UNIVERSITI PUTRA MALAYSIA

QUANTIFICATION OF BIOACTIVE COMPOUNDS IN INSTANT COFFEE AND THEIR EFFECTS ON GASTRIC RELEASE USING HGT-1 CELLS

WAN SYAMIMI BINTI WAN KAMARUL ZAMAN

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By

WAN SYAMIMI BINTI WAN KAMARUL ZAMAN

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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Chairman : Associate Professor Loh Su Peng, PhD
Faculty : Medicine and Health Sciences

Coffee has been found to have been linked with gastrointestinal issues, particularly to the avid coffee drinker. Prepacked instant coffee is a common drink in most Malaysian households but its influence on stomach acid release was insufficiently studied. This study was carried out to determine the gastric release effect of instant coffee and quantifying the putative compounds responsible for gastric release (chlorogenic acid, caffeine, and N-methylpyridinium). Seven types of instant coffee namely regular (REG), low sugar (LS), low fat (LF), white coffee (WC), white coffee low acid (WCA), decaffeinated (DC), and instant black coffee (BC) were used. The quantification utilizes the high-performance liquid chromatography-diode array detector (HPLC-DAD) system. The *in vitro* study and flow cytometry analysis (BD FASCANTO II) uses argon laser line (500 mW of the 488 nm) to excite the dye and obtained fluorescent bands in calculating the IPX value for gastric release effect. Statistical analysis of One-way ANOVA analysis was used in HPLC quantification and IPX values between different coffee samples. One-sample T-test was performed for the HGT-1 cell viability ≥70% compared with untreated cells. Independent t-test was used for the comparison between omeprazole or histamine with the non-treated control cells for flow cytometry assay calibration. HPLC results showed caffeine content is significantly higher ($p>0.05$) in BC (60,212 ± 212 µg/ml) and significantly lower ($p>0.05$) in DC as compared to other instant coffee samples. The order of caffeine content are as follows: BC > LS > WCA > LF > REG > WC > DC. In addition, the chlorogenic acid content was significantly higher ($p>0.05$) in the BC sample (35,779 ± 3027 µg/ml) as compared to other instant coffee samples. Meanwhile, there is no significant difference ($p>0.05$) of chlorogenic acid content between the instant coffee other than BC (BC > LS, WCA, LF, REG, WC, DC). As for N-MP content, the result showed BC (565 µg/ml) is significantly higher compared to other instant coffee samples. The amount of N-MP in WC (52 µg/ml) is significantly lowest

($p>0.05$) when compared with BC, DC, and LS. However, NMP in WC was not significantly different ($p>0.05$) in comparison to LF (65 µg/ml) and WCA (71 µg/ml). The order of N-MP content are as follows: BC > DC > LS > REG > WCA > LF > WC. The IPX values of gastric release activity of REG (-0.17 ± 0.007) and DC (-0.16 ± 0.005) are not significantly different ($p>0.05$) from each other. But both are significantly higher ($p>0.05$) gastric release when compared to other instant coffee samples (Gastric release order: DC, REG > BC, WC > WCA, LF, LS). Pearson correlation data showed no significant correlation ($p>0.05$) between the quantitative amount of chlorogenic acids, caffeine, and N-MP with the IPX values in each coffee sample. To conclude, the number of putative compounds in coffee has no significant correlation with the gastric release effect produced. Other pre-existing compounds that make up instant coffee warrant further identification and investigation such as pyrogallol and catechol.

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

KUANTIFIKASI KOMPOSISI BIOAKTIF DALAM KOPI SEGERA DAN KESAN PENGELUARAN ASID GASTRIK MENGGUNAKAN SEL HGT-1

Oleh

WAN SYAMIMI BINTI WAN KAMARUL ZAMAN

Disember 2020

Pengerusi : Profesor Madya Loh Su Peng, PhD
Fakulti : Perubatan dan Sains Kesihatan

