ANTI-HYPERLIPIDEMIC POTENTIAL OF A COMBINATION OF *Zingiber officinale* Roscoe, *Allium sativum* L., *Citrus lemon* (L.) Osbeck, HONEY AND *Malus domestica* Borkh. CIDER VINEGAR

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

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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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Intervention of herbal combination is widely used to decrease the risk of metabolic disorders such as cardiovascular diseases, hyperlipidemia, diabetes, and obesity. Hyperlipidemia is known as an abnormal lipid metabolism presents in the bloodstream which associated with co-morbidities and mortalities that grossly rising worldwide. The study aims to investigate the anti-hyperlipidemia activities of a combination of ZACAH mixture (*Zingiber officinale* Roscoe (ginger), *Allium sativum* L. (garlic), *Citrus lemon* (L.) Osbeck, Honey, and *Malus domestica* Borkh. Cider Vinegar in hyperlipidemic rats. High-performance liquid chromatography (HPLC) was performed to identify the phytochemical component that presents in the ZACAH mixture. 36 Sprague dawley (SD) rats were divided into 6 groups. ZACAH mixture (1ml/kg, 3 ml/kg, 5 ml/kg) was administered along with a high cholesterol diet (HCD) via oral gavage, daily for 18 weeks. Simvastatin 10 mg/kg was used as a standard drug. At end of week 18, the rats were sacrificed and blood and organs were collected for further experiments. The blood collection was performed for lipid profile (TC, TG, LDL), blood toxicity (Creatinine, AST, ALT), and enzymatic activity (HMG-CoA reductase, LCAT, ACAT2). Besides, liver, kidney and adipose tissue were performed for histological examination by using hematoxylin & eosin (H&E) stain. ZACAH mixture had ORAC value 2000 µmol TE/100 mL, TPC (7537 ± 54.5mg/100g GAE), 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity (27.34 ± 2.71%) , Elastase inhibitory assay (29.29 ± 1.65%) and Lipoxygenase inhibitory assay (98.58 ± 1.42%). The phytochemical component found in the ZACAH mixture is hesperidin. Bodyweight, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) reduced and an increase in high density lipoprotein (HDL) was observed in ZACAH mixture treated groups compared to the positive control (PC). ZACAH mixture treated groups reduced HMG-CoA reductase and ACAT2 activity led to a reduction of TC, TG, LDL and an increase in HDL. Histological examinations revealed that lipid accumulation was reduced in the liver tissue and the size of adipocytes was

suppressed in the ZACAH mixture treated group as compared to the PC group. The findings demonstrate that the ZACAH mixture at 5ml/kg BW significantly ($p<0.05$) has a strong hyperlipidemia activity that can be an alternative approach to combat hyperlipidemia treatment.

Keywords: ZACAH mixture, Hyperlipidemia, High cholesterol diet

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

POTENSI ANTI-HIPERLIPIDEMIK GABUNGAN *Zingiber officinale* Roscoe, *Allium sativum* L., *Citrus lemon* (L.) Osbeck, MADU DAN CUKA SIDER *Malus domestica* Borkh

