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# Mood, Cognitive Function and Quality of Life Improvements in Middle Aged Women Following Supplementation with *Polygonum minus* Extract

(Penambahbaikan *Mood* dan Kualiti Kehidupan dalam Kalangan Wanita Pertengahan Umur Selepas Pemberian Ekstrak *Polygonum minus*)

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ABSTRACT

Polygonum minus *is a plant rich in flavonoids and antioxidants beneficial for reducing oxidative stress and lipid peroxidation in neuronal membranes. This randomized, double-blind, placebo-controlled study evaluated the potential benefits of* P. minus *extract (LineMinus™) towards improving cognitive function, mood status and quality of life. Thirty five middle-aged women (35-55 years old) were randomized into intervention (*n*=17) and control group (*n*=18). Two capsules of* P. minus *(250 mg) or placebo (100 mg maltodextrin) each were taken once daily for six weeks. Cognitive tests, mood and anthropometric measurements were measured at baseline, week 3 and week 6, whilst biomarkers were measured at baseline and week 6. Parameters related to mood and quality of life including energy/fatigue, social functioning and general health significantly improved from baseline to week 6 in the intervention group (*p*<0.05). Mean score for cognitive tests (i.e. digit span, comprehensive trail making test (CTMT) and three domains of CNS vital sign (CNSVS)] improved significantly in both intervention and control groups (*p*<0.05). There was a significant decrease of mean uric acid, estimated glomerular filtration rate (eGFR), total cholesterol and glycated hemoglobin (HbA1C) in the intervention group from baseline to week 6.* P. minus *supplementation has the potential to improve mood and quality of life and no adverse effects were reported by the participants after 6 weeks supplementation.*

*Keywords: Flavonoid; mood;* Polygonum minus*; phytochemicals; quality of life; supplement*

ABSTRAK

Polygonum minus *adalah tumbuhan yang kaya dengan flavonoid dan antioksidan serta bermanfaat untuk mengurangkan tekanan oksidatif dan peroksidasi lipid pada membran neuron. Kajian ini berbentuk rawak, dwi-buta dan plasebo terkawal untuk menilai potensi faedah ekstrak* P. minus *(LineMinus™) dalam meningkatkan fungsi kognitif, status mood dan kualiti hidup. Tiga puluh lima wanita pertengahan umur (berumur 35-55 tahun) dibahagikan secara rawak ke dalam kumpulan intervensi (*n*=17) dan kumpulan kawalan (*n*=18). Dua kapsul* P. minus *(250 mg) atau plasebo (100 mg maltodekstrin) telah diambil setiap sehari selama enam minggu. Ujian kognitif, mood dan beberapa ukuran antropometri telah diukur pada peringkat dasar, minggu 3 dan minggu 6, manakala penanda biologi diukur pada peringkat dasar dan minggu 6. Parameter yang berkaitan dengan mood dan kualiti hidup termasuk tenaga/keletihan, fungsi sosial dan kesihatan meningkat secara signifikan pada peringkat dasar hingga minggu 6 untuk kumpulan intervensi (*p*<0.05). Min skor untuk ujian kognitif seperti* Digit Span, Comprehensive Trail Making Test *(CTMT) dan tiga domain* CNS Vital Sign *(CNSVS)] meningkat secara signifikan dalam kedua-dua kumpulan intervensi dan kawalan (*p*<0.05). Terdapat penurunan yang signifikan dalam min asid urik, anggaran kadar penapisan glomerular (EGFR), jumlah kolesterol dan hemoglobin glycated (HbA1C) dalam kumpulan intervensi pada peringkat dasar dan minggu 6. Pemberian* P. minus *mempunyai potensi untuk memperbaik mood dan kualiti hidup serta tiada kesan buruk dilaporkan oleh peserta selepas pengambilan selama 6 minggu.*

*Kata kunci: Fitokimia; flavonoid; kualiti hidup; mood;* Polygonum minus*; suplemen*

## INTRODUCTION

Globally, there is an increase in the number of individuals with mental disorders related to neurological, behavioural and substances usage. The number has been predicted to increase up to 15% in the year 2020 (WHO 2004). There has been growing interest in the use of complementary and alternative medicines as a natural method for treating or preventing numerous mental disorders and improving cognitive function and mood. Several traditional herbs including passion flower, valerian root and kava have been utilized for centuries as remedies to assist in mind calmness and mood enhancement (Lakhan & Viera 2010). Furthermore, numerous studies have attempted to identify the efficacy and safety of utilizing alternative medicines in treating psychological problems specifically mental health such as anxiety disorder (Garcia-Garcia et al.

2008; Kinrys et al. 2009; Saeed et al. 2007). The usage of herbal and other natural remedies for the management and treatment of psychological conditions is timely due to the rising cost of prescription medications and their potential unwanted side effects to the patients.

Herbs may improve cognitive function or reduce the risk of cognitive decline. For example, supplementation of American ginseng (*Panax quinquefolius*) was reported to increase the working memory performance up to 10% among young adults in Australia (Scholey et al. 2010). A modest improvement was found in the accuracy of working memory task after 14 day administration of *Ginkgo biloba* extract among middle-aged adults (Silberstein et al. 2011). In addition, supplementation of SuperUlam, a mixture of herbs containing about 14.5% *Polygonum minus* as well as other ingredients such as sireh extract, pegaga extract, turmeric extract, curry leaves extract and selasih extract have shown to improve cognitive function among healthy individual aged 35-65 years old (Udani 2013).

