



**ANTI-OBESITY ACTIVITIES OF EDIBLE BIRD NEST ON 3T3-L1
ADIPOCYTES AND HIGH FAT-CHOLESTEROL DIET INDUCED-OBESE
RABBITS**

By

RAMLAH BINTI MOHAMAD IBRAHIM

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

June 2022

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In loving memory of Allahyarhamah Prof Dr. Maznah Ismail

This thesis is dedicated to

My parents Mohamad Ibrahim & Fatimah

For their affection, support and prayers which made me able to complete this work

My husband Noor Muhammad

For making everything possible with his love and patience

My children Aira Tasneem, Adleena, Hafeedh, Meera

I hope this will be an inspiration for them

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For always being together with me in this journey

&

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For their dedication in sharing knowledge, guidance, and encouragements

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RAMLAH BINTI MOHAMAD IBRAHIM

June 2022

Chair : Professor Md. Zuki Abu Bakar @ Zakaria, PhD
Institute : Bioscience

Obesity has become a global public health issue with increasing prevalence in the recent decade. Managing obesity with anti-obesity drugs have been marked by numerous adverse effects. Therefore, current research focuses on commonly consumed foods to provide multi-target functions beyond their traditional nutritive values which would likely prevent obesity. Edible bird nest (EBN) is made from saliva of swiftlets which was deemed as an important ethno-medicinal commodity for its nutritional and healing values. Growing evidence suggests EBN as a potential functional food for managing metabolic disorders, which has initiated the present study to explore the therapeutic benefit of EBN to prevent obesity and its related disorders. The present study evaluated the comparative analysis in nutrient compositions between two different shapes of house-farmed EBN which are half cup and stripe-shape EBN. Nutrient analysis showed half cup EBN has significantly higher protein, carbohydrate, calcium and sulfur content compared to stripe-shaped EBN ($p < 0.05$). Next, stew extract (SE) and full stew (FS) was prepared from half cup EBN to determine sialic acid (SA) content and subsequently evaluated for their antioxidant effects and enzyme inhibition activities. Stew extract exhibited higher SA content than FS and both EBN showed significantly greater antioxidant and enzyme inhibition activities at concentration of 10 mg/mL ($p < 0.05$). *In vitro* anti-adipogenic potential of SA standard (1 mg/mL), SE and FS (10 mg/mL) on 3T3-L1 adipocytes showed significant reduction in lipid accumulation, lipase and G3PDH enzymes level ($p < 0.05$). The anti-obesity effect of EBN were further evaluated in high fat-cholesterol diet (HFCD)-induced obese rabbits for 12 weeks. Both SE and FS groups significantly prevented weight gain and improved Lee Index as well as reduced white adipose tissue and liver weights compared to HFCD group ($p < 0.05$). Also, the EBN groups significantly improved serum lipid profile, free fatty acids, leptin, adiponectin, IL-6, MCP-1 and catalase levels ($p < 0.05$). Gene expression studies revealed that the anti-obesity effects of EBN were associated to regulation of adipokines and adipogenesis along with *AMPK* activation which significantly improved genes involved in lipid metabolism pathway. Furthermore, SE and FS significantly inhibit *NF- κ B* signalling pathway which in turn downregulated the expression of pro-inflammatory

(*IL-6*, *CRP*, *MCP-1*) and insulin resistance (*IRS1*) genes. Supplementation of SE and FS significantly enhanced the expression of antioxidant genes such as *SOD3*, *CAT*, *GSR* and *PONI* ($p < 0.05$). Additionally, both SE and FS supplementation prevented the toxicity effect of HFCD reflected with significant reduction of ALT and GGT enzymes level ($p < 0.05$). In conclusion, the present study indicates that EBN via synergism of SA and other nutrients provide anti-obesity action through regulation of genes involved in adipokines, adipogenesis, lipid metabolism along with improvement in obesity-mediated inflammation, insulin resistance and antioxidants.