Kopi didapati mempunyai kaitan dengan masalah gastrousus terutama dikalangan peminum kopi yang tegar. Kopi segera yang dibungkus adalah minuman biasa di kebanyakan isi rumah di Malaysia, tetapi pengaruhnya terhadap pelepasan asid perut tidak banyak dikaji. Kajian ini dilakukan untuk mengetahui kesan pelepasan gastrik dari kopi segera dan mengkuantifikasi sebatian bioaktif yang bertanggungjawab untuk pembebasan gastrik (asid klorogenik, kafein, dan N-methylpyridinium). Tujuh jenis kopi segera iaitu biasa (REG), gula rendah (LS), rendah lemak (LF), kopi putih (WC), kopi putih asid rendah (WCA), tanpa kafein (DC), dan kopi hitam segera (BC) telah digunakan. Kuantifikasi sebatian kopi menggunakan kromatografi cecair berprestasi tinggi (HPLC)-diod tinggi (HPLC-DAD). Kajian in vitro dan analisis aliran sitometri (BD FASCANTO II) menggunakan garis laser argon (500 mW dari 488 nm) untuk membangkitkan pewarna dan memperoleh jalur pendarfluor dalam mengira nilai IPX untuk kesan pelepasan gastrik. Analisis statistik ANOVA Sehala digunakan dalam mengkuantifikasi HPLC dan nilai IPX antara sampel kopi yang berbeza. Satu sampel Ujian-T terhadap 70% dilakukan untuk daya maju sel HGT-1 yang diuji dengan sampel kopi. Dua sampel Ujian-T digunakan untuk perbandingan antara omeprazole atau histamin dengan sel kawalan yang tidak dirawat untuk penentukuran uji aliran sitometri. Hasil HPLC menunjukkan kandungan kafein jauh lebih tinggi ($p > 0.05$) pada BC (60.212 ± 212 µg / ml) dan jauh lebih rendah ($p > 0.05$) di DC berbanding dengan sampel kopi segera yang lain. Susunan kandungan kafein adalah seperti berikut: BC> LS> WCA> LF> REG> WC> DC. Di samping itu, kandungan asid klorogenik jauh lebih tinggi ($p > 0.05$) dalam sampel BC (35.779 ± 3027 µg / ml) berbanding dengan sampel kopi segera yang lain. Sementara itu, tidak ada perbezaan yang signifikan ($p > 0.05$) kandungan asid klorogenik antara kopi segera selain BC (BC> LS, WCA, LF, REG, WC, DC). Bagi kandungan N-MP, hasil menunjukkan BC (565 µg / ml) jauh lebih tinggi dibandingkan dengan sampel kopi segera yang lain. Jumlah N-MP dalam WC (52

µg / ml) jauh lebih rendah (p >0.05) jika dibandingkan dengan BC, DC dan LS. Walau bagaimanapun, NMP di WC tidak jauh berbeza (p >0.05) dibandingkan dengan LF (65 µg / ml) dan WCA (71 µg / ml). Susunan kandungan N-MP adalah seperti berikut: BC> DC> LS> REG> WCA> LF> WC. Nilai IPX aktiviti pelepasan gastrik REG (-0,17 ± 0,007) dan DC (-0,16 ± 0,005) tidak berbeza secara signifikan (p >0.05) antara satu sama lain. Tetapi keduanya jauh lebih tinggi (p >0.05) pelepasan gastrik jika dibandingkan dengan sampel kopi segera yang lain (Urutan pelepasan gastrik: DC, REG> BC, WC> WCA, LF, LS). Data korelasi Pearson tidak menunjukkan korelasi yang signifikan (p >0.05) antara kuantiti asid klorogenik, kafein dan N-MP dengan nilai IPX dalam setiap sampel kopi. Untuk menyimpulkan, jumlah sebatian putatif dalam kopi tidak mempunyai hubungan yang signifikan dengan kesan pelepasan gastrik yang dihasilkan. Kebarangkalian, kajian terhadap sebatian bioaktif lain dalam kopi segera memerlukan penyiasatan lebih lanjut seperti pyrogallol dan catechol.

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Loh Su Peng, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Norhaizan Mohd Esa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

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

Date: 8 July 2021

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Name and Matric No: Wan Syamimi Binti Wan Kamarul Zaman, GS42338

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LIST OF ABBREVIATIONS

3-CQA	3-Caffeoylquinic acid
4-CQA	4- Caffeoylquinic acid
5-CQA	5- Caffeoylquinic acid
ADB	1,4-diacetoxy 2,3_dicyanobenzenel
ATP	Adenosine triphosphate
ATF-1	Cyclic AMP-dependent transcription factor
AKT-1	Serine/threonine-protein kinase
$A^{Extract\ 570}$	Absorbance of tested sample extract
$A^{Control\ 570}$	Absorbance without tested sample extract
ANOVA	one-way analysis of variance
BC	Black coffee
BCECF	2',7'-Bis-(2-Carboxyethyl)-5-(and-6) Carboxyfluorescein
CGA	Chlorogenic Acid
CV	coefficient variation
CAFF	Caffeine
CQA	Chloroquinic acid
C_5HT	N-Alkanoyl-5-hydroxytryptamides
CQL	chlorogenic acid lactones
Cl^-	Chlorine
cAMP	Cyclic adenosine monophosphate
$CaCL_2$	Calcium chloride
DC	Decaffeinated
DCH	2,3-dicyanohydroquinone
DMEM	Dulbecco's Modified Eagle Medium

