

## Abstrac

**Objectives:** To assess efficacy of aromatherapy on cognition and BPSD symptoms in patient with mild cognitive impairment in Prasat Neurological Institute.

**Methods:** This study is prospective study at Prasat Neurological Institute, 35 patients who diagnosed with mild cognitive impairment between May1, 2017 and September 30, 2017 were included in this study. Intervention consists of inhalation essential oil rosemary (*Rosmarinus officinalis* L.) about 30 minutes before bedtime for 6 weeks. MOCA, The Hamilton rating scale for anxiety (HAM-A), NPI-Q tests were evaluated before and after aromatherapy intervention.

**Results:** 35 patients with MCI were enrolled in the study. Baseline MOCA score before intervention was 22 that was not different after intervention. In subgroup analysis, domain of delayed recall was improved significantly in statistic ( P value 0.007). NPI-q distress score and HAM-A after intervention had improvement significantly ( both P value 0.001). Median NPI-q severity score was not different before and after intervention.

**Conclusion:** Rosemary aromatherapy seems to be safe and effective for improving cognitive and behavioral problems in people with MCI.

**Keywords:** Aromatherapy, Non-pharmacological therapy, Mild cognitive impairment, Dementia, Essential oil

## Background

Mild cognitive impairment (MCI) is a condition of decline in one or more cognitive domains such as memory, visuospatial skills, executive function, attention and language that is greater than would

# Effect of Aromatherapy on Patient with Mild Cognitive Impairment in Prasat Neurological Institute

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be expected for patient's age and educational background. Amnesic MCI is mostly common. They may take more time and more errors in complex tasks that they could perform well previously such as shopping, paying bills. Nevertheless, they can still maintain their independence of function in daily life. Previous studies showing that MCI increased risk of progression to dementia. Dementia presents as a major healthcare challenge with people suffering from this condition worldwide. Current pharmacological for dementia are merely palliative. The better choice is to slow down the progressive course from clinical of MCI to dementia<sup>1</sup>.

There are several trials of therapeutic drugs that inhibit progression but no specific drug that is silver bullet recently. No diseased-modifying agents that proved to be effective now. Acetylcholinesterase Inhibitors cannot prevent evolution of disease from MCI stage to dementia. It is also known that serious side effects of these drugs such as bradycardia must be cautioned. Several studies found that non-pharmacological treatments may have benefits in MCI patients. Nowadays, the traditional non-pharmacological treatments include behavioral therapy, reality orientation approach and validation therapy, cognitive therapy, multisensory therapies and aromatherapy<sup>2</sup>.

Essential oils have been used to treat symptoms and diseases for thousands of years. The term aromatherapy was used by a French chemist Gattefosse who had published a text in 1936. Aromatherapy is the therapeutic use of essential oil from herbs, and other plants. Essential oils evaporated readily and particles travel directly through the olfactory bulb to the limbic system. An essential oil can also be anticipated to have a strong sedative agent. Rosemary (*Rosmarinus officinalis* Linn.) be-

longing to the family of Lamiaceae bear small pale blue flowers that has three varieties (silver, gold and green stripe); it's the green variety that is used for its medicinal properties. Rosemary had been widely investigated for a potential role in reducing cognitive decline. Orhan et al. proposed the effect of rosemary were determined by slightly modifying the spectrophotometric method developed by Ellman method and found that rosemary has effect on inhibition of acetylcholinesterase (ACh) and butyrylcholinesterase enzymes (BuChE)<sup>3</sup>.

From the mechanism that inhibits cholinesterase especially BuChE, rosemary essential oil had been widely studied in many researches such as healthy group, normal elderly group and Alzheimer's group. In our study, we focus on mild cognitive impairment group.

There are studies reporting on the high olfactory threshold and a decline in olfactory function in Alzheimer's disease (AD). It is certain that olfactory perception declines over time, however the ability to recognize aromas remains. The majority of patients with AD do not completely lose their sense of smell. The nose contains 10-100 million receptors for olfaction. Olfactory membranes contain millions of nerve endings causing the sense of smell<sup>4</sup>. The limbic system of the brain plays a primary role in a range of emotions, including pain, pleasure, affection, and anger. It controls more subtle responses of emotion, and memory. The olfactory nerves are directly connected to the limbic system of the brain, thus the stimulation by the aroma also effects on mood and memory function.

Therefore, the aim of this study is to assess efficacy of aromatherapy *Rosmarinus officinalis* L. on cognition and BPSD symptoms in patients with mild cognitive impairment in Prasat Neurological Institute.

## Objective

To assess efficacy of aromatherapy on cognition and BPSD symptoms in patient with mild cognitive impairment in Prasat Neurological Institute.

