ENHANCEMENT OF γ-AMINOBUTYRIC ACID PRODUCTION BY *Lactobacillus plantarum* Taj-Apis362 AND ITS BIOACTIVITIES IN YOGHURT WITH ANTIHYPERTENSIVE EFFECT ON RATS

By

FARAH SALINA BINTI HUSSIN

Thesis Submitted to School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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To my beloved sons Ariff, Aiman and Amsyar

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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γ-aminobutyric acid (GABA) has been well known to play a critical role in the central and peripheral nervous systems in terms of blood pressure regulation. Numerous foods have been reported to naturally contain GABA; for example, fruits and vegetables but in trace amounts. Therefore, this study aims to produce high GABA naturally via fermentation in yoghurt by using lactic acid bacteria (LAB), at a low glutamate concentration while eliminating the use of cofactor, pyridoxal-5' -phosphate (PLP) which is typically needed during GABA production. The GABA-producing ability of three novel strains of lactic acid bacteria (*L. plantarum* Taj-Apis362, assigned as UPMC90, UPMC91, and UPMC1065) co-cultured with starter culture in yoghurt was evaluated. A combination of UPMC90 + UPMC91 with starter culture symbiotically revealed the most prominent GABA-producing effect. Response surface methodology revealed the optimized fermentation conditions at 39.0 °C, 7.25 h, and 11.5 mM glutamate substrate concentration to produce GABA-rich yoghurt (29.96 mg/100g) with desirable pH (3.93) and water-holding capacity (63.06%). GABA content was further enhanced by the addition of simple sugars and commercial prebiotics where simple sugars induced more GABA production (42.83–58.56 mg/100g) compared to the prebiotics (34.19–40.51 mg/100g), with 2% glucose promoting the most GABA production in yoghurt (58.56 mg/100g) surpassing the control sample with added PLP (48.01 mg/100 g). The yoghurt prepared with glucose also had the highest probiotic count (9.31 log CFU/g). The effect of sugars and prebiotics on the rheological properties of yoghurt were not significant when compared to standard yoghurt in terms of consistency index (K), yield stress and dynamic oscillatory measurements. However, the addition of FOS and inulin showed significant effects on firmness, consistency and cohesiveness in texture profile analysis. The microstructure of yoghurt supplemented with inulin, FOS, and GOS was found to have more crosslinks interconnected, forming a compact protein network with small serum pores, than standard yoghurt and also those supplemented with glucose, sucrose, and fructose. A comparison study on the presence of bioactive components showed significant differences in peptide content and ACE-inhibitory activity between GABA rich yoghurt and standard yoghurt. The antioxidant activity measured by using ferric reducing ability of plasma (FRAP) assay was significantly higher for GABA-rich yoghurt (53.64 µM) than for standard yoghurt (47.61 µM) and the results were vice versa in 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay. Metabolomics profiling using ^{1}H-NMR was also conducted and revealed different metabolite concentrations of amino acid, sugar and organic acid in GABA-rich and standard yoghurt. Simulated gastrointestinal digestion of this GABA-rich yoghurt showed a non-significant reduction in GABA content and probiotic viability, demonstrating the resistance towards a highly acidic environment (pH 1.2). Refrigerated storage up to 28 days improved GABA production (83.65 mg/100 g) compared to fresh GABA-rich yoghurt prepared on day 1. In *in vivo* study, a blood pressure-lowering efficacy at 0.1 mg/kg GABA dosage (equivalent to 30 mg/kg GABA-rich yoghurt) was demonstrated in spontaneous hypertensive rats and no toxicity was observed for GABA-rich yoghurt up to 1500 µg/mL of concentration via the zebrafish model. These results successfully mitigate the over-use of glutamate substrate and omit the use of PLP cofactor at a shorter fermentation time during GABA enhancement in yoghurt, offering an economical approach to produce a probiotic-rich dairy food that also has high bioactive components with an antihypertensive effect.

