UNIVERSITI PUTRA MALAYSIA

PROBIOTIC CHARACTERISTICS, ANTI-INFLAMMATORY AND ANTI-CANCER EFFECT OF SHORT CHAIN FATTY ACID-PRODUCING Escherichia coli ISOLATED FROM HEALTHY HUMAN MICROBIOTA

ATCHAREEYA NAKKARCH

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By

ATCHAREEYA NAKKARCH

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June 2020

Chairman : Professor Hooi Ling Foo, PhD
Faculty : Biotechnology and Biomolecular Sciences

Human intestine is a great reactor to decompose dietary fiber to short chain fatty acids (SCFA) by indigenous gut microbiota that serve as energy for their growth and as anti-inflammation agents in human gut. Therefore, this research was aimed to isolate and characterize short chain fatty acid-producing bacteria from human feces. Five gut microbiota that isolated from three healthy volunteers were identified as the highest butyric producing bacteria, which were subsequently verified for their survivability under acid and bile condition, antimicrobial activity, hemolytic activity and mucin adhesion. The selected butyric producing bacteria were identified as *Escherichia coli* by 16s rRNA analyses. As for the probiotic, anti-cancer and anti-inflammatory characteristics, *E. coli* KUB-36 was identified as the most potentials probiotic bacteria among the SCFA producing *E. coli* strain that were isolated from human gut microbiota. The outer membrane of *E. coli* strain may contain the potent immunostimulatory lipopolysaccharide molecules. Hence, the toxin genes were investigated for *E. coli* KUB-36 and the results showed the lack of some endotoxin genes that related to LPS synthesis and absence of enterotoxin genes that related to diarrheas incidences, indicating that *E. coli* KUB-36 is presumptive safe bacterium. Moreover, LPS was extracted from *E. coli* KUB-36 has low effect to induce inflammatory cytokine on THP-1 macrophage cell line. The anti-cancer and anti-inflammatory effects of *E. coli* KUB-36 metabolites and individual SFCA that presents in *E. coli* KUB-36 metabolites were further investigated by using breast and colon cancer cell lines and macrophage cell. The cytotoxicity activity showed that *E. coli* KUB-36 produced anti-cancer effect on both cancer cell lines, while exhibited limited cytotoxicity effect on normal cells. Moreover, amongst the SCFA that present in the metabolite of *E. coli* KUB-36, acetic acid demonstrated higher cytotoxicity activity. As for the anti-inflammatory activity, *E. coli* KUB-36 metabolites and its SCFA suppressed inflammatory cytokine and induced anti-inflammatory cytokine simultaneously. In conclusion, the results in this research

suggested that *E. coli* KUB-36 have vast potential as probiotic bacterium since it has the ability to survive under acidic and bile condition, did not possess endo- and exotoxins but exhibited favorable anticancer and anti-inflammatory effects.

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

CIRI-CIRI PROBIOTIK, KESAN ANTI-RADANG DAN ANTI-KANSER *Escherichia coli* YANG MENGHASILKAN ASID LEMAK RANTAI PENDEK YANG DIPENCILKAN DARIPADA MIKROBIOTA MANUSIA YANG SIHAT

Oleh

ATCHAREEYA NAKKARCH

Jun 2020

Pengerusi : Profesor Hooi Ling Foo, PhD
Fakulti : Bioteknologi dan Sains Biomolekul

