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*Labisia pumila* (Blume) Fern.-Vill. known as *Kacip Fatimah*, is a herbal medicine that has been widely used for women’s health. The extensive use of this plant has led to many speculations and studies on its phytochemical identification, biological and toxicological activities. Phytoestrogen is one of many phytochemical properties found in the herbal extract and has beneficial effects for post-menopausal diseases. This systematic review highlights the phytoestogenic properties of *Labisia pumila* for the prevention and/or treatment of post-menopausal diseases. A comprehensive search was conducted in Scopus, EBSCO host and Ovid Medline for related studies published between the years 1946 to August 2016. The main inclusion criteria were research articles published in English, and studies had to report the phytoestrogenic effects of *Labisia pumila* in the prevention and treatment of post-menopausal diseases. The literature search identified 142 potentially relevant articles, whereby 12 met the inclusion criteria. Eleven animal studies and one human study were included in this review. All of the studies reported positive effects of *Labisia pumila* on post-menopausal diseases due to estrogenic deficient state. This systematic review focused on the potential of *Labisia pumila* being used for treatment or prevention of diseases in the post-menopausal state.

**Keywords:** *Labisia pumila*, *Marantodes pumilum*, Ovariectomized, Osteoporosis, Metabolic disorders, Cardiovascular diseases

**IPC Int. Cl.**: A61K 36/00, A01D 9/00, A61P 13/00, A61P 15/00, A01D 14/01, A01D 12/00

Menopause stage of women starts when their monthly menses cease. It is a normal part of aging and marks the end of a woman's fertility. Menopause typically occurs in women during late 40s to early 50s. At this stage, the ovaries have stopped releasing eggs or ovums and production of most estrogen. Many effects of estrogen on the skin are based on changes in post-menopausal women. During this stage, most women will have experienced hot flashes, night sweats and/or cold flashes, insomnia, irritability, mood swings, mild depression, dry skin, dry eyes or dry mouth, vaginal dryness, discomfort during sex, urinary urgency, and so on. Moreover, post-menopausal women are at an increased long-term health risks, such as osteoporosis, metabolic disorder, heart disease and various type of cancer like breast, uterine or ovarian cancer due to lower level of estrogen. Estrogen binds to its receptors on the specific body site, causing the release of chemical mediators which can alleviate estrogen deficient diseases. Studies with women who took ERT found higher risk for many diseases such as breast cancer, ovarian cancer, heart attack, thromboembolism, brain stroke, and Alzheimer’s disease. These adverse-effects of ERT have led to many post-menopausal women searching for alternatives for their post-menopausal symptoms that are comparable in effectiveness to estrogen but with minimal adverse effects. Some potential alternative agents discovered were soy, blueberry and *Achyranthes bidentata* Blume. Recently, the use of *Labisia pumila* has gained traction due to its many beneficial effects similar to estrogen and estradiol.

*Labisia pumila* a plant from the genus Myrcinaceae family, is a common herb in Indonesia, Indo-China and Malaysia. There are three variants, *Labisia pumila* var. *alata*, var. *pumila* and var. *lanceolata* which are available in Malaysia. *Marantodes pumilum* (Blume) Kuntze is a synonym of *Labisia*

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It is commonly known as “Kacip Fatimah” in Malaysia. The extract of the plant can simply be prepared by boiling the leaves, roots or the whole plant in water and taken orally by the local people of Malaysia. Various preparations Labisia pumila including capsules and drinks are available in local market. It is used exclusively by women to shrink the uterus, improve menstrual irregularities, facilitate labor and as post-partum rejuvenation medicine. Its use as a women’s health supplement has led to the belief that Labisia pumila is rich in phytoestrogens, a compound with similar chemical structure to estrogen. It was found that estradiol bound with antibodies and induced a specific estrogenic effect on human endometrial adenocarcinoma cells (Ishikawa-Var I line). It mimicked estrogen action by inhibiting the shrinkage of uterus due to estrogen deficiency in ovariectomized rats and initiate lipolysis in adipose tissue. It can also down-regulate gene expressions in adipose tissues and also reduce serum corticosterone levels in ovariectomized rats.