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

PENINGKATAN PENGELUARAN ASID γ-AMINOBUTIRIK OLEH *Lactobacillus plantarum* Taj-Apis362 DAN BIOAKTIVITINYA DI DALAM YOGURT DENGAN KESAN ANTIHIPERTENSI KE ATAS TIKUS

Oleh

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Asid γ-aminobutirik (GABA) telah terkenal memainkan peranan penting dalam sistem saraf pusat dan periferi dari segi pengawalan tekanan darah. Banyak makanan telah dilaporkan mengandungi GABA secara semula jadi; contohnya, buah-buahan dan sayur-sayuran tetapi dalam jumlah surih. Oleh itu, kajian ini bertujuan untuk menghasilkan GABA yang tinggi secara semula jadi melalui fermentasi dalam yogurt dengan menggunakan bakteria asid laktik (LAB), pada kepekatan glutamat yang rendah di samping menyingkirkan penggunaan kofaktor, pyridoxal-5' -fosfat (PLP) yang biasanya diperlukan semasa penghasilan GABA. Keupayaan menghasilkan GABA bagi tiga jenis LAB baru (*L. plantarum* Taj-Apis362, dengan nama umpukan UPMC90, UPMC91, dan UPMC1065) yang dikultur dengan kultur pemula di dalam yogurt telah dinilai. Kombinasi UPMC90 + UPMC91 bersama kultur pemula menunjukkan kesan simbiotik yang paling ketara dalam penghasilan GABA. Kaedah tindakbalas permukaan menunjukkan keadaan fermentasi yang dioptimumkan pada suhu 39.0 °C, 7.25 jam, dan substrat glutamat berkepekatan 11.5 mM untuk menghasilkan yogurt diperkaya GABA (29.96 mg/100g) dengan pH 3.93 dan muatan simpanan air sebanyak 63.06%. Kandungan GABA ditingkatkan lagi dengan penambahan gula ringkas dan prebiotik komersial di mana gula ringkas menyebabkan lebih banyak penghasilan GABA (42.83–58.56 mg/100g) berbanding dengan prebiotik (34.19–40.51 mg/100g). Penambahan glukosa pada kepekatan 2% mendorong penghasilan GABA paling banyak dalam yogurt (58.56 mg /100 g) melebihi sampel kawalan iaitu yogurt dengan penambahan PLP (48.01 mg/100 g). Yogurt yang ditambah dengan glukosa juga mempunyai kiraan probiotik tertinggi (9.31 log CFU/g). Kesan gula dan prebiotik terhadap reologi yoghurt tidak menunjukkan perbezaan ketara jika dibandingkan dengan yogurt biasa dari segi indeks konsistensi, K, tegasan alah dan pengukuran osilatori dinamik. Walau bagaimanapun, penambahan FOS dan inulin menunjukkan kesan yang signifikan terhadap keteguhan, konsistensi dan daya lekitan dalam analisis profil tekstur. Mikrostruktur yogurt yang dilengkapi dengan inulin, FOS, dan GOS didapati mempunyai lebih banyak pautan silang yang saling berkaitan, membentuk rangkaian protein padat dengan liang serum kecil,

daripada yogurt standard dan juga yogurt yang ditambah dengan glukosa, sukrosa, dan fruktosa. Kajian perbandingan mengenai kehadiran komponen bioaktif menunjukkan perbezaan yang signifikan dalam kandungan peptide dan aktiviti rencatan ACE di antara yogurt diperkaya GABA dan yogurt biasa. Aktiviti antioksidan yang diukur dengan menggunakan ujian kuasa antioksidan penurunan ion ferik (FRAP) jauh lebih tinggi untuk yogurt diperkaya GABA (53.64 μM) daripada yogurt biasa (47.61 μM) dan mmenunjukkan hasil yang sebaliknya dalam ujian asid 2,2'-azino-bis-(3-etilbenzotiozolin-6-sulfonik) (ABTS). Profil metabolit menggunakan ^{1}H-NMR juga dilakukan dan menunjukkan kandungan metabolit asid amino, gula dan asid organik yang berbeza dalam yogurt diperkaya GABA dan yogurt biasa. Simulasi pencernaan yogurt diperkaya GABA menunjukkan penurunan yang tidak ketara dalam kandungan GABA dan kebolehhidupan probiotik, menandakan ketahanan terhadap persekitaran yang sangat berasid (pH 1.2). Penyimpanan sejuk sehingga 28 hari meningkatkan penghasilan GABA (83.65 mg/100g) berbanding dengan yogurt diperkaya GABA yang disediakan pada hari pertama. Dalam kajian *in vivo*, keberkesanan penurunan tekanan darah pada dos 0.1 mg/kg GABA (bersamaan dengan 30 mg/kg yogurt diperkaya GABA) didemonstrasi pada tikus hipertensi spontan dan tiada ketoksikan yang diperhatikan untuk yogurt diperkaya GABA sehingga kepekatan 1500 µg/mL melalui model zebrafish. Hasil ini berjaya mengurangkan penggunaan substrat glutamat yang berlebihan dan mengelakkan penggunaan kofaktor PLP pada waktu fermentasi yang lebih pendek semasa peningkatan GABA dalam yogurt, menawarkan pendekatan ekonomi untuk menghasilkan makanan tenusu yang kaya dengan probiotik, mempunyai komponen bioaktif yang tinggi serta mempunyai kesan antihipertensi yang rentan.