DNA	Deoxyribonucleic acid
DMSO	Dimethyl sulfoxide
DAD	diode-array detector
EU	European Union
FDA	Food and Drug Administration
FD	Functional dyspesia
GERD	Gastroesophageal Reflux Disease
GORD	Gastro-oesophageal reflux disease
GAS	Gastric acid secretion
HPLC	High-performance liquid chromatography
HGT-1	Human gastric adenocarcinoma
HCL	Hydrochloric acid
H.*pylori*	Helicobacter pylori
HEPG2	Human liver cancer cell line
HIS	Histamine
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
ICH	International Conference on Harmonization
IBS	Irritable bowel syndrome
IPX	Intracellular pH index
KCl	Potassium chloride
LOD	Limit of detection
LOQ	Limit of quantification
LF	Low fat
LS	Low sugar
LC-MS	Liquid chromatography-mass spectrometry

LEGEND	Longitudinal Examination to Gather Evidence of Neurodegenerative Disease
MANS	Malaysian Adult Nutrition Survey
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
$MgSO_4$	Magnesium sulphate
NMP	N-methylpyridinium
NSAIDS	Nonsteroidal anti-inflammatory drugs
Na^+	Sodium
NaCl	Sodium Chloride
ND	Not detected
NaOH	Sodium hydroxide
OM	Omeprazole
OTC	Over the counter
OTA	Ochratoxin A
PU	Peptic ulcer
PPIS	Proton pump inhibitors
pHi	Intracellular pH
pH	Potential of Hydrogen
pHe	Extracellular pH
PBS	Phosphate-buffered saline
RSD	Relative standard deviation
REG	Regular
RT	Retention time
SNARF-AM	carboxy-Seminaphtharhodafluor - acetoxymethyl ester
SNARF-1	Seminaphtharhodafluor
TCGA	Total Chlorogenic Acid

TAS2R	Taste receptor 2 member 38
UV	Ultraviolet
V/V	Volume/Volume
WC	White coffee
WCA	White coffee- Low acid

CHAPTER 1

INTRODUCTION

1.1 Background

The word coffee according to the linguists is meant by "The Drink". The name was claimed to be originated and adapted from the Turkish word known as *Kahveh* which means coffeehouse and the word *Kahwa* which originally means wine in the Arabic language (International Institute of Agriculture Bureau of Statistics, Antonio di Fulvio, 1947). Coffee was widely accepted to have been originated from Ethiopia and was introduced in the 16th century to the Arab region before moving to the West part of the world (Hatzhold, 2012; International Institute of Agriculture Bureau of Statistics, Antonio di Fulvio, 1947). In the 17th century, coffee classification to *Coffea Arabica L* and *Coffea Canephora* was made known to botany scientists which have the most important economic contribution among all species of coffee plants (Bigger, 2007; International Institute of Agriculture Bureau of Statistics, Antonio di Fulvio, 1947).

Ever since its unveiling to the western world, there has been an unrelenting growing demand for coffee from all over the world particularly coming from countries such as Canada, EU, Japan, Norway, Switzerland, and USA. There was a worldwide increment of coffee production by 18,808 bags of coffee produced in 2014 (141 850 bags) as compared to the year 2009 (123 042 bags) (International Coffee Organization, 2015). Unlike the western part of the world where coffee is freshly brewed from roasted coffee beans, most Malaysians get their source of daily caffeine from prepacked coffee particularly the 3-in-1 instant coffee mixture and instant white coffee (Euromonitor, 2013). In addition, the coffee drinks produced in Malaysia mostly comprise a mixture of roasted coffee, margarine, sugar, and wheat which follows the Food Regulations 1985 where coffee bean composition shall not be lower than 50 percent of the total mixtures of coffee product.