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Gabungan herba digunakan secara meluas untuk mengurangkan risiko gangguan metabolik seperti penyakit kardiovaskular, hiperlipidemia, kencing manis, dan obesiti. Hiperlipidemia dikenali sebagai metabolisme lipid yang tidak normal yang terdapat dalam aliran darah yang dikaitkan dengan komorbiditi dan kematian yang meningkat secara mendadak di seluruh dunia. Kajian ini bertujuan untuk menyiasat aktiviti anti-hiperlipidemik gabungan ZACAH daripada *(Zingiber Officinale* Roscoe (halia), *Allium sativum* L. (bawang putih), limau sitrus, Madu, dan cuka *Malus domestica* (epal) dalam tikus hiperlipidemik. 36 ekor tikus Sprague dawley (SD) dibahagikan kepada 6 kumpulan. Gabungan ZACAH (1mg/kg, 3 mg/kg, 5 mg/kg) diberikan bersama diet kolesterol tinggi (HCD) melalui gavage oral, setiap hari untuk 18 minggu. Simvastatin 10 mg/kg mengikiut berat badan digunakan sebagai ubat standard. Pada akhir minggu ke-18, tikus telah dikorbankan dan darah serta organ dikumpulkan untuk eksperimen selanjutnya. Pengumpulan darah dilakukan untuk profil lipid (TC, TG, LDL), ketoksikan darah (Creatinine, AST, ALT), dan aktiviti enzimatik (HMG-CoA reductase, LCAT, ACAT2). Selain itu, hati, buah pinggang dan tisu adipos telah dilakukan untuk pemeriksaan histologi menggunakan hematoxylin & eosin (H &E). Campuran ZACAH mempunyai nilai ORAC 2000 µmol TE/100 mL, TPC (7537 ± 54.5mg/100g GAE), 2,2-diphenyl-1-picrylhydrazyl (DPPH) aktiviti penghapusan radikal bebas (27.34 ± 2.71%), akitiviti elastase (29.29 ± 1.65%) dan ujian perencatan lipoxygenase (98.58 ± 1.42%). Komponen fitokimia yang terdapat dalam campuran ZACAH ialah hesperidin. Kumpulan rawatan campuran ZACAH mengurangkan aktiviti HMG-CoA reduktase dan ACAT2 membawa kepada pengurangan tahap TC, TG, LDL dan peningkatan dalam HDL. Pemeriksaan histologi mendedahkan bahawa pengumpulan lipid dikurangkan dalam tisu hati dan saiz adiposit berkurang dalam kumpulan rawatan campuran ZACAH berbanding dengan kumpulan PC. Penemuan menunjukkan bahawa campuran ZACAH pada 5ml/kg berat badan (BW) mempunyai aktiviti hiperlipidemia yang kuat yang boleh menjadi pendekatan alternatif untuk memerangi rawatan hiperlipidemia.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ABCA1	ATP-binding cassette transporter A1
ACAT2	Acyl-coa cholesterol acyltransferase 2
AST	Aspirate aminotransferase
ALT	Alanine aminotransferase
BW	Bodyweight
CE	Cholesterol ester
DC	Drug control
DMAPP	Dimethylallyl diphospate
DMSO	Dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
FC	Free cholesterol
FPP	Famesyl diphospate
GPP	Geranyl pyrophosphate
HCD	High cholesterol diet
HDL	High-density lipoprotein
H&E	Hematoxylin & eosin
HMG- CoA	3-Hydroxy-3-methylglutaryl CoA
HPLC	High-performance liquid chromatography
IPP	isopentyl pyrophosphate
LCAT	Lecithin cholesterol acyltransferase
LDL	Low-density lipoprotein
LSD	Lleast significant difference
NBF	Neutral buffered formalin
NC	Negative control
OD	Optical density

ORAC	Oxygen radical absorbance capacity
PC	Positive control
RCT	Reverse cholesterol transport
SANA	Succ-(Ala)3-pnitroanilide
SD	Sprague dawley
SEM	Standard error of mean
TC	Total cholesterol
TG	Triglyceride
TPC	Total phenolic content
TX	Treatment
UPM	Universiti Putra Malaysia
VLDL	Very-low density lipoprotein
ZACAH	*Zingiber Officinale, Allium Sativum, Citrus Lemon*, Honey and *Malus Domestica* Cider Vinegar

CHAPTER 1

INTRODUCTION

1.1 Background of study

Hyperlipidemia is defined as an elevated amount of lipids in the bloodstream that rise in low-density lipoprotein cholesterol (LDL), total cholesterol (TC), and triglyceride (TG) levels and lower the high-density lipoprotein cholesterol (HDL) (Gill et al., 2021; Hill & Bordoni, 2022). As stated in National Health and Morbidity Survey 2019, an unhealthy amount of cholesterol is taken into account when it exceeds 5.2 mmol/L or higher. There is a primary and secondary types of hyperlipidemia. The primary type of hyperlipidemia happens due to consuming high fats and cholesterol-rich foods as well as genetic defects. While the secondary type of hyperlipidemia happens due to metabolic disorders and endocrine diseases (Nelson R, 2013). The complications that caused by hyperlipidemia are atherosclerosis, cardiovascular diseases, hypertension, and diabetes mellitus.

