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ORIGINAL RESEARCH

The effect of *Polygonum minus* extract on cognitive and psychosocial parameters according to mood status among middle-aged women: a randomized, double-blind, placebo-controlled study

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Background: *Polygonum minus* (PM) o[r] locally kn[o]n in Ma[l]aysia, as "kesum" is rich in micronutrients and natural antioxidant[s]. H[o]wever, its ben[e]f[i]cial effect on outcome associates with oxidative stress including cognitive fun[c]tion is yet to be discovered. We assessed the efficacy of PM extract (LineMi[n]us PM) on cogniti[v]e function and psychosocial status among middle-aged women in Kla[n] Valley of Malaysia.

Methods: A randomized, d[o]uble-blind, pl[a]cebo-controlled trial among 35 healthy middle-aged women was performed, and s[u]bjects were r[a]ndomized to receive either 250 mg PM or placebo of 100 mg malto[d]extrin each w[h]ich take[n] twice daily for 6 weeks. Subjects were assessed for neuropsychologic[a]l tes[t]s, psychosocial status, and anthropometric at baseline, week 3, and week 6. Biomarker[s] were also d[e]termined at baseline and week 6.

Resul[t]s: PM supple[m]entation of PM showed significant intervention effect on Digit Span test (P<0.05) so[c]ial funct[i]oning domain of 36-Item Short Form Health Survey (P<0.05) among s[u]bjects w[i]th mood disturbance. While, among subjects with good mood, PM supplementation impr[o]ved Wechsler Abbreviated Scale of Intelligence (WASI) for IQ verbal (P=0.016) and Full Scale IQ [o]f WASI (P=0.004). There were no adverse effects reported for the supplementation as indicated [u]sing biomarkers, including liver function and clinical symptoms.

Conclusion: Supplementation of PM is safe to be consumed for 6 weeks, with potential benefits to a[t]tention, short-term memory, improved quality of life, and mood, as well as IQ.

Keywords: cognitive function, *P. minus*, psychosocial, women, phytochemicals, quality of life

Introduction

Polygonum minus (PM) or locally known in Malaysia, as "kesum" has been proven to be a potent natural source of antioxidant due to its high antioxidant activity.[1,2] The PM leaves are used to treat dandruff,[3] and to warm up the body, and were believed to be good for blood circulation.[4] Nutritionally, PM is rich in antioxidant vitamins such as carotenes, retinol equivalents, and vitamin C, α-tocopherol (vitamin E), and minerals such as calcium, phosphorus, iron, sodium, potassium, magnesium, copper, and zinc.[5] Several studies have reported positive effect of such micronutrients and herbs on mood and cognitive function. For example, a placebo-controlled trial among 300 healthy adults involving 4 weeks administration of a vitamin B complex with vitamin C and minerals (Berocca Calmag®) reported that the supplementation improved subjective ratings of stress, anxiety, and psychological well-being.[6] Similarly, a study was carried out to assess the effects of a similar supplement for 4 weeks among 80 healthy

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men also reported significant attenuated subjective stress and anxiety.[7] In addition, antioxidant-rich natural herbs such as pine bark extract supplementation for 5 weeks have also been reported to improve cognitive function among middle-aged men, as assessed using spatial working memory and immediate recognition tasks.[8]

Recently, SuperUlam, containing several natural herbs including PM, has been reported to improve cognitive function and mood.[9] However, little is known about the beneficial effect of a single extract of PM. Furthermore, the former study[9] excluded those with poor mood status. According to the World Health Organization (WHO), 12% of Global Disease Burden in 2000 was due to mental and behavioral disorders and it is predicted to increase to 15% by 2020, and indeed, depression causes the largest amount of years lived with disability (YLDs).[10] Thus, this study aimed to determine the effect of natural herbs, ie, PM supplementation on cognitive function and psychosocial parameters among healthy middle-aged working women according to mood status, either poor or good mood. The working middle-aged women were chosen to be the study population, because many studies and cohort stated that women had more anxiety and mood disorders than men[11–13] and double prevalence of depression compared with men,[14,15] and this trend can persist until 54 years.[16] Among working adults, a study has reported that the stress score and mood disturbances were higher among middle-aged adults compared with young and older adults.[17] In addition, one study reported that the women have more job stresses and higher risk of depression compared with men in a 6-year cohort study.[18] Generally, mental health problems were shown to increase with age, and there are significant sex differences affecting this increase.[19] Generally, all the subjects were below the mean age of menopause of 51 years old, in Malaysia.[20] For these reasons, the study subjects were chosen from middle-aged, working females.

Materials and methods

Study design

A randomized, placebo-controlled trial was conducted among 35 healthy middle-aged women recruited from three schools and a governmental organization in Klang Valley, central Malaysia. The inclusion criteria included women, aged 35–55 years and body mass index (BMI) <40.0 kg/m^2. Subjects with medical conditions (eg, uncontrolled diabetes and kidney problem), had a history of substance or alcohol abuse, smoking, history of major depression, bipolar disorder, pregnant, or lactating, were excluded. Subjects were randomized to either intervention group receiving PM (250 mg of PM) or placebo group (100 mg maltodextrin) twice daily. The study protocol was approved by the Medical Research Ethics Committee of the Universiti Kebangsaan Malaysia, and informed consent was obtained from each subject in accordance with the principles suggested in the Declaration of Helsinki,[21] and Good Clinical Practice Guidelines.

Intervention (herbal product) and placebo

The supplements capsule containing 250 mg of PM extract (LineMinus™ Biotropics Malaysia Berhad, Selangor, Malaysia), of which the structural formula for the extract standardized based on quercetin 3-glucuronide and quercitrin (Table 1). The standardized extract was prepared by a water extraction with dried leaves of PM to plant extract ratio (1:20) using the unique cost-available method of aqueous extraction technology.[22,23] The product was obtained from a manufacturer with good manufacturing practice, free from *Salmonella*, *Escherichia coli*, and *Staphylococcus aureus*. The levels of heavy metals of lead, arsenic, cadmium, and mercury contents were less than 1.0, 1.0, 0.2, and 0.05 ppm and within the regulated limits of 10.0, 5.0, 0.3, and 0.5 ppm, respectively. Every bottle was closed with inner seal white caps to ensure its safety, prior to consuming.

Subjects were provided with two bottles containing 60 capsules throughout the intervention period of 6 weeks. The placebo used was a sensory-identical capsule. The energy, carbohydrate content, and appearance of the placebo

Table 1 Energy, nutrient, and bioactive profile of kesum (*Polygonum minus*) and placebo capsules

Constituents (per 100 g)	Placebo	*Polygonum minus*
Energy[a]		
kJ	386	305
kcal	1,621	1,281
Macronutrients[a]		
Fat (g)	0	0
Carbohydrate (g)	94	67.6
Protein (g)	2.6	8.6
Micronutrients[b,c]		
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 (%)[c]		
Quercetin-3-glucuronide	–	0.4
Quercitrin	–	0.1

Notes: [a]Determined by Method of Analysis for Nutritional Labeling, AOAC, 1993.[54] [b]Determined by US Environmental Protection Agency (EPA) method revision 2, 1995.[55] [c]Determined by high performance liquid chromatography.
Abbreviation: AOAC, Association of Official Agricultural Chemists.

were designed to be similar as the PM. Both groups were required to take two capsules once daily after breakfast, lunch, or dinner. The dosage of two capsules (ie, 500 mg/day) was determined based on a toxicity study on Wistar rats of which no-observed-adverse-effect level of PM extract, at more than 1,000 mg/kg body weight, following oral administration for 8 days.[23]

