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Review Article
Therapeutic Effects of *Labisia pumila* on Estrogen-deficiency Related Disorders: An Evidence Based Review

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Abstract

This study explores the therapeutic effects of *Labisia pumila* (LP) in protection against estrogen-deficiency disorders. A systemic review of the literatures was conducted to identify the relevant studies on LP. A comprehensive search was conducted in Medline via Ebscohost and Scopus for relevant studies published between the years of 1946-2014. The main inclusion criteria were research articles published in english, studies had to report the association or the therapeutic effects of LP in various pathological conditions which are related to lifestyle variables, aging or experimentally-induced conditions. The literature search identified 97 potentially relevant articles, whereby 11 met the inclusion criteria. Altogether, there were nine animal studies and two human studies included in this study. There were eleven articles on protection against estrogen-deficiency disorders. In conclusion, LP may be used as an alternative treatment of estrogen deficiency orpost-menopausal-related diseases.

Key words: *Labisia pumila*, estrogen deficiency, menopause, aging

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Natural product-based medicine has been used widely for many years probably since thousands of years ago. The medicinal use from natural sources such as plants, herbs and fruits has evolved with discovery of alternative medicine. Our earliest ancestors discovered the importance of natural product in therapeutic use for relieving pain, wound healing and treating injuries[1].

Labisia pumila (LP) from Myrsinaceae family is locally known in Malaysia as kacip fatimah. Other common names are kunci fatimah, selusoh fatimah, rumput fatimah and akar fatimah. There are three types of LP, which are varalata, var pumila and var lanceolata[2]. Decoction of the whole plant of LP is traditionally used by generations of Malay women for women health purposes such as to treat menstrual irregularities, improve fertility, facilitate child birth and as postpartum medicine[3]. Recently, there is a high demand in the application of LP as an alternative treatment, especially with reports on the side effects of several synthetic drugs.

Bioactive compounds discovered in aqueous extracts of LP include flavanoids, ascorbic acid, β-carotene, anthocyanin and phenols[4]. The LP was reported to have a wide range of biological activities including antioxidant, anti-inflammatory, antimicrobial, antifungal and antinociceptive[5-8]. Three flavonols (quercetin, myricetin and kaempferol), two flavanols (catechin and epigallocatechin) and nine phenolic acids were identified from the active fraction of LP by ultra-performance liquid chromatography/ electrospray-mass spectrometry (UPLC–ESI-MS/MS)[9].

Interestingly, LP has been shown to have higher antioxidant activity than ascorbic acid[10]. The more superior antioxidant activities of LP were associated with its high content of phenolic and flavonoids compounds[9]. Recently, Effendy and Shuid[11] confirmed that LP have increased the antioxidant enzyme levels and reduced malondialdehyde (MDA) level, which is the end product of lipid peroxidation and marker of oxidative stress.

With the growing interest in the potential health benefits of phytoestrogens, many reports were published on the beneficial effects of phytoestrogens on post-menopausal women. Phytoestrogens have a pair of hydroxyl group and a phenolic ring which are required for binding to Estrogen Receptors (ER)[12]. They bind to Estrogen Receptor (ER) at low levels compared to endogenous estrogen. Once bound to a receptor, phytoestrogens may exert both estrogenic and anti-estrogenic effects[13]. It was also reported that LP may act as a Selective Estrogen Receptor Modulators (SERMs) and exerted actions on certain tissues. To date, several studies have confirmed the phytoestrogenic properties of LP. The bioactive compound in LP was able to displace estradiol and binds to antibodies against estradiol[13]. The ethanolic extract of the root of LP exhibited significant estrogenic effect on human endometrial adenocarcinoma cells (Ishikawa var 1 cell line), resulting in enhanced secretion of alkaline phosphatase[14].

The LP was able to increase estrogen and testosterone levels and suppress Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) in ovariectomised rats. This resembles the action of endogenous estrogen[15]. It is well documented that LP has profound phytoestrogenic effects on various estrogen-deficiency related diseases such as insulin resistance, cardiovascular diseases and osteoporosis. The phytoestrogenic properties of LP have also been demonstrated by its uterotrophic effects and body weight regulation. The latter was achieved by modulating the secretions of leptin and resistin and expressions of adipokines in adipose tissue[16].