White coffee has different terminologies in different countries. About the British community, white coffee is a term for when the addition of milk, cream, or non-dairy creamer was made into the coffee drink to provide a source of energy and protein (Clarke & Macrae, 1988). Among the Lebanese people, white coffee or *Kahwa Bida (kah-wa bye-da)* in the Arabic language refers to a mixture of coffee and *Mazaher* (orange blossom water) which is commonly served after eating a meal to help promote a better digestion process (Al-Faqih, 2009). Meanwhile, in Malaysia white coffee was originated from Ipoh and was named so due to its distinctly light-colored coffee bean roasted with palm-oil margarine or butter without the involvement of sugar in the mixture. The result is served together with the addition of condensed milk (Richmond, 2010). The coffee-drinking culture in Malaysia differs from the western community where most of the coffee

consumptions derived from processed instant coffee which are less healthier in comparison to freshly brewed coffee or ground coffee drinks (Euromonitor, 2013).

Research has been done extensively in the west on epidemiological studies of coffee. Recently, numerous researches concluded that coffee has health benefits that defy previous epidemiological studies which assessed the risk of coffee intake towards health. Besides the famously known compound of caffeine, thousands of other chemicals such as carbohydrates, lipids, vitamins, minerals, alkaloids. and phenolic compounds can be found in a complex mixture of coffee which possesses beneficial characteristics to human health (Higdon & Frei, 2006). Phenolic compounds in coffee for instance were found to possess a protective role in humans against chronic and degenerative diseases such as diabetes mellitus, neurodegenerative disease, cancer, cardiovascular disease, and cataracts (Farah & Donangelo, 2006).

However, many consumers have claimed the experience of dyspepsia pain and/or gastroesophageal reflux symptoms (i.e. heartburn and regurgitation) concerning drinking coffee. Dyspepsia is a condition where a person is suffering from recurring pain in the upper abdomen region which causes prolong discomfort (Abdul Aziz, Hamzah, Tong, Nadeson, & Wan Puteh, 2009). The condition has affected the worldwide population with an estimation of 25% had developed coffee-induced dyspeptic symptoms. In the western countries including America, ¼ of the population has been diagnosed with dyspeptic symptoms whereby ¼ of them would seek treatment from the doctors while others opted for over-the-counter (OTC) drugs at the pharmacy.

1.2 Problem statement

Coffee is the most consumed beverage in the world and Malaysia's coffee productions are showing positive growth, indicating that coffee culture is the current gastronomical trend among Malaysians (Kong et al., 2011). Epidemiological studies had generated surprisingly positive results on coffee particularly regarding its ability in preventing diseases such as type 2 diabetes mellitus, Parkinson's disease, mental health diseases (i.e. suicide risk), as well as colorectal cancer, and few other types of cancer as well (Higdon & Frei, 2006). Nevertheless, some had also reported cases of gastric irritation originating from coffee consumption, likely as a manifestation of increased gastric acid secretion in the stomach (Boekema, Samsom, van Berge Henegouwen, & Smout, 1999). The first report on coffee causing gastric acid problems dated back to the 1940s (Chou & Benowitz, 1994).

Coffee prohibition by medical doctors is a common therapeutic solution for dyspeptic patients and patients with acid reflux symptoms (Fujioka & Shibamoto, 2008). Coffee was concluded by experts to stimulates gastric acid releases after consumption which consequently triggered the dyspepsia symptoms (Elta, Behler, & Colturi, 1990). Dyspepsia has a prevalence of 7-40%, based on the population

studies conducted worldwide, and was found to prevail among the Asian population. Malaysia on the other hand shows a higher prevalence of dyspepsia among the urban (25%) community compared to the rural (15%) populace (Goh, 2011).

Even though Malaysians are more currently inclined towards the coffee culture trend with instant 3-in-1 coffee being mostly consumed, there are still an insufficient amount of studies conducted to examine the influence of 3-in-1 instant coffee on the stomach acid release among the dyspeptic Malaysian population. Furthermore, extensive scientific-based evidence on the chemical compounds that existed in coffee and its mechanism in causing stomach discomfort is still lacking (Rubach et al., 2014).

Previously, roasted coffee which undergoes steam treatment was presumed to have reduced its content of compounds that causes gastric discomforts such as caffeine, chlorogenic acid, and C5HTs (Fehlau & Netter, 1990; Hoelzl et al., 2010; Pehl, Pfeiffer, Wendl, & Kaess, 1997). In contrast, health-benefiting properties were also discovered in other compounds found in coffee such as N-methylpyridinium which has been reported by multiple researchers to downgrade gastric-release in the stomach (Malte Rubach et al., 2014; Weiss et al., 2010). Furthermore, it was found that the Robusta (canephora) coffee beans are the main species of coffee beans being used in instant coffee production, presumably due to their higher production capacity (Farah, De Paulis, Trugo, & Martin, 2005). It was also found that different usage of coffee species and technological processes involved in coffee production could affect the percentage value of compounds in the final coffee product.

