Evaluation of Safety and Efficacy of Labeesity® for Weight Management and Fatigue in an Obese Female Patient with Hypothyroidism: A Case Report

Aman Shah Abdul Majid [A*], Elham Farsi [B], Natesan Vijayalakshmi [C], Syarifah Aisya Syed Amran [D], Mahibub Mahadmadsa Kanakal [E], Zarina Thasneem Zainudeen [F*]

Abstract

In this study, we aimed to evaluate the efficacy and safety administration of Labeesity® 125mg, an anti-obesity natural product supplement available in the market. A clinical obese female with medication-controlled hypothyroidism volunteered for this trial. The patient was supplemented with Labeesity® 125mg twice daily for 40 days. The hematological, serum biochemical, subject characteristic were recorded before and after treatment. When compared with the baseline reading, the treatment was favorable for weight loss, with hip and waist circumference reduction. It also improved the patient's general quality of life over the course of 40 days. There was no treatment related negative clinical symptoms except for mild bloating which dissipated after the second week of supplementation. Furthermore, there were no significant hematological and biochemical alterations, except for a slight fluctuation in uric acid. Labeesity® 125mg intake for the volunteer is assumed to be generally safe with moderate improvement in weight reduction, body composition and serum lipid profile. Longer period of observations on the effects of Labeesity 125mg would be required to evaluate if the positive effects seen would persist beyond 40 days of intervention. Therefore, strong evidence to support the potential effectiveness and long-term benefits of Labisia pumila extracts based products will require robust studies to be conducted utilizing larger patient numbers and over extended periods of time to rule out any potential toxic effects.

Key Words: *Labisia pumila*, Labeesity®, safety, efficacy, anti-obesity

Significance | *Labisia pumila* extracts based products will require robust studies to be conducted utilizing larger patient numbers and over extended periods of time to rule out any potential toxic effects.

*Correspondence: Assoc. Professor A.S. Abdul Majid at Centre for Natural Product and Angiogenesis Research, Department of Pharmacology, Faculty of Medicine, Quest International University, Perak, Malaysia.. Email: aman.shah@quip.edu.my and Zarina Thasneem Zainudeen at Advanced Medical and Dental Institute, Universiti Sains Malaysia, Penang, Malaysia., Email: zarinazainudeen@gmail.com

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Introduction

Worldwide increase in numbers of obese women among all populations and age groups has resulted in a significant increase risk in cardiovascular related mortality and morbidity. Obesity in women is associated with elevated risk of hypertension, metabolic syndrome, dyslipidemia, polycystic ovarian and systematic inflammation. Obesity has been introduced as the cause of many female cancers such as endometrial, postmenopausal breast cancer, also colon and kidney cancer. Female obesity occurs as result of many biological, hormonal and behavioral patterns (Kornstein & Clayton, 2010). Apparently, the endocrine system plays major role in obesity, as

Author Affiliation:
[A] Centre for Natural Product and Angiogenesis Research, Department of Pharmacology, Faculty of Medicine, Quest International University, Perak, Malaysia.
[B] EMAN Biodiscoveries Sdn Bhd. Penang, Malaysia.
[C] Department of Microbiology, Faculty of Medicine, Quest International University, Perak, Malaysia.
[D] Unit Farmasi, Klinik Kesihatan Teluk Bahang, Penang, Malaysia.
[E] Pharmaceutical Research, Faculty of Pharmacy, Quest International University, Perak, Malaysia.
[F] Advanced Medical and Dental Institute, Universiti Sains Malaysia, Penang, Malaysia.

