EVALUATION OF SERAI KAYU (*Sygyzium polyanthum*) LEAVES EXTRACT AS BLOOD PRESSURE LOWERING AGENT IN HYPERTENSIVE RAT'S MODEL

BY

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LIST OF SYMBOL AND ABBREVIATION

ACEIs	Angiotensin converting enzyme inhibitors
AESP	Aqueous Extract of *Syzygium polyanthum*
Ang	Angiotensin
ARBs	Angiotensin receptor blockers
ARF	Acute renal failure
AT_1	Type-1 angiotensin II receptor
AT_2	Type-2 angiotensin II receptor
BP	Blood Pressure
CCB	Calcium channel blockers
CMC	Carboxymethylcellulose
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DPX	Distrene plasticizer xylene
GFR	Glomerular filtration rate
GPCR	G-protein coupled receptor
H&E	Haematoxylin & Eosin
IF	Interstitial fibrosis
LVH	Left ventricular hyperthrophy
MESP	Methanolic extract of *S.polyanthum*
NHMS	National Health and Morbidity Survey
RAAS	Renin angiotensin-aldosterone system
ROS	Reactive oxygen species
SBP	Systolic blood pressure
SHR	Spontaneous hypertensive rats
TOD	Target organ damage
T&CM	traditional and complementary medicine
USAE	Ultrasonic-assisted extraction
WHO	World Health Organization

WKY	Wistar-Kyoto rats
%	Percent
≥	More or equal to
<	Less than
>	More than
°C	Degree celcius
±	Plus minus
d	Deci
g	Gram
mg	Miligram
mL	Milimeter
mmHg	Milimeter mercury

ABSTRAK

Syzygium polyanthum atau "serai kayu" sangat terkenal dalam masyarakat Kelantan sebagai ubat tradisional untuk antihipertensi. Kajian ini bertujuan untuk menilai kesan pengambilan ekstrak mentah akueus dan metanolik *S.polyanthum* (AESP dan MESP, masing-masing) secara oral ke atas tekanan darah dan penambahbaikan struktur histopatologi buah pinggang tikus hipertensi spontan (SHR) yang menerima rawatan. AESP dan MESP disediakan menggunakan teknik ekstraksi ultrabunyi-berbantu (sonikasi). Perubahan pada tekanan darah sistolik (SBP) direkodkan menggunakan kaedah teknik non invasif (kaedah pergelangan ekor) untuk jangka masa 24 jam (rawatan akut) dan 6 minggu (sub akut). Histopatologi buah pinggang telah dinilai pada akhir rawatan sub akut menggunakan pewarnaan Hematoxylin dan Eosin (H&E). AESP pada dos 1750 mg/kg telah menunjukkan penurunan secara signifikan dalam rawatan akut (p<0.001). Begitu juga dengan MESP pada dos 2000 mg/kg yang mana juga telah menunjukkan penurunan tekanan darah sistolik secara signifikan (p<0.001). Bagi rawatan sub akut, kedua-dua AESP dan MESP (pada dos 1750 mg/kg dan 2000 mg/kg, masing-masing) menunjukkan penurunan secara signifikan bermula pada minggu ke-2 (p<0.001) dan terus menurun sehingga minggu ke-6 selepas diberikan rawatan (p<0.001). Dalam penilaian histopatologi dalam buah pinggang tikus rawatan-MESP telah menunjukkan glomerulus dan kapsul Bowman kekal dalam keadaan baik. Bertentangan pula dengan AESP, yang mana tidak menunjukkan peningkatan yang sama. Keputusan ini menunjukkan bahawa walaupun kedua ekstrak menunjukkan profil yang sama dalam penurunan tekanan darah, hanya MESP sahaja yang menunjukkan peningkatan dalam histopatologi struktur buah pinggang dan mempunyai potensi sebagai agen antihipertensi.

