CHARACTERIZATION AND OPTIMIZATION OF BIOACTIVE COMPOUNDS EXTRACTED FROM HERBAL PLANTS USING MICROWAVE ASSISTED INFUSION

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Verily, with every hardship comes ease. (94:6)

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ABSTRACT

Phytochemicals study of herbal plants have received increased attention due to the biological benefits to human health, especially on oxidative stress related disease. Recently, microwave oven is favourable in extracting herbal plant phytochemicals due to the effectiveness in extracting the bioactive compounds. In this study, optimization of microwave assisted infusion (MAI) parameters based on selected herbal plants activities from conventional infusion was carried out. The parameters investigated were microwave power, brewing time and irradiation time. In conventional infusion, phytochemical content, antioxidant and antiacetylcholinesterase activities of six herbal plants of *Andrographis paniculata, Clinacanthus nutans, Morinda citrifolia, Piper sarmentosum, Strobilanthes crispus* and *Vernonia amygdalina* were evaluated. *P. sarmentosum* infusion showed antiacetylcholinesterase activity of 39.66% that was the highest among six medicinal plants. *P. sarmentosum* infusion also showed highest total phenolic content (TPC) and ferric reducing antioxidant power (FRAP) reducing activity at 245.64 mg GAE/L and 359.95 mg Fe^{2+}/L, respectively. *A. paniculata* infusion showed total flavonoid content (TFC) of 41.71 mg RE/L, whereas *S. crispus* infusion showed highest 2,2'-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) antioxidant activity with 59.92 mg AEAC/L. While *C. nutans* infusion showed 2,2-diphenyl-1-picrylhydrazyl (DPPH) inhibition activity of 64.09%. *P. sarmentosum* was chosen in MAI as this plant showed good activities in TPC, FRAP and AChE assay. The optimal conditions were 560 W, 495 sec of brewing time and 240 sec of irradiation time. Under optimal condition, the maximum recovery were TPC (141.48 ± 3.78 mg GAE/L), TFC (31.62 ± 0.45 mg RE/L), FRAP (327.7 ± 8.20 mg Fe^{2+}/L), DPPH and AChE inhibition (30.87 ± 0.27 %; 45.65 ± 0.69 %). From gas chromatography mass spectrometry (GC-MS) and Fourier transform infrared (FTIR) results, chemical compound of diethyl phthalate was identified in the MAI of *P sarmentosum* formulation. The finding of this study can be considered as the baseline study in exploring the use of microwave to aid in plant infusion preparation.

ABSTRAK

Kajian fitokimia tumbuhan herba mendapat perhatian ekoran faedah biologi terhadap kesihatan manusia, terutamanya penyakit berkaitan tekanan oksidatif. Ketuhar gelombang mikro lebih digemari dalam pengesktrakan fitokimia tumbuhan herba kerana keberkesanannya dalam mengeluarkan sebatian bioaktif. Pengoptimuman parameter bagi ekstrak infusi berbantukan ketuhar gelombang mikro (MAI) tumbuhan terpilih telah dijalankan berdasarkan dapatan aktiviti infusi konvensional. Parameter dikaji adalah kuasa gelombang mikro, tempoh renehan dan tempoh radiasi. Dalam infusi konvensional, kandungan fitokimia, aktiviti antioksida dan perencatan asetilkolinesterase enam pokok herba iaitu *Andrographis paniculata, Clinacanthus nutans, Morinda citrifolia, Piper sarmentosum, Strobilanthes crispus* dan *Vernonia amygdalina* telah dikaji. Aktiviti perencatan anti asetilkolinesterase infusi *P. sarmentosum* tinggi berbanding tumbuhan herba lain dengan nilai perencatan sebanyak 39.66 %. *P. sarmentosum* menunjukkan jumlah kandungan fenolik (TPC) dan penyahwarnaan antioksida (FRAP) tertinggi dengan 245.64 mg GAE/L dan 359.95 mg Fe^{2+}/L. *A. paniculata* menunjukkan kandungan flavonoid (TFC) tertinggi pada 41.71 mg RE/L, *S. crispus* menunjukkan aktiviti penyahwarnaan antioksida 2,2-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) tertinggi dengan nilai 59.92 mg AEAC/L. *C. nutans* menunjukkan perencatan 2,2-diphenyl-1-picrylhydrazyl (DPPH) sebanyak 64.09 %. *P. sarmentosum* dipilih dalam MAI kerana menunjukkan kadar aktiviti tertinggi TPC, FRAP dan AChE. Parameter optimum MAI adalah 560 W, 495 saat renehan dan 240 saat masa radiasi. Pada kadar optimum ini, hasil maksimum adalah TPC (141.48 ± 3.78 mg GAE/L), TFC (31.62 ± 0.45 mg RE/L), FRAP (327.7 ± 8.20 mg Fe^{2+}/L), perencatan DPPH dan AChE (30.87 ± 0.27 %; 45.65 ± 0.69 %). Berdasarkan gas kromatografi spektrometer jisim (GC-MS) dan Fourier pengubah inframerah (FTIR), sebatian kimia dietil phthalate telah dikenalpasti terkandung dalam MAI *P. sarmentosum*. Hasil kajian ini boleh dijadikan asas dalam kajian lanjut pengekstrakan infusi tumbuhan berbantukan ketuhar gelombang mikro.