Data collection, outcome measures, and follow-up

A preliminary health screening is performed through a self-administered questionnaire, and a collection of 20 mL fasting venous blood to determine biomarkers including HbA_{1C}, serum lipid, renal profile, liver function, and blood pressure was conducted on 63 subjects. Forty-three subjects were eligible and consented and further assessed for measuring primary outcomes including a neuropsychological tests by using Digit Span,[24] Rey Auditory Verbal Learning Test (RAVLT),[25] Comprehensive Trail Making Test (CTMT),[26] Wechsler Abbreviated Scale of Intelligence (WASI),[27] and CNS Vital Sign (CNSVS),[28] psychosocial test by using Profile of Mood States (POMS),[29] and quality of life using 36-Item Short Form Health Survey (SF-36).[30]

Their anthropometric measurements including body weight were measured using TANITA digital lithium scale HD319 to the nearest 0.1 kg (Tanita Corporation, Tokyo, Japan); height using SECA Leicester Portable Height Measure (SECA, Hamburg, Germany) and blood pressure was also measured using an automated monitor (Omron HEM 7321-E, OMRON Healthcare Co., Ltd, Kyoto, Japan). These measurements were taken at baseline, week 3, and week 6. Blood investigations were conducted again at week 6 to determine the same biomarkers as stated previously. On the testing days, subjects were advised to limit their consumption of caffeinated drinks not more than two cups daily. Subjects were then randomly allocated to either intervention or placebo controlled group. Subjects were asked to refrain from taking any vitamins, other herbal supplements throughout the study period. The supplements were provided to the subjects with instructions for consumption listed on the label. Compliance was checked regularly, and 98.3% of the capsules given were consumed by the subjects. A list of symptoms or any side effects experienced by the participant were recorded by the research assistants at each visit.

Compliance checking

Compliance was assessed by performing capsule count at the end of week 3 and week 6. Subjects were reminded by the researcher to take the capsule through a daily phone call or short message service. Subjects were required to record the time of consumption in a dose diary provided.

Statistical analysis

All analyses were performed using SPSS software (v 20.0; IBM Corporation, Armonk, NY, USA). The Shapiro–Wilk test was used to determine data normality. The results were expressed as the mean ± standard deviation (SD) or frequency and percentage, with 95% confidence interval. A two-way repeated measures ANOVA with adjustment of confounders including age, year of education, household income, BMI, and polyphenol intake was conducted according to two stratifications, ie, good mood (POMS ≤15) and mood disturbance (POMS >15).[8] All tests were two-tailed at a probability level of 0.05. Statistical analysis was performed under a double-blind protocol, meaning the treatment code was revealed to the researchers only after analysis of all study outcomes completed.

Results

A total of 31 subjects, from initially 43 recruited, completed the study (response rate 87.5%). Three subjects were dropped due to health problems, and two subjects were lost to follow-up (Figure 1). The mean age of subjects was 45±5.9 and 45±5.5 years, respectively, for both placebo (group A) and PM (group B). All the subjects were Malays, and both groups showed no significant difference with respect to socio-demographic profile (Table 2).

At baseline, there were no significant differences between groups on cognitive and psychosocial status. There was an interaction effect for Digit Span scale score ($P<0.05$) among subjects with mood disturbance, of which the mean of Digit Span scale improved among subjects intervention group when compared with placebo (Table 3). The mean of Digit Span scale increased among subjects in PM supplemented group from 9±2.2 at baseline to 10±1.5 at week 3 and maintained at 10±1.9 at week 6. While, among the placebo group, the value increased from 7±1.4 at baseline to 7±1.4 at week 3, but reduced to 9±2.9 at week 6 (Figure 2A). Furthermore, percentage of change of Digit Span continuously increased among the PM supplemented group, but it increased then decreased in the placebo group within subjects with mood disturbance (Figure 2B). Among those with good mood, there was a significant interaction effect for Verbal IQ ($P<0.05$) and Full Scale IQ of WASI ($P<0.05$) (Table 3). As shown in Figure 3A, within those with good, subjects supplemented with PM, the mean score of Verbal IQ improved

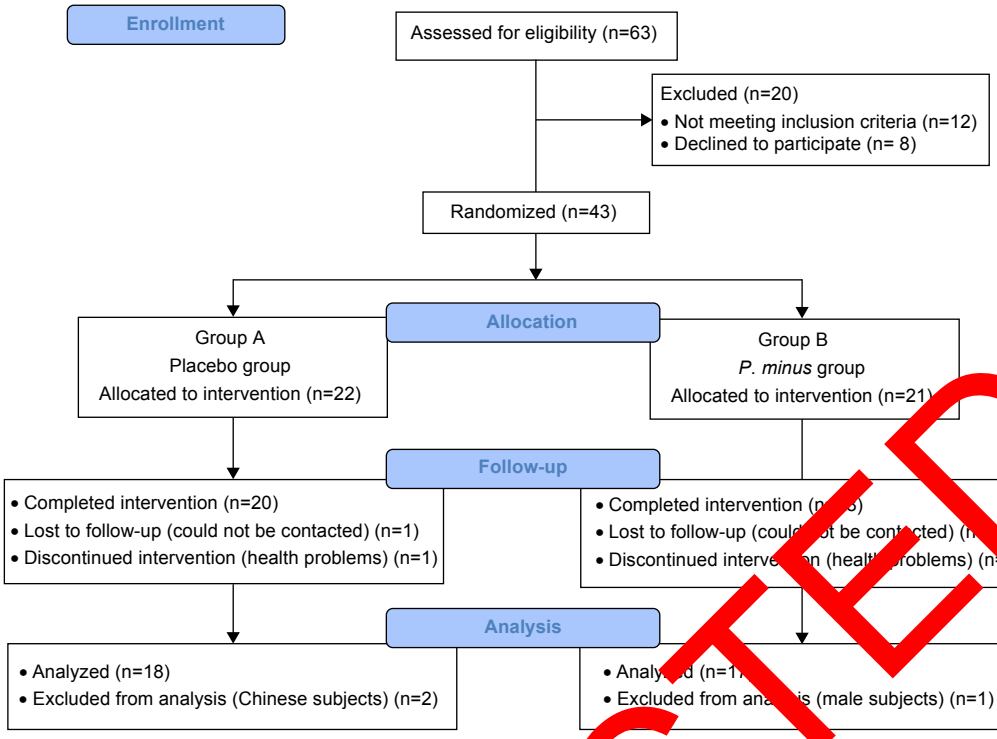

Figure 1 Study recruitment and flow chart.

from 107±4.4 at baseline to 110±8.6 at week 3 and slightly reduced to 109±6.7 at week 6, but the later value still higher than baseline (Figure 3A and B). Such increment was not notably seen in the placebo group. With respect to the Full Scale IQ of WASI, the mean score increased sharply from 105±10.4 at baseline in PM supplemented group to 115±9.4 at week 3 but slightly reduced to 115±9.4 at week 6, but the latter value still higher than baseline. However, such a sharp rise was not noted in the placebo group (Figure 4A). Thus, the percentage of change increased by 9% at 3 week and slightly reduced to 7.2% at week 6 in the PM supplemented group, when compared with a slight of increment only between 1% and 2% in the placebo group (Figure 4B). The difference in percentage of change between groups at week 3 was significantly differed.