The objective of this systematic review was to illustrate the outcomes of phytoestrogens found in Labisia pumila for the prevention and treatment of postmenopausal diseases. This review concentrates on postmenopausal diseases in estrogen deficient states.

Materials and methods

Search strategy

A systematic review of the literature was conducted to identify relevant studies about the phytoestrogenic properties of Labisia pumila. To conduct a comprehensive search of health science journals, we searched databases Scopus, EBSCOhost and Medline via Ovid Medline. We limited to publications between 1946 and August 2016. The search strategy involved a combination of the following two sets of keywords (1) Kacip Fatimah or Labisia pumila* or Marantodes pumilum* and (2) *estrogen* or *menopaus*. Furthermore, the references of all retrieved articles were reviewed for relevant citations.

Selection criteria

The results were limited to studies that were published in English language that included abstracts. Studies with these characteristics were included (1) reported the association or effect of Labisia pumila and/or (2) phytoestrogenic properties that have potential role in the prevention and/or treatment of postmenopausal diseases. Review articles, news, letter, editorials, non-primary research or case studies were excluded from this review.

Manuscript screening

Manuscripts were screened in three phases before being included in this review. In the first phase, any manuscripts that did not match the inclusion criteria based solely on the title were excluded. In the second phase, abstracts of the remaining manuscripts were screened and manuscripts that did not meet our inclusion criteria were excluded. In the final phase, the remaining manuscripts were read thoroughly to exclude any paper that did not meet our inclusion criteria. Duplicates were removed and the remaining manuscripts were again screened by two reviewers who are experts in Labisia pumila research independently. Both reviewers must agree that the manuscripts were of sufficient quality with bias risk assessment done before proceeding to the data extraction phase. Any differences in opinions were resolved through discussion between the reviewers. All data extraction was performed independently with the use of a data collection form.

Data extraction

The following data were recorded from the studies: (1) authors; (2) study design; (3) results; (4) outcomes of each study.

Results

Search results

The literature searches identified 142 potentially relevant articles (Scopus = 124, EBSCOhost = 14, Ovid Medline = 04). Two reviewers independently assessed all articles for inclusion or exclusion based on the title and abstract. 18 articles (EBSCOhost = 14 and Ovid Medline = 04) were removed due to duplication and 28 articles (reviews = 23, book = 02, book chapter = 02 and conference paper = 01) were excluded due to not being primary studies. After primary screening of abstracts, 96 articles remained. 84 of these articles were excluded because it did not contain information or outcomes related to phytoestrogenic effect of Labisia pumila and postmenopausal diseases. Twelve articles were retrieved for further assessment and data extraction. Differences of opinion between the reviewers regarding the inclusion or exclusion of the full articles were resolved by discussion. The remaining 12 articles fulfill all inclusion and exclusion criteria and were included for the purpose of this review.
Study characteristics

The summary of the characteristics of all studies is displayed in Table 1. All studies were published between the year 2008 - 2015 which consisted of eleven animal studies and one human study. Based on the types of post-menopausal diseases, 7 studies focused on osteoporosis23-25,28,30-32, 3 focused on metabolic disorders26,27,29 and two studies on cardiovascular diseases42,43,34. All animal studies used rat as the experimental model. The human study had used female patients who had been post-menopausal for at least 6 months. All studies were conducted using experimental design which compared the outcome of Labisia pumila treated groups with the control or sham group. Labisia pumila var. alata was used in all the studies using dried, powdered or fresh Labisia pumila processed from aqueous extract. Female rats were used in all of the studies with ovariectomized rat model used in all except, one study using polycystic ovary syndrome control rats29. Some rats were approximately 3 months old and 200-250 gm in body weight23,25,28 and some were 3-5 months30-32. Two studies26,27 stated 4 weeks old rats and another two studies29,33 used 9 weeks and 6 months old rats, respectively. Sample size in all animal studies was mentioned though the number of sample size was different from each other. Duration of treatment for rats depended on experimental design of individual study.