In this research, caffeine, chlorogenic acid and its isomers, (Caffeoylquinic acid; 5-caffeoylquinic acid, 3-caffeoylquinic acid, and 4-caffeoylquinic acid), as well as N-methylpyridinium, were analyzed for gastric release in the HGT-1 cells since these compounds were found to be abundant in a cup of brewed coffee.

1.3 Significance of study

Coffee drinking has become a lifestyle trend and its further widespread among the modern community was promoted by indication of positive health contribution of coffee in numerous researches. Despite the significant bioactive compounds in a cup of coffee, there are still reported cases of gastrointestinal problems among avid drinkers which directed the initial blame towards unhealthy coffee drinking habit. However, earlier seminal research had discovered that coffee can stimulate gastric release in the stomach, leading to a set of symptoms of dyspepsia (Elta, Behler, & Colturi, 1990). Demographically, dyspepsia prevalence in Malaysia is the highest among the urban population (25%) compared to the rural (15%) populace (Goh, 2011), in concurrence with income per capita influences on coffee drinking pattern found in previous research (Grigg, 2002).

The conclusion generated from this study will partly redound to the gastrointestinal health benefit of Malaysians and are able to improve their coffee intake management. In addition, the data in this research could instigate research advancement by other researchers to further explore the connection between coffee and gastrointestinal health by establishing more databases involving in-vivo, human clinical trials, and mechanistic studies. A well-established and resilient database is essential in performing comprehensive research to identify the potential side-effect of coffee on the gastrointestinal health of its consumer.

Furthermore, the outcome of the study could urge researchers to further study beyond the bioactive compounds in instant coffee that can potentially cause gastrointestinal turmoil. However, the possibilities of other vast compounds that existed and interacted within an instant coffee are crucial.

1.4 Objectives

General objective: To study the potential chemical compounds in instant coffee and their effect on gastric release.

Specific Objective:

(1) To determine and compare the amount of chlorogenic acid, caffeine, and N-methylpyridinium compounds that cause a gastric release in different types of instant coffee samples.
(2) To determine and compare the secretory activity of HGT-1 cells when subjected to different types of instant coffee samples using the flow cytometry method.
(3) To find the correlation between the amount of caffeine, chlorogenic acids, and N-MP with the acidity measurement of the HGT-1 cell released.

1.5 Hypothesis

1.5.1 Null Hypothesis

(1) There are no differences between caffeine, chlorogenic acid, and N-methylpyridinium compounds that cause gastric release between different types of instant coffee tested.
(2) There are no differences in secretory activity of HGT-1 cells between different types of instant coffee used.
(3) There is no correlation between the amount of chlorogenic acid, caffeine, and N-MP with the acidity measurement of the HGT-1 cell released.

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BIODATA OF STUDENT

Wan Syamimi binti Wan Kamarul Zaman was born on 29th August 1991 in Kuala Lumpur. In 2009, she was graduated with Malaysia School Certificate (SPM) at Adni Islamic School Taman Sri Ukay. She continued with Monash University Foundation Year (MUFY) while waiting for her SPM result at Sunway University College Subang Jaya. Upon finished with her foundation year, she continued her tertiary education in University College Sedaya International (UCSI) University in 2010 for 3-years program of Bachelor of Science (Hons) Food Science and Nutrition, which supported fully by her parents. After successfully completed her degree and graduated in 2013, she took a gap year before finally decided to do her master's degree in Master Science (Nutritional Science) under self-financial support from her parents. She has authored one review paper and under preparation of one more paper in different scientific journals.

LIST OF PUBLICATIONS

Wan Kamarul Zaman, W., Loh, S., & Mohd Esa, N. (2019). Coffee and gastrointestinal health: a review. *Malaysian Journal of Medicine and Health Sciences*, *15*(SP1), 96–103. (SJR 2021: 0.144)

Wan Kamarul Zaman, W., Loh, S., & Mohd Esa, N. (Accepted for publication 2022). Quantification of Selected Bioactive Compounds in Instant Coffee and Their Effect on Gastric Release using HGT-1 Cells. *Malaysian Journal of Medicine and Health Sciences*. (SJR 2021: 0.144)

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