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fat oxidation in women appears to be promoted by estrogen (D'Eon et al., 2015). Decrease in estrogen has been linked to changes in fat redistribution pattern as well as to insulin and leptin resistance (Azarbad & Gonder-Frederick, 2010). Reduced estrogen also contributes to dyslipidemia, elevated blood pressure, endothelial dysfunction, and vascular inflammation (Kornstein & Clayton, 2010). All these effects jointly cause in increased risk of obesity and cardiovascular disease. Obesity is associated with hyperlipidemia and characterized by decreased levels of HDL, increased levels of LDL, hypertriglyceridemia, and hypercholesterol (Jung & Choi, 2014). Currently, the use of available drugs in the market is costly and not devoid of side effects. The need for the replacement of current drugs, has turned sufferers' attention to natural product as a potential source for a more effective and safer anti-obesity drugs alternative.

Labisia pumila var. *alata* (LPva) (Primulaceae) is a plant commonly found in Southeast Asia and known as 'kacip fatimah'. It has been used traditionally for maintenance of general health and vitality of female reproductive system. It has been a remedy for regulating menstrual disorders, postpartum complications, pre and post-menopausal symptoms as well as weight management (Chua, Lee, Abdullah, & Sarmidi, 2012; Karimi, Jaafar, & Ghasemzadeh, 2016; Manda et al., 2014; Nurdiana et al., 2016; Samad 2018). LPva has been shown to exhibit pharmacological properties such as anti-photoaging (Choi et al., 2010), antioxidant(Fadlina Chany Saputri, 2011; Ibrahim & Jaafar, 2011; Karimi et al., 2016; Norhaiza, Maziah, & Hakiman, 2009), anti-cancer(Karimi et al., 2016), anti-inflammatory (Sanusi, Ab Shukor, & Sulaiman, 2013), antimicrobial and antifungal (Fazliana et al., 2011; Ibrahim, Jaafar, Karimi, & Ghasemzadeh, 2012; Karimi, Jaafar, & Ahmad, 2011), cardioprotective (Al-Wahaibi, Wan Nazaimoon, Norsyam, Farihah, & Azian, 2008; Dianita, Jantan, Amran, & Jalil, 2015), upregulation T helper1 cells (Pandey, Bani, Sangwan, & Koul, 2010), selective inhibition of CYP2C isoforms (Pan et al., 2012), anti-stress with adaptogenic potential (Kour et al., 2010). LPva regulates metabolism via regulation of insulin sensitivity and lipid profile by estrogenic effect, evidenced by increased uterus weight (Mannerås et al., 2010). Another study confirmed such an effect showing improved serum lipid profiles and modulation of serum antioxidants (Dianita, Jantan, Jalil, & Amran, 2016). The extract and its isolated active compound, Gallic acid, showed suppressed formation of fat droplets and triglyceride accumulation. In the study, gallic acids induced anti-obesity effect via inhibition of leptin secretion, triglyceride, LDL, VLDL, and promotion of HDL(Pandey, 2014). LPva extract consumption improved lipid profiles of pre- and postmenopausal women by regulation of total cholesterol as well as attenuating the effects of oxidative stress and inflammation. The consumption of the extract is assumed to be safe for postmenopausal women (Annie, Dale, Azreena, & Malkanthi, 2014).

There is still very little information or clinical data on the safety of LPva for human consumption and medical applications. In a recent animal safety study, no treatment related and mortality was reported in response to sub-acute oral toxicity aqueous extract of LPva (50, 250, 500, and 1000 mg/kg), however there was some toxicological concerns, evidenced by histopathological changes. These findings may suggest that aqueous extracts of LPva up to 1000 mg/kg/day statistically did not show any significant teratogenic effects in rats however it did dose-dependently affect the maternal body weight. However, the corrected maternal body weights were slightly higher in animals receiving low dose extracts (2 mg/kg/day) (Fuad, Sulaiman, & Islam, 2005). Another study reported aqueous extract of LPva posed no significant toxic effect, when tested on the estrous cycle, reproductive performance, post-natal growth and offspring survival of rats (Ezumi, Siti Amrah, Suhaimi, & Mohsin, 2007). Subcutaneous administration of petroleum-ether extract of LPva (0.025, 0.05, and 0.1 mg/ml) induced organ toxicity evidenced by degeneration in sinusoid area in liver and glomerulonephritis and nephrosis of the kidney (Effendy, Siti- Nurtahirah, & Hussin, 2006). Leaves extract of LPva contain flavonoids such as quercetin, myricetin, kaempferol, naringin, rutin, apigenin, anthocyanins, catechin, epigallocatechin and anthocyanins (Jaafar, Ibrahim, & Karimi, 2012; Karimi & Jaafar, 2011; Karimi et al., 2011; Norhaiza et al., 2009; Suan Chua et al., 2011), phenolic acids, salicylic acid, syringic acid, vanillic acid, protocatechin acid, gallic acid, coumaric acid, caffeic acid, chlorogenic acid, and pyrogallol, ascorbic acid and β-carotene (Karimi et al., 2011; Norhaiza et al., 2009)'(Karimi & Jaafar, 2011; Suan Chua et al., 2011) saponins (Karimi et al., 2011)'(Avula, Wang, Ali, Smillie, & Khan, 2011), and fatty acid (Karimi, Ze Jaafar, Ghasemzadeh, & Ebrahimi, 2015).