Estrogen is pivotal to the regulation of adipocyte differentiation, skeletal growth and bone homeostasis in both men and women. In humans, 17-β-estradiol (E2) is the most potent estrogen followed by estrone (E1) and estriol (E3). The effect of estrogens are mediated by two nuclear receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ)[17]. Estrogen plays a major role in distribution and deposition of adipose tissue. This tissue is an endocrine organ that is important for energy storage, regulation of fat mass, lipid metabolism, immune system and reproduction. Human subcutaneous and visceral/intraabdominal adipose tissues express both ERα and ERβ receptors[18,19] indicating that estrogen could directly affect adipose tissue metabolism. Estrogen reduces tissue adiposity by promoting the use of lipid as fuel. Estrogen deficiency results in adipose tissue proliferation, particularly in visceral fat, which are linked with obesity, cardiovascular diseases and metabolic disorders. Studies have shown that ovariectomised rats had increased food intake and gained body weight, which were reversed with estrogen[16]. Thus, adipose tissue regulation by estrogens is important to prevent the related complications.

Estrogen deficiency is also associated with insulin resistance, characterized by a decrease in the uptake of glucose by insulin target tissues such as adipose tissue and skeletal muscle. Adipose tissues release adipokines to modulate lipid and glucose metabolism. There are two types

of adipokines, the adipose-tissue specific such as leptin, resistin and adiponectin and non-tissue specific such as Plasminogen Activator Inhibitor-1 (PAI-1) and Tumor Necrosis Factor (TNF-α)[16]. Leptin, resistin and adiponeptin are very important biomarkers for pathogenesis of insulin resistance, which leads to obesity. Leptin controls the amount of body fat stored by regulating food intake and energy expenditure, via the hypothalamic response. Estrogen increased leptin sensitivity by controlling the expression of leptin-specific receptors. Disruption of leptin receptor expression in the pancreas directly affects β-cell growth and function, thus resulting in lower insulin production[20].

Aorta stiffness occurs with aging and worsens the arterial function, predisposing an individual to cardiovascular diseases including coronary artery disease. Statistical data showed that more than 30% of the female population in Malaysia who is at risk of coronary artery disease was in menopausal state[21]. It was also found that the aortic wall thickness were increased and become less elastic in estrogen-deficient rat model[22]. Norhayati *et al.*[23] reported that total cholesterol and low density lipoprotein cholesterol were higher in menopausal women.

An important transcription factor for adipocyte differentiation is peroxisome proliferator activated receptor gamma (PPARgamma). The expression levels of PPARgamma was the highest in adipose tissue compared to other metabolic organs, such as skeletal muscle and liver[24]. Jeong and Yoon[25] demonstrated that estrogen downregulated troglitazone-activated PPARgamma actions on adipogenesis and adipocyte-specific gene expressions.

Phystoestrogen such as LP may be beneficial in treating endocrine and metabolic disorders such as Polycystic ovary syndrome (PCOS) and osteoporosis. The PCOS is a disease which is associated with ovulatory dysfunction, hyperandrogenism, polycystic ovaries, insulin resistance, abdominal fat and obesity[26]. Osteoporosis is a common bone disease[27], which is defined as a progressive systemic skeletal disease that characterized by low bone mass and microarchitecture deterioration of bone tissue with a consequent increase in susceptibility to bone fragility and fractures[28]. According to the World Health Organization (WHO), osteoporosis occurs when the bone mineral density falls more than 2.5 Standard Deviations (SD) below the standard reference for maximum bone mineral density of young adult females[29]. After the age of 35-40, the bone mass in females begin to decline slowly, followed by a dramatic bone loss after menopause due to estrogen deficiency or surgical ovariectomy. Bone mass in women is only two-thirds of that in men by the age of 50 years. The lower bone mass combined with high rate of bone loss, resulted in a higher incidence of osteoporosis in elderly women compared to men[30]. Osteoporosis can be classified into primary and secondary osteoporosis. Primary osteoporosis occurs in hypogonadal women and men. This may occur in women after menopause or amenorrhea due to obsessive exercise programs or anorexia nervosa. In men, androgen-deficiencies due to castration or other conditions may contribute to hypogonadal or primary osteoporosis. Primary osteoporosis is also associated with the normal aging process in women and men, typically after the age of 60-70[31].

A proper systemic review will provide brief descriptions and updates of the therapeutic effects of LP in protection against estrogen-deficiency disorders.

