan berkemungkinan adalah selamat untuk kegunaan manusia.



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LIST OF ABBREVIATIONS

SCFA	Short chain fatty acids
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
WHO	World Health Organization
GRAS	Generally recognized as safe
QPS	Qualified Presumption of Safety
EFSA	European Food Safety Authority
ATCC	American type culture collection
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
Lact/L.	<i>Lactobacillus</i>
SPP.	Species
LAB	Lactic acid bacteria
LGG	<i>Lactobacillus rhamnosus</i> GG
LCs	<i>Lactobacillus casei</i> shirota
RAPD	Random amplified polymorphic DNA
BSH	Bile salt hydrolase
BA	Biogenic amine
MRS	De Man, Rogosa and Sharpe
BHI	Brain heart infusion
BSA	Bovine serum albumin
CFU	Colony forming unit
CIC	Critically ill children
PCR	Polymerase chain reaction
SPSS	Statistical package for social sciences
Peri	Perianal
PF	Posterior fornix
F.O.S	Fructo-oligosaccharide
G.O.S	Galacto- oligosaccharide
RCT	Randomized control trial
RDBCT	Randomized double blind control trial

CHAPTER 1

INTRODUCTION

1.1 Introduction

Diet and lifestyle related chronic diseases such as obesity, diabetes, and cardiovascular diseases are a major problem in most countries around the world (WHO, 2000). These diseases are non-reversible and greatly contributes to a country's economic burden. Extraneous factors such as physical inactivity and unhealthy diet (such as excessive calorie intake) contributes to the increasing incidence of these diseases. Likewise, the emergence of resistant microorganisms due to the increasing reliance on antibiotics, coupled with misuse and abuse of antibiotics has become a major public health problem and has led to the continuous manifestation of bacteria resistant to many available antibiotics. Infections caused by antibiotic resistant bacteria are extremely problematic, particularly in hospitalized patients, partly because hospitalized patients are likely to have a compromised immune defense mechanisms due to their underlying illnesses. In addition, infections due to antibiotic resistant microorganisms may lead to serious medical complications since they are difficult to treat (Imperial & Ibana, 2016).

The human body is colonized by many microorganisms including communities of bacteria, viruses and fungi that are specific to different body niches such as the gut, skin, urogenital system and the oral cavity. The advent of next-generation DNA sequencing has allowed more sophisticated analysis and sampling of these complex systems by culture-independent methods. The human microbiome project revealed that the cells of the microbiota are more than the total number of our own cells by 10 folds, and the bacterial microbiome itself, is a thousand times more than the total number of genes in the human genome (Turnbaugh et al., 2007). The interesting thing about this is that each individual has a unique set of microbiota, both in terms of composition and diversity. The gut has been described as the organ with the highest population of microorganism and comprises of as many as 10-100 trillion of microbes, of which majority are found in the large intestine (Turnbaugh et al., 2007). These microbes exist in a symbiotic relationship with the host. It is widely accepted that this symbiotic relationship is crucial for host physiology since these microbes play important roles in host physiology and metabolism (discussed in section 2.1.1 of the next chapter). Recent studies have provided strong evidence that perturbations in the normal composition of the intestinal microbiota (e.g. due to recent antibiotic therapy), often referred to as 'dysbiosis' can lead to inflammatory diseases such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), metabolic diseases and neurological diseases (Evrensel & Ceylan, 2015; Pflughoeft & Versalovic, 2012). Therefore, treatment modalities such as the use of probiotics to modulate and restore balance to the microbiota is a good way to enhance and maintain our physiology.

The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) defined probiotics as "live" microorganisms, which when administered in adequate amounts, confer health benefits to the host (FAO/WHO). Various health

beneficial effects of probiotics have been reported, such as the modulation of the composition and function of microbiota, modulation of intestinal immunity, production of antimicrobial substances, prevention and treatment of various types of diarrheal diseases and so on. With the increase awareness of correlations between health and diet coupled with the perceived health benefits of probiotics, there have been increased medical and industrial interests in the isolation and characterization of new probiotic strains with beneficial health properties. Species of *Lactobacillus* and *Bifidobacterium* are the most widely used species for probiotic development. This is partly due to the fact that many species belonging to these genera are generally regarded as safe (GRAS) and are non-pathogenic members of the human microbiota. *Lactobacillus* spp. have a long history of safe consumption in traditional fermented foods for centuries. Probiotics have been safely used in many populations including the immunosuppressed and the critically ill patients without any adverse effects (Kukkonen et al., 2008; Ladas et al., 2016; M. K. Salminen et al., 2002; Srinivasan et al., 2006; Sullivan & Erik Nord, 2006).

Despite the reported health benefits of *Lactobacillus* as probiotics together with their “GRAS” status, they have been reported to be associated with clinical conditions such as bacteremia, endocarditis and localized infections (Salminen et al., 2004; Cannon et al., 2005; Cukovic-Cavka et al., 2006). Infection caused by probiotic bacteria are extremely rare, but few individual cases have been reported in patients with severe underlying diseases (Salminen et al., 2004; De Groote et al., 2005; Land et al., 2005). Therefore, it has become extremely important to assess the safety of a new probiotic strain as they cannot be assumed to share the same historical safety of traditional strains even if they are of the same species.

In this study, five (5) strains belonging to three different species of *Lactobacillus*, previously characterized with probiotic characteristics (such as acid and bile tolerance, adhesion to human epithelial cell line, co- and autoaggregation and antimicrobial activity against common human pathogens) were evaluated for their safety for human use.

1.2 Research objectives

1.2.1 General objective

To evaluate the safety of lactobacilli strains as potential probiotics using *in vitro* and *in vivo* tests.

1.2.2 Specific objectives

1. To assess the antimicrobial resistance patterns and hemolytic activities of the *Lactobacillus* strains.
2. To screen the strains for undesirable metabolites production using *in vitro* methods.
3. To evaluate the safety of the *L. reuteri* 29B *in vivo* in a sub-acute oral toxicity testing in mice.

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LIST OF PUBLICATIONS

Journal article

Meleh, H.U., Choo, S., Desa, M. N. M., Rangasamy, P., Hassan, H., Than, L. T. L. (2018). Isolation and safety characterization of *Lactobacillus* strains with antimicrobial properties for human use. *Plos one*- (submitted).

Proceedings

Hadiza Umar Meleh, Mohd Nasir Mohd Desa, Leslie Than Thian Lung. In vitro safety Evaluation of lactobacilli as probiotics for human use. Malaysian Society for Microbiology postgraduate Seminar (MSMPS), 9th October, 2018. University Teknologi MARA, Shah Alam, Selangor.

Hadiza Umar Meleh, Mohd Nasir Mohd Desa, Leslie Than Thian Lung. Safety evaluation of potential probiotic *Lactobacillus reuteri* 29B in BALB/c mice. The 34th Symposium of the Malaysian Society for Microbiology 2018 (MSM2018), 7th – 10th December, 2018. Gurney Resort Hotel & Residences, Georgetown, Penang, Malaysia.



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