The present study assessed the responses of a single female subject to 40 days intake of Labeesity® 125mg, *Labisia pumila* standardized extract. The specific goals were to evaluate the safety and effect of test sample on weight management and fatigue. Patients' testimonies provided by the manufacturer indicate that the consumption of the standardized extracts in capsule form was associated with reports of general wellbeing, body weight and fat loss. Nevertheless, caution on interpreting the results should be exercised, as randomized, placebo-controlled clinical trials have not been carried out. There were also no records of any safety data such as blood test results measuring effects on liver function and renal function.

Methods

Labeesity®

Labeesity® is a patent pending (Patent No. WO 2016093692 A1) 100% natural herbal extract made from standardized Kacip Fatimah (*Labisia pumila*) extract (SKF7™) with each capsule containing N.L.T 4.5% Gallic Acid. Labeesity® 125mg is a recently marketed product by Orchid Life Sdn Bhd, and also the product registration holder approved by Malaysia National Pharmaceutical Regulatory Agency (NPRA) with registration number MAL16125022TC. Labeesity®

125mg capsules were analyzed for microbial and heavy metal content prior to the commencement of studies.

Pretreatment and follow-up studies

Patient

The patient was a 59-year-old female university lecturer with a medical background of hypothyroidism on 100 mg thyroxine for 5 years. The patient was assessed to be clinically obese when volunteered for this study. She was confirmed not to be on any extra ordinary weight management dietary program in the past or during the inclusion phase. After obtaining full informed consent to participate in the study, the patient was requested to maintain her regular diet and activities throughout the study period. Any deviations from her daily routine caloric intake or physical activities were recorded in a study diary.

Labeesity® dosage and schedule

The patient consumed Labeesity® 125mg capsule, twice daily for 40 days, after meals i.e. after breakfast and after dinner. The 125mg capsule is chosen, as it is the standard recommended dose for the product in the market. The patient was then monitored fortnightly throughout the study period i.e. from (20/11/2016 to 6/1/2017).

Baseline and terminal assessment

The patient initially underwent general medical assessment; data were collected on blood pressure, heart rate, baseline anthropomorphic assessment, weight, body mass index (BMI), percentage body fat using 4-compartment model for Asian women as well as blood and biochemical assessment at Quest International University, Perak, School of Medicine Clinic/Laboratory. All assessments were carried out within one clinic session prior to and shortly after completion of the study period. The patient was assessed at baseline using an investigator delivered patient-reported outcome assessment i.e. Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue) to evaluate any difference in fatigue and general well-being.

Results

Baseline characteristic

The patient's characteristics are detailed in Table 1.

