BIOASSAY-GUIDED EXTRACTION OF *Andrographis paniculata* FOR INTERVENTION OF *IN-VITRO* PROSTATE CANCER PROGRESSION IN METABOLIC SYNDROME ENVIRONMENT

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DEDICATION

This thesis is dedicated to my family.

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Alhamdulillah, all praise to Allah, the Most Gracious and Most Merciful. He is true to His promise.

"Verily after every difficulty, there is a relief" (Surah Al-Inshirah)

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ABSTRACT

Metabolic syndrome (MetS) is considered to be a risk factor for prostate cancer (PCa) progression. This disease has become one of the most significant healthcare issues, and the demands for a proactive curing strategy is essential. Plants and their bioactive compounds are promising sources for anticancer drug discovery. In this study, *Andrographis paniculata* (AP) or locally known as Hempedu Bumi has been selected due to its many reported medicinal values, particularly in the treatment of cancer, hyperglycemia and dysregulated lipid profile, and in the management of obesity. However, successful extraction of the active compounds from AP is crucial for maximum activity, which is influenced by extraction parameters particularly the solvent. Therefore, the current research aimed to discover the most potential AP extract as an agent to intervene PCa progression in metabolic syndrome environment. Strategically, bioassay-guided extraction of AP was conducted. Five AP extracts, each prepared with different solvent system using ultrasound-assisted extraction, designated as APE1 (aqueous), APE2 (absolute methanol), APE3 (absolute ethanol), APE4 (40 % methanol), and APE5 (60 % ethanol) were tested on *in vitro* MetS and PCa conditions utilizing the 3T3L1 adipocytes and DU145 cells, respectively. For extraction yield, APE4 (18.29 ± 2.02 %) resulted in the highest yield followed by, APE5 (15.78 ± 2.04 %), APE1 (14.76 ± 1.44 %), APE2 (8.81 ± 1.72 %), and APE3 (6.81 ± 0.24 %). Based on high-performance liquid chromatography analysis, APE2 was found to contain the highest andrographolide (andro) content at 1.34 ± 0.05 mg/mL. Similarly, the phenolic content of APE2 (8.85 ± 0.63 GAE/g DW) and APE3 (8.75 ± 0.06 GAE/g DW) significantly among the highest in this study. APE3 also displayed the highest flavonoid content at 11.52 ± 0.80 RE/ g DW. In the 1,1-diphenyl-2-picrylhydrazyl scavenging activity, APE2 resulted in the most potent activity (EC_{50} = 397.0 µg/mL). APE2 also exhibited the most potent antiproliferative action on DU145 PCa cell line with IC_{50} equivalent to 57.5 ± 11.8 µg/mL. APE2 and APE3 significantly inhibited the migration activity of DU145 after treatment with the concentration of 125 µg/mL for 24 hr. During adipogenesis inhibition in 3T3-L1 cells, APE3, APE4, and APE5 significantly reduced the lipid formation with a more considerable margin than APE2. Nevertheless, the inhibition by APE2 was still statistically significant compared to the untreated control. APE2 also demonstrated significantly higher insulin-sensitizing activity. Likewise, APE2, together with APE3 and APE5, simultaneously mimic insulin's action. The bioassay-guided extraction resulted in APE2 as the most potential AP extract. Leptin (10 – 100 ng/mL) progressively induced the proliferation of DU145. Similarly, adipocyte conditioned media (CM) induced the growth of DU145 at 10 % concentration. Co-treatment of DU145 with leptin/CM and APE2 successively diminished the proliferative effects through cell cycle arrest and apoptotic event. In conclusion, an andrographolide-rich AP extract shows high potential to ameliorate PCa progression induced by MetS factors, particularly leptin.