*P. minus* is an aromatic plant originates from Southeast Asia, belonging to the family Polygonaceae and locally known as *kesum*. It has been used as a traditional remedy and for cooking purpose to provide flavour and fragrance. Previous study has reported that *P. minus* extract showed the highest antioxidant activity as compared to other popular herbs such as 'pegaga' and curry leaves (Huda-Faujan et al. 2009). *P. minus* is usually consumed as salad or 'ulam' (a Malaysian practice of complementing raw plants with rice dishes) (Al-Qari 2006; Cheah et al. 2008; Joseph et al. 2005; Sumazian et al. 2010; Tanaka 1976). Traditional usage of *P. minus* leaves decoctions includes treatment for dandruff, diarrhoea and indigestion (Herbal Medicine Research Centre 2002; Norliza et al. 2013). Nutrients found in *P. minus* include carotenes, retinol equivalents and L-ascorbic acid, α-tocopherol (vitamin E), calcium, phosphorus, iron, sodium, potassium, magnesium, copper and zinc (Ching & Mohamed 2001). It has been proven to be a potent natural source of antioxidant due to high antioxidant activity among other selected Malaysian plants (Azlim Almey et al. 2010; Qader et al. 2011). There were numerous compounds previously isolated from *P. minus* leaves including flavonoids namely myricetin, quercetin, isorhamnetin, catechin and rutin (Narasimhulu & Mohamed 2014; Qader et al. 2012).

Until recently, reports on the effect of *P. minus* on mood and quality of life are still limited. There is a need to explore the potential effect of *P. minus* on cognition and mood status since we have previously shown that 6 weeks supplementation of *P. minus* had improved short term memory and attention among subjects with poor mood and improved IQ among those with good mood (Suzana et al. 2015). Therefore, this study aimed to evaluate the benefits of *P. minus* supplementation towards mood and cognitive function among middle aged women.

## Materials and Methods

### Study Design

This study was a randomised, double-blind, placebo-controlled trial assessing the effect of *P. minus* extract (LineMinusTM) on cognition and mood status among middle aged women in Klang Valley, Malaysia. Subjects were randomised into two groups, namely placebo or *P. minus*. Randomisation was conducted using random sample cases decided by statistical computer programme, Statistical package for Social Sciences version (SPSS). Blinding procedure is ensured by labelling the *P. minus* and placebo capsules as either A or B Only so that the manufacturer knew the coding for both A and B labelled capsules.

### Data Collection

A total of 63 subjects were recruited from the screening process which involved self-administered questionnaires, anthropometric and blood pressure measurement and a collection of 20 mL fasting venous blood after 8 to 10 h fasting for the analysis of HbA1C, serum lipid, renal profile and liver function. The inclusion criteria include women aged 35 to 55 years with body mass index (BMI) of less than 40.0 kg/m$^2$. The exclusion criteria included individuals with or had a history of substance or alcohol abuse, history of major depression (marked as depressed mood most of the day) and bipolar disorder, had medical conditions problems (e.g. uncontrolled diabetes and kidney problem), pregnancy or lactation. A total of 35 subjects participated in the study and were randomly assigned into either placebo or intervention group. This study has obtained approval from the Medical Research Ethics Committee of the Universiti Kebangsaan Malaysia (NN-2014-060) and subjects have given their informed consent in accordance with the principles in the declaration of Helsinki (World Medical Association declaration of Helsinki, 2000) and Good Clinical Practice Guidelines.

### Intervention

This study was performed over a 6 week intervention period which includes three visits within the study period. Data collection was conducted from October until December 2014 at a few schools and a government office in Klang Valley in Malaysia. Each subject was randomly chosen where 17 subjects were selected from schools and the other 18 subjects were from government office. These subjects were evaluated for outcome measures including a cognitive function test battery, mood test and quality of life at three time points (baseline, week 3 and week 6). Blood profiles including HbA1C, serum lipid, renal profile, liver function and blood pressure were analyzed at baseline and week 6 to measure the effect of *P. minus* supplementation on health status. Subjects were advised to restrict their intake of caffeinated drinks no more than two cups daily on the testing days and to abstain the intake of any vitamins, other herbal supplements during the study period.

The subjects were provided with two bottles of supplement each containing 60 capsules throughout the intervention period. The treatment group received capsules containing *P. minus* extract whilst the controlled group received placebo capsules containing 100 mg maltodextrin. The placebo used was a sensory-identical capsule. Both groups were required to take two capsules once daily preferably in the morning. Subjects were required to record the time of consumption each day and noted down the reason for not taking the products if any in a diary provided to them for compliance checking. Both diary and capsules were brought back to the study site during scheduled visits and daily reminder was performed through phone call or short message service (SMS). Compliance of the subjects was monitored regularly whereby about 98.3% of the given capsules were consumed by the subjects.

