

Potential Role of *Labisia pumila* in the Prevention and Treatment of Chronic Diseases

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Abstract

Labisia pumila (Myrsinaceae), also called Kacip Fatimah, is a herbal medicine that has been widely used in South East Asian communities mainly for women's health. The extensive use of this plant has led to many speculations and studies on its phytoestrogenic properties. This review highlights the studies that involved *Labisia pumila*, which include phytochemical profiling and its safety. In addition, we also look into its use as an alternative to hormonal therapy in postmenopausal women, and its role in cardiovascular protection and osteoporosis. Further studies are needed to highlight the potential benefits of this plant in promoting advantageous health properties.

Keywords: *Labisia pumila*, postmenopausal, safety profiles, cardiovascular risk factors and phytoestrogen

1. Introduction

Chronic diseases are diseases of long duration and generally slow in progression. These include diseases such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes. They are by far the leading causes of mortality and morbidity in the world. Plants have been one of the sources of medicine to treat various illnesses since ancient time. Currently in Malaysia, it was estimated that 2,000 species of plants with medicinal and therapeutic properties have been identified. A study on herbal drug use among multi-ethnic patients in Malaysia found that about 63% of patients used herbal medicine (Saw et al., 2006). Subsequently, more plants have been investigated for their phytochemical properties.

In Malaysia, among the famous herbs that have been widely used and studied are *Labisia pumila* (Kacip Fatimah), *Eurycoma longifolia* Jack (Tongkat Ali), *Orthosiphon stamineus* (Misai Kucing), *Quercus infectoria* (Manjakani) and *Piper sarmentosum* (daun Kaduk) (Nadia et al., 2012). *Labisia pumila*, a long known herb for Malay women has received much attention since more than a decade ago. This review will be focusing on the potential role of *Labisia pumila* in the management of chronic diseases.

Labisia pumila or popularly known in Malaysia as Kacip Fatimah, is a member of the small genus of slightly woody plants of the family Myrsinaceae (Burkill, 1935). The locals identify it by the name as *Seluruh Fatimah*, *Rumput Siti Fatimah*, *Akar Fatimah*, *PokokPinggang*, and *Belangkas Hutan* (Burkill, 1935; Rasadah & Zainon, 2003). There are at least four known varieties of *Labisia pumila* found in Malaysia. However, only three of them are popularly used by the Malays, which are *Labisia pumilavar. pumila*, *Labisia pumila var. alata* and *Labisia pumila var. lanceolata* (Stone, 1988). These plants have been utilized by many generations of Malay women. The plants are usually boiled and the water-soluble extract is taken as a drink. In daily practice, it is used for the general well-being and vitality of women, maintaining the figure and appearance, aiding in reducing symptoms related to hormonal imbalance, and increasing libido in women (Burkill, 1935; Prosea, 2003; Wan, 2007; Runi, 2000). Its exclusive use by women has led to the belief that it exhibits (phyto)-estrogenic activity, contains compounds with similar chemical structures to estrogens (Jamia et al., 2003) and therefore is able to relieve menopausal symptoms (Bhatena & Velasquez, 2002).

There are numerous scientific researches on *L. pumila* carried out to identify the bioactive phytochemicals that contribute to the pharmacological properties. Recently, phyto-chemical studies identified flavonoid, isoflavonoid and phenolic compounds as bioactive ingredients in leaf extracts of the three varieties of *L. Pumila* (Chua, 2011; Karimi et al., 2011; Karimi & Jaafar, 2011). Flavonoids mainly apigenin, kaempferol, rutin and myricetin were

identified from *L. pumila* var *alata*, along with phenolic contents such as gallic acid, pyrogallol and caffeic acid (Karimi et al., 2011; Karimi & Jaafar, 2011).

A genotoxicity assessment of the herb was carried out using *in vivo* rodent micronucleus assay where at doses of up to 2000 mg/kg body weight, *L. pumila* extract demonstrated no mutagenic potency (Zaizuhana et al., 2006). Clinical trial on human for 6 months duration also has been done to show that this plant extract is safe in terms of biochemical and haematological profiles (Hussain et al., 2009). Long term study is needed to assess the complication of the use of these extract that may happen after longer periods of use.