The prevalence of hyperlipidemia in Malaysia is major contributor that lead to cardiovascular disease (Ministry of Health Science, 2015). 8 million adults have a high level of cholesterol where 45% of females and 32% of males (NHMS, 2019). According to World Health Organization (WHO), approximately 2.6 million death are caused annually due to the rise of cholesterol. By the year 2030, it will be the world's biggest killer that affecting about 23.6 million people worldwide (WHO, 2015). Hyperlipidemia is associated with increase levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and subsequently dropped in high-density lipoprotein (HDL). Cholesterol is known as a component that regulates the fluidity and permeability of the cell membranes. Physiologically, cells are protected from the intracellular excessive deposition of cholesterol by regulating its synthesis, influx and efflux (Han, Yeung, Ip, & Mak, 2018). The primary rate-limiting enzyme for the cholesterol synthesis is 3-Hydroxy-3-methylglutaryl CoA (HMG- CoA) reductase. While cholesterol influx is facilitated by the LDL receptor, the efflux is majorly regulated by ATP-binding cassette transporter A1 (ABCA1) (Weibel et al., 2014). Alteration in this mechanism leads to excessive deposition of cholesterol, which may subsequently result in end-organ damage, characterized by increased necrosis and cell death (Li et al., 2015).

The available synthetic lipid-lowering drugs are statins and fibrates that are used to treat hyperlipidemia. Statins are widely used to reduce cholesterol levels via the cholesterol biosynthetic pathway by inhibiting HMG- CoA reductase. However, most of the drugs consist of undesirable side effects including liver poisoning, liver dysfunction, reduced liver enzyme, myopathy and complications with long term use (Ballantyne et al., 2003; Xu et al., 2014). Therefore, the use of natural and herbal medicine products have been increased in the development

of hyperlipidemia drugs due to fewer side effects, low toxicity (Perumal et al., 2019) cheap and easily available. On the other hand, phytochemicals, and bioactive components of herbs or plant origin help in the prevention of diseases (Sen, Chakraborty, Sridhar, Reddy, & De, 2010). In spite of the available drugs are effective but the side effects and mortality that caused by hyperlipidemia are worried high.

Nowadays, modern medicine highly substitutes natural and herbal sources. Natural and herbal sources that consist of Zingiber officinale (ginger), *Allium sativum* (garlic), Citrus lemon, Malus domestica (apple) vinegar and Honey [ZACAH mixture] are widely used for centuries due to their rich sources and numerous treatments including hyperlipidemia, obesity, and cardiovascular (Saravanan, Ponmurugan, Deepa, & Senthilkumar, 2014).

Zinger officinale is a ginger that belongs to zingi-beraceae family that is used as dietary supplement in food and drinks and has ability to decrease lipid concentration (Bhandari, Kanojia, & Pillai, 2005; Singletary, 2010). *Allium sativum* is a garlic that originated in Central Asia (Hosseini & Hosseinzadeh, 2015) and used in food as a spice and home remedies as a medicinal purpose for various diseases (Mikaili, Maadirad, Moloudizargari, Aghajanshakeri, & Sarahroodi, 2013). Citrus lemon comes from the Rutaceae family which is originated from tropical and subtropical Southeast Asia (Chaturvedi & Shrivastava Suhane, 2016). It is well known for sore throat soothing with the mixture of honey, helps in weight loss, is anti-inflammatory, and balances pH in the body (Chaturvedi & Shrivastava Suhane, 2016).

Honey is a sweetener that has vitamins, minerals, acids as well as enzymes (Chepulis & Starkey, 2008) that enhanced antioxidant capacity, lipid regulation, and improve the immune system (Cortés, Vigil, & Montenegro, 2011). Apple cider vinegar is made by fermenting apples that are consumed as flavoring as well as a preservative agent (Khezri, Saidpour, Hosseinzadeh, & Amiri, 2018). Into the bargain, compounds that present in ZACAH mixture to have been reported have anti-hyperlipidemia, anti-oxidant, and cardio protective properties (Naseem, Shamim, & Khan, 2016) (Ajamzibad, Baloochi Beydokhti, Mohtasham, & Nematollahi, 2021).

In spite of medicinal properties that mentioned, there is insufficient studies on the hyperlipidemia activity of ZACAH mixture. Moreover, the potential of ZACAH mixturet as HMG-CoA reductase has not yet been investigated. Therefore, this present study proposed that ZACAH mixture work as a natural cholesterol-lowering agent that interferes with the mevalonate synthesis pathway through the inhibition of HMG-CoA reductase activities.