Usus manusia adalah reaktor biologik yang hebat untuk menukar serat makanan kepada asid lemak rantai pendek hasil penguraian dari mikrobiota usus. Ia akan digunakan sebagai tenaga untuk pertumbuhan usus bakteria dan sebagai agen anti-radang pada usus manusia. Oleh itu, kajian ini bertujuan untuk mengasingkan dan mencirikan bakteria penghasil asid lemak rantai pendek dari tinja manusia. Lima bakteria yang diasingkan dari tiga sukarelawan yang sihat dikenalpasti sebagai bakteria penghasil asid butirik tertinggi, yang kemudiannya pencirian lain disahkan seperti kemandirian hidup bakteria tersebut di persekitaran ekstrim, aktiviti antimikrob, aktiviti hemolitik dan lekatan musin. Hasil analisis rRNA 16S mendapati, bakteria penghasil butirik yang dipilih dikenalpasti sebagai *Escherichia coli*. Ciri-ciri probiotik lain, seperti anti-kanser dan anti-radang juga dikaji, di mana *E. coli* KUB-36 didapati sebagai isolat berpotensi tinggi. Membran luar *E. coli* mungkin mengandungi molekul lipopolisakarida yang menyebabkan kesan imunostimulasi yang poten. Oleh itu, gen toksin untuk *E. coli* KUB-36 telah diselidik dan hasil kajian menunjukkan kekurangan beberapa gen endotoksin yang berkaitan dengan sintesis LPS dan ketiadaan gen enterotoxin yang berkaitan dengan kejadian cirit-birit, menunjukkan andaian bahawa *E. coli* KUB-36 adalah bakteria selamat. Tambahan pula, LPS telah diekstrak daripada *E. coli* KUB-36 mempunyai kesan yang rendah untuk merangsang keradangan cytokine pada garisan sel macrophage THP-1. Kesan anti-kanser dan anti-radang metabolit *E. coli* KUB-36 dan asid lemak rantai pendek yang terdapat dalam metabolit *E. coli* KUB-36 disiasat dengan menggunakan sel barah payudara dan usus besar dan sel makrofag. Analisis sitotoksisiti menunjukkan bahawa *E. coli* KUB-36 memberi kesan anti-kanser pada kedua-dua sel kanser, sementara menunjukkan kesan sitotoksisiti terhad pada sel normal. Selain itu, asid asetik didapati menunjukkan aktiviti sitotoksi yang lebih tinggi di antara asid lemak rantai pendek yang terdapat dalam metabolit *E. coli* KUB-36. Bagi aktiviti anti-radang, metabolit E. *coli* KUB-36 dan asid lemak rantai pendek yang diasingkan dari

E. coli KUB 36 menghambat aktiviti sitokin inflamasi dan mengaruh aktiviti sitokin anti-radang secara serentak. Kesimpulannya, dalam kajian ini, *E. coli* KUB-36 yang diasingkan dari tinja manusia berpotensi besar sebagai bakteria probiotik kerana mempunyai kemandirian hidup bakteria tersebut di persekitaran ekstrim yang tinggi, tidak memiliki endo- dan eksotoksin dan memberi anti-kanser dan anti-keradangan ke atas sel manusia.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Hooi Ling Foo, PhD
Professor
Faculty of Biotechnology and Molecular Sciences
Universiti Putra Malaysia
(Chairman)

Ulaiwan Withayagiat, PhD
Assistance Professor
Faculty of Agro-Industry
Kasetsart University, Thailand
(Member)

Sunee Nitisinprasert, PhD
Associate Professor
Faculty of Agro-Industry
Kasetsart University, Thailand
(Member)

Adelene Ai Lian Song, PhD
Senior Lecturer
Faculty of Biotechnology and Molecular Sciences
Universiti Putra Malaysia
(Member)

Nur Elina Abdul Mutalib, PhD
Scientist
National institutes of Biotechnology Malaysia
Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 10 December 2020

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LIST OF ABBREVIATIONS

ATCC	American type culture collection
BSA	Bovine serum albumin
CD	Crohn's disease
cfu	Colonies forming unit
cGMP	Cyclic guanosine monophosphate
CLSI	Clinical and laboratory standards institute
Ct	Cycle threshold
°C	Degree Celsius
DMEM	Dulbecco's modified eagle medium
DMSO	Dimethylsulfoxide
E. coli	*Escherichia coli*
FBS	Fetal bovine serum
FDA	Food and drug administration
FFAR	Free fatty acid receptor
g	G- force
GC	Gas chromatography
GI	Gastrointestinal
GRAS	Generally Recognized as Safe
g/l	Gram/liter
IBD	Inflammatory bowel diseases
IBS	Irritable bowel syndrome
IL	Interleukin
kg	Kilogram
LPS	Lipopolysaccharide

LT	Heat labile
LTA	Lipoteichoic acid
min	Minute
ml	Milliliter
mm	Millimeter
mM	Millimolar
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
µg	Microgram
NFκB	Nuclear factor kappa B
NOS	Nitric oxide synthase
OS	Oligosaccharide
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
PYY	Peptide YY
RPMI	Roswell park memorial institute medium
RT	Reverse transcription
SCFA	Short-chain fatty acid
SLAPs	Surface layer associated proteins
ST	Heat-stable
TNF-α	Tumor necrosis factor alpha
UV	Ulcerative colitis
VRE	*Vancomycin-resistant enterococci*
v/v	Volumn/volumn
w/v	Weight/volumn

CHAPTER 1

INTRODUCTION

The human gastrointestinal (GI) tract contained around 300–500 different species of microbial communities and have over 50 bacterial phyla (Noverr *et al.,* 2004). The common bacteria type which are presented in human GI tract are *Bacteriodetes, Bifidobacterium, Eubacterium, Fusobacterium, Clostridium, Lactobacillus, Enterococcus* and *Enterobacter* (Noverr *et al.,* 2004). Generally, Probiotic bacteria belong to *Lactobacillus* or *Bifidobacteria* genera. Moreover, some strains of *Streptococcus, Candida,* and *E. Coli* also play a key role in probiotic products. These strains secrete compounds that inhibit pathogen colonization, enhance immune function and assist digestion (Hill *et al.,* 2014).