ABSTRACT

Syzygium polyanthum or "serai kayu" is popular among Kelantanese as traditional antihypertensive medicine. This study aimed to evaluate the effects of oral crude aqueous and methanol extracts of *S.polyanthum* (AESP and MESP, respectively) on blood pressure of spontaneous hypertensive rat (SHR) and the histopathology improvements on the kidney of treated-SHR. AESP and MESP were prepared using ultrasound-assisted (sonication) extraction technique. The changes of systolic blood pressure (SBP) were recorded using non-invasive technique (tailed cuff method) over period of 24 h (acute study) and 6 week (subacute study) of daily gavage. The kidney histopathology was evaluated at the end of subacute study using hematoxylin and eosin (H&E) stain. AESP at 1750 mg/kg significantly reduced SBP in the acute study ($p<0.001$). Similarly, MESP at 2000 mg/kg significantly reduced SBP ($p<0.001$). For subacute study, both AESP and MESP (at 1750 mg/kg and 2000 mg/kg, respectively) significantly reduced SBP started at week 2 ($p<0.001$) and continue up until week 6 of intervention ($p<0.001$). In histopathology assessment, the kidney of MESP-treated SHR showed a well-preserved glomerulus and well capsulated Bowman's capsule. In contrast, AESP did not showed the similar improvements. These results showed that despite both extracts had similar profile on blood pressure reduction, only MESP improved the histopathology of the kidney and to be potential antihypertensive agents.

CHAPTER 1

INTRODUCTION

1.1 *Syzygium polyanthum*

Syzygium polyanthum (Wight) Walp. (synonym *Eugenia lucidula* miq and *Eugenia polyantha* Wight) is a member of Myrtaceae, mainly distributed in Malaysia, Indonesia, Myanmar, Thailand, Indochina and also in Suriname (Wartini, 2009) This deciduous tropical tree (Raden *et al.*, 2009) is called differently in each country or province : "serai kayu", "salam", "samak kelat" (Malaysia), "meselangan" (Sumatra), "salam" (Java, Sunda, Madura). "gowok" (Sunda), "manting" (Java) or "kastolam" (Kangean) (Dalimartha , 2005; Suganda & Ruslan , 2007).

The tree of *S. polyanthum* has a single trunk and clear, dense canopy shape and can reach 25 meter high (Figure 1.1). It has dark brown and rough grooved bark. Single leaves are arranged opposite elliptic-round shaped or obovate with a pointed tip (Figure 1.2). Compact white flowers are fragrant and reddish (Figure 1.3). Sweet fruit is round with a diameter of 8-9 mm and red to dark red (Figure 1.4) (Backer & Bakhuizen van den Brink, 1963).

Fresh and dried leaf of *S. polyanthum* are useful in culinary (Katzer, 2004) because of its scent, colour and flavour. The leaves are slightly astringent or sour and the flavour develops more after frying. It has long been used as spices in cooking (Azizah *et. al*,

2014). In Malaysia, the leaf are important ingredient in nasi kerabu and kerabu perut or eaten raw as ulam. It is also can be used to treat haemorrhoids, stomach-ache, diarrhae (Kloppenburg- Versteegh, 1983), diabetes, itchiness, gastritis, astringent and scabies (Wijayakusuma, 1995), hypertension, high cholesterol and skin disease (Raden *et al.*, 2009).

Figure 1.1: *S. polyanthum* tree (personal photo)

Figure 1.2: *S. polyanthum* leaves (personal photo)

Figure 1.3: *S. polyanthum* flowers (Adapted from Ahmad Fuad, 2012)