A systematic review of the literature was carried out to identify relevant studies on the therapeutic effects of LP. In order to conduct a comprehensive search of the health science journals, we used Medline via EBSCwwOhost (published between 1946 and March 2012) and Scopus (published between 1946 and 2012). The search strategy involved a combination of the following four sets of key words: (1) Kacip fatimah or *Labisia pumila**, (2) Anti* or treatment* or medic* or cure, (3) Therapeutic and (4) Effect* or activit*.

SELECTION OF RESEARCH ARTICLES

The results were limited to studies that were published in english language and have abstracts. Studies with these characteristics were included: (1) Reported the therapeutic effects of LP and the pathological changes related to estrogen deficiency and (2) The pathological changes should be related to lifestyle variables, aging or experimentally-induced conditions. Review articles, news, letter, editorials or case studies were excluded from the review.

DATA EXTRACTION AND MANAGEMENT

Papers were screened in three phases before included in the review. First, any paper that did not match the inclusion criteria based solely on the title was excluded. In the second phase, abstracts of the remaining papers were screened and papers that did not meet our inclusion criteria were excluded. In the final phase, the remaining papers were read thoroughly to exclude any paper that did not meet our inclusion criteria. Duplicates were removed and the remaining papers were again screened. The inclusions of full papers were agreed by

reviewers before the data extraction phase. Any differences in opinions were resolved through discussion between the reviewers. In order to standardize the data collection, all data extraction was performed independently with the use of a data collection form. The following data were recorded from the studies: (1) The therapeutic effect of LP, (2) The type of study, (3) The type of LP extract used in the study, (4) A brief description of the sample population of the study, (5) A brief description of the methods used in the study, (6) The brief description of the results of the study and (7) Comments and conclusion of the study.

The search of literature found 21 articles in total after filtering all the inclusion and exclusion criteria. At the beginning, 40 articles had potential to be reviewed. By screening the titles and abstracts, 9 papers were excluded as they reported studies which did not focus on LP as the primary study or they were review articles. The process of obtaining the articles and the flow chart is shown in Fig. 1.

STUDY GROUP AND CHARACTERISTICS

The articles obtained were discussed according to the study of interest, which was protection against estrogen-deficiency disorders. There were 11 articles on protection against estrogen-deficiency disorders. The summary of all the results were discussed in Table 1.

The types of LP extracts used were given attention as they might produce different results. All the extractions were done using the LP plant sample. No commercialized product of LP was used in all the studies selected. In fact, several studies have examined the effects of the different parts of LP plant on the same parameters. This systematic review includes both *in vitro* and *in vivo* studies. The *in vivo* studies involved human and animal studies. There may be some difficulties in comparing the studies because of the different methodologies and sample populations.

In this review, various therapeutic uses of LP were discussed. The LP is known to have phytoestrogenic effects which produce similar effects to estrogen. It is well known that phytoestrogenic plants such as LP may have both estrogenic and anti-estrogenic effects and thus, may act as Selective Estrogen Receptor Modulators (SERMs). The LP is safe to be used as alternative treatment for estrogen-deficiency related diseases[23], particularly in postmenopausal woman. The actions of LP in relation to the pathogenesis or mechanism of estrogen deficiency including body weight gain, increased adipocity, insulin resistance, cardiovascular disease and osteoporosis have been well studied.

In most of the animal studies, ovariectomised rat was used as the post-menopausal model to examine the effects of LP on estrogen-deficiency related diseases. Human studies