Table 2 Baseline characteristics of subjects

Baseline characteristics	Group A (n=18)	Group B (n=17)	*P*-value
Age (years), mean ± SD	46±6.1	45±4.6	0.829[a]
Anthropometric status, mean ± SD			
Weight (kg)	67±9.7	67±11.7	0.929[a]
Height (cm)	156±5.0	154±5.5	0.412[a]
BMI (kg/m^2)	27.6±4.3	28.2±5.0	0.734[a]
Marital status, n (%)			
Married	18 (100.0)	16 (94.1)	0.296[b]
Single	0 (0.0)	1 (5.9)	
Level of education, n (%)			
Secondary school	8 (44.4)	4 (23.5)	0.362[b]
Certificate/diploma	2 (11.1)	4 (23.5)	
Degree	8 (44.4)	9 (52.9)	
Occupation, n (%)			
Teacher	8 (44.4)	9 (52.9)	0.615[b]
Non-teacher	10 (55.6)	8 (47.1)	
Household income per month (RM), mean ± SD	7,591±3,904.2	8,251±5,125.1	0.670[a]

Notes: [a]Independent *t*-test; [b]chi-squared test.
Abbreviations: BMI, body mass index; RM, Ringgit Malaysia; SD, standard deviation.

The time effect was noted in CTMT composite index ($P<0.05$) among subjects with mood disturbance and CTMT (Trail 3) ($P<0.05$) for subjects with good mood.

With respect to psychosocial, there was a significant interaction effect for SF-36 subscale, ie, social functioning ($P<0.05$), of which there was an increased in the mean score among intervention group with mood disturbance from 74±19.4 (baseline) to 89±10.0 (week 3), and 90±9.1 (week 6), when compared with the decrease in placebo group (Table 4 and Figure 5A). Thus, the percentage of change in the PM supplemented group increased by 30% at week 3 and reduced to 15% at week 6, when compared with a reduction by 3% in the placebo group (Figure 5B). However, a significant interaction and time effect was also observed with subjects with mood disturbance in control group showed an improvement in vigor (subscale in

Table 3 Cognitive function at baseline, week 3, and week 6 according to mood status (mean ± SD)

Scale	Mood disturbance		Group effect		Time effect		Intervention effect		Good mood		Group effect		Time effect		Intervention effect	
	A (n=7), mean ± SD	B (n=13), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2	A (n=11), mean ± SD	B (n=4), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2
Digit Span[a] scale score																
Baseline	7±1.4	9±2.2	0.470	[illegible]	0.080	0.177	0.037*	0.224	9±1.8	9±3.7	0.572	0.042	0.701	0.043	0.886	0.015
Week 3	11±3.6	10±1.5							9±3.1	9±1.4						
Week 6	9±2.9	10±1.9							10±2.1	10±2.5						
RAVLT[b]																
Baseline	53±5.4	50±7.8	0.41[illegible]	0.053	0.603	0.030	0.313	0.083	48±11.7	58±8.9	0.965	0.00	0.430	0.086	0.294	0.139
Week 3	55±7.4	48±10.1							46±12.1	54±5.4						
Week 6	52±5.4	51±7.6							48±10.6	54±4.3						
Recall																
Baseline	38±6.4	41±6.9	0.839	0.003	0.071	[illegible]185	[illegible]91	0.027	47±11.6	53±6.2	0.975	0.00	0.104	0.246	0.394	0.110
Week 3	50±5.8	48±6.1							48±10.9	53±8.2						
Week 6	52±5.4	50±7.8							47±12.2	51±8.5						
CTMT[c]																
Trail 1																
Baseline	38±6.4	41±6.9	0.839	0.003	0.071	0.1[illegible]5	[illegible]027		39±11.2	37±7.1	0.431	0.079	0.777	0.031	0.946	0.007
Week 3	50±5.8	48±6.1							48±7.7	47±7.6						
Week 6	52±5.4	50±7.8							[illegible]	48±10.0						
Trail 2																
Baseline	42±5.7	45±8.4	0.751	0.008	0.961	0.003	0.149	[illegible]36	46±10.1	39±4.1	0.301	0.132	0.207	0.179	0.235	0.165
Week 3	54±14.6	45±4.7							50±9.1	[illegible]7±5.4						
Week 6	51±11.6	52±12.1							53±12.4	43[illegible]4						
Trail 3																
Baseline	41±7.7	42±10.1	0.736	0.009	0.158	0.132	0.168	0.128	42±11.9	43±8.3	0.416	0.084	0.029*	0.358	0.236	0.165
Week 3	46±7.4	49±10.5							47±11.6	43±8.9						
Week 6	49±11.0	46±7.2							50±10.6	47±8[illegible]						
Trail 4																
Baseline	39±7.8	40±6.8	0.818	0.004	0.321	0.084	0.349	0.078	42±10.6	[illegible]±1.3	0.554	0.046	0.149	0.212	0.276	0.149
Week 3	43±12.9	44±8.1							44±10.2	39[illegible]3						
Week 6	40±9.4	46±8.6							47±7.6	43±4.8						
Trail 5																
Baseline	46±6.5	45±6.0	0.612	0.020	0.582	0.041	0.917	0.007	40±8.4	42±4.3	0.429	0[illegible]0	0.757	0.034	0.062	0.293
Week 3	48±11.7	45±8.0							46±9.6	43±6.9						
Week 6	51±9.8	50±6.4							51±7.3	44±10.1						

(*Continued*)

Table 3 (*Continued*)

Scale	Mood disturbance		Group effect		Time effect		Intervention effect		Good mood		Group effect		Time effect		Intervention effect	
	A (n=7), mean ± SD	B (n=13), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2	A (n=11), mean ± SD	B (n=4), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2
Composite index																
Baseline	40±5.4	41±	0.947	0.00	0.026*	0.246	0.619	0.036	41±9.8	39±5.1	0.382	0.097	0.206	0.179	0.284	0.146
Week 3	48±8.1	45±6.1							46±9.4	40±6.6						
Week 6	48±8.4	48±7.0							50±9.8	44±6.8						
WASI[d] IQ verbal																
Baseline	104±9.8	109±11.7	0.1	104	0.918	0.007	0.568	0.043	114±11.4	107±4.4	0.260	0.177	0.179	0.218	0.016*	0.447
Week 3	107±8.5	106±6.7							110±4.3	110±8.6						
Week 6	108±6.8	109±5.7							110±5.5	109±6.7						
WASI[e] IQ performance																
Baseline	107±11.8	108±9.7	0.288	0.086	25	0.06	0.390	0.070	113±8.5	104±18.5	0.426	0.093	0.082	0.301	0.891	0.016
Week 3	112±12.2	115±6.0							120±8.3	116±10.3						
Week 6	114±6.8	121±6.0							120±3.7	114±13.6						
WASI[f] IQ full																
Baseline	106±10.4	110±10.1	0.198	0.124	0.794	0.0	57	0.003	115±6.9	105±10.4	0.176	0.245	0.514	0.091	0.004*	0.542
Week 3	110±10.4	111±5.9							117±5.2	115±9.4						
Week 6	113±5.7	116±5.0							116±4.3	113±9.0						
CNSVS																
Visual memory[g]																
Baseline	90±20.1	85±8.4	0.591	0.023	0.498	0.052	0.383	0.07	80±17.	97±21.0	0.691	0.021	0.642	0.054	0.440	0.097
Week 3	83±15.0	88±14.5							78±14.6	88±9.4						
Week 6	80±22.2	84±18.1							85±21.2	93±5.3						
Psychomotor speed[h]																
Baseline	97±11.0	100±15.0	0.286	0.087	0.451	0.059	0.292	0.0	26.1	9	0.938	0.001	0.551	0.072	0.492	0.085
Week 3	94±10.9	99±14.9							88±19.5	7±14.3						
Week 6	93±15.6	104±17.6							97±13.8	102±15.0						
Reaction time[i]																
Baseline	94±15.6	81±18.7	0.969	0.000	0.133	0.144	0.520	0.049	91±17.4	94±	0.	0.030	0.266	0.153	0.324	0.131
Week 3	95±19.0	89±15.7							96±13.4	4.9						
Week 6	97±12.3	91±11.6							98±11.1	14.6						
Cognitive flexibility[j]																
Baseline	103±15.1	92±12.1	0.322	0.075	0.581	0.041	0.746	0.022	93±14.0	101±9.4	05	0.0	0.973	0.003	0.937	0.008
Week 3	105±16.4	101±12.0							103±16.4	105±16.5						
Week 6	109±12.8	107±11.6							108±6.8	106±12.0						
Processing speed[k]																
Baseline	107±17.3	99±13.8	0.741	0.009	0.591	0.040	0.577	0.041	98±13.0	116±7.7	0.290	0.138	0.126	0.228	0.765	0.033
Week 3	110±16.7	104±15.7							104±15.1	117±20.3						
Week 6	110±21.0	112±24.5							109±12.8	125±25.1						