Phytoestrogenic effects of LP for animal study

Eleven animal studies were included in this paper. Of the seven animal studies on osteoporosis, Fathilah et al.25 analyzed structural, dynamic and static bone histomorphometric parameters and found that Labisia pumila extract had been able to improve all parameters significantly. In another study, Labisia pumila could protect bone against estrogen deficiency induced changes by regulating Osteoprotegerin (OPG), Receptor Activator of Nuclear Factor kappa B Ligand (RANKL), Macrophage Colony Stimulating Factor (MCSF) and Bone Morphogenetic Protein 2 (BMP 2) gene expressions23. It was found that Labisia pumila had the potential to protect against osteoporotic fractures in the post-menopausal or estrogen deficient state24. Study by Shuid et al.28 demonstrated that Labisia pumila was able to prevent

<table>
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<th>Outcomes</th>
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<tr>
<td>Fathilah SN, et al.23</td>
<td>Eight weeks in vivo animal study 32 female Wistar rats (3 months old and 200-250 gm) were divided into 4 groups.</td>
<td>† RANKL gene expression. † OPG &amp; BMP-2 gene expression in treated groups than control groups.</td>
<td>LPva may protect bone at estrogen deficient state.</td>
</tr>
<tr>
<td>Fathilah SN, et al.24</td>
<td>Eight weeks in vivo animal study 32 female Wistar rats (3 months old and 200-250 gm) were divided into 4 groups. The biomechanical properties of the femoral bones were assessed.</td>
<td>† Significantly of biomechanical properties such as load, stress, strain and modulus elasticity in treated groups than control groups.</td>
<td>Improved osteoporotic fractures at estrogen deficient state.</td>
</tr>
<tr>
<td>Fathilah SN, et al.25</td>
<td>Eight weeks in vivo animal study 32 female Wistar rats (3 months old and 200-250 gm) were divided into 4 groups. Duration of treatment is 8 weeks. Bone histomorphometry parameters such as structural, static and dynamic were assessed.</td>
<td>Structural, static and dynamic parameters were positively result in treated groups than control groups.</td>
<td>Protect osteoporosis at estrogen deficient state.</td>
</tr>
<tr>
<td>Fazliana M, et al.26</td>
<td>Thirty days in vivo animal study 42 female Sprague Dawley rats (4 weeks old) were divided in six groups. Plasma CORT levels and HSD11B1 protein levels were measured.</td>
<td>† Plasma CORT levels and † significantly HSB11B1 protein levels in treated groups than control groups.</td>
<td>LPva may contain compounds with estrogenic activities.</td>
</tr>
<tr>
<td>Fazliana M, et al.27</td>
<td>Thirty days in vivo animal study 42 female Sprague Dawley rats (4 weeks old) were divided in six groups. Plasma leptin &amp; adipokine levels and mRNA expression of adipokine tissue were measured.</td>
<td>† Significantly plasma leptin levels and † mRNA gene expression in treated groups than control groups.</td>
<td>Regulated body weight at estrogenic state.</td>
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changes in bone biochemical markers but unable to prevent bone calcium loss using post-menopausal osteoporosis rat model. In the study by Effendy et al., rats with post-menopausal osteoporosis supplemented with *Labisia pumila* were able to induce bone strength and prevent bone loss. *Labisia pumila* has the potential to be used as an alternative treatment and prevention of post-menopausal osteoporosis. Of the three animal studies on metabolic disorders, Fazliana et al. investigated plasma corticosteroid (CORT) levels, RNA quantification, cDNA and cRNA synthesis, cRNA fragmentation and hybridization reactions, hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1) proteins identification from the microarray and real-time RT-PCR in rat model induced by *Labisia pumila* extract. The extract increased the protein levels in both adipose and liver tissues and decreased circulating CORT levels of treated groups in estrogen deficiency state.