Body composition

The results of measurement before and after 40 days treatment shows the subject with the BMI of 33.2 kg/m^2 is identified as class one obese in lower cut-off point (32.50 - 34.99 kg/m^2). After administration of Labeesity®, the subject experienced 2.51% decrease in body weight (90.5 vs. 88.2 kg). These reduction results in BMI of 32.40 kg/m^2, which is in the upper cut-off point (30.00 - 32.49 kg/m^2) of class one obesity categories. There was a respectively 2.5 % and 2.95 % decrease in waist and hip circumferences. At the end of treatment with Labeesity®, 9 % decrease was observed in total body fat (Table 2).

Safety analysis

The patient generally did not experience any treatment-related adverse event during and by the end of intervention except for some mild sensation of bloating and gas which lasted during the first week of treatment commencement. There was no significant deviation in the full blood count and other hematological indices. The renal profile and liver function test also showed no apparent adverse effects or derangements in key biochemical markers except for significant raise in uric acid ($P < 0.05$) (Appendix 1- Table 2). Full laboratory report on blood parameters and other biochemical profiles taken prior to consuming Labeesity® and after last dosage were within average population reference range, as provided in Appendix 1.

Lipid profile

Significant deviations from baseline parameters in the lipid profile as well as uric acid were noted following 40 days of study initiation (Table 3). The result shows patient experienced significant ($P <0.05$) decline in in total cholesterol, triglycerides, LDL – cholesterol, total Chol/HDL-Chol, uric acid by the end of treatment period. It further shows the HDL- cholesterol is significantly ($P < 0.05$) improved by Labeesity® administration.

Fatigue index

The FACIT-fatigue scale was measured before and after treatment. All negatively expressed items (e.g., I feel listless), showed lowered score, while the positively worded items (e.g., I have energy) showed the higher score. Compared to baseline response, there was an improvement of total score of all items from 34 to 48. Except for general feeling of fatigue, which was same prior and after treatment, there was an improvement in all other items. The subject felt less tired and more energetic. She was capable of performing her daily activities with greater stamina, without frustration and need of a daily nap. The subject also was able to participate in her usual active work and social activities.

Discussion

Overall, the patient reported significant improvement on many aspects of her quality of life. Patient had also reported an overall improvement based on FACIT-F scores after consuming the product. Although weight loss was not relatively prominent over 40 days, but there was nevertheless improvement in BMI from lower cut-off point to upper cut-off point of class one obesity. There were significant decreases in body measurements, i.e. waist and hip circumferences. Significant decrease in percentage body fat was also noted. It is also noteworthy that there were significant

Table 1. Patient's baseline characteristics

Item	Unit	Reading	Category
Gender		Female	
Age	Years	59	(>18 and < 65 years)
Race		Malaysia Indian	
Occupation		University lecturer	
Height	m	1.65	
Weight	Kg	90.5	
BMI	Kg/m2	33.2	Class 1 obese
Waist circumference	cm	103	
Hip circumference	cm	120	
Body fat	Percentage	43 %	
Blood pressure		135/67	
Heart rate		85	

Table 2. Body measurements before and after consuming Labeesity® 125mg

Item	Unit	Before	trial	Percentage
Height	m	1.65	1.65	0 %
Weight	Kg	90.5	88.2	2.51%
BMI	trial	33.2	32.4	-
Waist circumference	cm	103	100	2.95 %
Hip circumference	cm	120	117	2.5 %
Body fat	cm	43 %	42 %	1 %

Table 3. Serum lipid profile before and after consuming Labeesity® 125mg

Lipid profile	Unit	Before	After	Normal range
Total cholesttrialmmol/l)	(mmol/l)	5.28	*4.82	<5.18
Triglyceride (mmol/l)	(mmol/l)	2.01	*1.97	<1.7
HDL (mmol/l)	(mmol/l)	1.1	*1.2	>1.0
LDL(mmol/l)	(mmol/l)	3.3	*2.8	< 2.6
Total cholesterol /HDL ratio	-	4.9	*4.1	Risk indicate if > 4.5

improvements in all parameters of lipid profile. Significant reduction in LDL and Total Chol/HDL-Chol ratio was also noticed. It is also clear from patient's blood laboratory investigations, there were no significant deviations in blood and biochemical parameters including liver and renal profile after 40 days on Labeesity® 125mg. It was noted that uric acid was mildly raised from the previous baseline. However, it is difficult to interpret if this small rise is related to the test article or a physiological response to its effects on cellular metabolism. The anti-obesity mechanisms of LPva in human and laboratory animal were mainly attributed to improvement of serum lipid profile, regulation of insulin sensitivity, attention of oxidative stress, and inhibition of leptin in obese model (Annie et al., 2014; Dianita et al., 2016; Mannerås et al., 2010; Pandey, 2014).