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LIST OF SYMBOLS AND ABBREVIATIONS

%	-	percentage
^{o}C	-	degree celcius
α	-	alpha
µg	-	microgram (s)
µL	-	microlitre (s)
µm	-	micrometre (s)
cm^{-1}	-	per centimetre
g	-	gram (s)
Hz	-	Hertz
I%	-	Scavenging effect
min	-	minute (s)
mg	-	milligram (s)
mL	-	millilitre (s)
sec	-	second (s)
AEAC	-	ascorbic acid equivalent antioxidant capacity
ABTS	-	2,2′-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)
AD	-	Alzheimer’s disease
ACh	-	Acetylcholine
AChE	-	Acetylcholinesterase
ATCI	-	Acetylthiocholine
BBD	-	Box-behnken design
CCD	-	central composite design
DNA	-	Deoxyribonucleic acid
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
DTNB	-	5,5′-Dithiobis [2-nitrobenzoic acid]
FE	-	Ferrous sulphate equivalent
FRAP	-	Ferric reducing assay power

FTIR	-	Fourier transfrom infrared
GAE	-	Gallic acid equivalent
GCMS	-	Gas chromatography mass spectrometry
HPLC	-	High performance liquid chromatography
MAE	-	microwave assisted extraction
MAI	-	microwave assisted infusion
NPMAE	-	nitrogen-protected microwave assisted infusion
OH	-	hydroxyl radical
R^2	-	Coefficient of determination
RE	-	Rutin equivalent
ROS	-	reactive oxygen species
RNS	-	reactive nitrogen species
RSM	-	response surface methodology
SEM	-	scanning electron microscope
TCMCS	-	Temperature controlled microwave closed system
TPC	-	Total phenolic content
TFC	-	Total flavonoid content
TPTZ	-	2,4,6-Tris(2-pyridyl)-s-triazine
UHPLC	-	Ultra high performance liquid chromatography
UMAE	-	Ultrasonic microwave assisted infusion
VMAE	-	Vacuum microwave assisted infusion

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CHAPTER 1

INTRODUCTION

1.1 Background of study

The extraction technique is one of the key factors in the isolation of phytochemicals from plants (Ghasemzadeh *et al.*, 2014). The extracted biometabolites from plants are largely dependent on the extraction techniques and conditions. Extraction types can be distinguished into 2 main groups that are conventional extraction and advanced extraction. The conventional extraction techniques include maceration, hydro distillation, steam distillation, infusion, decoction, shaking, reflux extraction and Soxhlet extraction (Zhao *et al.*, 2013). The advanced extraction techniques include microwave-assisted extraction, microwave-assisted infusion, supercritical fluid extraction, pressurized liquid extraction, solid phase extraction, solid phase microextraction and ultrasonic extraction (Chan *et al.*, 2011). Conventional extraction techniques involved simple and easy application. The drawbacks in conventional extraction techniques are longer extraction time and larger solvent consumption that may costly for research purpose. The use of advanced extraction techniques may solve the drawbacks of conventional extraction techniques. The advanced extraction techniques require shorter extraction time with low solvent consumption as compared to conventional extraction techniques.

Conventional infusion extraction technique involved soaking of plant material in the solvent, usually boiled water for a specific time. This conventional infusion technique is frequently used in the herbal tea preparation process. Infusion techniques are applied since hundreds of years ago globally in China, Taiwan (Lin *et al.*, 2013), Brazil (Amoah *et al*., 2015), Europe (Guimarães *et al*., 2013) and other Asia countries.

Many research had shown significant results of infusion extract with anti-inflammatory activity and antimicrobial activities due to the presence of phytochemical constituents in the herbal plants.

Microwave oven utilization in the extraction technique has been used since the last decade due to environment-friendly and green approach especially in polyphenol recovering process (Dragović-Uzelac *et al.*, 2012; Panja, 2017). Microwave-assisted extraction (MAE) involved utilization of microwave energy to move sample matrix analytes into the solvent (Dai & Mumper, 2010). The advantages of MAE are lower in cost and in energy consumption with reduced extraction time and solvent volume with higher quantity and quality of extract. Moreover, MAE may minimize the carbon dioxide emission into the atmosphere when compared to hydrodistillation (Benmoussa *et al.*, 2018). In order to assist and provide more convenient and efficient MAE, some modifications were usually made to suit the research purpose. Microwave-assisted infusion (MAI) uses the combination of conventional extraction techniques of infusion with microwave. Herbal plants were known to benefit in health and currently most people extract the herbal plants in infusion form.