Executive function[l]														
Baseline	105±15.3	93±11.7	0.339	0.070	0.655	0.032	0.701	0.027	97±13.2	101±9.7	0.848	0.005	0.923	0.010	0.903	0.013
Week 3	105±17.1	101±12.4							105±11.1	106±15.7						
Week 6	109±13.1	107±12.2							107±7.0	107±11.6						
Motor speed[m]																
Baseline	92±14.9	100±13.7	0.123	0.173	0.834	0.014	0.614	0.037	81±29.7	86±11.8	0.598	0.036	0.744	0.036	0.682	0.047
Week 3									81±22.5	86±8.1						
Week 6									89±12.1	87±5.2						

Notes: *$P<0.05$ significant using ANCOVA with age, years of education, household income, BMI, and polyphenol intake as covariates. A, placebo group; B, *Polygonum minus* group. Mood disturbance = POMS >15; good mood = POMS ≤15. Higher score represents – [a]good short term memory; [b]good learning ability and memory; [c]higher executive function; [d]higher IQ verbal; [e]higher IQ performance; [f]higher score overall IQ; [g]higher visual memory; [h]higher psychometer speed; [i]longer reaction time; [j]higher level of executive functioning; [k]longer processing speed; [l]higher level of executive functioning; and [m]higher level of motor speed.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CNS Vital Sign; CTMT, Comprehensive Trail Making Test; η_p^2, partial eta squared; POMS, Profile of Mood States; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; WASI, Wechsler Abbreviated Scale of Intelligence.

POMS), when compared with intervention group ($P<0.05$ for both) (Table 3). The mean score of vigor decreased from 91±15.7 at baseline in the placebo group to 89±19.7 at week 3 and 88±12.5 at week 6. However, an increment was noted in the intervention group (Figure 6A and B). Among subjects with good mood, only a significant time effect in anger subscale of POMS was found ($P<0.05$).

There were no significant interaction effects on anthropometric parameters and blood biomarkers in Tables 5 and 6, respectively. However, there was a significant time effect for weight, BMI, and diastolic blood pressure; sodium, uric acid, creatinine, total protein, globulin, total cholesterol/high density lipoprotein, and HbA_{1C} ($P<0.05$) for all parameters. No significant adverse effects were reported in both placebo and intervention groups.

Discussion

To the best of our knowledge, this is the first clinical trial to evaluate the cognitive and psychosocial effects of PM in human specifically in middle-aged women, with its safety as evidenced by blood biomarkers have also been proven. Recently, interest in products aimed at improving cognitive performance and mood is steadily increasing. However, those products were not supported by scientific evidence. There is a trend that most individuals preferred a natural option for improving cognitive function and mood rather than pharmaceutical agents which have been reported to have some side effects.[31] In one study, Laditka et al found that most of adults used supplements to treat or cure their cognitive problems rather than to prevent them.[32] Hence, this study provides scientific evidence of beneficial effect of natural herbs, ie, PM extract in improving cognitive function and psychosocial parameter.

In this study, PM supplementation exerts positive effect on IQ, by 2.1% for verbal and 7.3% for Full Scale IQ of WASI, for subgroup with good mood (POMS ≤15). PM is a natural herb rich in phytochemicals particularly flavonoid (ie, flavonols, myricetin quercetin, methyl flavonol, and flavones),[33] higher than total flavonoid when compared with other indigenous plants.[34] In addition, PM water extract had higher antioxidant activity when comparing with ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*), measured by the total phenolic content, 2,2-diphenyl-11-picrylhydrazyl free radical and ferric reducing antioxidant power.[34,35] These phytochemicals have strong antioxidant capacities play an important role in delaying or preventing degenerative diseases caused by oxidative damage of living cell components and its free radical scavenging properties

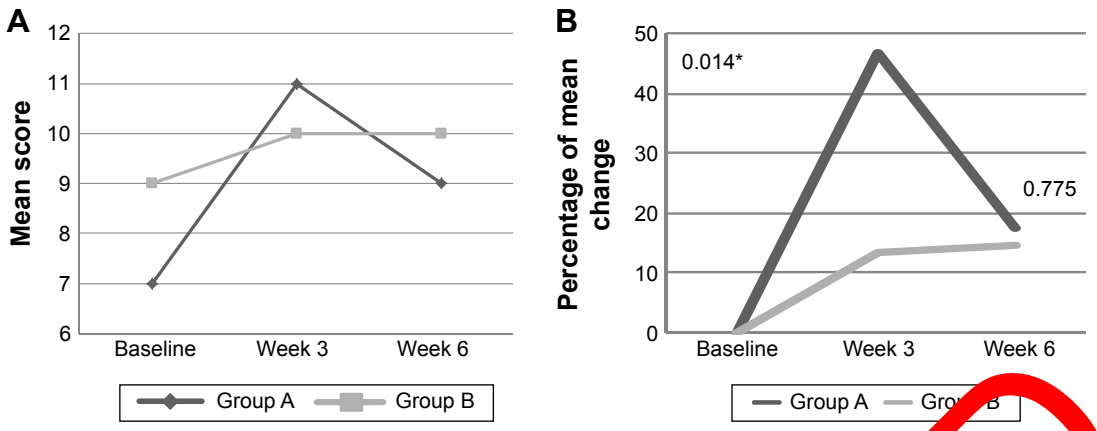

Figure 2 (**A**) The mean score of Digit Span at baseline, week 3, and week 6 among subjects with mood disturbance according to study groups. (**B**) The percentage of mean change for Digit Span from baseline to week 3 and week 6 among subjects with mood disturbance according to study groups.
Notes: A, placebo group; B, *Polygonum minus* group. Mood disturbance = POMS >15. *$P<0.05$ independent *t*-test.
Abbreviation: POMS, Profile of Mood States.

may help to reduce oxidative stress and lipid peroxidation in neuronal membrane, further results in positive effect on memory, cognition, and improved cerebrovascular blood flow.[36]