### STUDY PRODUCT

The supplements capsule, LineMinusTM was a standardized water extract of *P. minus* leaves with a ratio of water to dried leaves of *P. minus* (1:20) (George et al. 2014; Ming et al. 2013). A finished product contained 250 mg of *P. minus* extract for each besides containing about 0.4% and 0.1% Quercetin-3-glucuronide and Quercitrin, respectively. Table 1 shows the constituents of both placebo and *P. minus*. This product has passed microbial limit test with absence of several microbes in the products and were reported to be free from *Salmonella*, *Escherichia coli* and *Staphylococcus aureus*. The level of several heavy metals such as arsenic, cadmium, lead and mercury were analyzed and passed within the regulated limits. Reference from previous study that stated no-observed-adverse-effect level (NOAEL) of *P. minus* extract in Wistar rats following oral administration for 28 days at more than 1000 mg/kg body weight was used to determine the dosage of two capsules (i.e. 500 mg/d) (Ming et al. 2013). According to the manufacturers' guidelines, this supplement only can be used traditionally for general health and not recommended for pregnancy and lactation women due to lack of sufficient data.

### OUTCOME MEASURES

Cognitive function, mood and quality of life are the primary outcome of this study. These variables were measured through Digit Span (Groth-Marnat 2000), Rey Auditory verbal learning test (RAVLT) (Rey 1964), comprehensive trail making test (CTMT) (Reynolds 2002), Wechsler abbreviated scale of intelligence (WASI) (Wechsler 1999) and CNS vital sign (CNSVS) (Gualtieri & Johnson 2006), profile of mood states (POMS) (McNair et al. 1971) and 36-Item short form health survey (SF-36) (Brazier et al. 1992). Anthropometry and body composition measurements were the secondary outcomes and measured at baseline, week 3 and week 6. The anthropometric parameters were measured with minimal clothing using TANITA digital lithium scale HD319 to the nearest 0.1 kg, (TANITA Corporation, Japan) for body weight and Leicester Portable Height Measure (SECA, German) for height. A total of 20 mL of fasting blood samples were taken for analysis of fasting serum lipid, liver and renal function test (triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol) and HbA1C were measured at baseline and 6 weeks. Blood pressure measurement was performed using an automated monitor (Omron HEM 7321-E, Netherlands). At each visit, subjects were asked by research assistants for any symptoms or side effects that they experienced.

TABLE 1. Energy, nutrient, and bioactive profile of *P. minus* preparation, LineMinusTM and placebo capsules

| Constituents (per 100 g) | Placebo | *P. minus* preparation, LineMinusTM |
|---|---|---|
| Energy[1] | | |
| (kJ) | 386 | 305 |
| (kcal) | 1621 | 1281 |
| Macronutrients[1] | | |
| Fat (g) | 0 | 0 |
| Carbohydrate (g) | 94 | 67.6 |
| Protein (g) | 2.6 | 8.6 |
| Micronutrients [2,3] | | |
| Calcium (mg) | 6.3 | 38.5 |
| Iron (mg) | 0.4 | 1.4 |
| Vitamin A (µg) | 0 | 0 |
| L-ascorbic acid (mg) | 10.6 | 27.0 |
| α-tocopherol (mg) | 0 | 0 |
| Bioactive content (%)[3] | | |
| Quercetin-3-glucuronide | - | 0.4 |
| Quercitrin | - | 0.1 |

[1] Determined by Method of Analysis for Nutritional Labeling, AOAC 1993
[2] Determined by U.S Environmental Protection Agency Method (EPA) revision 2, 1995
[3] Determined by High Performance Liquid Chromatography (HPLC)

### STATISTICAL ANALYSIS

Data was analysed using Statistical package for Social Sciences version (SPSS) 20 (v 20.0; IBM Corporation, Armonk, NY, USA). Data normality was determined from the Shapiro-Wilk test. The results were stated as either mean ± standard deviation (SD), frequency or percentage or with 95% confidence interval. The variations between the treatment and the placebo groups were analysed using independent student t-test and chi squared test. Paired sample t-tests were used for within subjects means comparisons between control and intervention groups at baseline, Week 3 and Week 6. All tests were 2-tailed with p values less than 0.05 were considered statistically significant.

## RESULTS

A total of 63 subjects were screened, with 43 were eligible and consented to participate. However, 35 were included in the final analysis, as four had health problems that interfered with the protocol of the study and one subject was lost to follow up giving with 87.5% response rate (Figure 1). After randomisation, a total of 18 subjects in placebo group and 17 subjects in the intervention group were allocated. Demographic profiles of the subjects according to the supplementation group are presented in Table 2. Mean age of the subjects were 45.6±6.1 and 44.7±4.6 years, for placebo and *P. minus*, respectively. All of the subjects were Malays and both groups showed no significant difference with respect to socio-demographic profile. Anthropometric status which includes weight, height and BMI showed no significant difference between groups.