Antioxidants are dietary plant secondary metabolites that able to neutralize free radicals caused by oxidative stress either by scavenging, reducing or quenching the activities. Some of the antioxidants reported in herbal plants are phenolic compounds, flavonoids, carotenoids, benzoic acids and derivatives, coumarins, proanthocyanidins stilbenes and lignins (Lusia *et al.*, 2015). The oxidative stress in human may lead to neurodegenerative, cancer, cardiovascular disease, diabetes, asthma, atherosclerosis and rhinitis as human cell oxidative damage occurs due to excessive production of free radicals and reactive oxygen and nitrogen species (RONS) (Li *et al.*, 2013). Antioxidant protective roles to combat RONS have triggered the interest in antioxidants based dietary intake to enhance antioxidant body defense as well as to prevent against oxidative stress-induced disease.

Phytochemicals are chemical compounds in plants that act as plant secondary metabolites. The largest phytochemical group, that is phenolics composed of more than one aromatic rings with hydroxyl groups attached to it. These phenolic compounds were the major contributor to plant antioxidant activities. Apart from possessing antioxidant properties against oxidative stress, phenolics also attribute in plant colours as well as protecting against ultraviolet light, plant pathogens and parasites (Dai & Mumper, 2010; Mustapa *et al.*, 2015). The largest phenolic groups,

that are flavonoids comprise up to four thousand plant phenolics (John *et al.*, 2014) benefit in biological activities such as antimicrobial, antiulcer, anticancer, antidiabetic and protein kinase inhibition (Atangwho *et al.*, 2013). The polyphenolic functional groups presented in flavonoids enable them to act as antioxidant scavenger towards free radicals of superoxide and hydroxyl radicals.

There are two types of cholinesterase presented in human bodies that are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) (Talesa, 2001). AChE can be found in nervous tissue, muscles, plasma and blood cell and functions in cell proliferation, differentiation and amyloid formation (Talesa, 2001). The main function of AChE is to hydrolyse neurotransmitter acetylcholine (ACh) at the cholinergic synapses. However, the functions of BuChE still remain unclear and is said to mimic AChE. Apart from contributes to Parkinson disease (PD), dementia and heart disease, excess hydrolyses of ACh by AChE could lead to neurodegenerative disease of Alzheimer's disease (AD). Potential acetylcholinesterase inhibitors (AChEI) derived from plants were often studied as several AChEI plant-based compounds had been proven to improve in AD treatment.

1.2 Problem statement

Medicinal plants have been used traditionally in treating the disease from hundreds of years back due to richness of plant secondary metabolites properties. Moreover, some of the chemical compounds presented in the medicinal plants had been synthetically developed for medication purpose. About 80 % of the world populations, mainly Europe and Asia have high dependency on traditional medicine practices with 85 % of the traditional medicine comes from plant extracts in aqueous form for their primary healthcare (Ghasemzadeh, Jaafar, & Rahmat, 2015; Mckay & Blumberg, 2006). Nowadays, most of the population in developing countries still committed to using medicinal plants for healthcare purposes (Okhuarobo *et al.*, 2014). Malaysia has great biodiversity of its flora and fauna which give great opportunities to discover its medicinal plants potential to be used in daily healthcare.

Microwave oven had gained great attention these days as an important household item as it is easy, convenient and require shorter food preparation time. Over the years, the increasing demands of processed food had led to the innovation in microwave manufacturing. Most of the microwave nowadays comes with selections of cooking programmes depending on menus the consumers wish to have. However, the programme selection was found to be lack of herbal infusion preparation. With the increasing interest among the community in having herbal infusion drink, it is beneficial to study the optimum conditions to extract the phytoconstituents of the herbal infusion with the aid of microwave. Moreover, studies on antioxidant in *Camellia sinensis* (green tea) revealed that the use of microwave may extract higher antioxidant value compared with conventional infusion techniques (Vuong *et al.*, 2012).

Lack of cholinergic transmission or “cholinergic hypothesis” is one of the neuropathological features of AD (Choi *et al.*, 2014). Degradation of the neurotransmitter acetylcholine by hydrolysis with acetylcholinesterase enzyme may trigger AD. Finding new acetylcholinesterase inhibitor will be a therapeutic approach in dealing with AD. Synthetic AChE inhibitors such as donepezil, tacrine, and rivastigmine help in cognitive dysfunction and memory loss that related to AD, however some side effects of gastrointestinal disturbances were reported later (Mukherjee *et al.*, 2007b). The alkaloidal compound of galanthamine that is isolated from plants of Amaryllidacea had become AChE inhibitors standard and is used in AD

treatment (Heinrich & Teoh, 2004). This finding becomes a key factor in discovering more AChE inhibitor derived from medicinal plants. Thus, discovering new potential of AChE inhibitor with minimal side effects will be beneficial in AD treatment.