Flavonoids and their metabolites are shown to modulate neuronal signaling through tyrosine kinase, phosphoinositide 3-kinase, protein kinase C, and mitogen-activated protein kinase pathways.[36] These signaling cascades a also critical for the control of inflammatory processes i the brain, including the activation of microglia i sponse to cytokines and the induction of inducib nitric xide synthase and nitric oxide production.[37] B ffecti pathways, flavonoids can be seen innova e dietary strategies for reducing the effe neuroinfla mation in the brain. In addition, its attributi can also have a direct impact o memory quisi on (learning), consolidation (s rag of labile ta memory), and storage process through the i uction of new protein synthesis in neuro s. Moreover, flav oids may induce increases in cere ral blood fl w which eventually give an impact on acu cognitive p rformance, or may lead to an increase in hipp campal ascularization capable of inducing new neuronal growth.[38] Thus, PM has the ability to improve cogniti including attention and short-term memory, indicated by an improvement in Digit Span by 14.7% as being seen in this study, among individuals with poor mood or having some degree of mood disturbance. Similar findings were observed in other studies involving natural herbs as neuroprotective supplementations in improving cognitive functions.[8,9]

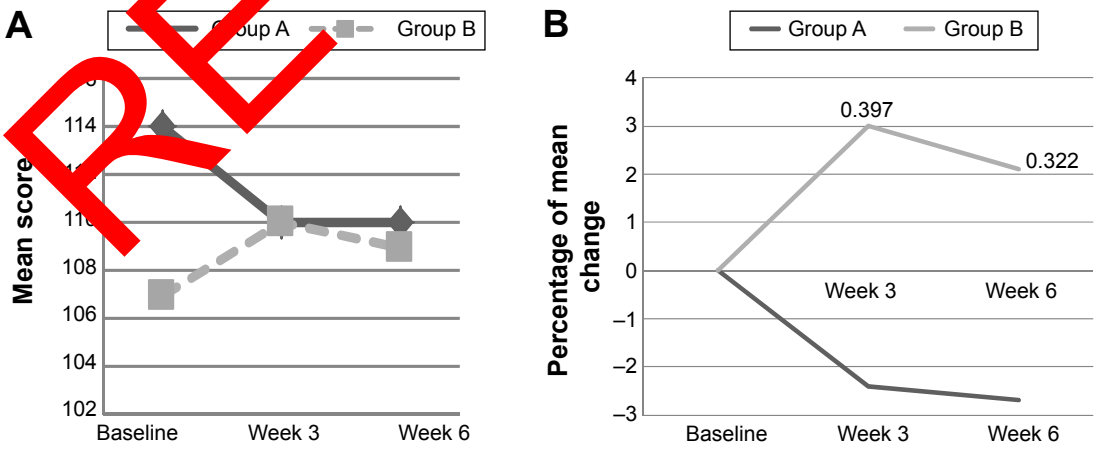

Figure 3 (**A**) The mean score of Verbal IQ of WASI at baseline, week 3, and week 6 among subjects with good mood according to study groups. (**B**) The percentage of mean change for Verbal IQ from baseline to week 3 and week 6 among subjects with mood disturbance according to study groups.
Notes: A, placebo group; B, *Polygonum minus* group. Good mood = POMS ≤15. Non-significant independent *t*-test.
Abbreviations: POMS, Profile of Mood States; WASI, Wechsler Abbreviated Scale of Intelligence.

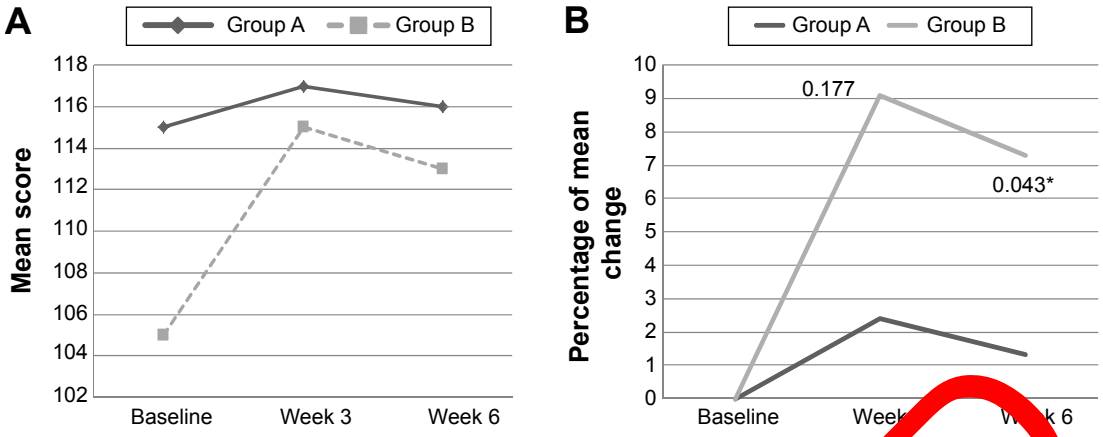

Figure 4 (**A**) The mean score of Full IQ of WASI at baseline, week 3, and week 6 among subjects with good mood according to st[illegible] groups. (**B**) The [illegible]ercentage of mean change for Full IQ of WASI from baseline to week 3 and week 6 among subjects with mood disturbance according to study [illegible]oups.
Notes: A, placebo group; B, *Polygonum minus* group. Good mood = POMS ≤15. *$P<0.05$ independent *t*-test.
Abbreviations: POMS, Profile of Mood States; WASI, Wechsler Abbreviated Scale of Intelligence.

In this study, the ability of PM supplementation in improving cognition among those with mood disturbance will further improve general well-being such as the social functioning in SF-36. Stress is a risk factor for low physical strength lead to poor well-being. PM composed of quercetin and quercetin-3-glucuronide as its bioactive chemical act as anti-depression agent.[39] Moreover, those flavones including hyperin and isoquercitrin had a potential structure fo[illegible] depression.[40] Quercetin and quercetin-3-glucuronide [illegible]ere reported to impact the gamma-aminobutyri[illegible]d recep[illegible] producing sedation, anxiolytic, or antic[illegible]vulsiv[illegible]effects.[41] Animal studies showed that quercet[illegible] dose [illegible]ently increases social interaction, de[illegible]eases [illegible]obility time, and minimizes changes in beh[illegible]r in anima[illegible]periments, such as the swim test or forced [illegible]mobilization which designed to create anxi[illegible]y and behavio[illegible]despair.[42,43] Thus, it might explain the [illegible]bility of quercetin in improving social functioning (exte[illegible]or f[illegible]quency of physical health and emotions pr[illegible]lem in[illegible]acting [illegible]h normal social activities) in S[illegible]36. F[illegible]ther, i[illegible] studies showed that quercetin r[illegible]duced s[illegible]-induced brain corticotropin-releasing factor (C[illegible] expression (CRF has been implicated in anxiety and d[illegible]ression).[42,44] It also attenuates stress-induced increases of plasma corticosterone and adrenocorticotropic hormone.[44]

In this study, only one of eight domains in POMS, ie, vigor showed significant intervention effect upon supplementation of PM. This beneficial effect was seen in placebo group with mood disturbance. This might be due to differences in subject measurements. Different individuals may have different ways of experiencing emotion. Moods can easily fluctuate and constantly change over period of time and thi[illegible]makes m[illegible]d cha[illegible]es difficult to measure. Mood ca[illegible]fi[illegible]t by a numb[illegible] environmental or external factors (ie, socia[illegible]nteractions or stressful life events) and in[illegible]a[illegible] factors (ie, [illegible]rcadian rhythms or menstrual cycle [illegible] women).[45] The six distinct mood states in POMS are not [illegible]laim to capt[illegible]e the entire content domain of mood.[46] The u[illegible] of more [illegible]bjective measurements such as eye-tracking method to monitor emotions based on pupil dilations,[47] or [illegible]ing BioM-10 Mood Panel,[48] a peripheral biomarker set of low vs high mood states are recommended for future studies.

