

Ginger Supplementation Enhances Working Memory of the Post-Menopause Women

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Abstract: Problem statement: Cognitive impairment is one important problem in post-menopausal women. Although hormone therapy can improve this condition, it also produces adverse effect. Recent findings showed that this condition could be mitigated by the herb. Ginger or *Zingiber officinale* Roscoe, a plant in a family of Zingiberaceae, was previously demonstrated the neuroprotection and cognitive enhancing effects. Therefore, this study was set up to determine whether ginger rhizome extract could improve attention and working memory of the post-menopausal women. **Approach:** Sixty healthy post-menopausal women were randomly assigned to receive either placebo or standardized plant extract at doses of 400 and 800 mg once daily for 3 months. After the assessment of biographic information, they were evaluated the working memory and cognitive function using computerized battery test and the auditory oddball paradigm of event related potential before and after 3-month of intervention. **Results:** The ginger treated group decreased N100 and P300 latencies but increased N100 and P300 amplitudes in accompany with the enhanced working memory including the power of attention, continuity of attention, speed and quality of memory. **Conclusion:** Our results suggested that ginger is the potential cognitive enhancer for post-menopausal women. However, further researches are still required.

Key words: Ginger rhizome, *Zingiber officinale*, attention impairment, working memory, post-menopausal women, computerized battery, ginger extract, intellectual function

INTRODUCTION

Episodic memory decline and attention impairment are recognized as the important disturbances commonly found in post-menopausal period and normal aging (Weber and Mapstone, 2009; Perfect and Maylor, 2000; Halbreich *et al.*, 1995). Several lines of evidence demonstrated that cognition declined progressively over the menopause, with significant diminution processing speed and working memory (Greendale *et al.*, 2010;

Schaafsma *et al.*, 2010). Recent findings showed that this condition could be improved by Hormone Replacement Therapy (HRT) (Khoo *et al.*, 2010; Sherwin, 2005; Rocca *et al.*, 2010). However, numerous adverse effects were reported (Anderson *et al.*, 2003; Beral, 2003; Beral *et al.*, 2007; Calle *et al.*, 2009; Rugg and Coles, 1995; Hildebrand *et al.*, 2010; Daniel and Bohacek, 2010). Due to the limitation of therapeutic efficacy, many post-menopause women preferred using Complementary and Alternative

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Medicine (CAM) therapies (Borrelli and Ernst, 2010). Herbal medicine and dietary supplements is the most commonly used strategies among various alternative strategies (Low, 2005; Kronenberg and Fughh-Berman, 2002; Wattanathorn *et al.*, 2008a; 2008b; Tong-Un *et al.*, 2010). Ginger or *Zingiber officinale* is belonging to Zingiberaceae family. It has been long-term used as both spicy and medicine in Asian, Indian and Arabian folklore. The rhizome of *Z. officinale* exhibits a wide range of pharmacological properties including antilipidemia (Verma and Bordia, 2001), anti-emetic (Langner *et al.*, 1998), anti-inflammation and anti-arthritis (Srivastava and Mustafa, 1992). In Ayurveda, Traditional Chinese Medicine and Arabic Medicine, ginger has been reported to use for managing memory impairment either as ginger extract, ginger tea or as ingredient in food formulations and preparation (Keith, 2006). Recently, it was found that ginger could suppress acetylcholinesterase (Oboh *et al.*, 2010) and improved memory impairment in animal model of stroke (Wattanathorn *et al.*, 2011). Although ginger has been long-term used in traditional folklore to enhance memory, less clinical evidence is available until now. Therefore, the present study was carried out to determine the effect of ginger extract on working memory and attention in postmenopausal women.