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

AKTIVITI ANTI-OBESITI SARANG BURUNG WALIT PADA SEL ADIPOS 3T3-L1 DAN ARNAB OBES YANG DIARUH DIET TINGGI LEMAK-KOLESTEROL

Oleh

RAMLAH BINTI MOHAMAD IBRAHIM

Jun 2022

Pengerusi : Profesor Md. Zuki Abu Bakar @ Zakaria, PhD
Institut : Biosains

Obesiti telah menjadi isu kesihatan awam dengan peningkatan kadar pada dekad terkini. Rawatan obesiti menggunakan ubat-ubatan telah mendatangkan pelbagai kesan buruk. Oleh itu, penyelidikan semasa memfokuskan pada makanan fungsian yang mempunyai nilai terapeutik melebihi nilai nutrisi asas yang berkemungkinan mencegah obesiti. Sarang burung walit (EBN) diperbuat daripada air liur burung walit dianggap sebagai komoditi etno-perubatan penting kerana nilai pemakanan dan penyembuhannya. Peningkatan bukti saintifik mencadangkan EBN sebagai makanan fungsian yang berpotensi untuk melindungi gangguan metabolik yang mana telah memulakan kajian ini bagi meneroka manfaat terapeutik EBN untuk mencegah obesiti dan gangguan metabolik yang berkaitan dengannya. Kajian ini menilai perbandingan analisis dalam komposisi nutrien antara dua bentuk EBN dari rumah penternakan burung walit iaitu bentuk cawan dan bentuk jalur. Analisis nutrien menunjukkan bahawa EBN bentuk cawan mempunyai kandungan protein, karbohidrat, kalsium dan sulfur yang lebih tinggi berbanding EBN bentuk jalur ($p < 0.05$). Seterusnya, “stew extract” (SE) dan “full stew” (FS) disediakan dari EBN bentuk cawan bagi menentukan kandungan asid sialik (SA) dan kemudiannya dinilai untuk kesan antioksidan dan aktiviti perencatan enzim. “Stew extract” mempamerkan kandungan SA yang lebih tinggi berbanding FS dan kedua-dua EBN menunjukkan aktiviti perencatan antioksidan dan enzim yang signifikan pada kepekatan 10 mg/mL ($p < 0.05$). Potensi anti-adipogenik secara *in vitro* bagi SA (1 mg/mL), SE dan FS (10 mg/mL) pada sel adipos 3T3-L1 menunjukkan pengurangan yang signifikan terhadap pengumpulan lemak, paras enzim lipase dan G3PDH ($p < 0.05$). Kesan anti-obesiti EBN seterusnya dinilai menggunakan arnab yang diaruh obesiti melalui diet yang tinggi lemak dan kolesterol (HFCD) selama 12 minggu. Kedua-dua kumpulan SE dan FS secara signifikan menghalang penambahan berat badan dan mengawal Indeks Lee serta mengurangkan berat tisu adipos putih dan hati berbanding kumpulan HFCD ($p < 0.05$). Juga, kumpulan EBN secara signifikan telah memperbaiki tahap serum profil lemak, asid lemak bebas, leptin, adiponektin, IL-6, MCP-1 dan katalase ($p < 0.05$). Kajian ekspresi gen mendedahkan bahawa kesan anti-obesiti EBN dikaitkan dengan pengawalan adoksin dan adipogenesis bersama-sama dengan pengaktifan AMPK secara

signifikan memperbaiki gen yang terlibat dalam laluan metabolisme lemak. Tambahan pula, SE dan FS dengan signifikan menghalang laluan isyarat *NF-Kb* yang seterusnya menurunkan ekspresi gen pro-radang (*IL-6*, *CRP*, *MCP-1*) dan rintangan insulin (*IRS1*). Suplemen SE dan FS meningkatkan dengan signifikan ekspresi gen antioksidan seperti *SOD3*, *CAT*, *GSR* dan *PON1* ($p < 0.05$). Tambahan pula, kedua-dua suplemen SE dan FS menghalang kesan ketoksikan HFCD yang dicerminkan melalui pengurangan signifikan tahap enzim ALT dan GGT ($p < 0.05$). Kesimpulannya, kajian ini menunjukkan bahawa EBN melalui sinergi SA dan nutrien lain memberikan kesan anti-obesiti melalui kawalatur gen yang berkait dengan adipokin, adipogenesis, metabolisme lemak bersama-sama dengan penambahbaikan keradangan, rintangan insulin dan antioksidan berantarkan obesiti.