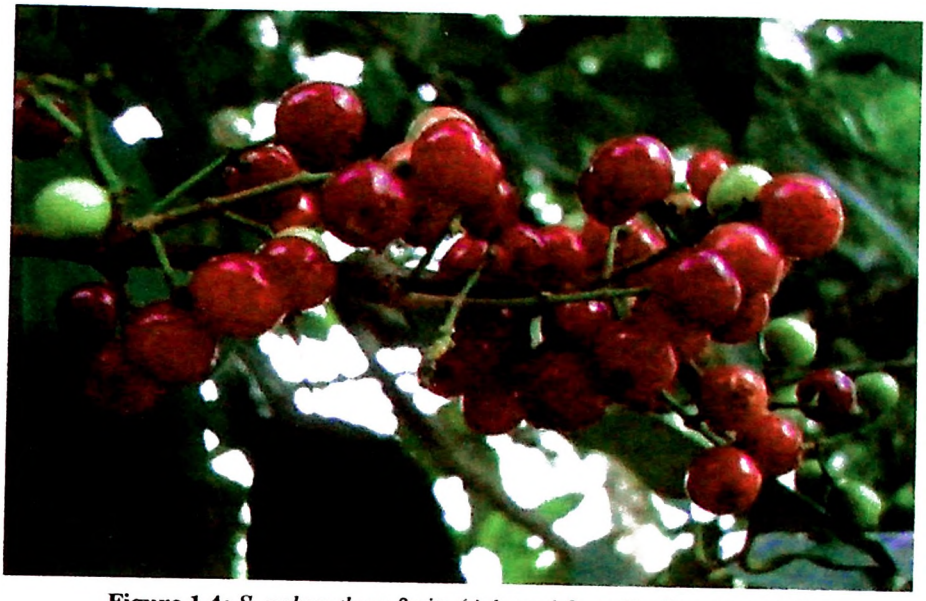

Figure 1.4: *S. polyanthum* fruits (Adapted from Fazlisyam, 2009)

1.2 Prevalence of Hypertension

Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more, or taking antihypertensive medication (Benjamin *et al.*, 2017). Hypertension is a major contributor to the global disease burden and was responsible for 7.0% of all disability-adjusted life years in 2010 (Ikeda *et al.*, 2014). It is associated with at least 7.6 million deaths per year worldwide (13.5% of all deaths), making it the leading risk factor for cardiovascular disease (CVD) (Chow *et al.*, 2013). It also an important cause of morbidity and mortality in the elderly (Rashid & Azizah, 2011). Hypertension has been associated with increased risk of coronary artery disease and is an independent risk factor for cardiovascular and cerebrovascular diseases (Wu *et al.*, 2013). A meta-analysis also reported that low range pre-HPT (value/range) is associated with higher risk of cardiovascular disease and also with chronic kidney diseases (Huang *et al.*, 2013).

The majority of patients' BPs remain uncontrolled in all societies and the decline in CVD, particularly stroke, has raised in some countries. Lim *et al.*, (2012) stated that complications of hypertension account for 9.4 million deaths worldwide every year. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke (WHO, 2008). Based on National Health and Morbidity Survey 2015 (Volume II) stated that the prevalence of individual with known hypertension was 13.1% while the prevalence of individual with unknown hypertension was 17.2%.

Specifically, in Kelantan, hypertension is common disease and associated with other risk factors for cardiovascular disease. The prevalence is likely to increase with increasing affluence and to become a major health problem causing significant morbidity and mortality in the near future (Mafauzy *et al.*, 2003).

The rising prevalence of hypertension is due to population socioeconomic status (Colhoun *et al.*, 1998) and behavioral risk factors. Socioeconomic status does not directly impact the cardiovascular system but exerts its cardiovascular effects via a complex interaction of biobehavioral factors, such as exercise and diet. Socioeconomic status is "a composite measure that typically incorporates economic status, measured by income; social status, measured by education; and work status, measured by occupation" (Dutton & Levine, 1989). Ironically, individuals higher in the social hierarchy typically enjoy better health than do those below; socioeconomic differences are found for rates of mortality and morbidity from almost every disease and condition (Antonovsky, 1967; Illsley & Baker, 1991).

Low socioeconomic status also could have led to limited access to health care and ignorance of the complication of uncontrolled hypertension. In addition, some studies from less industrialized countries, such as a study of Nigerian civil servants have found a positive association between socioeconomic status and chronic disease (Markovic *et al.*, 1998). Low educational attainment may be a proxy for low income. Low socioeconomic status could lead to limited access to health care, and to ignorance of the complications

of uncontrolled hypertension (Naing *et al.*, 2016). Recent reports have provided evidence that increasing rates of non-communicable diseases, including hypertension, are associated with other determinants like increases in rapid unplanned urbanization, globalization, and sociodemographic and nutritional transition (Contractor *et al.*, 2014). The World Health Organization has highlighted that hypertension disproportionally effects populations in low-income and middle-income countries where the health system is weak (WHO, 2013). Besides that, the behavioral risk also contribute to the increasing prevalence of hypertension. This includes unhealthy diet, consume excessive of alcohol, physical inactivity, obesity and tobacco used (CDC, 2016).