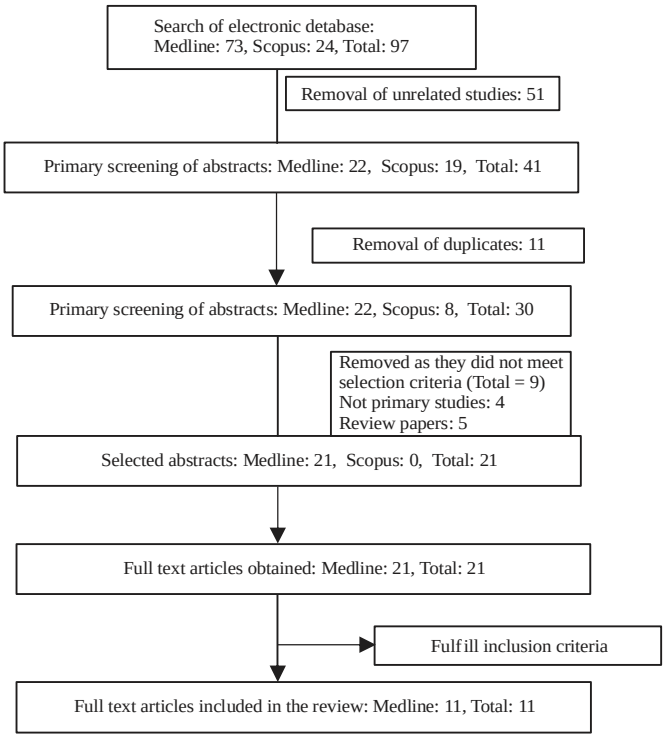

Fig. 1: Flow chart to show the selection process of the articles in this study

Table 1: Summary of therapeutic studies of *Labisia pumila* (LP)

Therapeutic uses	References	Type of study	LP extract	Sample population	Methodology	Result	Comments/outcomes
Estrogen deficiency: Body weight regulation	Fazliana *et al.*[16]	Animal study	Hot water extraction of LPva	Ovariectomised Sprague-Dawley rats	Rats were administered orally 10 (Lpva 10), 20 (Lpva 20) or 50 (Lpva 50) mg kg^{-1} day^{-1} of LPva, parameters: • Uterine to body weight ratio, plasma glucose and insulin • Food intake • Plasma levels of adipokines (leptin, resistin and adiponectin) • Gene expressions of adipokines	• Lpva 50-treated OVX rats showed lower weight gain, higher leptin level and expression and lower plasma resistin • There was a dose dependent increase in uterus to body weight ratio with Lpva treatment	LPva exerted uterotrophic effect and regulated body weight gain by modulating secretion of leptin and resistin and adipokines expressions
Estrogen deficiency: Body weight regulation	Fazliana *et al.*[22]	Animal study	Hot water extraction of LPva	Ovariectomised Sprague-Dawley rats	Rats were administered orally 10 (Lpva 10), 20 (Lpva 20) or 50 (Lpva 50) mg kg^{-1} day^{-1} of Lpva, parameters: • Body weight • Protein and gene expressions of HSD11B1 • Plasma corticosterone	LPva-treated rats showed • Less weight gain • Down-regulation of HSD11B1 expressions in liver and adipose tissues • Lower corticosterone level	LPva extract reduced weight gain by decreasing HSD11B1 expressions and corticosterone level in adipose and liver tissues
Estrogen deficiency: Cardiovascular risk	Al-Wahaibi *et al.*[36]	Animal study	Hot water extraction of LPva	Ovariectomised Sprague Dawley rats	Parameters: Elasticity and thickness of the aortic wall	LPva reduced the thickness of aortic wall	LP modulated cardiovascular risk in estrogen deficiency
Estrogen deficiency: Post-menopausal health	Norhayati *et al.*[23]	Human study	LP water extract	197 subjects	Parameters: • Quality of life profile • Hormonal profile • Safety profile • Cardiovascular risk profile • Total bone mineral density • Adverse events	• LP group showed improved memory/concentration, vasomotor symptoms and menstrual symptoms • LP group had lower Total Cholesterol (TC) and Low Density Lipoprotein Cholesterol (LDLC) • Two adverse events (Aes) occurred in LP group (cough and headache)	LP water extract was safe and could improve the quality of life and cardiovascular risks factors (TC and LDL-C)
Estrogen deficiency: Post-menopausal health	Kadir *et al.*[39]	Pilot human study	LPva water extract was packed in a sachet form	63 patients	Menopausal symptoms were assessed at baseline and at 6 months, parameters: • Blood pressure • Body mass index • Waist circumference • Fasting blood sugar • Lipid profile • Hormonal profile (follicle stimulating hormone/luteinizing hormone/estradiol)	LPva lowered triglycerides levels	LP reduced e triglyceride values in postmenopausal women