Table 3 shows the result of blood biomarkers changes from baseline after 6 weeks of supplementation in both group placebo and *P. minus*. Both placebo and *P. minus* group showed no significant difference in blood biomarkers at baseline. In the intervention group, there was a significant decrease ($p<0.05$) of mean in uric acid, estimated glomerular filtration rate (eGFR), ratio total cholesterol to HDL and HbA1C from baseline (303.2±71.3 umol/L, 95.1±19.9 mL/min/1.73m$^2$, 3.3±1.0 mmol/L and 5.7±0.4) to week 6 (271.2±57.2 umol/L, 86.0±18.2 mL/min/1.73m$^2$, 3.2±0.7 mmol/L and 5.4±0.3). The mean of

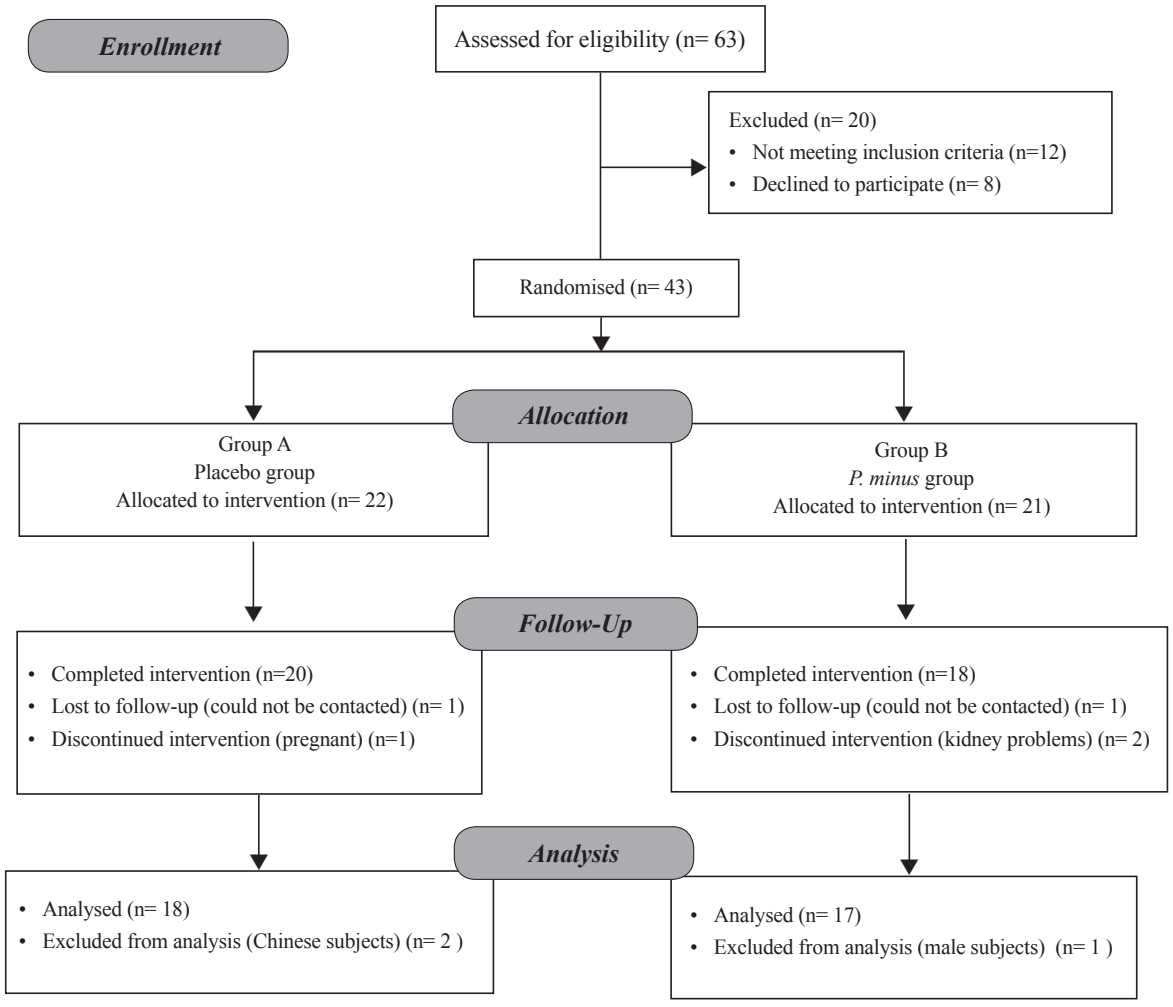


FIGURE 1. Flow diagram of study

TABLE 2. Baseline characteristics of participants by intervention and placebo group

| Baseline characteristics | Placebo (*n*= 18 ) | *P. minus* (*n*= 17) | P value |
|---|---|---|---|
| Mean age (year)[1] | 45.6±6.1 | 44.7±4.6 | 0.623[1] |
| Marital status[2] | | | |
| Married | 20 (100.0%) | 17 (94.1%) | 0.296 [2] |
| Single | 0 (0.0%) | 1 (5.9%) | |
| Level of education[2] | | | |
| Secondary school | 8 (44.4%) | 4 (23.5%) | 0.362 [2] |
| Certificate/Diploma | 2 (11.1%) | 4 (23.5%) | |
| Degree | 8 (44.4%) | 9 (52.9%) | |
| Occupation[2] | | | |
| Teacher | 8 (44.4%) | 9 (52.9%) | 0.615 [2] |
| Non-teacher | 10 (55.6%) | 8 (47.1%) | |
| Mean household income (RM)[1] | 7591.1±3904.2 | 8250.6±5125.1 | 0.670[1] |
| Anthropometric status[1] | | | |
| Weight (kg) | 67.3±9.7 | 66.9±11.7 | 0.929[1] |
| Height (cm) | 155.7±5.0 | 154.3±5.5 | 0.412[1] |
| BMI (kg/m$^2$) | 27.7±3.9 | 28.2±5.0 | 0.734[1] |