ABSTRAK

Sindrom metabolik (MetS) merupakan faktor risiko kepada perkembangan barah prostat (PCa). Penyakit ini telah menjadi satu daripada isu kesihatan yang penting dan permintaan utama kepada strategi rawatan yang proaktif. Tumbuh-tumbuhan dan sebatian bioaktifnya merupakan sumber yang berpotensi dalam penyelidikan ubat anti-kanser. Dalam kajian ini, *Andrographis paniculata* (AP) atau nama tempatan dikenali sebagai hempedu bumi telah dipilih kerana banyak nilai perubatan yang telah dilaporkan, terutamanya dalam rawatan barah, hiperglisemia dan kecelaruan profil lemak, dan dalam pengawalan obesiti. Namun, pengekstrakan sebatian aktif daripada AP adalah penting bagi aktiviti biologi yang maksimum yang dipengaruhi oleh parameter pengekstrakan, terutamanya jenis pelarut. Oleh itu, kajian ini bertujuan untuk menemukan ekstrak AP yang paling berpotensi sebagai agen untuk menghalang perkembangan PCa dalam persekitaran sindrom metabolik. Secara strategik, pengekstrakan AP berpandukan bioasai telah dijalankan. Lima ekstrak AP yang masing-masing diekstrak dengan sistem pelarut yang berbeza menggunakan kaedah pengekstrakan berbantu ultrabunyi, ditetapkan sebagai APE1 (akueus), APE2 (metanol mutlak), APE3 (etanol mutlak), APE4 (40 % metanol), dan APE5 (60 % etanol) telah diuji pada keadaan MetS dan PCa secara *in vitro* menggunakan sel 3T3L1 adiposit dan DU145. Untuk hasil pengekstrakan, APE4 (18.29 ± 2.02 %) memberikan hasil tertinggi diikuti oleh, APE5 (15.78 ± 2.04 %), APE1 (14.76 ± 1.44 %), APE2 (8.81 ± 1.72 %), dan APE3 (6.81 ± 0.24 %). Berdasarkan analisis kromatografi cecair berprestasi tinggi, APE2 didapati mengandungi jumlah andrografolida (andro) tertinggi pada 1.34 ± 0.05 mg/mL. Begitu juga, kandungan fenolik APE2 (8.85 ± 0.63 mg GAE/g DW) dan APE3 (8,75 ± 0.06 mg GAE/g DW) nyata sekali lebih tinggi dari ekstrak-ekstrak lain. APE3 juga menunjukkan kandungan flavonoid tertinggi pada 11.52 ± 0.80 mg RE/g DW. Dalam penyingkiran radikal 1,1-difenil-2-pikrilhidrazil, APE2 menghasilkan aktiviti terkuat (EC_{50} = 397.0 µg/mL). APE2 juga memperlihatkan kesan antiproliferatif paling kuat ke atas DU145, dengan IC_{50} bersamaan 57.5 ± 11.8 µg/mL. Aktiviti migrasi DU145 secara ketara direncat oleh APE2 dan APE3 setelah dirawat pada kepekatan 125 µg/mL selama 24 jam. Dalam perencatan adipogenesis pada sel 3T3-L1, APE3, APE4, dan APE5 secara ketara telah mengurangkan pembentukan lemak dengan lebih banyak daripada APE2. Namun, aktiviti APE2 masih signifikan berbanding sampel kawalan. APE2 juga menunjukkan aktiviti pemekaan insulin yang lebih kuat. Begitu juga, APE2 bersama APE3 dan APE5, menyamai tindakan insulin. Pengekstrakan berpandukan bioasai menghasilkan APE2 sebagai ekstrak AP yang paling berpotensi. Leptin (10-100 ng/mL) secara progresif menyebabkan percambahan DU145. Begitu juga, media terkondisi (CM) adiposit mendorong pertumbuhan DU145 pada kepekatan 10 %. Rawatan serentak keatas DU145 dengan leptin/CM dan APE2 telah mengurangkan percambahan sel DU145 melalui kekangan kitaran sel dan peristiwa apoptosis. Kesimpulannya, ekstrak AP yang kaya dengan andrografolida menunjukkan potensi untuk menghalang perkembangan PCa yang disebabkan oleh faktor dari MetS, terutamanya leptin.

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Akt	-	Protein kinase B
AMPK	-	AMP-Activated Protein Kinase
Andro	-	Andrographolide
AP	-	*Andrographis paniculata*
APS	-	Antiphospholipid Syndrome
AR	-	Androgen Receptor
ASODN	-	Antisense oligonucleotide
ATP III	-	Adult Treatment Panel III
BF%	-	Body Fat Percentage
BMI	-	Body Mass Index
CRP	-	C-Reactive Protein
CRPC	-	Castration-resistant PCa
CVD	-	Cardiovascular Disease
CXCL12	-	C-X-C Motif Chemokine 12
CXCR4	-	C-X-C Motif Chemokine Receptor 4
Deoxy	-	Deoxyandrographolide
DHT	-	Dihydrotestosterone
EMT	-	Epithelial-Mesenchymal-Transition
EPS	-	Expressed Prostatic Secretion
ERK1/2	-	Extracellular signal-regulated kinase 1/2
FOXO1	-	Forkhead box protein O1
GLUT-4	-	Glucose Transporter 4
GWAS	-	Genome-Wide Association Studies
HBV	-	Hepatitis B
HDL-C	-	High Density Lipoprotein Cholesterol
HFD	-	High-Fat Diet
HPLC	-	High Performance Liquid Chromatography
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
IL-6	-	Interleukin – 6