Table 1: Continue

Therapeutic uses	References	Type of study	LP extract	Sample population	Methodology	Result	Comments/outcomes
Estrogen deficiency: Osteoporosis	Fathilah *et al.*[4]	Animal study	LPva root extract	Ovariectomised Wistar rats	Parameter: Bone-related gene expressions	• LPva extract prevented ovariectomy-induced elevation of RANKL and OPG genes expressions • LPva prevented ovariectomy-induced reduction of BMP-2 gene expression	LPva prevented estrogen-deficient osteoporosis by regulating RANKL, OPG and BMP-2 expressions
Estrogen deficiency: Osteoporosis	Fathilah *et al.*[41]	Animal study	LPva root extract	Ovariectomised Wistar rats	Parameters: • Bone histomorphometry structural parameters • Bone histomorphometry static parameters • Bone histomorphometry dynamic parameters	• LPva restored the bone structural measurement of ovariectomised rats • LPva prevented the bone static parameter changes induced by ovariectomy • LPva prevented the bone dynamic parameter changes induced by ovariectomy	LP prevented the bone histomorphometric changes-induced by estrogen deficiency
Estrogen deficiency: Osteoporosis	Fathilah *et al.*[43]	Animal study	LPva root extract	Ovariectomised Wistar rats	Parameters: • Bone biomechanical test • Extrinsic parameter • Intrinsic parameter	• LPva prevented ovariectomy-induced reduction in the bone strain and modulus of elasticity	LPva promoted bone strength to prevent osteoporotic fractures
Estrogen deficiency: Osteoporosis	Shuid *et al.*[42]	Animal study	LPva root extract	Ovariectomised Wistar rats	Parameters: • Biochemical analysis: Osteocalcin and C-terminal telopeptide of type 1 collagen (CTX) • Bone calcium content measurement	• LPva increased the osteocalcin levels • LPva reduced the CTX levels	LP prevented the bone marker changes-induced by estrogen deficiency
Estrogen deficiency: Bone/osteoporosis	Effendy and Shuid[11]	Animal study	LPva whole plant extract	Ovariectomised Sprague-Dawley rats	LPva at doses of 20 (LP 20) and 100 (LP 100) mg kg^{-1}, parameters were measured at 3rd, 6th and 9th weeks of treatment: • Bone superoxide dismutase (SOD) level • Bone glutathione peroxidase (GPx) level • Bone lipid peroxidation (MDA) level	• LPva increased the bone SOD level • LPva increased the bone GPx level • LPva reduced the bone MDA level • LP at the dose of 100 mg kg^{-1} and 9th week of treatment were the best LP treatment regimen	LPva increased the bone anti-oxidative enzymes and reduced the oxidative stress in estrogen-deficient rat model
Estrogen deficiency: Bone/Osteoporosis	Effendy *et al.*[40]	Animal study	LPva whole plant extract	Ovariectomised Sprague-Dawley rats	LPva at doses of 20 (LP 20) and 100 (LP 100) mg kg^{-1}, Micro-CT analysis of femoral bones were carried out at 3rd, 6th and 9th weeks of treatment	• Rats treated with LPva showed the best bone microarchitecture • LPva at the dose of 100 mg kg^{-1} and 9th week of treatment were the best LP treatment regimen	LPva promoted the bone microarchitecture of estrogen-deficient rat model

were carried out to investigate the efficacy and safety of LP extract on the quality of life, menopausal symptoms, cardiovascular risk factors and hormonal profiles of post-menopausal women.

ESTROGEN-DEFICIENCY

Body weight regulation: Estrogen-deficiency was associated with increased food intake and body weight gain. Kishida *et al.*[32] demonstrated that estrogen replacement in ovariectomised rats were able to reduce food intake and body weight. Fazliana *et al.*[16] studied the LP protection against body weight and adipocity related to estrogen deficiency. It was proven that LP was able to exert uterotrophic effect and regulates body weight gain. These were achieved by modulating the secretion of adipokines such as leptin, resistin and adiponectin in adipose tissues[16]. Adipokines are adipose tissue-derived hormones which play a central role in signalling to organs of metabolic importance including brain, liver, skeletal muscles and the immune system[33]. Leptin is responsible for controlling appetite and hence, the body weight. The LP supplemented to ovariectomised rats were able to elevate the leptin levels and reduce their body weight[34]. On the other hand, LP extract may regulate body weight by regulating glucocorticoid levels. Hydroxysteroid (11-β) dehydrogenase type 1 (HSD11B1) and corticosterone are hormones that regulate glucocorticoid levels. The HSD11B1 reduces inactive 11-dehydrocorticosterone to the active corticosterone that binds to glucocorticoid receptors. Reductions of these two biomarkers in ovariectomised rats affected glucose homeostasis, insulin action and adipocity, leading to obesity and type II diabetes[35]. The LP extract was found to reduce HSD11B1 and corticosterone level expressions in both adipose and liver tissues, thus reducing the body weight[22]. As a whole, *in vivo* study showed LP was able to exhibit uterotrophic effect and regulates body weight gain by modulating adipokines secretion and regulating glucocorticoid levels.