MATERIAL AND METHODS

Participants: Sixty healthy Thai middle aged women (mean age 53.40 ± 3.57 years) were recruited to participate in this project, which was approved by the Ethical Committee of Faculty of Medicine, Khon Kaen University. Prior to the investigation, each volunteer must sign an inform consent form, completed the medical healthcare questionnaire and the participants must also be screened for physical health by the physician in order to assure the health condition. Inclusion criteria are included healthy, middle-aged women between the ages of 50 and 60, who has experienced at least twelve consecutive months of amenorrhea. Exclusion criteria included any history of cardiovascular diseases, respiratory diseases, neuropsychological diseases, head injury, diabetes, cancer, alcohol addiction, smokers of more than 10 pieces per day. Any persons taking prescribed and non-prescribed drugs or nutraceutical compounds influencing the function of the nervous system were excluded. The study target was not elderly postmenopausal women. We also excluded very young and oophorectomized woman whom a fall in hormones could have more intense effect. The participants were randomly divided into 3 separated groups including placebo, *Zingiber officinale* 400 and 800 respectively.

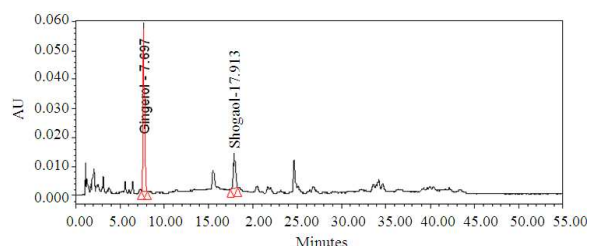


Fig. 1: HPLC Chromatogram (high performance liquid chromatography) of *Zingiber officinale* extract. Column: Luna C₁₈ 4.6×150 mm. Mobile phase: water/acetonitrile (gradeint)

The preparation of the standardized extract of *Zingiber officinale*:

A standardized extract of *Zingiber officinale* was prepared by the Thailand Institute of Scientific and Technological Research in Pathumthani, Thailand. Standardization and conformity of the extract were assured by strict in-process controls during manufacture and complete analytical control of the resulting dry extract. In brief, the dried ginger rhizome powder was extracted with 95% ethanol in a stainless steel tank for 5-10 days. The filtrate was evaporated to dryness under a vacuum at 35°C on a rotary evaporator. The production yield of the extract was 6.84% w/w. The phenolic compound of standardized ginger extract contained 7.33% w/w of 6-gingerol and 1.34% w/w of 6-shogaol. *Zingiber officinale* was analyzed by HPLC (high performance liquid chromatography) as shown on Fig. 1. This fingerprint has been prepared by Mrs. Tanwarat Kajsongkram, Thailand Institute of Scientific and Technological Research (TISTR), Pathumthani, Thailand

Procedures and treatments: This study was conducted as a 3 month, double-blind, placebo-controlled and randomized trial. A random list of numbers was generated by computer. After being randomly assigned to various treated groups, each participant received one capsule of either placebo or ginger extract at various doses ranging from 400 and 800 mg once daily. The placebo and ginger capsules had the same color, texture, size and odor. All participants were screened for their baseline intellectual function using Standard Progressive Matrices (SPM) in order to avoid confounding error induced by the intellectual function problem. Then, they were assessed the cognitive processing ability and working memory after 3 months of treatment.

ERP recording: All subjects were assessed for cognitive performance using the classic “oddball paradigm” of auditory event-related potentials (N100 and P300 amplitudes and latencies) (Kennedy *et al.*, 2003). The Electroencephalogram (EEG) was recorded

via Cz and linked mastoids were used as reference for the electrode. The resistance of the electrodes was kept below 5 kohm. The analog filter band pass was 1-100 Hz (Drake *et al.*, 1989). For each stimulus, an epoch of 500-ms duration including a 100-ms pre-stimulus period was extracted from the continuous EEG. Epochs with a voltage change below 0.1 μ V or above 70 μ V were rejected from further analysis.

ERP measurement: The subjects listened to a train of tone bursts presented binaurally through headphones. The standard stimuli had a tonal frequency of 650 Hz (60 dB, 200 ms) and occurred with a tonal frequency of 80%. The target stimuli had a tonal frequency of 1 kHz (60 dB, 200 ms) and occurred with a probability of 20%. All participants were informed to pay attention and mentally count infrequent target tones. Inter-stimulus intervals varied randomly between 1250 and 3000 ms. The N100 latency range was determined to be 65-135 ms and the P300 latency range was determined to be 280-375 ms. Both the latency and maximum amplitudes were measured for N100 and P300 deflections. Any peaks outside of this range were measured manually and all peaks were visually examined prior to measurement.