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Md. Zuki bin Abu Bakar @ Zakaria, PhD

Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Rozi binti Mahmud, MBBS, MMed

Professor (Medical)
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Nor Asma binti Ab. Razak, PhD

Research Officer
Institute of Bioscience
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD

Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

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Signature: _____
Name of Chairman of
Supervisory
Committee: Prof. Md. Zuki bin Abu Bakar

Signature: _____
Name of Member of
Supervisory
Committee: Prof. Datin Dr. Rozi binti Mahmud

Signature: _____
Name of Member of
Supervisory
Committee: Dr. Nor Asma binti Ab. Razak

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LIST OF ABBREVIATIONS

AABA	Aminobutyric acid
Abs	Absorbance
ACAC α	Acetyl-CoA carboxylase alpha
ACLY	Acetyl-CoA by ATP-citrate lyase
ACC1	Acetyl-CoA carboxylases 1
ADP	Adenosine diphosphate
ADIPOQ	Adiponectin
AKT	Protein kinase B
ALT	Alanine transaminases
ALP	Alkaline phosphatase
AMP	Adenosine monophosphate
AMM	Adipocyte maintenance medium
AMPK	Adenosine monophosphate activated protein kinase
AOAC	Association of Official Analytical Chemists
ATGL	Adipose triglyceride lipase
ATP	Adenosine triphosphate
ATR	Attenuated Total Reflectance
BAT	Brown adipose tissue
β -AR	$\beta_{1/2}$ -adrenergic receptors
BSA	Bovine serum albumin
cAMP	Cyclic adenosine monophosphate
CAT	Catalase
CCM	Complete culture media
CCL2	Chemokine (C-C motif) ligand 2
CE	Cholesterol esters
C/EBP	CCAAT/enhancer-binding protein

CETP	Plasma cholesteryl ester transfer protein
CPT1	Carnitine palmitoyltransferase 1
cGMP	Cyclic guanosine monophosphate
ChoRE	Carbohydrate response elements
ChREBP	Carbohydrate response element-binding protein
CPG	Clinical Practice Guideline
CRI	Castelli Risk Index
CRP	C reactive protein
DAG	Diacylglycerol
DEX	Dexamethasone
DNL	De novo lipogenic
EAA	Essential amino acids
EBN	Edible bird nest
EDI	Estimated daily intake
EGF	Epidermal growth factor
FABP4	Fatty acid binding protein 4
FAD	Flavine adenine dinucleotide
FAO	Food and Agriculture Organization
FASN	Fatty acid synthase
FFA	Free fatty acid
FFAR2	Free fatty acid receptor 2
FTIR	Fourier Transform Infrared
FS	Full Stew
G3P	Glycerol-3-phosphate
G3PDH	Glycerol-3-phosphate dehydrogenase
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GAG	Chondroitin glycosaminoglycans

GC-MS	Gas Chromatography–Mass Spectrometry
GGT	Gamma glutamyl transferase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
GSSG	Glutathione disulfide
HDL	High-density lipoproteins
HED	Human equivalent dose
HFCD	High fat-cholesterol diet
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPLC	High Performance Liquid Chromatography
HSL	Hormone-sensitive lipase
IBMX	Isobutylmethylxanthine
ICP-MS	Inductively coupled-plasma mass spectrometry
ICP-OES	Inductively coupled plasma-optical emission spectroscopy
IL	Interleukin
IR	Insulin resistance
IRS1	Insulin receptor substrate 1
JECFA	Joint Expert Committee on Food Additives
JNK	c-Jun N-terminal kinase
LDL	Low-density lipoprotein
LEP	Leptin
LIPE	Hormone sensitive lipase
LOD	Limit of detection
LPL	Lipoprotein lipase
LXR	Liver X receptor
MAG	Monoacylglycerol