Hypertension is the most common modifiable risk factor for cardiovascular disease (CVD) and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. There are many synthetic antihypertensive drugs available; such as diuretics, beta blockers, calcium channels blocker (CCBs), angiotensin – II receptor blocker (ARBs) and angiotensin converting enzyme inhibitors (ACEIs). However, World Health Organization (2013) has identified the side effects of conventional anti-hypertensive drugs is one of the main factors that influence people into seeking for alternative traditional medicines. The synthetic antihypertensive drugs also cause undesirable effect; such as depression, delirium, potassium deficiency and sexual dysfunction (Sulaiman *et al.*, 2009).

A report by NHMS 2015 (Volume IV) on traditional and complementary (T&CM) has shown that 40.4% of Malaysian respondents choose T&CM as primary treatment before seeking conventional treatment. Among these, 18.3% used T&CM practices solely (Institute for Public Health, 2015b). Therefore, herbs and medicinal plants are gaining interest because of their potential to produce natural products, which are known to be good sources to provide better health. Besides, herbs and medicinal plants also claim to have minor side effects and has well therapeutically performance (Maghrani *et al.*, 2005). Thus, in Malaysia, one of the local herbs known which is *S.polyanthum* is said to be one of the potential alternative medicine due to its biological properties (Lee Wei & Ismail, 2012).

1.3 Scope of Research

Syzygium Polyanthum is well-known as traditional medication for various illnesses such as cataract, diarrhoea, gastritis, hypercholesterolemia, skin disease and diabetes mellitus (Sumono, 2008).

However, less study has been carried out with *S.polyanthum* and its effect on blood pressure and histology of kidney. In this research, *in vivo* approach has been employed. Methanol extract and aqueous extract of *S. polyanthum* has been orally administered on normotensive Wistar-Kyoto (WKY) and Spontaneously Hypertension Rats (SHR).

1.4 Aim of Research

Generally, the aim of this study to evaluate the effect of serai kayu (*Sygyzium polyanthum*) leaves extract as blood pressure lowering agent in SHR.

The specific objective of this study are:

i. To determine the present of gallic acid compound in the extract using thin layer chromatography (TLC).
ii. To evaluate the effect of equeous and methanol extract as blood pressure lowering agent by using non-invasive SHR.
iii. To evaluate the effect of extract on kidney histology of SHR using Hematoxylin and Eosin (H&E) staining.

1.5 Hypothesis

The orally administered of MESP and AESP extract are able to significantly reduce the blood pressure in normotensive WKY and SHR.

CHAPTER 2

LITERATURE REVIEW

2.1 *Syzygium polyanthum*

2.1.1 Family Myrtaceae

The family Myrtaceae comprises of around 121 genera (Stefanello *et al.*, 2011) and over 5800 species (WCSP, 2015) with centres of diversity in Australia, Southeast Asia, tropical, subtropical America and a small representation in Africa (Wilson *et al.*, 2001). Myrtaceae is unusual in having four genera of over 500 species; two of these *Myrcia* (Lucas *et al.*, 2011), *Eugenia* (Mazine *et al.*, 2014) and *Syzygium* (more than 700 spp., more than 1050 spp. and more than 1050 spp. respectively) (WCSP, 2015). They are predominantly from tropical rainforest and are ubiquitous in the Atlantic forest biome. *Eugenia* and *Syzygium* genera sharing much morphological similarities that has led to their repeated synonym (Lucas *et al.*, 2011). The distinguished features of the family are leaf containing oil glands, half inferior to inferior ovary, numerous stamens, internal phloem and xylem vessels with vestured pits (Wilson *et al.*, 2001). Worldwide, Myrtaceae is used as medicinal hygenic, edible and ornamental purposes (Ghannadi & Dezfuly, 2011). The uses of Myrtaceae as traditional medicine have led to the screening of some species for the essential oil and their biological activities (Stefanello *et al.*, 2011).

2.1.2 Genus *Syzygium*

Syzygium is a large genus of flowering plant which consists of over 1,040 species (Govaerts *et al.*, 2008), or about 1,200 species (Parnell *et al.*, 2007) which widely distributed in the tropics and subtropics of the old world from Africa, mainland Asia, Malaysia, Australia, New Zealand and the western Pacific (Biffin, 2005). It has been noted that there were 156 species of *Syzygium* found in Borneo (Merrill & Perry, 1939) and at least 52 species of *Syzygium* found in Java, 20 of which could be found in East Java (Backer & Bakhuizen van den Brink, 1963). It is around 140 genera (Ayyanar & Babu, 2012), occurring as evergreen trees, shrubs and suffrutices.