IR	-	Insulin Resistance
IRS-2	-	Insulin Receptor Substrate 2
JAK	-	Janus kinase
LDL	-	Low-Density Lipoprotein
LKB1	-	Liver Kinase B1
MAPK	-	Mitogen-Activated Protein Kinase
mCRPC	-	Metastatic castration-resistant prostate cancer
MetS	-	Metabolic Syndrome
MMP-9	-	Matrix Metalloproteinase 9
MOH	-	Ministry of Health
NCEP	-	National Cholesterol Education Program
Neo	-	Neoandrographolide
NF-κB	-	Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells
Notch-1	-	Translocation-Associated Notch Protein TAN-1
PAI-1	-	Plasminogen Activator Inhibitor–1
PCa	-	Prostate Cancer
PI3K	-	Phosphoinositide 3-kinases
PTEN	-	Phosphatase and tensin homolog
PTP1B	-	Protein Tyrosine Phosphatase 1B
RR	-	Relative Risk
Rx	-	Pharmacological Treatment
SNS	-	Sympathetic Nervous System
SHBG	-	Sex-hormone-binding globulin
STAT3	-	Signal transducer and activator of transcription 3
STZ	-	Streptozotocin
SVF	-	Stromal Vascular Fraction
T2DM	-	Type 2 Diabetes Mellitus
TFC	-	Total Flavonoid Content
TG	-	Triglyceride
TLC	-	Thin Layer Chromatography
TNF-α	-	Tumor Necrosis Factor α
TPC	-	Total Phenolic Content
TRAMP	-	Transgenic Adenocarcinoma of The Mouse Prostate

TSC1/2	-	Tuberous Sclerosis Proteins 1 and 2
VEGF	-	Vascular Endothelial Growth Factor
VEGFR2	-	Vascular Endothelial Growth Factor Receptor 2
ZEB1	-	Zinc Finger E-Box Binding Homeobox 1

CHAPTER 1

INTRODUCTION

1.1 Research Background

The prevalence of prostate cancer (PCa) is increasing in our community. In the Asian regions, the incidence rate of PCa has been on the rise, reported to grow at a rate of 7.2% per year from 2004 to 2009 (Chen *et al.*, 2014; Sim and Cheng, 2005) and there is no sign of this trend abating. At present, PCa is the sixth most frequent cancer among Asian men (Chen *et al.*, 2014). It is expected that by 2030, 1.7 million new PCa cases and 499,000 deaths will occur in the entire world, and this cancer will be the most common in men in the future (Pakzad *et al.*, 2015). Even though the incidence of PCa is still relatively low in Malaysia compared to the reported global incidence, the number of the annually reported cases continues to be on a steady trend. In a recent report published by the Ministry of Health of Malaysia (MOH), 3132 cases were reported between 2007-2011. Following that, between 2012-2016, the total reported case increased to 4189 (Azizah *et al.*, 2019).

Several well-established risk factors of PCa include advanced age, ethnicity, genetic factors, and family history (Rawla, 2019). The disease is more common among older men in terms of age, with a median age at diagnosis of above 60 years (Tao *et al.*, 2015). Other factors that are positively associated with PCa include diet, obesity and physical inactivity, inflammation, hyperglycaemia, infections, and environmental exposure to chemicals or ionising radiation (Rawla, 2019). However, it has been observed that the progression is worse among individuals with metabolic syndrome (MetS). A meta-analysis conducted on previously published academic manuscripts reported that MetS was associated with a 12% increase in PCa risk. But the association was only significant in the studies conducted in Europe but not in those conducted in the U.S. and Asia. The same report also emphasised that hypertension and waist circumference of >102 cm were associated with a significantly higher risk of PCa at

15% and 56% respectively (Esposito *et al.*, 2013). However, another meta-analysis reported that men with MetS have a lower relative risk to develop PCa and its associated mortality than those without MetS. Nevertheless, the author highlighted those men with MetS are more likely to suffer from high-grade PCa and more advanced disease. They were also at a greater risk of disease progression after radical prostatectomy and were more likely to succumb to PCa-specific death (Xiang *et al.*, 2013).