As this is the first study, to the best of our knowledge, to assess the effects of PM extract on cognitive function and psychosocial status, only few comparisons can be made with the existing research in improving cognitive with herbs supplementation. *Curcuma longa* or turmeric is commonly used to make curries in Asia, has been portrayed as having antioxidant and has the effect of neuron.[49] Flavonoid and polyphenols have been long studied for their strong antioxidant capacities, and as scavenging agents for reactive oxygen species thus it have potential role in preventing aging and oxidative stress-related diseases.[50,51] American ginseng (*Panax quinquefolius*) has been found to improve working memory performance.[52] Recently, the product known as SuperUlam has been reported to improve cognitive function and mood after 3 weeks supplementation among middle-aged healthy individuals. SuperUlam is a mixture of several natural plant extracts including PM extract.[9] In an animal study, the potent antioxidant in PM extract was capable of entering into and protecting cells from oxidative damage, and produce favorable effects of cognitive function, because the brain has a high level of metabolism and required a high amount of

Table 4 Psychosocial status at baseline, week 3, and week 6 of intervention according to mood status (mean ± SD)

Scale	Mood disturbance		Group effect		Time effect		Intervention effect		Good mood		Group effect		Time effect		Intervention effect	
	A (n=7), mean ± SD	B (n=13), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2	A (n=11), mean ± SD	B (n=4), mean ± SD	*P*-value	η_p^2	*P*-value	η_p^2	*P*-value	η_p^2
POMS[a] tension																
Baseline	11±4.5	12±3	.763	0.007	0.921	0.006	0.831	0.014	7±2.0	6±3.5	0.843	0.005	0.290	0.143	0.917	0.011
Week 3	8±6.0	8±5.3							11±6.1	9±7.4						
Week 6	10±3.3	9±5.5							7±6.3	6±1.8						
Depression																
Baseline	9±4.9	15±4.4	0.7	0.0	0.939	0.005	0.809	0.016	3±2.2	3±2.4	0.533	0.050	0.266	0.152	0.621	0.058
Week 3	6±10.1	7±8.1							11±10.5	12±13.5						
Week 6	9±9.2	10±8.6							6±11.5	2.5±2.6						
Anger																
Baseline	13±4.6	13±3.9	0.733	0.009	.724	0.0	.606	0.028	5±3.9	6±3.6	0.958	0.000	0.029*	0.375	0.861	0.019
Week 3	6±4.2	9±4.7							11±9.0	11±11.6						
Week 6	12±6.5	10±6.6							7±3.7	5±1.3						
Vigor																
Baseline	19±7.2	19±5.0	0.834	0.004	0.003*	0.35	0.027*	0.244	20±7.4	21±6.7	0.159	0.232	0.173	0.197	0.864	0.018
Week 3	17±5.2	17±6.0							20±4.7	19±1.7						
Week 6	21±5.0	18±3.9							19±6.2	22±5.5						
Fatigue																
Baseline	9±2.1	10±3.7	0.270	0.093	0.554	0.044	0.800	0.017	4±2.5	5±2.9	0.249	0.162	0.239	0.164	0.918	0.011
Week 3	5±3.4	7±5.2							9±6.4	10±5.7						
Week 6	8±4.5	8±4.6							6±6.3	5±4.2						
Confuse																
Baseline	7±2.7	9±1.9	0.194	0.126	0.753	0.022	0.788	0.018	5±1	4±	0.662	0.025	0.373	0.116	0.885	0.015
Week 3	6±3.9	7±2.9							8±3.9	±4.4						
Week 6	7±3.4	7±3.5							6±4.5	5±1.4						
TMD																
Baseline	30±10.8	41±17.2	0.807	0.005	0.648	0.023	0.594	0.030	4±9.0	4±	0.3	0.118	0.766	0.033	0.877	0.016
Week 3	19±27.9	20±28.7							29±31.5	41.7						
Week 6	26±24.9	26±25.3							13±32.1	2± 2						
SF-36[b] physical functioning																
Baseline	95±6.5	79±19.6	0.356	0.071	0.634	0.024	0.606	0.028	87±12.9	94±4.8	958	0.0	0.589	0.064	0.379	0.114
Week 3	91±11.0	85±14.5							88±12.9	93±5.0						
Week 6	94±6.1	84±13.8							90±11.4	96±4.8						
Role limitation due to physical health																
Baseline	82±37.4	75±32.3	0.732	0.009	0.269	0.096	0.474	0.056	70±35.0	94±12.5	0.429	0.080	0.762	0.033	0.236	0.165

Week 3	82±31.3	77±33.0							68±37.2	69±47.3						
Week 6	89±28.3	85±37.6							61±42.4	100±0.0						
Role limitation due to emotional problems																
Baseline	90±25.2	72±40.5	0.51	0.034	0.710	0.018	0.396	0.063	88±30.8	100±0.0	0.771	0.011	0.796	0.014	0.384	0.103
Week 3	95±12.6	82±32.2							100±0.0	83±33.3						
Week 6	90±25.2	95±							91±30.2	83±33.3						
Energy/fatigue																
Baseline	59±8.4	58±13.9	.111	0.183	.685	0.029	0.842	0.013	73±16.0	76±15.5	0.500	0.059	0.541	0.054	0.815	0.010
Week 3	69±7.5	68±13.5							75±17.5	75±14.7						
Week 6	65±13.5	65±12.7							74±21.7	79±12.5						
Emotional well-being																
Baseline	75±9.4	70±13.2	0.261	0.096	0.671	0 .30	0.391	0.070	80±11.0	84±9.8	0.377	0.098	0.799	0.028	0.588	0.064
Week 3	77±5.0	76±13.2							86±9.7	84±14.2						
Week 6	71±19.4	73±12.4							81±15.6	85±9.5						
Social functioning																
Baseline	91±15.7	74±19.4	0.356	0.066	0.571	0.0	0.02	0.249	80±21.1	97±6.3	0.335	0.116	0.741	0.037	0.265	0.153
Week 3	89±19.7	89±10.0							89±13.1	94±12.5						
Week 6	88±12.5	90±9.1							84±16.9	97±6.3						
Pain																
Baseline	80±19.5	63±12.0	0.069	0.232	0.685	0.029	52	.14	78±19.4	92±16.3	0.680	0.022	0.697	0.044	0.245	0.161
Week 3	84±13.8	77±15.5							83±14.8	84±14.2						
Week 6	85±19.9	70±6.0							82±20.7	87±10.3						
General health																
Baseline	68±12.5	62±15.9	0.534	0.030	0.606	0.038	0.278	0. 4	72±21.1	8±15.5	0.476	0.065	0.684	0.046	0.654	0.052
Week 3	69±17.0	71±15.7							78±17.5	7 3.5						
Week 6	69±17.4	69±14.4							2.6	8						

Notes: *$P<0.05$ significant using ANCOVA with age, year of education, household income, BMI, and polyphenol intake as covariates. A, p bo group; B, *Polygonum minus* group. Mood disturbance = POMS >15; good mood = POMS ≤15. [a]Score 0–4, higher score indicates anxiety, emotional suppression, and psychological distress. [b]Score 0–100, with higher scores ecting better qu of life, except for physical pain, which is reversed.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; η_p^2, partial eta squared; POMS, Profile of Mood States; SD, sta d deviation; SF 36-ite Short Form Health Survey; TMD, total mood disturbance.