Some species of the genus *Syzygium* were formerly classified as Eugenia and many references may still list these species as Eugenia. Most Eugenia species originated from America and the West Indies whereas *Syzygium* species originated from the Indo-Malaysian region. Merrill & Perry (1939) reported that Species of Eugenia are diagnosed as having a pericarp which is easily crushed and the seed is free, the taste is smooth, chartaceous to cartilaginous and mostly lustrous, and the cotyledons are mechanically inseparable, i.e., they have grown together in such a way that often the line of their opposing faces is scarcely distinguishable whereas *Syzygium*, one of the segregate genera, is described as having fruits that when dried are not too easily broken, and, when opened, the embryo (not the entire seed) falls out leaving the roughish seed coat more or less loosely adhering to the pericarp; the embryo has two distinct cotyledons usually attached near the middle of the opposing faces which conceal the hypocotyl within. There has been a lot of ways of grouping e.g. based on the succulency of fruits, leaf shape, number of

pairs of lateral veins etc. (Chaffey, 1999), geographical Old World and New World (Schmid, 1980).

Some key species of genus *Syzygium* are *Syzygium cuminutesi, Syzygium aromaticum, Syzygium polyanthum, Syzygium jambos, Syzygium malaccense* and *Syzygium aqueum.* Several species of the *Syzygium* are grown and consumed for their edible fruits such as *Syzygium jambos, Syzygium aqueum, Syzygium samarangense* and *Syzygium malaccense.* All four species presumably originated in south-east Asia and in peninsular Malaysia are planted in home gardens, as ornament as well as for their edible fruits (Verheij & Coronel, 1991). Some of *Syzygium* species are used in traditional medicine to treat inflammation (Chauduri *et al.*, 1990), asthma (Alma *et al.*, 2007), various allergic disorders by oral administration (Kim *et al.*, 1998), sore throat, bronchitis, thirst, dysentery and ulcers (Ayyanar & Babu, 2012). Besides, some species also exhibited antiseptic properties and the commercial antiseptic from this genus is Clove (Mohanty & Cock, 2010). In addition, some species of *Syzygium* also claim to reduce blood pressure and heart rate of rats *in vivo* (Lahlou *et al.*, 2004).

2.1.3 *Syzygium polyanthum* species

Dalimartha (1999) state that *Syzygium polyanthum* is named as Eugenia polyantha Wight and known as "serai kayu" or "samak kelat" among the local, comes from the family of Mythaceae. It has been utilized as traditional remedy including the leaf, bark, root and fruits. The leaves are slightly astringent or sour and the flavour develops more after frying. It has long been used as spices in cooking (Azizah *et. al.*, 2014). The roots and fruits extract have ability to neutralize overdoses of alcohol consumption. In addition, the leaves, roots, stems and fruit also have antidiabetes, antihypertension and antidiarrhoea (Seidemann, 2005). Besides medicinal usage, the young shoots of *S.polyanthum* were commonly consumed as fresh salad (ulam) whereas the mature leaves were regularly added as a flavour enhancer in Malays cuisines.

Tropilab (2016) stated that *S.polyanthum* plant can reach a height of 90 feet although 60 feet is more common. Besides, Wijayakusuma (2002) also have reported that this plant can be found in lowlands until 400 meters above sea level and have straight root, round trunk and smooth surface. Bay trees have small, white, and fragrant flowers. The leaf has 2.-8.0 centimeters long leaf with flat margins, the tip is blunt and the base of the leaf stretch along length and tight (Utami & Tim, 2005). The bark of *S.polyanthum* are grey round bark that fissured and scaly.

2.1.4 *Syzygium polyanthum* Phytochemicals.