High adiposity, hyperglycaemia, hypertension and dyslipidemia are the components of MetS (Zhang *et al.*, 2015) that are implicated in the aggressiveness of PCa development. However, this area of research is still new, and more information is yet to be discovered. Nonetheless, some of the previous researchers have linked the role of hyperglycaemia and high adiposity with PCa progression. A report from the Asian Pacific Journal of Cancer Prevention indicated that those with a marked impairment in glucose regulation have a higher risk of developing PCa (Pandeya *et al.*, 2014). At the same time, a 50% increased probability of disease recurrence has also been reported among those with high glucose levels at the time of PCa diagnosis (Wright *et al.*, 2013). Similarly, another study demonstrated a higher PCa incidence among those with high abdominal adiposity and suggested central adiposity as the predictive criterion in the determination of PCa risk (Nemesure *et al.*, 2012). One of the mediators between MetS and PCa is leptin, a hormone secreted by adipocytes. Long-term exposure to high leptin levels significantly worsens the PCa prognosis due to increased proliferation, migration, and invasion of the cancer cells (Noda *et al.*, 2015a). Additionally, the action of leptin is more pronounced in the androgen-resistant PCa cells, thus possibly explaining the recurrence of the disease even after radical prostatectomy (Hoda *et al.*, 2012b).

Based on the above understanding, treatment approach by using leptin antagonist has gained a great amount of research interest in cancer research arena. This method is viewed as the most direct approach for the treatment of this disease relationship. For example, a leptin antagonist called LDFI has been successfully synthesised in a previous study. The antagonist was derived from amino acids, and it was discovered to have growth and migration inhibitory effects on breast cancer cells

after further testing (Catalano *et al.*, 2015). Leptin antagonist has also been derived from plant phytochemicals. Honokiol from *Magnolia grandiflora* was found to be able to antagonise the activity of leptin. It can negatively mediate the growth of breast cancer cells by inhibiting leptin-induced epithelial-mesenchymal-transition (EMT) and mammosphere-formation along with a reduction in the expression of stemness factors (Avtanski *et al.*, 2015). This finding provides a great insight into the potential of plant-derived bioactive as one of the candidates for the intervention of MetS-PCa co-disease.

In the arena of plant-derived drug discovery research, *Andrographis paniculata* (AP) is among the mostly studied plant candidates. In particular, this plant has been found to inhibit the growth of cancer cells as well as potentiate chemotherapy prognosis. Apart from that, components of AP and its derivatives are also associated with the ability to manage manifestation of MetS (Islam, 2017). The anticancer properties of AP have been reported to originate from andrographolide, neoandrographolide, and deoxyandrographolide (Pfisterer *et al.*, 2010; Varma *et al.*, 2011) whereas in the management of MetS component, it was reported to originate from deoxyandrographolide and andrographolide (Arha *et al.*, 2015; Ding *et al.*, 2014).

Therefore, good sample preparation process vital in any study. AP extracts that is rich with the aforementioned bioactives is highly dependant on the choice of extraction method and its parameters such as solvent system, time, and temperature. In a recent study, the use of the reflux method for one hour with methanol as the solvent produced higher analytical values of andrographolide as compared to other methods (Sharma and Sharma, 2018). The locality of the bioactives also plays a role in this aspect. It has been reported that these compounds can be found in high abundance in the leaves of both young and mature AP. (Chua *et al.*, 2013). Thus, to obtain AP extract rich with its bioactives, appropriate extraction techniques and parameters should be considered apart from selecting the most suitable plant part.

Hence, armed with this understanding, the current research aims to utilise AP as a candidate to intervene disease linkage between MetS and PCa. At the same time, bioassay-guided technique was employed to screen for the best preparation of AP. To the best of author's knowledge, no researcher has attempted this strategy.

1.2 Problem Statement

Obesity in MetS has direct impact on the development of PCa. Specifically, the adipokine, leptin, has been reported as one of the causative factors that worsens the progression of PCa. Despite a better understanding of the relationship, diagnosis method, and treatment approaches, the mortality rate of patients with co-disease of PCa and MetS is still high. As a result, many researchers have begun to look for an alternative intervention method. One of the most promising alternatives is phytotherapy. Among the various types of plants, AP appears to be one of the most extensively studied. However, the potential of AP in MetS-PCa, has not yet been reported. Thus, in this study, the therapeutic effect of AP on MetS-PCa was investigated.