Computerized assessment battery test: The computerized assessment battery test was modified from the CDR computerized assessment battery test used in hundreds of European and North American drug trials. It is sensitive to acute cognitive improvements as well as impairments with a wide variety of substances (Moss *et al.*, 1998; Wesnes, 2001). Presentation was performed using notebook computers with a high-resolution VGA colour monitor and, with the exception of written word recall tests, all responses were recorded via a two-button (yes/no) response box. The entire selection of tasks took approximately 20 min. Tests were administered in the following order: word presentation, picture presentation, simple reaction time, digit vigilance task, choice reaction time, spatial working memory, numeric working memory, delayed word recognition and delayed picture recognition.

Word presentation: Fifteen words, matched for frequency and concreteness, were presented in sequence on the monitor for the participant to remember. The stimulus duration was 1 s, as was the inter-stimulus interval.

Picture presentation: A series of 20 photographic images was presented on the monitor at the rate of 1 every 3 s, with stimulus duration of 1 s, for the participant to remember.

Simple reaction time: The participant was instructed to press the 'yes' response button as quickly as possible every time the word 'yes' was presented on the monitor. Fifty stimuli were presented with an inter-stimulus interval that varied randomly between 1 and 3.5 s. Reaction times were recorded in milliseconds.

Digit vigilance task: A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the centre of the screen at the rate of 80/min and the participant was required to press the 'yes' button as quickly as possible every time the digit in the series matched the target digit. The task lasted 1 min and there were 15 stimulus-target matches. Task measures were accuracy (%), reaction time (milliseconds) and false alarms.

Choice reaction time: Either the word 'no' or the word 'yes' was presented on the monitor and the participant was required to press the corresponding button as quickly as possible. There were 50 trials of which the stimulus word was chosen randomly with equal probability, with a randomly varying inter-stimulus interval between 1 and 3.5 s. Reaction times (millisecond) and accuracy (%) were recorded.

Spatial working memory: A pictorial representation of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorize the position of the illuminated windows. In 36 subsequent presentations of the house, one of the windows was illuminated and the participant decided whether or not this matched one of the lighted windows in the original presentation. The participant made their response by pressing the 'yes' or 'no' response button as quickly as possible. Mean reaction times were measured in milliseconds and the accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages used to derive a 'percentage greater than chance performance' score.

Numeric working memory: Five digits were presented sequentially for the participant to hold in memory. This was followed by a series of 30 probe digits for each of which the participant decided whether or not it had been in the original series and pressed the 'yes' or 'no' response button as appropriate and as quickly as possible. This was repeated two further times with different stimuli and probe digits. Mean reaction times were measured in milliseconds and the accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages that were used to derive a 'percentage greater than chance performance' score.

Delayed word recognition: The original words and 15 distractor words were presented one-at-a-time in randomized order. For each word, the participant indicated whether or not she recognized it as being included in the original list of words by pressing the 'yes' or 'no' button as appropriate and as quickly as possible. Mean reaction times were measured in milliseconds and the accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages that were used to derive a 'percentage greater than chance performance' score.

Delayed picture recognition: The original pictures and 20 distractor pictures were presented one-at-a-time in a randomized order. For each picture, participants indicated whether or not it was recognized as being from the original series by pressing the 'yes' or 'no' button as appropriate and as quickly as possible. Mean reaction times were measured in milliseconds and the accuracy of responses to both original and novel (distractor) stimuli were recorded as percentages that were used to derive a 'percentage greater than chance performance' score.

Statistical analysis: Comparison between doses was made using Analysis of Variance (ANOVA) and followed the recommendations of Keppel and Wickens (2004), with planned comparison being made between the placebo and each of the two active treatments utilizing t tests. Statistical significance was regarded at p-value <0.05

RESULTS

Demographic data of subjects: The baseline data about characteristic of subjects in all groups were shown in Table 1. No significant difference of all parameters among various groups was observed.