[1]Continuous data were presented as mean ± standard deviation, [2]Categorical data were presented as number (%), RM: Ringgit Malaysia

TABLE 3. Data on blood biomarkers at baseline and 6 weeks of intervention in control and intervention group (mean ± SD)

| Parameters | Placebo (*n*=18) | | *P. minus* (*n*=17) | |
|---|---|---|---|---|
| | Baseline (mean ± SD) | Week 6 (mean ± SD) | Baseline (mean ± SD) | Week 6 (mean ± SD) |
| Renal profil | | | | |
| Sodium (mmol/L) | 140.7±1.6 | 142.7±1.9$^c$ | 140.8±2.1 | 141.5±2.6 |
| Potassium (mmol/L | 4.2±0.2 | 4.5±0.5$^a$ | 4.3±0.4 | 4.4±4.2 |
| Urea (mmol/L) | 3.7±1.1 | 3.7±0.9 | 3.7±0.8 | 3.5±1.0 |
| Uric acid (umol/L) | 302.4±65.4 | 290.7±69.5 | 303.2±71.3 | 271.2±57.2$^a$ |
| Creatinine (umol/L) | 59.8±7.6 | 65.1±8.8$^c$ | 61.3±9.1 | 66.6±10.0$^c$ |
| eGFR (mL/min/1.73m$^2$) | 96.1±15.5 | 87.0±13.0$^c$ | 95.1±19.9 | 86.0±18.2$^c$ |
| Liver function test | | | | |
| Total protein (g/L) | 78.1±3.4 | 76.9±3.0$^a$ | 79.4±3.3 | 77.6±4.6 |
| Albumin (g/L) | 44.8±2.1 | 44.5±1.9 | 44.9±2.9 | 44.3±3.3 |
| Globulin (g/L) | 33.2±3.7 | 32.5±2.9 | 34.6±3.5 | 33.5±4.5 |
| Bilirubin (umol/L) | 10.8±5.9 | 10.4±6.5 | 10.6±4.9 | 9.2±3.4 |
| Alkaline phosphatase (U/L) | 73.9±20.2 | 73.8±19.7 | 72.6±14.7 | 76.9±23.5 |
| GGT (U/L) | 27.0±21.1 | 27.4±20.0 | 28.5±12.9 | 34.8±41.6 |
| Aspartate transferase (AST) (U/L) | 22.6±7.1 | 24.0±11.4 | 21.2±6.7 | 32.4±30.4 |
| Alanine transaminase (ALT) (U/L) | 21.9±11.9 | 19.7±9.8 | 19.9±14.5 | 33.3±40.6 |
| Lipid profile | 71±18.0 | 74±17.5 | 66±16.8 | 72±14.9 |
| Total cholestrol (mmol/L) | 5.4±0.9 | 5.4±0.9 | 5.3±1.2 | 5.4±1.3 |
| Triglycerides(mmol/L) | 0.9±0.4 | 0.9±0.3 | 0.9±0.2 | 1.0±0.5 |
| HDL (mmol/L) | 1.5±0.3 | 1.5±0.3 | 1.7±0.4 | 1.7±0.4 |
| LDL (mmol/L) | 3.5±0.9 | 3.5±0.8 | 3.2±1.0 | 3.3±0.7 |
| Total cholestrol/HDL (mmol/L) | 3.7±1.1 | 3.8±1.0 | 3.3±1.0 | 3.2±0.7$^a$ |
| HbA1C (%) | 5.9±0.8 | 5.6±7.4$^b$ | 5.7±0.4 | 5.4±0.3$^c$ |

*$p$<0.05 mean difference between placebo and *P. minus* at baseline
**$p$<0.05 mean changes between placebo and *P. minus* from baseline and week 6
$^a p$<0.05, $^b p$<0.01, $^c p$<0.001
HDL: High density lipoprotein, LDL: Low density lipoprotein, HBA1c: Glycated hemoglobin

creatinine increased significantly ($p$<0.05) from baseline (61.3±9.1 umol/L) to week 6 (66.6±10.0 umol/L). In placebo group, mean of renal profile include sodium, potassium and creatinine had significantly increase from baseline (140.7±1.6, 4.2±0.2 and 59.8±7.6 umol/L) to week 6 (142.7±1.9, 4.5±0.5 and 65.1±8.8 umol/L). Meanwhile decreasing in mean was noted in eGFR and HbA1c from baseline (96.1±15.5 mL/min/1.73 $m^2$ and 5.9±0.8) to week 6 (87.0±13.0 mL/min/1.73$m^2$ and 5.6±7.4) in placebo group. However, no significant difference in mean changes between both groups after 6 weeks of intervention.

There was no significant difference in psychosocial status for both groups at baseline except for depression, fatigue, confusion and total mood disturbance. A significant decrease of mean POMS (tension, depression, anger and TMD (Total Mood Disturbance)) were observed in the intervention group from baseline (10.9±4.5, 11.8±6.4, 11.7±4.9 and 32.0±21.8) to week 6 (8.6±5.0, 8.1±8.2, 8.7±6.1 and 21.1±25.1) with $p$ value of 0.038, 0.019, 0.011 and 0.010, respectively (Table 4). Mean changes in POMS (anger) was significantly difference in *P. minus* group compared to placebo from baseline to week 6. Furthermore, mean of quality of life (energy/fatigue, social functioning and general health) in the intervention group have significantly increased from baseline (62.4±15.9, 79.4±19.7, 65.6±16.8) to week 6 (68.2±13.7, 91.9±8.8 and 71.8±14.1) with $p$ value of 0.022, 0.008 and 0.028, respectively. There were no significant difference in both parameters of mood and quality of life in placebo group.