The previous studies showed that saponins, triterpenes, alkaloids and 0.05% essential oil consists of citral, tannins, flavonoids, sesquiterpenes, lactone and phenol are present in *S.polyanthum* (Soedarsono *et al.*, 2002). The essential oil of *S.polyanthum* can be obtain from the leaf, stem, fruits and barks. Wartini (2009) reported that the essential oils obtained from steam-distillation without using n-hexane as solvents contained 27 compounds while the essential oil extracted from steam distillation using n-hexane yielded 25 compounds. The main compounds were cis-4-decenal, octanal, α-pinene, farnesol, β-ocimene, α- caryophyllene, trans-caryophyllene, citronellol and nerolidol. Another study reported that citric acid, eugenol and methyl chavicol (Sumono & Agustin, 2008) were the main compounds of *S.polyanthum* oils. Sembiring (2003) have reported the presence of octanal, 3, 7-dimethyl-1-octene and cyclohexane while Agusta (2000) also reported 3, 7-dimethyl-1-octene but with the presence of n-decanal, patchoulin, D-nerolidol and caryophyllene oxide. Eugenol is the major compound in the essential oils of clove, a member of the genus Syzygium. The main class of compounds listed above was aliphatic compounds and oxygenated sesquiterpenes. The largest content of *S.polyanthum* is eugenol and methyl chavicol (Hanindra, 2012).

Besides that, *S. polyanthum* also contain gallic acid compound. The gallic acid is used as an antihypertensive in Spontaneous Hypertensive Rats (SHR) (Ismail *et al.*,2013; Ramli *et al.,* 2014). Gallic acid is a component of naturally occurring esters of gallic acid that belong to the larger group of plant polyphenols known as gallotannins. Gallotannins are polyphenolic compounds found in legumes, vegetables, fruits and beverages (Okuda *et*

al., 1995). Gallotannins were reported to possess multiple biological activities including anticancer, antioxidant, antimicrobial activities and cardioprotective effects (Zenebe & Pechanova, 2002). In recent years, gallotannins have been also studied for their antihyperglycemic, lipid lowering and antioxidant activities (Li *et al.*, 2005).

2.1.5 *Syzygium polyanthum* Uses

Culinary

Syzygium polyanthum Wight (walp.) var. Polyanthum leaves are commonly consumed by Malays as fresh salad and flavour enhancer in culinary (Azizah *et al.*, 2014). The crushed or ground leaf releases more desired fragrance than the whole leaf. In order to release the fragrance, it is suggested to leave the leaf cook for some time. The leaves are slightly astringent or sour and flavour develops more after frying. Usually it is eaten after boiling it (Seidemann, 2005).

Medicine

S.polyanthum is proven to cure diarrhoea in mice, which was observed in amount, consistency of the feces, and the duration of the diarrhoea (Sundari, 2010). Adnyana *et al.*, (2005) claim that the water extract can lowers cholesterol in rat's heart cell culture. Pidrayanti (2008) also found that the anticholesterol effect in Wistar rats. Both of the researches indicated significant effect of the *S.polyanthum* extract compared to negative control. Another pharmacological effect of *S.polyanthum* infuse is lowering uric acid in male mice induced by potassium (Ariyanti *et al.*, 2007). Although the effect is not similar to allopurinol as positive control, the infuse lower uric acid level compared to the negative control. Antioxidant activity of *S.polyanthum* is found to be highest when extracted with combination of methanol-water. Antihyperglycemia activity test of *S. polyanthum* has been conducted in alloxan-induced mice. Extract administration for 7 days significantly lowered blood glucose level the most compared to control (Studiawan, 2005). The hypoglycemia activity of the ethanolic extract was also tested in rabbits by Glucose Tolerance Test (GTT) (Wahyono & Susanti, 2008). Besides showing significant

hypoglycemic effect, it was suggested that the mechanism of the blood glucose lowering was different from Andrographis paniculata. The evaluation of *S.polyanthum* leaves absorption was observed by analyzing the metabolites in feces, blood and urine (Anggowati *et al.*, 2004).

Other than that, *S.polyanthum* can be used for hypertension, drunks and skin diseases (Raden *et al.*, 2009). The plant also has other benefits such as diuretic and analgesic effect. It roots and fruits extract have the ability to neutralize overdoses of alcohol consumption. Beside those two utilities, *S.polyanthum* extract is usually used to stop diarrhoea, gastritis, diabetes mellitus, itchy, astringent and scabies. It can also be used to treat patients with high uric acid (Agus & Agustin, 2008) and can be used as a safe, reliable and economical natural source in pharmaceutical and food industry.