2. Phytoestrogenic Property of *Labisia pumila* for Estrogen Replacement Therapy

Women now live more than one third of their life in the menopausal years (Kinlay et al., 1992). The increase in life expectancy in women will predispose them to suffer from morbidities due to the loss of ovarian function (Kinlay et al., 1992). Menopause is associated with chronic conditions such as increased cardiovascular risk, osteoporosis, declined cognitive function and other problems linked with obesity (Kinlay et al., 1992). Postmenopausal women may also experience vasomotor symptoms such as hot flushes, night sweats, insomnia, vaginal dryness and urinary symptoms (Kinlay et al., 1992). The current treatment for postmenopausal symptoms and diseases related to estrogen deficiency is hormone replacement therapy. However, recent studies have changed this practice due to adverse effects as regards to hormone replacement therapy (HRT) (WHI, 2002). For this reason, there is tremendous growth in the use of alternative therapies to relieve postmenopausal symptoms.

In regard to *L. pumila*, Malaysian women extensively use this plant especially in assisting childbirth and during postpartum period. This practice has led to the speculation that this plant exhibit (phyto)-estrogenic activity, a compound that has similar effect with estrogen hormone (Turner et al., 2007). It was also postulated that this plant have certain effect either they are full estrogen agonists or antagonist or partial agonist. Theoretically, this plant extracts act by binding to the estrogen receptors and exerting weaker estrogenic effect compared to the female hormones (IFST, 2001). Researches have shown that *Labisia pumila* acts as selective estrogen receptor modulators (SERMs) which is a partial antagonist (Malaysian Herbal Medicine Research Center, 2011). In view of the initial evidence that it is a phytoestrogen, it is postulated that this plant have a beneficial effect to the postmenopausal women in terms of its positive effects on the lipids and hormonal profile.

Report had showed that the plant displayed a non-significant response to *in vitro* estrogen activity (Houghton et al., 1999). A study by Husniza et al. showed that the water extracts of *L. pumila* were able to displace estradiol binding to antibodies raised against estradiol, making it similar to other estrogens such as estrone and estradiol (Husniza, 2002). In other study, Jamal et al. found that ethanol extract of *Labisia pumila* exhibited a weak estrogenic activity in an *in vitro* assay in Ishikawa cells, but none was observed from the leaf extract. However, he could not find the same activity in the aqueous extract from the same roots (Jamal et al., 2003).

In an animal study done in ovariectomized rats, it showed that this plant extract was able to increase estradiol level and suppress Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) levels which resemble the effect of estrogen therapy (Wahab et al., 2011).

The most trustworthy evidence and the best scientific design for herbal efficacy should come from trials on human and randomized, double blind, placebo controlled trials in order to guarantee the most dependable results. However, there are still limited trials conducted in human to support the efficacy of the herbal products.

There is a randomized, double blind placebo- controlled study done to assess the effects of water extract of *Labisia pumila* var *alata* on postmenopausal women (Azidah et al., 2012). In the study, there was no significant difference in terms of menopausal symptoms, cardiovascular profile (blood pressure, body mass index (BMI), waist circumference, fasting blood sugar and hormonal profile (FSH, LH and estradiol) between the placebo and active groups on *Labisia pumila* (Azidah et al., 2012). However, in that study, there was significant reduction of triglyceride levels in the active group at 6 months of treatment compare to placebo (Azidah et al., 2012). The study showed that *Labisia pumila* did not have any effects on the hormonal profile in the postmenopausal women; however in animal model study it showed that *Labisia pumila* takes longer time (almost twice) to the time needed by estrogen to exert its effects on the female hormones. Therefore, a longer study would be beneficial. Currently, there is still inadequate evidence to show that *Labisia pumila* has estrogenic activities or could work as phytoestrogen. Therefore, it is too early to recommend the use of *Labisia pumila* over conventional hormone replacement therapy. There was also no evidence to conclude that this plant could reduce menopausal symptoms.