Improvement in the mean score of digit span, CTMT (Trail 1, Trail 2, Trail 5 and Composite Index), WASI (IQ performance and IQ full) and CNSVS (cognitive flexibility, psychomotor speed and executive function) from baseline to week 6 was found for both groups (Table 5). However, only CTMT (Trail 3) shows significantly difference in mean changes between treatment and placebo group at week 3 and baseline. In addition, CTMT (Trail 5) shows a significant difference in mean changes between both groups at baseline and week 6. Mean score for digit span improved from baseline to week 6 ($p$=0.030) in *P. minus* group and in placebo group ($p$=0.005). Both groups showed an increment in the mean score for CTMT composite index for baseline and week 6. In addition, *P. minus* exert highly significant difference ($p$=0.001) as compared to the placebo group ($p$<0.05) from baseline to week 6 in the Full Scale IQ of WASI. Similar trend was observed for executive function in CNSVS which shown higher significant level in *P. minus* group as compared to placebo group. Besides, significant improvement in cognitive flexibility domain in CNSVS was seen from week 3 for *P. minus* group, but was only

TABLE 4. Data on psychosocial status at baseline, 3 weeks and 6 weeks of intervention in control (mean ± SD) and intervention group (mean ± SD)

| Parameters | Baseline (mean ± SD) | | Week 3 (mean ± SD) | | Week 6 (mean ± SD) | |
|---|---|---|---|---|---|---|
| | Placebo ($n$=18) | *P. minus* ($n$=17) | Placebo ($n$=18) | *P. minus* ($n$=17) | Placebo ($n$=18) | *P. minus* ($n$=17) |
| POMS | | | | | | |
| Tension | 8.3±3.8 | 10.9±4.5 | 9.7±6.0 | 8.6±5.6 | 8.4±5.4 | 8.6±5.0[c] |
| Depression | 5.3±4.7 | 11.8±6.4* | 9.2±10.4 | 7.9±9.4 | 7.2±10.5 | 8.1±8.2[c] |
| Anger | 8.3±5.4 | 11.7±4.9 | 9.3±7.7 | 9.1±6.5 | 8.9±5.4 | 8.7±6.1***[c] |
| Vigour | 19.6±7.1 | 19.2±5.2 | 18.8±5.1 | 17.7±5.3 | 19.7±5.7 | 18.6±4.6 |
| Fatigue | 6.2±3.4 | 9.1±4.2* | 7.7±5.6 | 7.4±5.3 | 6.4±5.6 | 7.3±4.6 |
| Confusion | 5.6±2.3 | 7.6±2.6* | 7.3±4.0 | 6.7±3.2 | 6.7±4.0 | 6.6±3.2 |
| Total mood disturbance | 14.2±16.2 | 32.0±21.8* | 24.8±29.7 | 21.2±30.9 | 18.1±29.4 | 21.1±25.1[c] |
| SF-36 | | | | | | |
| Physical Functioning | 90.0±11.4 | 82.6±17.6 | 89.2±11.9 | 86.8±12.6 | 91.7±9.7 | 86.9±13.3 |
| Role limitation due to physical health | 75.0±35.4 | 79.4±29.6 | 73.6±34.8 | 75.0±35.4 | 72.2±39.2 | 88.2±33.2 |
| Role limitation due to emotional problems | 88.9±28.0 | 78.4±37.2 | 98.1±7.7 | 82.4±31.4 | 90.7±27.5 | 92.2±22.1 |
| Energy/fatigue | 67.2±14.8 | 62.4±15.9 | 72.8±14.6 | 69.4±13.7[a] | 70.3±19.0 | 68.2±13.7[c] |
| Emotional wellbeing | 78.0±10.5 | 73.2±13.7 | 82.4±9.1 | 77.9±13.4 | 77.3±17.5 | 76.0±12.6 |
| Social functioning | 84.0±19.6 | 79.4±19.7 | 88.9±15.4 | 90.4±10.4[a] | 85.4±15.0 | 91.9±8.8[c] |
| Bodily pain | 79.0±18.9 | 69.9±17.8 | 83.6±14.0 | 78.4±15.1 | 83.2±19.8 | 73.8±10.1 |
| General health | 70.6±18.0 | 65.6±16.8 | 74.4±17.5 | 72.1±14.9 | 71.7±20.3 | 71.8±14.1[c] |

*$p$<0.05 mean difference between placebo and *P. minus* at baseline
**$p$<0.05 mean changes between placebo and *P. minus* from baseline and week 3, ***$p$<0.05 mean changes between placebo and *P. minus* from baseline and week 6
[a] $p$<0.05 at baseline and week 3, [b] $p$<0.05 at Week 3 and Week 6, [c] $p$<0.05 at baseline and Week 6
POMS: Profile of Mood States, SF-36: 36-Item Short form Health Survey