Leptin is adipocyte-specific protein, with direct correlation to the size of body fat mass in human and some other mammalian. In the obese experimental cases, excessive leptin induces resistance and deficiency in its brain receptor, which promotes fat storage (Sorensen, Echwald, & Holm, 2011). Under this circumstance, suppression of leptin may reverse the process and improve dyslipidemia in obese (Pandey et al., 2010). The high levels of leptin also contribute to the insulin resistance. Insulin resistance plays a role in pathophysiology of much chronic disease such as dyslipidemia. Increase insulin sensitivity contributes to regulation of dyslipidemia and metabolism of fat, which consequently accelerate weight loss (Sah, Singh, Choudhary, & Kumar, 2016). Phytoestrogenic activity of LPva may also be the reason behind weight loss (Avula et al., 2011). Dietary phytoestrogens has also been shown to suppress adipose differentiation on lipid accumulation (Taxvig, Specht, Boberg, Vinggaard, & Nellemann, 2013). Previous studies suggest oral administration of phytoestrogens is associated with improved lipid metabolism, the reduction of LDL levels and elevation of HDL levels in

postmenopausal women (Okamura et al., 2008). Another study confirmed the positive effect of phytoestrogen on triglyceride metabolism and metabolic cardiovascular condition in postmenopausal women (de Kleijn, van der Schouw, Wilson, Grobbee, & Jacques, 2002). Gallic acid rich Labeesity® 125mg induced weight loss possibly via activation and modulation of the angiogenesis cascade in fat tissue. Gallic acid, a phenolic entity identified in different preparations of LPva, has been reported to exert a notable antiangiogenic activity in animal model (He, Chen, Rojanasakul, Rankin, & Chen, 2016). Modulation of anti-angiogenesis thus has been recently proposed as a potential pharmacological target for anti-obesity and weight management in human after success in preclinical models (Bråkenhielm et al., 2004; Cao, 2007). With regard to toxicity and safety, it is important to note that except in rare cases, studies conducted in experimental animals have not reported increased mortality or significant toxicity in humans. The dose administered to the human volunteer in this study is well below the NOAEL in animals of 50 mg/kg and as such, there were no observed or reported adverse or side effects. A phase 1 pilot study is nevertheless required to establish a proper dose response relationship as well as evaluating a range of dosing regimens to determine the most efficacious and safe dose of the product. In summary, this case study indicates significant antihyperlipidemic activity of Labeesity® 125mg in a 59 years old clinically obese women. The treatment was favorable for weight loss, hip, and waist circumference reduction. It also improved the quality of life of the patient over the course of 40 days. With no major record of treatment hazards throughout the intervention and no significant hematological and biochemical alteration, except for the slight modification in uric acid, Labeesity® 125mg intake in this study can be assumed to be safe. It is difficult to say however whether the effects of Labeesity® 125mg would persist beyond 40 days of intervention. Therefore, strong evidence to support the potential effectiveness and long-term benefits of *Labisia pumila* extracts based products will require robust studies to be conducted utilizing larger patient numbers and over extended periods of time to rule out any potential toxic effects.

Author Contributions

ASAM designed the study and wrote the manuscript. EF, SASA, MMK and ZTZ collect and analyzed the data and wrote the draft. ASAM, EF, NV, SASA, MMK and ZTZ contributed to critical discussion. All authors read and approved the final manuscript.

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Competing financial interests

The author(s) declare no competing financial interests.

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