3. Cardiovascular Effect of *Labisia pumila*

Menopause is known to have a link with weight gain and adiposity due to estrogen deficiency, and the theory behind this is that adipocytes increased in size followed by increased in number (Kinlay et al., 1992). The increased in adiposity is associated with cardiovascular risks. Since *Labisia pumila* is thought to behave as phytoestrogen, the actions of this plant with adiposity have been studied. Animal model of ovariectomized rats showed that there is an increased in size and vasculature of adipose tissue observed by using transmission electron microscope (Ayida et al., 2006). Thickening of the adipocyte membrane were also observed in the ovariectomized rats. However, it was found that in rats given *Labisia pumila* and estrogen treatment, there are fragmentation of collagen fibres that hold the adipocytes together. Hence, in this study it showed that there is possible role for *Labisia pumila* in modulating postmenopausal adiposity through lipolysis process in adipose tissue (Ayida et al., 2006).

Aorta stiffness is associated with atherosclerosis and it worsens arterial function. Indirectly, it is one of the factors associated with cardiovascular risk (Boutouyrie et al., 2002). Thus, aortic stiffness is presented as a useful measure of cardiovascular health, which has predictive value in cardiovascular morbidity and mortality (Boutouyrie et al., 2002). In the animal model, it has been showed that the water extract of *Labisia pumila* has the capability in maintaining the elastic lamellar architecture of aortae in the ovariectomized rats in a manner comparable to that of the normal rats (Boutouyrie et al., 2002). This result also indicates that *Labisia pumila* extract might be able to modulate postmenopausal cardiovascular risk but probably not through the mechanism of phytoestrogen (Boutouyrie et al., 2002).

In a separate animal study done by Fazliana et al., it has been shown that both estrogen replacement therapy and *Labisia pumila* were able to suppress weight gain in ovariectomized rats by increasing leptin, decreasing resistin levels and expression of the adipokines in adipose tissues (Fazliana et al., 2009). The study by Fazliana et al. showed that *Labisia pumila* appears to show promising results in regulating body weight through the secretion of leptin and thus might affect insulin sensitivity (Fazliana et al., 2009). The effect of *Labisia pumila* in polycystic ovarian syndrome (PCOS) rats induced with dihydrotestosterone was also studied (Manneras et al., 2010) based on the results by the study done by Fazliana et al. (Fazliana et al., 2009). PCOS is an endocrine and metabolic disorder that is associated with obesity, insulin resistance and type 2 diabetes. In the study, it showed that PCOS induced rats treated with *Labisia pumila* has increased insulin sensitivity without influencing weight gain or adiposity. There was no difference in body fat or body weight between *Labisia pumila* treated rats and controls. After treatment with *Labisia pumila*, the Polycystic Ovarian Syndrome (PCOS) rats also had decreased levels of Total Cholesterol and triglyceride levels. However, there were no changes seen in High Density Lipoprotein - C (HDL-C) and Low Density Lipoprotein - C (LDL-C) levels (Manneras et al., 2010). A study done by Azidah et al in human trials also showed that there was beneficial effect of *Labisia pumilavar alata* in reducing triglyceride level in postmenopausal women (Azidah et al., 2012). The extract was derived from the leaves of the plant and the marker compound is 3,4, 5-trihydroxybenzoic acid (Azidah et al., 2012). However, the mechanism underlying the lowering of triglyceride level is unclear. Human trial also showed that there were no significant changes in terms of body weight, BMI and waist circumference between the group treated with *Labisia pumila* and placebo (Azidah et al., 2012).

4. Role of *Labisia pumila* in Prevention of Osteoporosis

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Consensus Development Conference, 1993). Osteoporosis related fractures have been recognized as a major health problem, particularly in the elderly. Postmenopausal women are at higher risk to develop osteoporosis due to the decline in estrogen level during menopause. The decline in estrogen level leads to a decline in bone formation and an increase in bone resorption activity.

Estrogen Replacement therapy (ERT) is effective for prevention and treatment of postmenopausal osteoporosis (CPG, 2012). ERT reduces the risk of spine, hip and other osteoporotic fractures by 33-40% (Cauley et al., 2003; The WHI Initiative Steering Committee, 2004). However, Women's Health Initiative study found that there are adverse effects of estrogen replacement therapy (ERT) which increases the risk of breast cancer, stroke and thromboembolic disease. Due to this effect there are many controversial on the use of ERT.