Nowadays, butyric acid-producing bacteria in the GI system have gained recognition as anti-inflammatory functional responsive bacteria. Most butyric acid-producing bacteria in the human intestine belong to the Firmicutes phylum such as *Eubacterium rectale* and *Faecalibacterium prausnitzii* which are two most predominant species in the human intestine (Rivière *et al.,* 2016). Butyric acid-producing bacteria species in the human colon are *Roseburia* spp., *Anaerostipes* spp., *Eubacterium* spp., and *Butyricicoccus pullicaecorum* (Rivière *et al.,* 2016). These strains are useful bacteria (Roberfroid *et al.,* 2010; Gibson *et al.,* 2017) because they produce the short chain fatty acid (SCFA) especially butyric acid which has the intestinal health effects to reducing inflammation and enhancing gut barrier integrity (Canani *et al.,* 2011).

SCFA; Butyric acid generated in the large intestine by gut microbiota fermentation. Three predominant SCFA; acetic, butyric and propionic acids are normally found in a ratio of 3:1:1 in the GI tract (Thursby and Juge, 2017). The SCFA have an important role in promoting gut health. These SCFA can be absorbed and utilized for energy by epithelial cells in the GI tract that related to the cellular process regulation (Louis and Flint, 2009; Sokol *et al.,* 2008). Acetic acid is produced by most gut anaerobes, whereas two pathways, the succinate or propanediol pathway are known for the propionic acid formation and butyric acid is produced from carbohydrates through acetoacetyl CoA and glycolysis (Louis and Flint, 2017).

SCFAs act as important signals in the immune system (Górska *et al.,* 2019), especially butyric acid has anti-cancer properties along with anti-inflammatory (Ploger *et al.,*2012; Van Zanten *et al.,* 2012). The inhibitory effect of SCFA presented in several cancer cell lines (Arun *et al.,* 2019; Yonezawa *et al.,* 2007). The *Lactobacillus* and *Bifidobacterium* supernatant were enriched with SCFA and they can initiate the apoptotic signaling that leads to cell death of HT-29 colon cancer cells. (Arun *et al.,* 2019). Moreover, butyric acid exhibited the anti-cancer effect by signaling via the stress-responsive p38 MAPK/HSP27 pathway in the breast cancer MCF-7 cell line (Yonezawa *et al.,* 2007). Besides, butyric acid enabled to decrease 60 % of the viability of U9-37 leukemia cells via p38 MAPK pathway (Pulliam *et*

al., 2016). A study with relevance to inflammatory bowel disease reported that SCFA TNF-α release stimulated by LPS from blood-derived neutrophils of human. Furthermore, SCFA had an anti-inflammatory effect in human colon adenocarcinoma cell line by inhibit TNF-α activation in NF-κB pathway (Tedelind *et al.,* 2007). Also, butyric acid had anti-inflammatory effects in macrophage cell line via activation of FFA3 receptors that resulted in the reduction of IL-6, TNFα, MCP-1 and NOS production (Ohira *et al.,* 2013).

These data presented that the metabolism of gut microbiota related with the host immune system and inflammatory responses. Therefore, this research aims to isolate butyric acid-producing bacteria and characterize their probiotic properties, anti-cancer and anti-inflammatory effects. Bacteria were isolated from feces of healthy adult. These isolates were investigated their acid bile tolerance, antimicrobial activity, antibiotic sensitivity, mucin adhesion ability and SCFA production for probiotic potentials. The bacteria safety which were hemolytic activity, and harboring of the LPS production and toxin genes were elucidated. Finally, anti-cancer and anti-inflammatory of the selected bacteria metabolite were investigated under this research.

The main aims to characterize high butyric acid-producing bacteria from human feces with probiotic, anti-cancer and anti-inflammatory potentials and the specific objective was proceeded.

1. To isolate and identify butyric acid-producing bacteria from human.
2. To determine the probiotic characteristics of selected butyric acid.
3. To detect endotoxin and exotoxin genes from selected butyric acid producing bacteria isolated from human feces.
4. To determine anti-cancer and anti-inflammatory activity of the selected butyric acid-producing bacteria isolated from human feces.

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