MAPK	Mitogen activated protein kinase
MCE	Mitotic clonal expansion
MCP-1	Chemoattractant protein-1
MDA	Malondialdehyde
MDI	Induction media
MGL	Monoacylglycerol lipase
MUFA	Mono-unsaturated fats
MSCs	Mesenchymal stem cells
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NC	Normal control
NCDs	Non-communicable diseases
NEAA	Non-essential amino acids
NF- κ B	Nuclear factor-kappa B
NHMS	National Health and Morbidity Survey
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NPR-A	Natriuretic peptide receptors
OMA	Obesity Medicine Association
ORO	Oil Red O
PAI-1	Plasminogen activator inhibitor type 1
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PKG	Protein kinase G
PNPG	Nitrophenyl- β -D- glucopyranoside
PLIN1	Perilipin 1
PON 1	Paraoxonase 1
PUFA	Poly-unsaturated fatty acids

PPAR α	Peroxisome proliferator activated receptor alpha
PPAR- γ	Peroxisome proliferator activated receptor gamma
PTWI	Provisional tolerable weekly intake
RBP4	Retinol binding protein 4
RNI	Recommended Nutrient Intakes
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RXR	Retinoid X receptor
SA	Sialic acid
SAMM	Accreditation Scheme of Malaysia
SCD1	Stearoyl-CoA desaturase-1
SE	Stew extract
SFA	Saturated fatty acids
SOD	Superoxide dismutase
SOP	Standard Operating Procedure
SREBP1	Sterol regulatory element-binding protein 1
TAC	Total antioxidant capacity
TC	Total cholesterol
TCA	Tricarboxylic acid
TCM	Traditional Chinese Medicine
TG	Triglycerides
TNF- α	Tumor necrosis factor- α
UCP	Uncoupling protein
VLDL	Very low-density lipoproteins
WAT	White adipose tissue
WC	Waist circumference
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Study background

Overweight and obesity are among the world's critical health problems in which the rates have nearly tripled in recent decades. This problem affects people of all ages from entire social groups. It was once considered a problem of developed nation, but now obesity is prevalent in low and middle-income countries as well. Globally, incidence of overweight in adults aged 18 years and above is 39%, while the prevalence of obese is 13%. According to the World Health Organization (WHO), about 65% of the world's population live in nations in which mortality rate of obesity is higher than underweight problem (WHO, 2016). In a national front, the current trend of obesity in Malaysia continues to rise compared to previous report of National Morbidity Survey (NHMS) in year 2015 with latest national prevalence of overweight and obesity among adults were 30.4% and 19.7%, respectively. The current NHMS report indicate that relatively at least one-in-two adults were overweight and obese which is an alarming trend of obesity epidemic in Malaysia (NHMS, 2019).

Overweight and obesity are complex, multi-factorial condition characterized by accumulation of excessive fat which possess a health threat to those affected individuals. The most established and commonly used index to classify overweight and obesity in adults is based on body mass index (BMI), defined as weight in kilograms divided by the square of the heights in meters (kg/m^2). Based on WHO classification, the cut-off points for overweight and obesity is 25 and 30 kg/m^2 , respectively (WHO, 2000). Obese individuals are at a higher risk of developing various non-communicable diseases such as hypertension, type 2 diabetes, cirrhosis, stroke, cancers etc. which may affect nearly all parts of the body (Zhang et al., 2014). Among the main pathological hallmarks of obesity includes adipogenesis, insulin resistance, dysregulation of lipid metabolism, inflammation, and oxidative stress (Kim et al., 2020; Dlundla et al., 2018; Saltiel and Olefsky, 2017; Sears and Perry, 2015; Sung et al., 2011). The increasing epidemic, growing threat of obesity related co-morbidities and economic burden urges the need for various approaches to prevent obesity.