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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:

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GABA	γ -aminobutyric acid
UPMC90	*L. plantarum* Taj-Apis362 intracellular
UPMC91	*L. plantarum* Taj-Apis362 extracellular
UPMC1065	*L. plantarum* Taj-Apis362 wild-type
PLP	Pyridoxal 5'-phosphate
K	Consistency index
FOS	Fructooligosaccharide
GOS	Galactooligosaccharide
ACE	Angiotensin-converting enzyme
FRAP	Ferric reducing antioxidant power
ABTS	2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate)
GAD	Glutamate decarboxylase
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
BP	Blood pressure
SHR	Spontaneously hypertensive rats
GDAR	Glutamate-dependent acid-resistance
LVR	Linear viscoelastic region
SGF	Simulated-gastric-fluid
SIF	Simulated-intestinal-fluid
WHC	Water holding capacity
NMR	Nuclear magnetic resonance
TA	Titratable acidity

GY	GABA-rich yoghurt
SY	Standard yoghurt
hpe	Hours of post exposure
LC	Lethal concentration

CHAPTER 1

INTRODUCTION

1.1 Background of study

Hypertension is an underlying health complication that relates directly to the prevalence of cardiovascular diseases, including heart failure, coronary artery disease, stroke, atrial fibrillation, and peripheral vascular disease (Carey et al., 2018). A continuous hypertension without proper treatment may lead to kidney failure, cognitive decline, and dementia (Vaes et al., 2015). According to WHO (2020), 25% of men and 20% of women were diagnosed with hypertension in the year 2015, resulting in the occurrence of worldwide premature death. Along with the increasing health awareness and consumer demand towards food products that provide beyond basic nutrition (carbohydrate, protein, fat), food scientists are driven towards developing functional foods with additional health benefits.

One of the active constitute in foods receiving such attention is γ-aminobutyric acid (GABA), a non-proteinaceous amino acid that has been demonstrated to play a vital role in both the central and peripheral nervous system to consequently regulate blood pressure (Hayakawa et al., 2004; Yang et al., 2012). Physiologically, GABA reduces stress (Nishimura et al., 2016), inhibits cancer cell proliferation (Kim & Ji, 2015) decreases blood pressure (Yoshimura et al., 2010) and prevents diabetes (Soltani et al., 2011). GABA is naturally produced in various fermented foods, including sourdough (Coda et al., 2010), cheese (Pouliot-Mathieu et al., 2013), fermented milk (Nejati et al., 2013) and fermented sausage (Ratanaburee et al., 2013), mainly as a result of lactic acid bacteria (LAB) metabolism. In LAB, L-glutamate substrate is actively converted into GABA via the irreversible α-decarboxylation reaction, catalyzed by the presence of glutamic acid decarboxylase (GAD) enzyme in the microorganism. GABA is produced mostly by lactic acid bacteria (LAB), specifically *Lactobacillus brevis (L. brevis)*, *Lactobacillus paracasei (L. paracasei)*, *Lactobacillus plantarum (L. plantarum)*, and *Lactococcus lactis (L. lactis)*, via the enzymatic reaction of GAD, which requires pyridoxal 5' - phosphate (PLP) as cofactor (Ohmori et al., 2018).