### Table 1—Characteristics of studies included in the review

<table>
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<th>Authors</th>
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<tr>
<td>Manneras L, et al.²⁹</td>
<td>Fourteen weeks <em>in vivo</em> animal study</td>
<td>↑ Plasma resistin level and Improved lipid profile &amp; insulin levels in treated groups than control groups. No significant changes of body composition and adipocyte size among the groups</td>
<td>Regulated body metabolites</td>
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<tr>
<td>Effendy NM, et al.³⁰</td>
<td>Nine weeks <em>in vivo</em> animal study</td>
<td>↑ Bone strength parameters such as maximum load, displacement, stiffness, stress, and Young Modulus in treated groups than control groups</td>
<td>Induced bone biomechanical changes at estrogenic state</td>
</tr>
<tr>
<td>Effendy NM, et al.³¹</td>
<td>Nine weeks <em>in vivo</em> animal study</td>
<td>↑ Significantly of SOD and GPx levels and significantly MDA levels in treated groups than control groups</td>
<td>Prevent bone loss at estrogenic state</td>
</tr>
<tr>
<td>Effendy NM, et al.³²</td>
<td>Nine weeks <em>in vivo</em> animal study</td>
<td>↑ Significantly of connectivity density, trabecular bone volume, trabecular thickness, trabecular separation and trabecular number in treated groups than control groups</td>
<td>Revealed bone osteoporotic changes at estrogenic state</td>
</tr>
<tr>
<td>Al-Wahaib A, et al.³³</td>
<td>Three months <em>in vivo</em> animal study</td>
<td>↑ Aortic wall in treated groups than control groups. Elastic lamellae architecture was normal in treated groups than negative control.</td>
<td>Reduced cardiovascular risk at estrogenic state</td>
</tr>
<tr>
<td>Kadir AA, et al.³⁴</td>
<td>Six months <em>in vivo</em> human study</td>
<td>No significant changes in all parameters except TG levels between the groups ↓ significantly TG levels in treated group than Placebo control group</td>
<td>Maintained cardiovascular health</td>
</tr>
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†↑ Increased, ↓ Decreased, LPva = *Labisia pumila var alata*, BMP-2 = Bone Morphogenetic Protein-2, OPG = Osteoprotegerin, RANKL = Receptor Activator of Nuclear Factor kappa-B Ligand, MCSF = Macrophage-Colony Stimulating Factor, CORT = Corticosterone, HSD11B1 = Hydroxysteroid (11-beta) Dehydrogenase 1, CTX = C-terminal telopeptide of type 1 collagen, SOD = Superoxide dismutase, GPx = Glutathione peroxidase, MDA = Malondialdehyde, FBG = Fasting Blood Glucose, LDL = Low Density Lipoprotein, HDL = High Density Lipoprotein, TG = Triglycerides, LH = Luteinizing Hormone, FSH = Follicle Stimulating Hormone.
were increased and lipid profile was improved, while leptin mRNA expressions were decreased in the treated groups. In addition, Al-Wahaibi et al.\textsuperscript{33} investigated using \textit{Labisia pumila} extract on aorta of ovariectomized Sprague Dawley rats. They concluded that \textit{Labisia pumila} has the ability to modulate post-menopausal cardiovascular risk by changing aortic wall and elastic lamellae architecture similar to that of estrogen.