The medicinal function of AP depends on its phytochemicals which can be obtained through solid-liquid extraction. However, no standardized methods have been developed for AP. Additionally, variation on solvent systems have been known to exert diverging magnitude of bioactivities. Nevertheless, ultrasound-assisted extraction (UAE) has been reported as one of the best method for AP preparation in comparison to other methods. But none of the reported methods were designed for the intervention of MetS-PCa co-disease. To overcome this limitation, a bioassay-guided screening technique was applied in this study to find out the best solvent system for the extraction of AP for the purpose of MetS-PCa treatment.

Pathologically, MetS interacts with PCa through several mediators. To replicate this environment for *in vitro* testings, a co-culture system comprising adipocyte and PCa cells could be employed. However, this system has many limitations that need to be addressed, rendering it not practical for an *in vitro* experiment. The growth of one cell type could overwhelm the other, causing mixed responses exerted by both cells. To address this issue, the strategy of using a conditioned media (CM) was used instead. But CM also contains other components besides leptin that could interact with PCa cells. Thus, a control group exposed with only leptin was included in this study for comparison.

1.3 Objective of the Study

The objectives of this study were as follow:

i. To investigate the effect of *Andrographis paniculata* (AP) extract on the anti-proliferative activity of DU145 prostate cancer (PCa) cell lines through bioassay-guided technique.
ii. To investigate the effect of AP extract on the anti-hyperglycemic and anti-obesity activities on 3T3-L1 adipocyte cell lines through bioassay-guided technique.
iii. To evaluate the effects of andrographolide-rich AP extract on the progression of PCa cells exposed with metabolic syndrome (MetS) microenvironment.

1.4 Scope of the Study

The scopes of this study were as follow:

i. Extraction of *Andrographis paniculata* (AP) using five different solvent systems by ultrasound-assisted extraction technique.
ii. Phytochemical analysis of the extracts using high-performance liquid chromatography (HPLC), total phenolic content (TPC), total flavonoid content (TFC), and antioxidant activity.
iii. Evaluation of *in vitro* anti-obese activity of the AP extracts through adipogenesis inhibition on 3T3-L1 cells.
iv. Evaluation of *in vitro* anti-hyperglycemic activity of the AP extracts by measuring its insulin-sensitising and mimicking actions on 3T3-L1 cells.
v. Evaluation of *in vitro* anti-cancer potential of the AP extracts by determining antiproliferative and anti-migratory activities on PCa cell line DU145.
vi. Investigation of the effect of MetS microenvironment on DU145 by treatment with 3T3-L1 conditioned media and recombinant leptin.
vii. Investigation of andrographolide-rich extract capability in arresting growth cycle of DU145 exposed with recombinant leptin or adipocytes conditioned media using flow cytometry.
viii. Investigation of andrographolide-rich extract capability in inducing apoptosis of DU145 exposed with recombinant leptin or adipocytes conditioned media flow cytometry.

1.5 Significance of the Study

The herbal industry has been previously perceived as classic industry and deemed as not profitable. However, with the advancement of research and development, many benefits dan industrial values based on herbs have started to emerge. This is also partly contributed by giant industrial players that has been promoting the added values of plant-based products. As a result, demand on herbal industry has been blooming and this requires engineering solutions to accommodate the market challenges.

One of the highly expected merit from an herbal industry is for its medicinal usage in cancer treatment. This comes from the consideration that there are still rooms for improvement in the currently utilized treatment strategy. Therefore, this study could provide as the starting point for the discovery of novel treatment approach in cancer treatment using AP, particularly in the treatment of PCa in patients with MetS. The current study also could spark ideas for future researchers on improvement for better research design and strategy.

Particularly to the population who is directly affected by the disease in question, this study could offer broader treatment options. It goes without saying that chemotherapy brings along undesirable side effects. For some people, these side effects are hardly tolerable. Therefore, with this discovery, along with ample future research, AP could hopefully be considered as an effective treatment option.

Malaysia is a country that bears tropical climate, suitable for the cultivation of AP. This study imposes additional benefits for the plant. This could help in the commercialisation and potentiate this country as the major producer of the herbal plant in the future. Thus, indirectly contribute in the economic development.

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