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# CHAPTER 1

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## INTRODUCTION

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Hypertension is a medical term used to refer to a condition in which blood pressure of the arteries is elevated from the normal level. Blood pressure is measured according to two indicators named systolic and diastolic. Systolic indicates the arterial pressure when the heart beats while diastolic is the arterial pressure generated when the heart relaxes between heartbeats. A normal blood pressure is considered when the systolic blood pressure (SBP) is less than 120 mmHg and the diastolic blood pressure (DBP) is less than 80 mmHg. A person is categorized in pre-hypertension stage if the person SBP is between 120 to 139 mmHg and DBP is between 80 to 89 mmHg. However, when the SBP exceeds 140 mmHg and DBP exceeds 90 mmHg, the person is considered to suffer from hypertension (Chobanian *et al.*, 2003).

An analysis done found that more than a quarter of world's adult population suffered from hypertension in the year 2000. It was suggested that the value may increase up to 29 % by the year 2025 and occur higher in economically developing countries than developed countries (Kearney *et al.*, 2005). The high prevalence around the world has caused hypertension to become one of the major contributors to cardiovascular disease (CVD). In Malaysia, CVD has been the principal cause of admission and death in government hospitals (Zambahari, 2004).

Researchers have done enormous amount of studies to investigate the event of hypertension disease. Hitherto, the exact causes for the occurrence of hypertension are not apparently known. It is classified as 'silent killer' since it has no specific symptoms and can cause death. However, there are several possible factors that associated with the elevation of blood pressure.

Salt is one of the important ingredients in dietary intake where it provides good taste to food and indeed is required by human to maintain their metabolic balances. However, excess salt intake than recommended dietary requirement may result in rising

of the blood pressure (Dahl, 2005). At high salt intake of more than 50 mmol per day, renin-angiotensin-aldosterone system (RAAS) is not able to substantially suppress the level of sodium-retaining hormone, aldosterone, and consequently blood pressure increases.

Cigarette smoking has been found to be one of the major risk factors for cardiovascular diseases (Erhardt, 2009). The adverse effects are due to the presence of over 4,000 harmful chemical constituents in the cigarette smoke inhaled by the smokers such as nicotine, carbon monoxide, ammonia, hydrogen cyanide and formaldehyde (Villablanca *et al.*, 2000). Nicotine binds to nicotinic cholinergic receptors that can be found in the brain, autonomic ganglia and neuromuscular junction (Benowitz, 1996). This association triggers the production of endothelin-1 (Suzuki *et al.*, 1994) which then causes vasoconstriction of blood vessel.

Hypertension and diabetes mellitus are two chronic diseases which frequently coexist. Diabetes mellitus refers to a condition when the production of insulin in the body is insufficient, in that it causes blood glucose level to rise. Investigations done by Sowers (1990) as well as Edelson and Sowers (1993) showed a positive correlation between insulin resistance and hypertension. Nevertheless, the mechanism of how the insulin resistance contributes to hypertension is incompletely understood (Epstein and Sowers, 1992).

Another possible factor for hypertension is obesity. Obesity is clinically defined as body mass index (BMI) measurement of more than 30. Data from Framingham Study cohort showed that obesity by itself might contribute to 78 % and 65 % of essential hypertension in men and women, respectively (Kannel *et al.*, 1993). A rise of free fatty acids level in obese individual was found to enhance blood pressure via increasing the sympathetic vascular system (Grekin *et al.*, 1997) and activating the

renin angiotensin aldosterone system (Goodfriend *et al.*, 1998).

Uncontrolled hypertension may lead to severe conditions such as stroke, kidney failure, congestive heart failure, heart attack and blindness. Due to the rise of hypertensive patients globally, a holistic prevention and treatment should be done in order to reduce the occurrence of the disease. Practising a healthy lifestyle is a good way in preventing hypertension and would be the first line therapy for hypertensive patients. Salt intake should be restricted by taking less salty food and eliminating added salt to the diet. Besides, smoking habit should be avoided and by itself, is the risk factor for stroke and heart disease.

In situation where lifestyle modification alone could not adequately lowered the blood pressure, antihypertensive medications will be considered. There are several groups of medications available such as diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and calcium channel blockers. Although the synthetic antihypertensive agents are effectively lowering the blood pressure, they seem to cause several side effects.

Basically, blood pressure control is associated with a number of different biochemical pathways including renin-angiotensin-aldosterone system (RAAS). ACE plays a major role in RAAS and has become a key target in combating hypertension. A number of studies have revealed that bioactive peptides/proteins from food could inhibit ACE activity which then caused significant hypotensive effects. This brings to the fact that instead of being part of food products, ACE inhibitory peptides/proteins could be an alternative for the treatment and prevention of hypertension.

*Ganoderma lucidum* is a well-known medicinal mushroom particularly in China, Japan and Korea. For centuries, the fruiting bodies of *G. lucidum* have been adopted by old folks to treat various ailments including hypertension. Recently, people

are aware of the health improving properties of mycelia, thus triggers researchers to do comprehensive studies on it. To date, however, no study has been conducted to determine if *G. lucidum* mycelia proteins exhibit anti-ACE properties.

The significant advantage of the mycelia is that cultivation requires a shorter period compared to fruit bodies, thus reducing the time spent to obtain the product. Moreover, mycelia cultivated by submerged fermentation contain more consistent composition and higher nutritional value than the fruit bodies. In the present study, proteomic approach is applied in order to isolate and characterize the ACE inhibitory proteins from the mycelia. Employment of proteomic tools may generate extensive understanding in the nature of the proteins of interest.

Proteins from *G. lucidum* mycelia are viewed to be a promising alternative for treating hypertension in an economic and safe way. Hence, the aims of this study are:

- i. To cultivate *G. lucidum* mycelia by submerged fermentation
- ii. To extract proteins from *G. lucidum* mycelia and screen for anti-hypertensive activity via inhibition of ACE
- iii. To purify and identify protein(s) associated with anti-hypertensive activity