**Phytoestrogenic effects of LP for human study**

The human study included in this review is by Kadir \textit{et al.}\textsuperscript{34}, which was a pilot open-labeled study on cardiovascular risk during post-menopausal period of Malay women. The sample size was 63 participants aged 48 - 55 years with the body mass index ranging from 18 to 35 kg/m\textsuperscript{2} and had been post-menopausal for at least 6 months. After baseline studies were completed, subjects were randomly assigned to 6 months treatment with either: 1) Placebo sachets (n = 34); 2) \textit{Labisia pumila} (280 mg/day for 6 months, 140 mg x 2 sachets; n = 29); subjects ingested their study medication (placebo or \textit{Labisia pumila} sachets) daily at night for 6 months. Blood samples to measure fasting glucose levels, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol levels as study outcomes were taken at baselines and at two-month intervals. The subjects were followed up every 2 months for the total duration of 6 months. After the 6 months follow up trial with placebo and 280 mg \textit{Labisia pumila}, results showed similar in all baseline values except the cardiovascular risk factors and hormonal changes. The adjusted mean of TG in \textit{Labisia pumila} subjects was significantly lower than placebo (1.4 vs. 1.9 mmol/L). There were also comparatively lower means of the fasting plasma glucose and total cholesterol in the \textit{Labisia pumila} treatment group. The study concluded that \textit{Labisia pumila} has the potential to be a useful phyto-supplement for maintaining cardiovascular health in menopausal women.

**Discussion**

Seven animal studies have demonstrated that \textit{Labisia pumila} was able to prevent bone loss and promote bone formation with similar efficacy to ERT\textsuperscript{23-25,28,30-32}. Bone biomechanical test suggested that \textit{Labisia pumila} enhanced both extrinsic parameters (load) and intrinsic parameters of bone biomechanical properties and prevented the changes in bone biochemical markers in ovariectomized rats\textsuperscript{24,28}. It also induced the bone strength parameters such as maximum load, displacement, stiffness, stress and Young Modulus in both ERT and \textit{Labisia pumila} supplemented ovariectomized rats\textsuperscript{30}.

Findings on bone histomorphometry parameters of ovariectomized rats concluded that \textit{Labisia pumila} almost completely restored the deteriorations of the bone due to estrogen deficiency\textsuperscript{25,32}. Improvements of these parameters could be due to the positive regulation of bone formation activities and the reduction of bone resorption through modification of the RANKL, OPG, MCSF and BMP-2 by \textit{Labisia pumila}\textsuperscript{33}. Aging and hormonal disturbances in post-menopausal women can be related to oxidative stress. The study by Signorelli \textit{et al.}\textsuperscript{35} has reported that oxidative stress is higher in postmenopausal women, indicating that antioxidant status may be related to estrogen deficiency. Antioxidants may play an important role in suppressing the development of osteoporosis\textsuperscript{37}. Due to estrogen reduction following menopause, the body is subjected to a high level of free radicals and disruption of the oxidative stress defense system. This condition was shown to be associated with decreased bone mass and quality of bone in numerous studies\textsuperscript{38}. Previous study by Jagger \textit{et al.}\textsuperscript{39} has confirmed that thiol antioxidant defense is downgraded in rodent bone for estrogen deficiency state, resulting in accelerated bone loss. Effendy \textit{et al.}\textsuperscript{31} demonstrated that \textit{Labisia pumila} supplementations may reduce oxidative stress which in turn may prevent bone loss via its antioxidative property. The bones of the ovariectomized rat model were also shown to be protected from bone loss with the presence of potent anti-oxidants such as vitamin E\textsuperscript{41}. These studies have suggested that oxidative stress may be responsible for bone loss although inflammation may play a role in the pathogenesis\textsuperscript{43}. Either way, \textit{Labisia pumila} may be effective as it has both anti-inflammatory and anti-oxidative properties\textsuperscript{44}.