1.2 Statement of the problem

In spite of medicinal Hyperlipidemia severity is grossly increasing around the world (Hill & Bordoni, 2022). Hyperlipidemia treated drugs are available such as statin, bile acid sequestrants, and fibrates that inhibit excess lipid accumulation, cholesterol formation, and activation mevalonate pathway.

Based on GHO (Global health observatory data), hyperlipidemia causes one-third of ischaemic heart disease (WHO,2015). Besides, 2.6 million deaths were caused by the raised of total cholesterol. Hyperlipidemia major leads to cardiovascular diseases (CVD). This predicted the over the next 10 years, CVD will be the leading cause of death (Jørgensen et al., 2013 ; Shattat, 2015). The highest mortality was found in Eastern Europe and Central Asia (Benjamin et al., 2017).

Drug therapies are available for the management and treatment of lipid and lipoprotein levels in blood but they consist of limitations as well as side effects (Wilkinson, Laffin, & Davidson, 2014). Therefore, medicinal plants are widely used as an alternative treatment for hyperlipidemia due to minimal or no side effects. Isoflavones, phytosterols, saponins, fibres, polyphenols, flavonoids, and ascorbic acid are active compounds that are produced by plants that play a huge responsibility in lipid metabolism (Verma et al., 2010) ; (Bulku et al., 2010).

1.3 Justification of study

Many researchers have studied widely on a number of herbal combinations to treat diabetes, cardiovascular disease, and microbial activity that lowers total cholesterol, lipoproteins and blood sugar levels (Mothana et al., 2010 ; Bulku et al., 2010). Several Ayurveda drug manufacturers in India have been marketing herbal combination formulation drugs to treat various diseases such as Livergen (Standard Pharmaceuticals) used for liver problems that consist of 6 herbs, Tefroliv (TTK Pharma Pvt. Ltd.) used for hepatic disorders that made of 9 types of herbs and Pankajakasthuri (Herbals India Pvt. Ltd.) used for respiratory infections that have 14 herbs (Visavadiya & Narasimhacharya, 2011). Therefore, the present research aims to find effective combinations of herbals for the management and treatment of hyperlipidemia.

1.4 Objectives

1.4.1 Main objective

The general objective of this study is to determine anti-hyperlipidemic potential of a combination of *Zingiber officinale* Roscoe*, Allium sativum* L., *Citrus lemon* (L.) Osbeck, Honey and *Malus domestica* Borkh. Cider Vinegar (ZACAH) mixture in rats fed with high cholesterol diet.

Specific objectives

1. To determine ORAC (Oxygen radical absorbance capacity) assay, total phenolic content (TPC), elastase inhibitory assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, and phytochemicals using high-performance liquid chromatography (HPLC) in ZACAH mixture.

2. To measure the effects of ZACAH mixture on body weight, caloric intake and organs weight in rats fed with high cholesterol diet.

3. To determine lipid profiles [total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)] in rats fed with high cholesterol diet supplemented with ZACAH mixture.

4. To determine liver and kidney function tests [Creatinine, Aspirate aminotransferase (AST), Alanine aminotransferase (ALT)] in rats fed with high cholesterol diet supplemented with ZACAH mixture.

5. To evaluate the effects of ZACAH mixture on cholesterol metabolism [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, lecithin cholesterol acyltransferase (LCAT), acyl-coa cholesterol acyltransferase 2 (ACAT2)] in rats fed with high cholesterol diet.

6. To identify histological changes of liver, adipose tissue, kidney through Hematoxylin and Eosin (H&E) staining in rats fed with high cholesterol diet supplemented with ZACAH mixture.

1.5 Hypothesis

1. ZACAH mixture reduces the bodyweight, and organ weight in rats fed with high cholesterol diet.

2. ZACAH mixture decreases the lipid profiles [total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL)] and increases the high density lipoprotein (HDL) in rats fed with high cholesterol diet.

3. ZACAH mixture decreases the liver and kidney function tests [Creatinine, Aspirate aminotransferase (AST), Alanine aminotransferase (ALT)] in rats fed with high cholesterol diet.

4. ZACAH mixture reduce the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, acyl-coa cholesterol acyltransferase 2 (ACAT2) and increase lecithin cholesterol acyltransferase (LCAT), in rats fed with high cholesterol diet.

5. ZACAH mixture shows regeneration of liver, adipose tissue, and kidney toward normal architecture in rats fed with high cholesterol diet

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