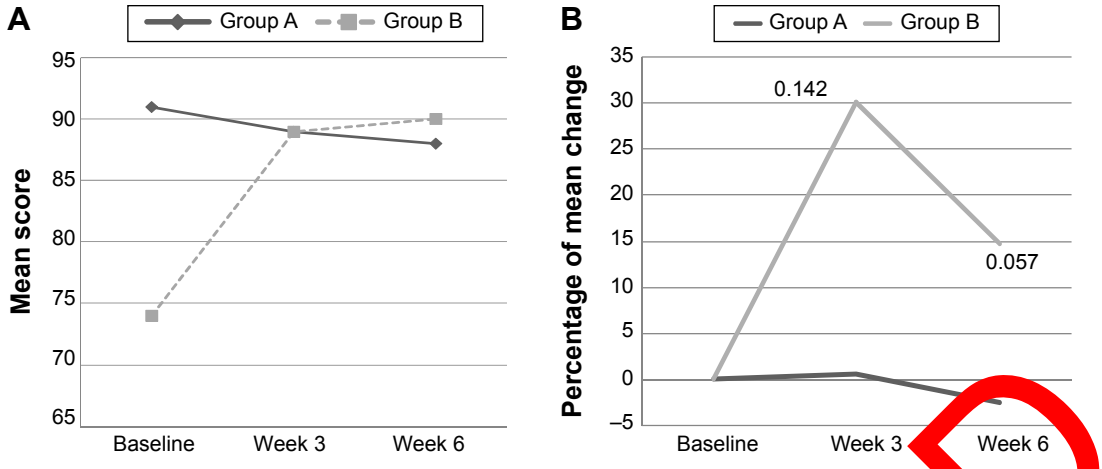

Figure 5 (**A**) The mean score of social functioning of SF-36 at baseline, week 3, and week 6 among subjects with mood disturbance according to study groups. (**B**) The percentage of mean change for social functioning of SF-36 from baseline to week 3 and week 6 among subjects with mood disturbance according to study groups.
Notes: A, placebo group; B, *Polygonum minus* group. Mood disturbance = POMS >15. Non-significant independent *t*-test.
Abbreviations: POMS, Profile of Mood States; SF-36, 36-Item Short Form Health Survey.

oxygen to do its function which is prone to oxidation by the free radicals.[22] Thus, PM extract, along with other natural herbs, has shown to have a neuroprotective effect in human as noted in this study.

The PM extract was safe to use as indicated by no significant changes in liver function, kidney function, and other blood indices in the study subjects, these findings were supported by findings from a recent study which also reported the safety of supplement contains a mixture of herbs, including PM extract on liver and kidney function.[53] However, in a retrospective review study on the risk assessment of using *Polygonum multiflorum*, on liver function, liver damage was reported in some cases. The safety of this herb may be affected by the type of the species, type of extract, dose, and duration of the intervention. It should be noted that this study documented the safety of another species of *Polygonum* which is PM aqueous extraction using a specific dose of 500 mg/day and 6 weeks intervention period.

This research has some strengths, including the use of randomized, placebo-controlled, double-blind study design, a full 6 weeks of supplementation, blood monitoring at baseline and post-treatment, and multiple assessments of many cognitive functions. However, this study also has

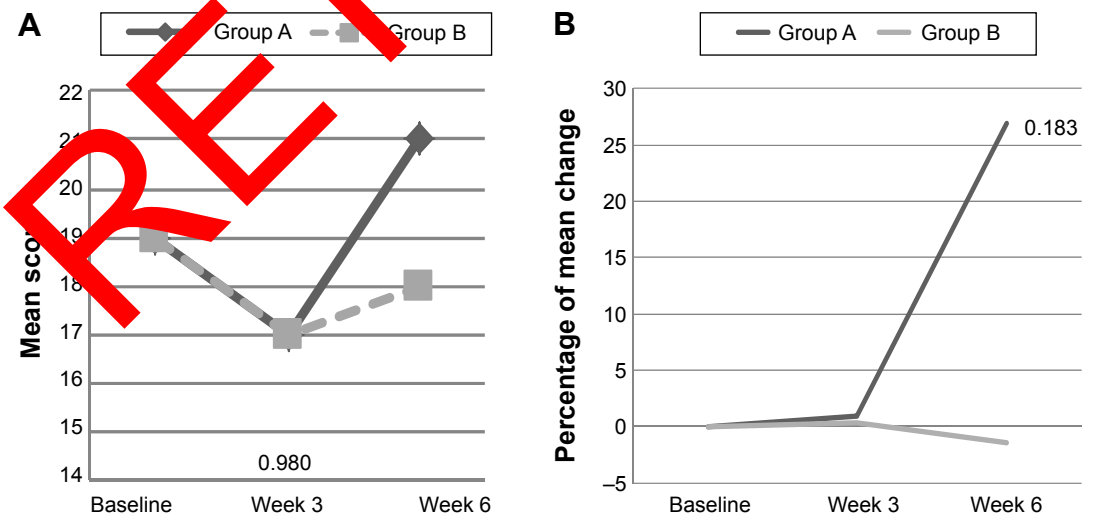

Figure 6 (**A**) The mean score of vigor at baseline, week 3, and week 6 among subjects with mood disturbance according to study groups. (**B**) The percentage of mean change for vigor from baseline to week 3 and week 6 among subjects with mood disturbance according to study groups.
Notes: A, placebo group; B, *Polygonum minus* group. Mood disturbance = POMS >15. Non-significant independent *t*-test.
Abbreviation: POMS, Profile of Mood States.

Table 5 Profile of anthropometric parameters at baseline, week 3, and week 6 according to mood status (mean ± SD)

Parameter	Group A (n=18), mean ± SD	Group B (n=17), mean ± SD	Group effect			Time effect			Intervention effect		
			P-value	η_p^2	Power	*P*-value	η_p^2	Power	*P*-value	η_p^2	Power
Weight (kg)											
Baseline	67.3±9.7	66.9±11.7	0.933	0.000	0.051	0.046*	0.089	0.598	0.611	0.015	0.128
Week 3	67.6±9.7	67.4±11.7									
Week 6	67.5±9.8	67.1±11.5									
BMI (kg/m^2)											
Baseline	27.7±3.9	28.2±5.0	0.728	0.004	0.063	0.045*	0.090	0.601	0.589	0.016	0.134
Week 3	27.8±3.8	28.4±5.0									
Week 6	27.8±3.9	28.2±5.0									
Fat percentage											
Baseline	37.8±5.0	37.3±4.9	0.789	0.002	0.058	0.253	0.041	0.291	0.991	000	0.051
Week 3	38.2±4.8	37.7±5.3									
Week 6	38.1±4.5	37.7±4.7									
Systolic (mmHg)											
Baseline	118±20.6	117±17.9	0.812	0.002	0.056	0.880	0.00	0.0	0.878	0.004	0.069
Week 3	119±16.1	117±15.0									
Week 6	117±12.3	117±13.6									
Diastolic (mmHg)											
Baseline	75±14.7	72±13.7	0.630	0.007	0.076	0.016*	0.1	0.739	0.627	0.014	0.124
Week 3	70±11.2	67±8.3									
Week 6	69±10.4	69±9.3									

Notes: *Significant at $P<0.05$ using two-way repeated measures ANOVA. A, placebo g up; B, *Polygonum* us group.
Abbreviations: ANOVA, analysis of variance; BMI, body mass index; η_p^2, partial eta squ d; SD, standard viation.

several limitations. For example, although the cognitive sts completed by the subjects were objective, st dized t based on well-known, validated measur of neu psych logical functioning, several of the subt s on th Vital Signs battery are relatively brief d ma t be sensitive enough to detect very subtle c es in neuro chological functioning.[28] Future resea h may ish to include objective assessments of c itive functi such as magnetic resonance imaging.