There were three animal studies investigating postmenopausal metabolic disorder. Fazliana \textit{et al.}\textsuperscript{26} investigated the effects of \textit{Labisia pumila} on body weight change, HSD11B1 expressions and CORT level in ovariectomized rats. \textit{Labisia pumila} treated rats showed less weight gain and had significant down-regulation of protein levels of HSD11B1 and CORT levels in both liver and adipose tissue.
Reduction of HSD11B1 expression cause reduced intrahepatic glucocorticoid action or increases insulin sensitivity. In another study by Fazliana et al., the effects of Labisia pumila was compared to ERT on body weight gain, uterus weight, protein levels of adipokines and adipose tissue mRNA in ovariectomized rats. The results showed that Labisia pumila has uterotrophic effect and regulates body weight gain by control of leptin and resistin secretion and adipokines expression in adipose tissues. In addition, Manneras et al. have studied the effect of Labisia pumila extracts on body composition and metabolic features in female rats. Before puberty, rats were treated continuously with dihydrotestosterone to induce polycystic ovarian syndrome (PCOS). Labisia pumila was able to increase uterine weight and insulin sensitivity measured by euglycemic hyperinsulinemic clamp. Plasma resistin levels were increased and lipid profile was improved in Labisia pumila treated rats. In adipose tissue, Labisia pumila decreased leptin mRNA expression but did not change the expression of adiponectin and resistin. No effects on body composition, adipocyte size, or plasma leptin levels were observed. Labisia pumila increased uterine weight and develops insulin activity and lipid profile in PCOS rats without affecting body composition which may indicate estrogenic effects of Labisia pumila.

With regards to cardiovascular diseases, there was an animal study and one in vivo human study. In the animal study, Labisia pumila maintained the elastic lamellae architecture of the ovariectomized rat aorta in a manner comparable to that of the normal rats. Phytoestrogen intake was also reported to be associated with a smooth structure of aorta lamellae. Thus, Labisia pumila would have a possible role in modulating postmenopausal cardiovascular risks, based on the estrogenic activity of the extract. The study of Kadir et al. on the effects of Labisia pumila on 63 women volunteers demonstrated that Labisia pumila has a beneficial effect of reducing triglyceride values. A major component of Adipose tissue is fat in the form of triglycerides. Excessive adipocytes are associated with estrogen deficient state that leads to cardiovascular risk and weight gain. Therefore, Labisia pumila may be a useful phyto-supplement for maintaining cardiovascular health in menopausal women.

Strength and limitations of this study

Studies on the effects of Labisia pumila on osteoporosis, metabolic disorders and cardiovascular diseases have shown some promising results in terms of protection against specific diseases. In the quest of seeking newer alternative treatments for postmenopausal diseases, a critical review is highly relevant. This study identified 11 research articles and to the best of our knowledge; this is the first critical review that highlight the effects of Labisia pumila extract on post-menopausal diseases. We have included animal and human studies in trying to have a better overview of the most recent and reliable evidence presented on this subject.

Some limitations were identified in this review. The Labisia pumila extraction method and sources used were not standardized. There was only one human study available and it focused on cardiovascular disease with a reduction in triglyceride value changes. The results generated were limited by the small number of volunteers but was able to provide highly relevant and important initial data.

There was no in vitro study in this review to investigate for the prevention and/or treatment of post-menopausal diseases.

Recommendations

The Labisia pumila extractions used for future studies need to be standardized to allow direct comparison of the study results. More studies are required to identify the precise Labisia pumila active ingredients and the exact molecular mechanisms involved in preventing and treatment of post-menopausal diseases. This should be followed by well-designed human studies. These steps will ensure better future meta-analysis of the study results to give a better understanding and true picture of the effects of Labisia pumila on post-menopausal diseases.

Conclusion

Labisia pumila has shown good outcomes on postmenopausal diseases especially for osteoporosis, metabolic disorders and cardiovascular diseases. Labisia pumila has elicited a high potential as a safe treatment and preventive agent for post-menopausal diseases and a good alternative to estrogen replacement therapy. Further studies are required to determine the bioactive component(s) and the exact mechanisms responsible for therapeutic activities, followed by more well designed human studies.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.
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AHMAD et al.: PHYTO-ESTROGENIC EFFECTS OF LABISIA PUMILA FOR THE PREVENTION AND TREATMENT