2.2 Hypertension

2.2.1 Definition of Hypertension

Hypertension is reported to have affected millions worldwide as it is account for 9.4 million deaths worldwide every year (WHO, 2015). According to National Health and Morbidity survey (2015), among others, one in three (30 per cent) or about 6.1 million people have hypertension (Azura, 2016). Hypertension also one of the most important causes of premature death worldwide and the problem is growing; in 2025, an estimated 1.56 billion adults will be living with hypertension (WHO, 2012). Overall, there was a rising trend in the prevalence of hypertension in adults ≥ 30 years: 32.9% (30%–35.8%) in 1996, 42.6% (37.5%–43.5%) in 2006, and 43.5% (40.4%–46.6%) in 2011 (Naing *et al.*, 2016). The World Health Organization (2008) reports that suboptimal BP (115 mm Hg SBP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by sex. High blood pressure also one of the most important modifiable risk factors for cardiovascular disease. It is an extremely common finding in the community and a risk factor for myocardial infarction, stroke, congestive heart failure, end-stage renal disease, and peripheral vascular disease (Whelton, 1994). In Malaysia, according to the National Health and Morbidity Survey (NHMS) (2015), the overall prevalence of hypertension among adults of 18 years and above was 30.3% and Kelantan has ranked the highest prevalence at 23.2% of undiagnosed hypertension. The criteria of staging hypertension can be seen in Table 2.1.

Table 2.1: Criteria for Staging Hypertension. Adapted from American Heart Association (2016).

Category	Blood Pressure (mmHg)
Normal	≤ 120/80
Prehypertension	≥120/80
Stage 1 Hypertension	≥140/90
Stage 2 Hypertension	≥160/100
Severe Hypertension	SBP ≥ 180 or DBP ≥ 110

2.2.2 Stages of Hypertension

Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. However, increasing evidence indicates that the cardiovascular (CV) risk associated with elevation of blood pressure (BP) above approximately 115/75 mm Hg increases in a log-linear fashion (Kikuya *et al.*, 2007). In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) a category of ''prehypertension'' was created using BP criteria of 120/80 mmHg to 139/89 mmHg (NHBPEP., 2003).

The cardiovascular status of an individual decides the individual is either normal or hypertensive. The progression of hypertension from early to advanced can be categorized into grade 1, 2 and 3 hypertensions (Table 2.2). Each stage of hypertension is characterized by the cumulative presence or absence of markers of hypertensive cardiovascular disease (CVD) and evidence of target organ regardless of the blood pressure level such as progression includes such parameters as microalbuminuria or evidence of left ventricular hypertrophy (Giles *et al.*, 2009). Since hypertension is a progressive cardiovascular syndrome, early markers of the syndrome are often present before blood pressure elevation is observed; therefore, hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs, and lead to premature morbidity and death (Giles *et al.*, 2009).

Table 2.2: Classification of clinic blood pressure levels in adults. Adapted from National Heart Foundation of Australia (2016).

Diagnostic Category	SBP (mmHg)		DBP (mmHg)
Optimal	<120	And	<80
Normal	<130	And/ or	<85
High Normal	130-139	And / or	85-89
Grade 1 (Mild) Hypertension	140-159	And/ or	90-99
Grade 2 (Moderate) Hypertension	160-179	And/ or	100-109
Grade 3 (Severe) Hypertension	≥180	And / or	≥110
Isolated Systolic Hypertension	>140	And	<90

Hypertension is a well-known risk factor for cardiovascular and cerebrovascular events such as heart attacks and strokes. In addition, it is associated with earlier changes in organ systems in the body, such as left ventricular hypertrophy (LVH), proteinuria and renal failure, retinopathy and vascular dementia which are grouped under the term "target organ damage" (TOD). There are many processes involved in the pathogenesis of TOD and these include endothelial activation, platelet activation, increased thrombogenesis changes in the renin aldosterone angiotensin system (RAAS), and collagen turnover. All these changes work hand in hand and lead to the production of hypertensive TOD.

2.2.3 Mechanism of Hypertension.

There are three main regulator of arterial blood pressure mechanism, which are rapidly acting mechanism for regulation of blood pressure, intermediate acting mechanism for control of blood pressure and long term mechanism for control of blood pressure (Figure 2.1). All of these mechanisms play some roles in regulation of blood pressure.