The cognitive asur in this study were administered 3 weeks ap thus s possi e that improvements in performa ce due o prac r learned effects may have obscu the a y to detect any direct effects of study products cognitive functioning. Future studies using alternative re arch designs with longer study duration may help to clarify th s concern. In addition to this, we attribute the lack of statistical significance in our study due to small sample size and short duration of study. Thus, a future higher-powered study is needed to investigate an appropriate number of individuals to generate further statistically significant results with a wide range of population that include different sex and races. Overall, the findings of this study were the first to demonstrate the cognitive function and psychosocial status following supplementation of water t of PM (LineMinus™) for 6 weeks with no adverse effect on blood biomarkers including liver and renal function and also blood sugar and fasting serum lipid. However, the results have to be taken with caution, because not all components of cognitive functions and psychosocial status were shown to be statistically significant. Further research is required to assess the neurocognitive effects of PM in other populations (eg, older individuals and those with cognitive problems).

Conclusion

This study showed that PM supplementation (LineMinus™) improved both attention and short-term memory and quality of life for social functioning domain among women with mood disturbance in this study. Analysis in a subgroup with good mood indicated that the supplementation improved the IQ of the women in this study. Supplement given at a dosage of 500 mg/day was also proved to be safe with no adverse or toxicity effect on health has assessed using several biomarkers. There is a need to further investigate the beneficial effect of the supplementation among other vulnerable groups such as older adults, for a longer period of study and involving objective measures and biomarkers associated with cognition.

Table 6 Profile of biochemical at baseline and week 6 according to mood status (mean ± SD)

Parameter	Group A (n=18), mean ± SD	Group B (n=17), mean ± SD	Group effect			Time effect			Intervention effect		
			P-value	η_p^2	Power	*P*-value	η_p^2	Power	*P*-value	η_p^2	Power
Sodium (mmol/L)											
Baseline	141±1.6	141±2.1	0.353	0.026	0.150	0.000*	0.323	0.971	0.072	0.095	0.437
Week 6	143±1.9	141±2.6									
Potassium (mmol/L)											
Baseline	4.2±0.2	4.3±0.4	0.762	0.003	0.060	0.045*	0.116	0.525	0.083	0.088	0.410
Week 6	4.5±0.5	4.4±0.4									
Urea (mmol/L)											
Baseline	3.7±1.1	3.7±0.8	0.830	0.001	0.055	0.323	0.030	0.164	0.210	0.047	0.237
Week 6	3.7±0.9	3.5±1.0									
Uric acid (μmol/L)											
Baseline	302±65.4	303±71.3	0.658	0.006	0.072	0.009*	0.189	0.767	[illegible]	0.04[illegible]	0.240
Week 6	291±69.5	271±57.2									
Creatinine (μmol/L)											
Baseline	60±7.6	61±9.1	0.596	0.009	0.081	0.000*	0.511	[illegible].000	[illegible].991	[illegible].000	0.050
Week 6	65±8.8	67±9.9									
eGFR (mL/min/1.73 m^2)											
Baseline	96±15.5	95±19.9	0.856	0.001	0.054	0.000*	[illegible].516	1.000	[illegible].99	0.000	0.050
Week 6	87±13.0	86±18.2									
Total protein (g/L)											
Baseline	78±3.4	79±3.3	0.354	0.026	0.150	[illegible]	0.166	[illegible]01	0.616	0.008	0.078
Week 6	77±3.0	78±4.6									
Albumin (g/L)											
Baseline	45±2.1	45±2.9	0.953	0.000	0.050	[illegible].112	[illegible]75	0.355	0.605	0.008	0.080
Week 6	45±1.9	44±3.3									
Globulin (g/L)											
Baseline	33±3.7	35±3.5	0.403	0.020	[illegible].131	[illegible]071	0.095	0.441	0.640	0.007	0.074
Week 6	33±2.9	33±4.5									
Bilirubin (μmol/L)											
Baseline	11±5.9	11±4.9	0.[illegible]	[illegible]4	[illegible]	0.083	0.088	0.411	0.330	0.029	0.161
Week 6	10±6.5	9±3.4									
Alkaline phosphatase (U/L)											
Baseline	74±20.2	73±14.7	0.709	0.004	0.066	0.407	0.021	0.129	0.395	0.022	0.133
Week 6	74±19.7	77±2[illegible]									
GGT (U/L)											
Baseline	27±21.1	[illegible]±12.9	0.[illegible]	0.010	0.087	0.437	0.018	0.119	0.491	0.014	0.104
Week 6	27±20.0	35±41.[illegible]									
Aspartate transferase (U/L)											
Baseline	23±7.1	[illegible]±6.7	0.422	0.020	0.124	0.093	0.083	0.389	0.191	0.051	0.254
Week 6	24±[illegible]	[illegible]±30.4									
Alanine transaminase (U/L)											
Baseline	22±11.[illegible]	20±14.5	0.354	0.026	0.150	0.222	0.045	0.227	0.092	0.084	0.393
Week 6	[illegible]	35±40.6									
Total cholesterol (mmol/L)											
Baseline	5.4±0.[illegible]	5.3±1.2	0.942	0.000	0.051	0.654	0.006	0.072	0.500	0.014	0.102
Week 6	5.4±0.9	5.4±1.3									
Triglycerides (mmol/L)											
Baseline	0.9±0.4	0.9±0.2	0.672	0.005	0.070	0.200	0.049	0.246	0.462	0.017	0.112
Week 6	0.9±0.3	1.0±0.5									
HDL (mmol/L)											
Baseline	1.5±0.3	1.7±0.4	0.112	0.075	0.354	0.128	0.069	0.328	0.362	0.025	0.146
Week 6	1.5±0.3	1.7±0.5									
LDL (mmol/L)											
Baseline	3.5±0.9	3.2±1.0	0.429	0.019	0.121	0.545	0.011	0.091	0.872	0.001	0.053
Week 6	3.5±0.8	3.3±1.0									

(*Continued*)

Table 6 (*Continued*)

Parameter	Group A (n=18), mean ± SD	Group B (n=17), mean ± SD	Group effect			Time effect			Intervention effect		
			P-value	η_p^2	Power	*P*-value	η_p^2	Power	*P*-value	η_p^2	Power
Total cholesterol/HDL (mmol/L)											
Baseline	3.7±1.1	3.2±0.7	0.142	0.064	0.309	0.019*	0.156	0.670	0.460	0.017	0.112
Week 6	3.8±1.0	3.4±0.9									
HbA_{1C} (%)											
Baseline	5.9±0.8	5.7±0.4	0.325	0.029	0.163	0.000*	0.559	1.000	0.285	0.035	0.184
Week 6	5.6±0.7	5.4±0.3									

Notes: Significant at *$P<0.05$ using two-way repeated measures ANOVA. A, placebo group; B, *Polygonum minus* group.
Abbreviations: ANOVA, analysis of variance; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA_{1C}, hemoglobin A_{1C}; HDL, high density lipoprotein; LDL, low density lipoprotein; η_p^2, partial eta squared; SD, standard deviation.

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Author contributions

SS had access to all data and was involved in the overall study design, interpretation of the data, and revising the manuscript. AFA was involved in interpretation of data, drafting, and revising the manuscript. NCD, ZAM and MMB made substantial contributions to conception and study design. Both NCD and MMB were also involved in the planning of statistical analyses and revising the manuscript. HMY contributed in conception of the study, supervising the fieldwork, and revising the manuscript. SSAI performed statistical analyses, interpreted the data, and revised the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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