Pharmacotherapy is a beneficial adjunct to lifestyle changes which is aimed to induced weight loss in overweight and obese individuals with co-morbidities. Several pharmacological drugs approved for obesity treatment includes orlistat, sibutramine and phentermine (Zainudin et al., 2014). However, safety concerns have been raised regarding the use of these weight-loss medications due to the adverse side effects which may outweigh their benefits and these drugs may not be appropriate for all overweight or obese individuals. Current approaches highlight the importance and possible health effects of certain foods, referred to as functional foods as a complementary approach for preventing and treating obesity with enhanced efficacy and less side effects (Nderitu et al., 2017). Moreover, numerous studies have showed that the consumption of functional foods irrespective of any form (whole foods, extracts, or bioactive fractions), could

considerably lower the risk of metabolic disorders including obesity via synergistic effects of its nutrient components (Martinez et al., 2019; Ntrigiou et al., 2019; Attari et al., 2017).

Edible bird nest (EBN) is made from the saliva of swiftlets. It is used as a renowned heritage delicacy due to its health promoting properties since the early Chinese dynasties (Ma and Liu, 2012). Moreover, the consumption of EBN for years among the consumers without any major safety concerns, prompting its continuous and widespread use (Murugan et al., 2020). Scientific evidence to prove the claimed medicinal properties of EBN is limited, and information on the bioactive and metabolic pathway on how the EBN responsible for its functional effects is also lacking. Previously, the cardio-protective efficacy of EBN has been scientifically proven in our laboratory. Treatment with EBN has demonstrated a cardio-protective effect in high fat diet-induced hyperlipidaemic rats through regulation of insulin resistance, oxidative stress and hypercoagulation, most probably due to the bioactive component in EBN which is sialic acid (Yida et al., 2015). Therefore, the former research project had opened the exploration into new therapeutic approach of EBN on other cardio-metabolic indices including obesity. Thus, this present study was aimed to investigate the antioxidant, enzyme inhibitory activities along with *in vitro* anti-adipogenic potential of EBN and its bioactive content, sialic acid. Following this, the functional properties of EBN to provide anti-obesity effect in high fat-cholesterol diet-induced obese rabbits and those underlying transcriptional regulation that been associated with obesity has also been evaluated.

In view of the increasing drive to use safer alternatives for the management of chronic diseases such as obesity, the findings from this study could have profound health implications to EBN consumers since it has been widely consumed by majority of people in Asia, where obesity being an increasing public health problem. Moreover, with the rising price and demand for EBN every year at the global level, more people are expected to consume EBN as a health food (Hidayah et al., 2019). However, the anti-obesity activity of EBN is yet to be explored and the exact mechanisms involved remains unknown. Therefore, the present study is expected to offer a novel therapeutic option in management and prevention of obesity and how it may contribute to the specific effect. This study will also provide an important basis for further development and commercialization of EBN and its bioactive components as functional food or anti-obesity nutraceutical.

1.2 Hypotheses

- i. The EBN samples are proven authentic via molecular fingerprint of its functional groups and chemical compositions is varied between the different shapes of EBN.
- ii. EBN and sialic acid exhibit good antioxidant and enzyme inhibitory potentials, in addition to the inhibition of adipogenesis in 3T3-L1 cell.
- iii. EBN possesses anti-obesity effect via regulation of biomarkers related to adipokines, adipogenesis and lipid metabolism in high fat-cholesterol diet-induced obese rabbits.
- iv. EBN exerts anti-inflammatory effect, improves insulin resistance and enhances endogenous antioxidants in high fat-cholesterol diet-induced obese rabbits.

1.3 Objectives

General objective

To investigate the anti-adipogenic and anti-obesity activities of EBN in *in vitro* and *in vivo* experimental models.

Specific objective

- i. To determine the authenticity of genuine EBN and chemical constituents in different shapes of EBN.
- ii. To investigate the antioxidant and enzyme inhibitory properties of EBN and sialic acid along with their anti-adipogenic effects in adipogenesis of 3T3-L1 cell.
- iii. To investigate the anti-obesity effect of EBN supplementation in high fat-cholesterol diet-induced obese rabbits via regulation of genes related to adipokines, adipogenesis and lipid metabolism.
- iv. To investigate the effect of EBN supplementation in high fat-cholesterol diet-induced obese rabbits on inflammation, insulin resistance and endogenous antioxidant defence system associated to obesity including the underlying actions.

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