To the best of my literature review, very little information is available regarding the antioxidant and acetylcholinesterase activities of conventional infusion of the selected plants species. Usually, microwave-assisted extraction is reported in context to certain parameters like types of solvents, microwave power, solvent to solid ratio and irradiation time, but there are very few reports on microwave-assisted infusion (MAI) of herbal plants. This study aimed to investigate the effect of microwave parameters by optimizing microwave power, brewing time and irradiation time on the antioxidant and anti-acetylcholinesterase activities of microwave - assisted infusion (MAI) of selected plant that are not yet reported in literature.

1.3 Objectives of the study

The objectives of this present study are:

i. To evaluate the phytochemical contents, antioxidant and enzymatic activities of plants by using the conventional infusion method.

ii. To characterize the phytochemical constituents and functional groups presented in the plants that were used in the microwave-assisted infusion technique.

iii. To optimize microwave parameter in terms of microwave power, brewing time and irradiation time on phytochemical activities, antioxidant activities and acetylcholinesterase inhibition activity of selected plants from the conventional infusion results.

iv. To compare the phytochemical activities in conventional infusion and microwave-assisted infusion.

1.4 Scope of study

The present research was carried out to optimize the microwave-assisted infusion of medicinal plants. In this context, the scope of this study includes the following:

i. 6 medicinal plants, *Andrographis paniculata*, *Clinacanthus nutans*, *Morinda citrifolia*, *Strobilanthes crispus*, *Piper sarmentosum*, and *Vernonia amygdalina* were subjected for the preliminary screening of conventional infusion.
ii. The total phenolic content and total flavonoid content were determined by using Folin-Ciocalteu and aluminium chloride colorimetric methods, respectively.
iii. The antioxidant activity was determined via DPPH, ABTS and FRAP assays.
iv. The antiacetylcholinesterase activity was carried out via Ellman's method.
v. The central composite design was used for the optimization of microwave-assisted infusion with α=2.
vi. The optimization of microwave-assisted infusion was carried out at microwave power (80-800) W, brewing time (495-1800) sec and irradiation time (60-300) sec.
vii. The compound's identification was carried out by using gas chromatography-mass spectrometry (GC-MS) and the presence of functional groups in the Microwave-assisted infusion (MAI) was identified by Fourier transform infrared spectrophotometer (FTIR).

1.5 Significance of study

Nowadays, the microwave oven had been used extensively as household items that function to improve food preparation time. Most of current conventional microwave was occupied with selection of dishes cooking styles. However, selection for infusion preparation by using microwave oven seems to be neglected. Herbal plants are well known for the health benefits due to richness of antioxidants and anti-inflammatory properties. With increasing interest among community on using herbal plants as herbal drinks for its beneficial health properties, the use of microwave oven to maximise the extracted phytoconstituents from the herbal plants is a great idea. Apart from that, the contribution of microwave-assisted extraction parameter in improving the herbal plants infusion quality in the optimization process were also evaluated.

CHAPTER 2

LITERATURE REVIEW

2.1 Medicinal plants extractions

Medicinal plants are plants that have medicinal properties that benefit consumers. Medicinal plants were used for thousands of years either to cure or to reduce the illness symptoms. World Health Organization (WHO) reported the used of medicinal plants are still relevant globally. Moreover, more than 70% of communities in developing countries still practice traditional medicine as their primary care (Cvetkovic & Rami, 2013). Research showed medicinal plants possess plant secondary metabolites that act as active substances that promote biological activity. Studies on antioxidant activity between medicinal plants, fruits and vegetables suggested some medicinal plants promote higher antioxidant values as compared to few fruits and vegetables (Li *et al*., 2013). This finding had promotes the intake of medicinal plants as great source of antioxidant sources to aid in body defense mechanism.

Determination of bioactive compounds in a plant sample largely dependent on extraction techniques. The basic purpose of extraction is to transfer possible soluble plant metabolites (alkaloids, glycosides, phenolics, terpenoids, and flavonoids) into the solvent that act as the carrier before being used in experimental studies (Azwanida, 2015; Chan *et al.*, 2017). They are two types of extraction techniques: i) conventional extraction techniques and ii) advanced extraction techniques. The conventional extractions techniques are maceration, infusion, decoction, vortex, shaking and Soxhlet are commonly used in small research setting (Azwanida, 2015). These extraction techniques used the principle of soaking the plant material in a solvent for selected time in order to transfer the bioactive materials of the plants into the solvent.

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