Effect of *Zingiber officinale* on event-related potential components (ERP): The effects of *Zingiber officinale* on ERP components were shown in Table 2 and Fig. 2. The pre-dose baseline data of latency and amplitude of both N100 and P300 of various groups showed no significant difference [$f(2,57) = 0.3765, p = 0.6879; f(2,57) = 0.1865, p = 0.8303; f(2,57) = 0.0408, p = 0.9600$ and $f(2,57) = 0.0138, p = 0.9863$, respectively]. It was found that when the treatment was prolonged further to 3 months, the subjects who received *Zingiber officinale* at doses of 400 and 800 mg showed the enhanced amplitudes of both N100 ($t = 3.6444, p = 0.0004; t = 4.1137, p = 0.0001$) and P300 ($t = 2.1654, p = 0.0183; t = 3.2504, p = 0.0012$) respectively compared to placebo treated group.

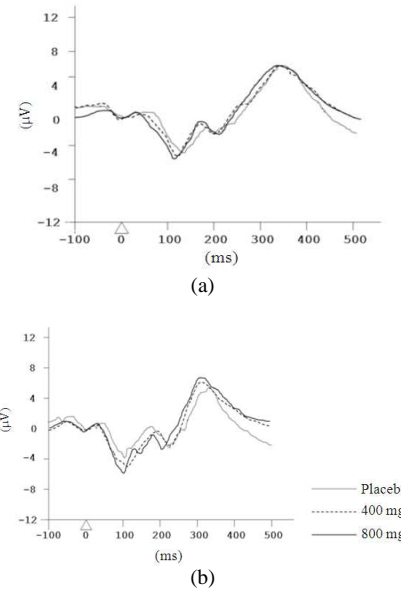


Fig. 2: Average waveforms of the auditory event related potential at electrode Cz at various periods of treatment; (a) Pre-dose baseline, (b) 3rd month after substance administration

Table 1: Demographic data of subjects

Baseline data	Placebo	400 mg	800 mg
Age (years)	53.92±3.82	54.33±4.12	54.33±3.17
Education (years)	5.50±3.70	5.40±3.68	5.15±2.74
Full scale IQ	98.95±4.42	99.75±4.23	98.85±6.01
Blood sugar	90.06±8.45	89.10±13.08	91.15±10.16
Body mass index	21.95±1.90	22.78±2.06	23.12±1.83
Systolic blood pressure (mmHg)	121.00±7.72	117. ±8.49	117.85±9.76
Diastolic blood pressure (mmHg)	82.25±2.53	82.80±2.73	80.50±3.73
Menstrual cessation (years)	3.95±1.60	3.75±1.48	4.05±1.57

Data were presented as mean ± SD. f and p-value were compared between groups (n = 20/group)

Table 2: Effect of *Zingiber officinale* on event-related potential

Wave	Pre-dose baseline score	Post-dose score 3 month
N100 latency	Placebo	116.80±1.385
	400 mg	114.35±11.44
	800 mg	114.05±8.31
N100 amplitude	Placebo	5.70±10.08
	400 mg	5.90±1.37
	800 mg	5.75±1.29
P300 latency	Placebo	332.70±12.96
	400 mg	332.25±13.81
	800 mg	332.90±10.20
P300 amplitude	Placebo	7.25±1.10
	400 mg	7.25±1.01
	800 mg	7.20±1.10

The amplitudes and latencies of event-related potential elicited by oddball paradigm at Cz electrode were measured. Data are presented as mean ±SD (n = 20/group). *, **, ***= P-value < 0.05, 0.01 and 0.001 compare to placebo treated group respectively

Table 3: Effect of *Zingiber officinale* on working memory assessing via computerized battery test