Currently, there is a growing interest from the food industry to produce GABA-enriched foods especially from Japan and Korea since consumer preferences are evolving toward health-promoting and functionally enhanced food products which lead to healthier lifestyles. Furthermore, GABA has been identified as a bioactive compound that promotes health by controlling blood pressure and treating anxiety and depression, meeting the criteria for the Development of Foods for Specified Health Use (FOSHU) (Martirosyan & Singh, 2015; Diez-Gutiérrez et al., 2020). Therefore it is crucial for the development of new products targetting the market of GABA-enriched foods that has been getting a huge attention among consumers.

1.2 Problem statement

Yoghurt is becoming the popular choice of fermented food among consumers. It is appreciated for its high nutritional value and positive health benefits, owing to the probiotic effects of the starter culture, i.e. lactic acid bacteria *Streptococcus thermophilus* (*S. thermophilus*) and *Lactobacillus delbrueckii* subsp. *bulgaricus* (*L. delbrueckii* subsp. *bulgaricus*), such as improved lactose digestion (Savaiano, 2014), prevention of diarrhoea (Linares et al., 2016) and stimulation of the gut immune system (Hong et al., 2015). Typically, yoghurt starter cultures have poor glutamate decarboxylase (GAD) activity, for instance, *S. thermophilus* exhibited GAD activity in the range of 0.65 to 11 μmol/g/min of protein (Zhang et al., 2014; Ohmori et al., 2018), while no GAD activity was reported for *L. delbrueckii* subsp. *bulgaricus* as reflected by extremely low GABA production (Valenzuela et al., 2019). Due to the various health benefits of GABA, production of yoghurt rich in GABA is highly necessary to represent a value-added functional dairy product that can be conveniently consumed regularly.

Previous studies revealed that the effective production of GABA required a high concentration of glutamate (20–507 mM), the presence of costly pyridoxal-5' -phosphate cofactor (PLP, 18–200 μM), and a long fermentation time (48–120 h) (Nejati et al., 2013; Hasegawa et al., 2018; Santos-Espinosa et al., 2020). These major obstacles make up a tall order that deters the production of GABA-rich fermented foods under minimum usage of glutamate and PLP at a reduced incubation time. Glutamate also produces a salty/savoury taste at high concentrations that is unfavourable for yoghurt products while PLP cofactor is a costly ingredient. Following this, using yoghurt as an example of a fermented food system, there is a need to evaluate on wild-type *L. plantarum* Taj-Apis362 (UPMC1065) and its self-cloned, recombinant cells; UPMC90 (intracellular) and UPMC91 (extracellular), that have been previously engineered to have high GAD activity by Tajabadi et al. (2015a), to produce high GABA in yoghurt. The author also worked on new strategy to optimise and enhance GABA production at a reduced incubation time by using response surface method (RSM) and induction technique by simple carbohydrates. To the best of my knowledge, there are only a few studies regarding the effect of sugar on enhancing GABA production in culture medium (Zhang et al., 2014; Ohmori et al., 2018;) and no work has been reported on the effect of prebiotics in culture medium or these simple carbohydrates in an actual food system.

It is hypothesized that natural GABA production could be optimized in yoghurt through co-culturing technique of *L. plantarum* Taj-Apis362 strains with starter culture, by using low glutamate content and without the addition of PLP. The addition of different carbohydrates will also induce GABA production in yoghurt with good rheological and textural properties. This yoghurt will have good stability in terms of GABA content and viability during simulated digestion and also storage. Furthermore, it will lower blood pressure effectively and showed no toxicity effects in *in vivo* models.

1.3 Objectives of the study

Therefore, this research was conducted to accomplish the following objectives:

1. To select and optimise the production of GABA yoghurt by using GABA-producing *L. plantarum* Taj-Apis362 via response surface methodology (RSM).
2. To investigate the effect of different simple sugars and commercial prebiotics on the enhancement of GABA and rheological properties of yoghurt.
3. To analyse the simulated gastrointestinal digestion, storage stability, physicochemical, microbiological properties and bioactive components of enhanced GABA yoghurt.
4. To evaluate the antihypertensive effects of high GABA yoghurt on spontaneously hypertensive rats *in vivo* and its toxicity effects on zebrafish embryos.

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