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Institutionen för Molekylär Medicin och Kirurgi

**Studies on *Labisia pumila* var. *alata* extract with
phytoestrogenic effects: impact on biological
activities and gene expression**

AKADEMISKA AVHANDLING

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ABSTRACT

In Malaysia, *Labisia pumila* var. *alata* (LPva) has been used by women for generations. Traditionally, the plant is boiled, either alone or in decoction with other herbs. It is claimed to have health benefits such as to contract the uterus after childbirth, allay painful menstruation and irregular periods and to generally alleviate fatigue. Therefore, we aimed to investigate the scientific basis of LPva phytoestrogenic activities in different animal models and cell lines.

In **Paper I**, we investigated the effects of a standardized water extract of LPva (10, 20 and 50 mg/kg body weight/day) and compared to estrogen replacement (ERT), on body weight gain, uterus weight, adipose tissue mRNA and protein levels of adipokines in ovariectomized (OVX) female Sprague-Dawley rats. After a month of oral treatment, ERT- and LPva-treated OVX rats showed significantly less weight gain compared to untreated OVX rats. Ovariectomy caused plasma leptin levels to decrease significantly but when treated with LPva or ERT, plasma leptin and mRNA levels increased to levels higher or comparable to that seen in the sham operated control rats (SHAM). In contrast, the elevated plasma resistin concentrations in OVX rats were significantly reduced in rats given ERT and LPva extracts. The uterus to body weight ratio of untreated OVX rats was significantly low compared to SHAM, but showed dose-dependent increase upon treatment with LPva. The study provides evidence that LPva exerts uterotrophic effect and regulates body weight gain.

In **Paper II**, we evaluated the effects of LPva on 11-beta hydroxysteroid dehydrogenase type-1 (*Hsd11b1*) and corticosterone (CORT) expressions in OVX rats. *Hsd11b1* was chosen because it was highly expressed in a microarray analysis of OVX rat liver compared to SHAM. Using samples from **Paper I**, *Hsd11b1* expressions were measured and found that mRNA levels in liver of OVX rats were significantly increased when compared to SHAM and restored to normal level after treatment with LPva or ERT. In adipose tissues, the *Hsd11b1* mRNA level of OVX group was increased by 55 % in comparison to SHAM, normalized in LPva. Protein levels of 11 β -HSD1 were down-regulated in both liver and adipose tissue of LPva- and ERT-treated rats, in comparison to OVX rats. CORT levels in OVX group increased significantly compared to SHAM. The results showed that the treatment with LPva normalized *Hsd11b1* mRNA expression and 11 β -HSD1 levels in OVX rats, in parallel with decreased CORT levels. Thus, LPva is useful for postmenopausal treatment based upon its regulation at body weight partially via inhibition of *Hsd11b1* expression in adipose tissue and liver.

In **Paper III**, we investigated the effect of LPva on body composition and metabolic features in a rat model of polycystic ovary syndrome (PCOS). LPva (50 mg/kg body weight daily) increased uterine weight (27%) and insulin sensitivity (36%) measured by euglycemic hyperinsulinemic clamp compared to control PCOS rats. Lipid profile was improved in LPva rats and plasma resistin levels were increased. In adipose tissue, LPva decreased leptin mRNA expression but did not affect expression of resistin and adiponectin. No effects on body composition, adipocyte size or plasma leptin levels were observed. Therefore, in this study, LPva increases uterine weight, indicating estrogenic effects, and improves insulin sensitivity and lipid profile in PCOS rats without affecting body composition.

In **Paper IV**, the effects of LPva treatment on urinary tract infection (UTI) were investigated in an infection model using uropathogenic *Escherichia coli* (UPEC) strain CFT073 and the bladder epithelial cell line, T24. Our results demonstrate that LPva treatment induced apoptosis and significantly reduced the number of intracellular *E.coli* in bladder epithelial cells. LPva-induced apoptosis was coupled with up-regulated expression of pro-apoptotic caveolin-1. LPva treatment down-regulated the expression of β 1 integrin as indicated by reduced levels of gene specific mRNA. However, LPva did not exhibit direct antimicrobial properties and did not influence antimicrobial peptide levels in cells. These findings suggest that LPva facilitates the exfoliation of infected bladder cells and may thereby mediate beneficial effects during UTI.

Key words: *Labisia pumila*, ovariectomy, PCOS, adipokines, apoptosis