Based on the possible estrogenic activities of *Labisia pumila*, it has been considered as an alternative to replace estrogen for the treatment and prevention of postmenopausal osteoporosis (IFST, 2001; Malaysian Herbal Medicine Research Center, 2011; Husniza, 2002). Nazrun et al. conducted a study to determine the effects of *Labisia pumila* on osteoporosis using ovariectomised rats as the model of postmenopausal osteoporosis (Nazrun

et al., 2011). Bone biomarkers were measured as indicators of bone formation and resorption, while bone calcium content was used as an indicator of bone loss in this model (Nazrun et al., 2011). The effects of *Labisia pumila* were compared to a group of ovariectomised rats given ERT as the gold standard of treatment (Nazrun et al., 2011). In the study, it showed that the supplementation *Labisia pumila* to ovariectomised rats was able to prevent the changes in bone biochemical markers but failed to prevent the bone calcium loss induced by ovariectomy (Nazrun et al., 2011).

The effects of *Labisia pumila* on the bone of ovariectomised rats was measured with histomorphometric parameters in another animal study (Fathilah et al., 2012a). It showed that supplementation of *Labisia pumila* to ovariectomized rats could prevent these osteoporotic changes, as effective as ERT (Fathilah et al., 2012a).

In a different study by Fathilah et al., bone biomechanical strength was assessed to see the effect of *Labisia pumila* in ovariectomized rats (Fathilah et al., 2012b). She demonstrated that *Labisia pumila* supplementation to the ovariectomized rats improved the femoral strength and may be as effective as ERT in preventing fractures due to postmenopausal osteoporosis (Fathilah et al., 2012b). Based on previous studies, there are a few postulated mechanisms of how *Labisia pumila* works in prevention and treatment of osteoporosis. It was postulated that it contains triperenone saponins, which were thought to interact with estrogen receptors (Bharathi et al., 2011). It was also postulated that this plant works through its antioxidative properties as those exhibits through beta carotene and flavonoids (Bharathi et al., 2011). Inhibition of cytokine called Tumour Necrosis factor- α (TNF- α) may be another possible way (Choi et al., 2010). TNF- α is a bone resorbing cytokine that promotes bone resorption by activating mature osteoclasts or by stimulating proliferation and differentiation of osteoclasts (Lerner & Ohlin, 1993). *Labisia pumila* has been shown to markedly inhibit the TNF- α production in an experimental study (Choi et al., 2010). As a conclusion, *Labisia pumila* has the potential to prevent postmenopausal osteoporosis.

5. Future Studies

Recent studies have shown that this plants has anti-oxidant and anti inflammatory properties. The anti-oxidant property is due to the presence of the phenolic compounds, including phenolic acids and flavonoids (Chua et al., 2011; Karimi et al., 2011; Karimi & Jaafar, 2011). The phenolic compounds include flavonoids (quercetin, myricetin, kaempferol and catechin) and other detected constituents (ascorbic acids, tocopherols, carotene and carotenoids) (Karimi et al., 2011). Studies have showed that the leaves of the plant from all the varieties showed higher antioxidant activities compared to the roots and stems. The presence of these anti-oxidant properties could be used to treat diseases involving oxidative stress such as cancer and certain aspect of cardiovascular disease.

This plant also has been shown to have anti-inflammatory activity. Experimental findings showed that this plant extract has the ability to markedly inhibit TNF- α production and the expression of cyclooxygenase (COX)-2. Cox-2 is an enzyme that is responsible for the production of mediators involved in inflammation. Pharmacological inhibition of COX-2 can provide relief from the symptoms of inflammation and pain thus can be used in the treatment of chronic disease such as arthritis or asthma. In-vivo study has shown that this plant extract exhibited bronchodilator activity and inhibition of the inflammatory mediators involved in asthma (Patrick et al., 2012).

6. Conclusion

Many studies have been done on the Asian plant-based or herbal medicines, and *Labisia pumila* is one of the herbal plant that has been extensively studied. The support of efficacy of botanical products can be derived from animal trials. However, animals may process herbal products differently from humans, thus, results are not necessarily reliable. It is important that the plant materials of herbal medicines being clinically evaluated in randomised double blind studies to examine the evidence-based benefits to consumers. Publication on *Labisia pumila* from a single well planned human trial had been done and is enough to launch this plant into medical limelight (Azidah et al., 2012). However, further studies in human are needed to assess the full potential of this product and not to only depend on animal studies. As for now, there are sizeable evidences to suggest that *Labisia pumila* is an alternative to be used as phytoestrogen, prevention and treatment of cardiovascular disease and also osteoporosis.

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