Measurement		Pre-dose baseline score	Post-dose score 3 month
1. Word recognition (%accuracy)	Placebo	72.99±8.97	75.00±9.70
	400mg	74.83±8.27	81.10±6.36*
	800mg	74.83±13.39	85.07±6.85***
2. Word recognition reaction time (msec.)	Placebo	1242.56±217.14	1241.26±201.04
	400mg	1226.06±161.82	1092.20±94.84**
	800mg	1261.14±176.75	1077.15±100.74**
3. Simple reaction time (msec.)	Placebo	619.05±222.35	621.70±146.77
	400mg	616.25±195.39	583.00±160.06
	800mg	623.25±191.43	568.35±59.91
4. Digit vigilance (%accuracy)	Placebo	43.35±6.84	43.75±6.47
	400mg	42.90±5.05	43.55±4.97
	800mg	44.75±5.63	50.35±5.62***
5. Digit Vigilance reaction time (msec.)	Placebo	631.65±140.92	627.20±109.61
	400mg	620.00±122.74	546.95±39.74**
	800mg	623.75±109.55	516.00±69.15***
6. Digit vigilance false alarm number	Placebo	8.85±2.39	8.2±1.39
	400mg	8.85±2.18	7.05±1.43**
	800mg	8.65±2.13	6.75±1.29***
7. Choice reaction time (%accuracy)	Placebo	79.90±7.40	80.45±7.18
	400mg	80.00±8.86	88.15±8.17**
	800mg	79.05±8.53	91.25±10.25***
8. Choice reaction time response (msec.)	Placebo	976.00±168.70	967.45±108.52
	400mg	964.55±191.10	880.95±100.66**
	800mg	980.35±197.24	860.65±108.11**
9. Numeric working memory (%accuracy)	Placebo	73.90±10.40	75.95±10.73
	400mg	75.50±8.67	83.95±9.19**
	800mg	76.45±9.69	84.90±5.66**
10. Numeric working memory reaction time (msec.)	Placebo	1334.50±226.25	1322.60±171.31
	400mg	1339.40±234.61	1310.70±174.98
	800mg	1335.60±260.95	1305.65±214.19
11. Picture recognition (%accuracy)	Placebo	72.99±8.97	75.00±9.71
	400mg	74.83±8.27	81.10±6.37
	800mg	74.83±13.39	85.07±6.86***
12. Picture recognition reaction time(msec.)	Placebo	1256.88±239.51	1241.26±201.04
	400mg	1224.88±185.08	1092.20±94.84
	800mg	1234.61±197.52	1077.15±100.74**
13. Spatial working memory (%accuracy)	Placebo	66.25±6.64	67.10±4.62
	400mg	66.11±5.47	70.73±4.37**
	800mg	66.33±6.88	71.90±3.51***
14. Spatial working memory reaction time(msec.)	Placebo	1799.25±33.45	1821.30±289.87
	400mg	1784.30±191.92	1695.65±255.55
	800mg	1712.75±219.45	1467.85±197.52 ***

Subjects were measured power of attention, continuity of attention, speed of memory and quality of memory by using computerized battery test. Data are presented as mean ± SD (n=20/group). *, **, ***= P-value < 0.05, 0.01 and 0.001 compare to placebo treated group respectively

The current data also showed that subjects who received *Zingiber officinale* at dose of 800 mg significantly decreased the latencies of both N100 (t = 3.3936, p = 0.0008) and P300 (t = 3.7677, p = 0.0003) compared to placebo treated group. However, the participants who obtained *Zingiber officinale* at dose of 400 mg showed the significant change only in P300 latency (t = 2.3654, p = 0.0116) compared to placebo treated group while no significant reduction of N100 latency was observed.

Effect of *Zingiber officinale* on working memory

Prior to the determination of *Zingiber officinale* on working memory, baseline data and mean pre-dose raw baseline scores for all three conditions (placebo, 400

and 800 mg *Zingiber officinale*) for each individual task scores were subjected to a one-way ANOVA. No significant changes of all parameters were observed.