TABLE 5. Data on cognition at baseline, 3 weeks and 6 weeks of intervention in control (mean ± SD) and intervention group (mean ± SD)

| Parameters | Baseline (mean ± SD) | | Week 3 (mean ± SD) | | Week 6 (mean ± SD) | |
|---|---|---|---|---|---|---|
| | Placebo (*n*=18) | *P. minus* (*n*=17) | Placebo (*n*=18) | *P. minus* (*n*=17) | Placebo (*n*=18) | *P. minus* (*n*=17) |
| Digit span | 8.2±1.8 | 8.8±2.5 | 10.1±3.3[a] | 9.5±1.5 | 9.8±2.5[c] | 9.8±2.0[c] |
| RAVLT | | | | | | |
| Learning | 48.7±10.4 | 51.8±9.3 | 50.2±12.1 | 50.4±6.1 | 49.1±10.7 | 51.2±7.9 |
| Recall | 50.1±9.9 | 51.4±7.4 | 50.4±10.1 | 49.4±9.6 | 49.0±10.3 | 51.0±7.5 |
| CTMT | | | | | | |
| Trail 1 | 38.8±9.5 | 40.2±7.0 | 48.6±7.0 [a*] | 47.6±6.3 [a*] | 52.0±10.0 [b, c*] | 49.8±8.1[c*] |
| Trail 2 | 44.8±8.7 | 43.6±7.9 | 51.7±11.3[a] | 42.9±5.8 | 52.1±11.8 [b, c] | 49.6±11.5[c] |
| Trail 3 | 41.6±10.2 | 42.6±9.5 | 46.6±10.0[a] | 47.2±10.2**[a] | 49.5±10.4[c] | 46.1±7.3 |
| Trail 4 | 41.2±9.5 | 39.1±6.0 | 43.4±11.0 | 42.9±7.8 | 44.1±8.7 | 45.5±7.9[c] |
| Trail 5 | 42.0±8.2 | 44.1±5.6 | 47.1±10.2 [a] | 44.8±7.6 | 50.9±8.0 [b, c*] | 48.3±7.5***[c] |
| Composite index | 40.6±8.0 | 40.8±6.6 | 46.7±8.7[a] | 44.2±6.4[a] | 49.2±9.1[b, c*] | 47.2±7.0[c*] |
| WASI | | | | | | |
| IQ verbal | 109.7±11.6 | 108.5±10.3 | 108.5±6.3 | 107.2±7.0 | 109.1±5.8 | 108.8±5.7 |
| IQ performance | 111.3±10.1 | 107.1±11.8 | 116.4±10.5[a] | 114.9±6.9[a] | 117.8±6.0[b, c] | 119.2±8.4***[c*] |
| IQ full | 111.6±9.3 | 108.7±10.0 | 114.2±8.2 | 112.2±6.6 | 114.5±5.0[c] | 115.6±6.0[c] |
| CNS Vital Sign | | | | | | |
| Visual memory | 83.7±18.6 | 87.8±12.7 | 80.2±14.5 | 88.3±13.2 | 83.0±16.3 | 85.8±16.3 |
| Psychomotor speed | 89.1±22.0 | 99.3±13.7 | 90.3±16.6 | 98.2±14.4 | 95.2±16.6 | 103.2±16.6[b] |
| Reaction time | 92.3±16.3 | 84.1±17.8 | 95.3±15.3 | 90.9±14.3[a] | 97.6±11.9 | 90.6±11.9 |
| Cognitive flexibility | 97.2±14.9 | 94.1±11.9 | 104.1±15.9 | 101.9±12.7[a] | 108.0±11.3[c] | 107.0±11.3[c*] |
| Processing speed | 101.5±15.1 | 102.6±14.4 | 106.4±15.5[a] | 107.0±17.2 | 109.6±24.5[c] | 114.8±24.5[b, c] |
| Executive function | 100.1±14.2 | 95.2±11.4 | 105.3±13.3 | 102.4±12.9[a] | 108.2±11.7[c] | 107.0±11.7[c*] |
| Motor speed | 85.2±25.1 | 97.0±14.3 | 83.3±18.3 | 93.4±15.9 | 87.5±13.2 | 94.5±13.2 |

*$p$<0.05 mean difference between placebo and *P. minus* at baseline
**$p$<0.05 mean changes between placebo and *P. minus* from baseline and week 3, ***$p$<0.05 mean changes between placebo and *P. minus* from baseline and week 6
[a]$p$<0.05 at baseline and Week 3,[a*]$p$<0.01 at baseline and Week 3,[b]$p$<0.05 at Week 3 and Week 6,[c]$p$<0.05 at baseline and Week 6,[c*]$p$<0.01 at baseline and Week 6
RAVLT: Rey Auditory Verbal Learning Test, CTMT: Comprehensive trail making test, WASI: Wechsler Abbreviated Scale of Intelligence, CNS Vital Sign: Central Nervous System Vital Sign

seen at week 6 for placebo group. No adverse effects were reported by the subjects from both groups throughout the study period.