Reduce risks of cardiovascular disease: Al-Wahaibi *et al.*[36] evaluated the effects of LP var alata (Lpva) to the cardiovascular risks associated with estrogen deficiency[36]. The LPva treatment was found to maintain the elastic lamellae architecture of ovariectomised rats. This suggested that LPva was able to modulate cardiovascular risk contributed by estrogen deficiency. There are similar studies using other phytoestrogen such as soy isoflavones, which were also found to improve the endothelial-dependent vascular activity and arterial elasticity[37,38]. Kadir *et al.*[39] showed that only triglycerides levels was significantly reduced in postmenopausal subjects receiving LP for 6 months compared to those receiving placebo[39].

Postmenopausal health: There were two studies conducted on the effects of LP on postmenopausal health[23,39]. The effects of LP were not seen on the menopausal symptoms and hormonal profiles of the subjects[39]. The lack of findings may be contributed by the small number of participants. In addition, longer duration of study may be required before the full effects of LP could be seen. In comparison[23] it is reported that treatment with LP for 4 months produced improvements in memory or concentration, vasomotor symptoms, menstrual symptoms and sleep problems. There were also improvements in the cardiovascular parameters but no changes in the relevant hormones such as Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and 17 β-estradiol. The LP was shown to be safe and effective for improving quality of life and cardiovascular risk factors including total cholesterol and low-density lipoprotein cholesterol[23]. The best regiment of LP for post-menopausal women was a daily dose of 400 mg and the effects could be seen after 4 months.

ANTI-OSTEOPOROTIC EFFECTS OF LP

As for the studies on osteoporosis, all the six animal studies demonstrated that LPva has potential as an alternative to ERT for treatment and prevention of estrogen-deficient osteoporosis[40]. In addition, LP did not cause any side effects and safe when used within its therapeutic doses[4,23]. This was much better than ERT, the current treatment and prevention of postmenopausal diseases, which were reported to increase the risks of ovarian cancer, breast cancer, heart attack, thromboembolism, strokeand Alzheimer's disease[4].

Bone histomorphometric studies by Fathilah *et al.*[4] indicated that LPva was as effective as ERT in protecting the bone structure from the deleterious effects of ovariectomy[41]. Both LP and ERT treatments have led to high number of osteoblast on bone surface and increase in bone formation. The dynamic parameters showed that both LP and ERT promoted the formation of the complete double-labelled surface as opposed to the incomplete single-labelled surface

in ovariectomised-control rats. These positive changes were also reflected by the elevated osteocalcin level and lowered CTX level, which indicated that LPva was as effective as estrogen in preventing the bone marker changes induced by estrogen deficiency[41]. Furthermore, a time and dose-dependent micro-computered tomography analyses of ovariectomised rats demonstrated that LP treatment resulted in denser trabecular bone microarchitecture, higher connectivity density, bone volume and trabecular number but less trabecular separation[42]. In terms of bone function, all the changes induced by LP were accompanied by increased bone strength, better ability to receive load, stress and strain and high modulus of elasticity[11].

Several studies have elucidated the mechanisms of bone protection offered by LP. Fathilah *et al.*[43] measured the factors involved in bone remodeling to investigate the bone-protective mechanism of LP. The LPva was shown to stimulate OPG production and down-regulate RANKL gene expression. The RANKL, which encoded the tumor necrosis factor receptor superfamily (TNFRSF) 11A and TNFSFF11 genes was an important factor in controlling bone resorption[4,44].

The LP also increased the anti-oxidative enzymes and reduced oxidative stress in an estrogen-deficient rat model. It increased the levels of superoxide dismutase (SOD), glutathione peroxidase (GPx) and lowered the level of malondialdehyde (MDA)[40]. These enzymatic antioxidants scavenged free radicals and protected against harmful effects of free-radicals[45], while MDA is a by-product of lipid peroxidation and act as the marker of lipid peroxidation[46]. The bone protective effects of LP may be contributed by its phytoestrogenic and anti-oxidant properties, combined with its ability to regulate factors involved in bone remodeling.

CONCLUSION

All the studies concluded that LP was effective in prevention and treatment of diseases related to estrogen deficiency. These abilities may be contributed by its pleurotropic actions including phytoestrogenic and anti-oxidant capabilities. The LP has potential to be developed as alternative treatment of estrogen deficient or postmenopausal-related diseases.

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