Mean raw baseline scores and changes from baseline scores for each condition across each session are presented in the Table 3. It was found that at 3 months, subjects who consumed *Zingiber officinale* at dose of 400 mg/day decreased the reaction time of word recognition time (t = 2.9989, p = 0.0024), digit vigilance test (t=3.0781, p= 0.0019) and choice reaction time (t = 2.6134, p = 0.0064) and increased %accuracy of word recognition (t = 2.3483, p = 0.0121), choice reaction (t = 3.1633, p = 0.0015), numeric working memory (t = 2.5332, p = 0.0078) and spatial working memory (t = 2.5505, p = 0.0075). The subjects who had consumed the plant extract at dose of 800 mg/day significantly increased %accuracy of word recognition (t = 3.7911, p = 0.0003), digit vigilance (t = 3.4431, p = 0.0007), choice reaction time (t = 3.8575, p = 0.0002), numeric working memory (t = 3.3002, p = 0.0011), picture recognition (t = 3.4512, p = 0.0007) and spatial working memory (t = 3.6946, p = 0.0003) and decreased the reaction times of numerous parameters including word recognition (t = 3.2638, p = 0.0012), digit vigilance (t = 3.8371, p = 0.0002), choice reaction time (t = 3.1178, p = 0.0017), picture recognition (t = 2.8422, p = 0.0036) and spatial working memory (t = 3.9179, p = 0.0002). Therefore, our data suggested that the plant extract at doses used in this study significantly improved the following parameters (1) power of attention indicating by the decreased reaction times of simple reaction time, choice reaction time and digit vigilance tests, (2) the continuity of attention or accuracy of attention reflecting by the elevation of %accuracy of the parameters mentioned above (3) the speed of memory which indicated by the reduction of reaction time of another parameters mentioned the computerized battery test used in this study (4) quality of memory indicating by the %accuracy of the same parameters as mentioned in 3).

DISCUSSION

Our data clearly demonstrated the cognitive enhancing effect of ginger extract in the post-menopausal women. The consumption of ginger rhizome extract for 3 months significantly enhanced both attention and working memory.

Presently, it is well established that the components of Event Related Potential (ERP) were sensitive to attention and working memory demand of task (Gevens *et al.*, 1996; McEvoy *et al.*, 1998). It was reported that a large positive voltage deflection in an

interval between 300-500 ms following stimulus onset which known as P3 or P300 (Picton, 1992) was corresponding to mental process such as recognition, categorization of stimuli and expectancy or short-term memory. The amplitude of this wave was correlated with individual differences in working memory capacity (Nittono *et al.*, 1999) while its latency was regarded as a measurement of relative timing of the stimulus evaluation process which in turn indicated stimulus evaluating time (Rugg and Coles, 1995). In addition, it was also reported that N100 latency reflected process of activation of attention, analysis of information on physical characteristics of the sound while its amplitude was associated with the enhanced memory performance (Parageorgiou *et al.*, 2009) such as attention (Picton and Hillyard, 1974), expectancy (Starr *et al.*, 1997) and tasks involving short-term memory (Kaufman *et al.*, 1992).

In addition to the event related potential, reaction time and %accuracy of numerous psychological tests were also used as validated tools for assessing attention and memory. It was reported that power of attention could be evaluated using reaction time in choice reaction time and digit vigilance tests while continuity of attention was also able to be evaluated by using the %accuracy tests mentioned earlier. Moreover, speed and quality of memory were also evaluated by using reaction time and %accuracy of numeric working memory, spatial memory and word and picture recognition (Kennedy *et al.*, 2007). It was reported that lateral prefrontal cortex and monoamine system especially dopamine and norepinephrine played an important role on the numeric, word and picture recognition memory (D'Esposito *et al.*, 1999; Smith and Jonides, 1999) while acetylcholine and serotonin in hippocampus simultaneously activated during performing spatial working memory (Moser and Moser, 1998; Stancampiano *et al.*, 1999).

Previous studies also demonstrated that ginger or *Zingiber officinale* could enhance the level of norepinephrine, epinephrine, dopamine and serotonin contents in cerebral cortex and hippocampus (Waggas, 2009), the areas contributing the important role on working memory (D'Esposito *et al.*, 1999; Smith and Jonides, 1999; Moser and Moser, 1998; Stancampiano *et al.*, 1999). It also enhanced the memory performance induced by cerebral ischemia by decreasing infarct volume in both cortical and subcortical area (Wathanatorn *et al.*, 2011). Furthermore, it could suppress AChE activity (Oboh *et al.*, 2010). Therefore, taken all together, we suggest that the cognitive enhancing effect of *Zingiber officinale* might be partly associated with the modulation effect of this plant

extract on the alteration of both monoamine system and the cholinergic system in cerebral cortex and hippocampus. However, the precise underlying mechanism is still required for further investigation.

CONCLUSION

In conclusion, the present study demonstrates that *Zingiber officinale* extract is the potential candidate cognitive enhancer for post-menopausal women. However, the precise underlying mechanism and the possible active ingredient further investigations are still required.

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