## Discussion

To date, most of previous studies have focused on assessing the efficacy of *P. minus* on animal (George et al. 2014; Ming et al. 2013; Norliza et al. 2013). Hence, there are a limited number of studies reporting on the efficacy of *P. minus* extract supplementation on cognitive function, mood status and quality of life in human. In this present study, 6 week supplementation of *P. minus* extract among healthy women aged 35 to 55 years was found to improve some domains in mood state and quality of life. Significant improvements were noted in POMS for tension, depression, anger and total mood disturbance and SF-36 domain including energy/fatigue, social functioning and general health in *P. minus* group. With respect to quality of life assessed by SF-36, the significant improvement was seen from week 3 onward for energy/fatigue and social functioning domain. Whereas, there was no improvement seen in the placebo group for mood and quality of life until week 6 of supplementation.

Several studies have reported that leaves of *P. minus* are high in phytochemicals particularly flavonoid which associated with their antioxidant activity (Maizura et al. 2011; Urones et al. 1990). Flavonoid possessed the ability to delay or prevent degenerative diseases caused by oxidative damage, thus facilitate in the reduction of oxidative stress and lipid peroxidation in neuronal membranes (Spencer 2009). To exert the effect on cognition or mood, flavonoids must arrive at the central nervous system (CNS) through the blood brain barrier (Jäger & Saaby 2011). Studies have shown that quercetin-3-glucuronide can be absorbed through the small intestine and reach the central nervous system (CNS) (Lee et al. 2001). In a cell culture study, quercetin extracted from onion has been reported to permeate across the blood brain barrier and has the ability to impede the neuron cell death by hydrogen peroxide (Dan et al. 2011). In an animal study, oral administration of quercetin has shown to reduce the increment of oxidative

stress in the brain thus proved the ability of this compound to permeate to the brain (Ishisaka et al. 2011). Although in the present study we have not measure the bioavailability of quercetin from *P. minus*, previous supplementation studies using quercetin have reported the increase in plasma level of quercetin after two week up to 12 weeks administration (Egert et al. 2008; Jin et al. 2010).

Quercetin and quercetin-3-glucuronide were reported to have an impact on gamma-aminobutyric acid (GABA) receptors producing sedation, anxiolytic or anticonvulsive effects (Jäger & Saaby 2011). In addition, structural formula of *P. minus* extract which consist of two flavonoids namely quercetin-3-glucoronide and quercitrin has been reported to possess anti-depression property (Pathak et al. 2013). Thus, these components found in *P. minus* extract might explain its ability in improving mood state particularly in tension, depression, anger and total mood disturbance and domain in SF-36 (energy/fatigue, social functioning and general health). Similarly, Udani (2013) has observed a significant improvement in tension, depression and anger of POMS after the supplementation of SuperUlam, a mixture of natural herbs including *P. minus*. The synergistic effect mixture of vitamins and minerals in *P. minus* capsule also might potentially affect the mood parameters. Previous study among elderly has reported that supplementation of multivitamin formulation consist of vitamins, minerals, antioxidants and herbal extracts has improved alertness and reducing negative mood symptom in the intervention group (Harris et al. 2011). Study by Tildesley et al. (2005) has suggested an improvement in mood after acute administration of *Salvia lavandulaefolia* in the form of capsule. Supplementation of *Nigella sativa* L. or also known as black cumin for four weeks has shown to improve mood and decrease anxiety through their potent antioxidant and anticholinesterase activities of the herbs (Sayeed et al. 2014). On the contrary, Panax ginseng has shown no effect on total mood disturbance after 8 weeks supplementation with different dosages (Cardinal & Engels 2001). The effect of herbal supplementation on mood can vary according to dosage, duration and the forms of supplementation given to the subjects.

In the present study, both *P. minus* and control group have shown an improvement in cognitive test administered. One of the possible explanations is due to practice effect. This term has been defined as the improvements in cognitive performance caused by practicing a task or repetition of the cognitive battery (Heiman 2002). Participants were required to repeat the same version of cognitive tests during baseline, week 3 and week 6, thus, this might exposed them to practice effect and led to an improvement in cognitive performance. In the present study, only computerized CNSVS had different test versions. Study by Collie et al. (2003) has reported a significant improvement due to practice effect after first and second administration of cognitive test battery to the subjects. However, the following administration did not show any improvement in the test performance. Although practice effect has been linked as a source of error, earlier study has suggested that it can be a beneficial tool to monitor cognitive status specifically among patients with neurodegenerative disorders at earlier stage (Duff et al. 2007).

There are some strengths in this study that enhance confident in the results obtained, including the use of randomised, double-blind, placebo controlled methods, a full 6 weeks supplementation, blood monitoring at baseline and week 6 of the study and multiple assessments of cognition test. However, this study is limited by a short duration of supplementation. In addition, only one male subject has successfully completed the study and the data was excluded from the analysis, thus no comparison between genders can be made. This research will serve as a base for future studies to investigate the benefits of P. minus supplementation on cognitive and mood in a wide range of population which include different genders and races. Moreover, it would be interesting to assess the mechanism of action of P. minus specifically on mood.

## CONCLUSION

In conclusion, this study suggested that 6 weeks supplementation of *P. minus* (LineMinus™) had significantly improved mood specifically in tension, depression, anger and total mood disturbance. Similarly, the same trend was found for quality of life components including energy/fatigue, social functioning and general health. On the other hand, improvements in cognitive functions were observed in both intervention and control group. Further investigations in determining the effect of *P. minus* at cellular and molecular level are strongly recommended.

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