## Material and Methods

### Types of studies

This is a prospective pilot study. The patients who were diagnosed mild cognitive impairment in Prasat Neurological Institute between May 1, 2017 to September 30, 2017 were included in this study. Mild cognitive impairment was diagnosed according to DSM V criteria.

### The criteria included

- (i) Clinical concern raised by the patient or an informant or observations made by the clinician.
- (ii) Cognitive impairment in one or more cognitive domains preferably relative to appropriated normative data for that individual.
- (iii) Preservation of functional independence
- (iv) No dementia.

### Inclusion criteria

- 1) The patients who were diagnosed mild cognitive impairment
- 2) Amnesic MCI (memory dysfunction) or nonamnesic MCI (language, visuospatial, executive dysfunction)
- 3) No structural brain lesion

### The exclusion criteria

- 1) Defective Thai language communication.
- 2) No relatives can record the consistency of attendance.
- 3) MCI patients who get ACEI medications or NMDA antagonist.
- 4) Functional deficit of CN I
- 5) Sensory deprivation of visual and hearing

sensation that are not Corrected.

- 6) Asthma, COPD, hyperactive airway diseases and other chronic lung diseases.

### Type of intervention

Aromatherapy was performed via inhalation route everyday for 6 weeks, 30 minutes per session before bedtime. MCI patients were exposed to the 0.05 ml of rosemary essential oils. The oil were placed on the water in diffuser with electric fan. (all essential oils and diffusers in the present study were produced by the Peace of Mind Company :Tokyo Japan) The distance between diffuser and participants must be within the area of 20 square metres. The patients' co-operation was checked by recording in the notebook by caregivers and randomly phone called with caregivers.

### Outcome measures

#### Primary outcome

I: Cognitive function : Montreal Cognitive assessment (MOCA) (Solaphat Hemrungronj MD. Thai version 2007) : score 0 to 30 (cut points scale of interpretation as normal results is above 25)

#### Secondary outcome

I: BPSD : Neuropsychiatric Inventory Questionnaire (NPI-Q) : score of severity ranged from 0 (normal) to 36 (very depression) and score of distress ranged from 0 (normal) to 60 (very distress).

II: Anxiety mood : Hamilton rating scale for ANXIETY (HAM-A) The scale consists of 14 items designed to assess the severity of a patient's anxiety. Each of the 14 items contains a number of symptoms, and each group of symptoms is rated on a scale of 0 to 4, with score of 4 being the most severe.

Data collections were compared between before and after 6 weeks of interventions.

### Ethical issue

Prasat Neurological Institute ethic committee approved for this study.

### Statistical analysis

Using Wilcoxon Signed Ranks test, as appropriate. All of the tests were two sided, and p-value less than 0.05 were considered as statistical significance. All statistical analyzes were performed using SPSS version 16 for Windows programme.

## Results

### Demographic data

35 patients who diagnosed as MCI at outpatient clinic in Prasat Neurological Institute between May 1 2017, to September 30 2017, met eligibility criteria based on the inclusion and exclusion criteria detailed in approved protocol and agreed to participate in the study were recruited. No participants be discontinued during the study. The demographic data of patients were showed in Table 1.

Male to female ratio was 0.4:1. Their mean age at onset was 61.06 years (range 52-67 years). There was no significant difference in education, age at onset of symptoms, age at diagnosis of MCI, current medication, BMI, underlying disease, insomnia problem, hearing and visual problems and the first clinical presentation. All MCI patients in this study were amnesic type of MCI .

### Cognitive test: MOCA

Baseline median score before intervention (median 22.00) was not different from after intervention (median 22.00). In subgroup analysis, the median score in domain of delayed recall were improved significantly in statistic after 6 weeks of intervention. (P value 0.007) No difference in other domains was found before and after intervention.

### Mood test: HAM-A

There was different in statically in median scores before and after 6 weeks of intervention (4.00 and 1.00, respectively, P-value < 0.001). In subgroup analysis, there were also different median score significantly in statistic in domain of insomnia and depressed mood (both P value < 0.001). No difference of median score found in other domains before and after intervention.

### BPSD: NPI-Q

There was different in median scores significantly in statistic of NPI-Q distress before and after 6 week aromatherapy intervention (3.00, 1.00 respectively, P-value < 0.001). In subgroup analysis, median scores in domain of nighttime behavior were improved statistically significant (P-value < 0.001). There was also different in median scores significantly in statistic in domain of motor disturbance before and after intervention (P-value < 0.001). About NPI-Q severity scores, there're not found different in median scores of any domains.

## Discussion

Several studies<sup>5-11</sup> found that aromatherapy has benefits on dementia patients for decrease agitation, restlessness, and insomnia. The six placebo controlled trials<sup>5-11</sup> reported significant beneficial effects on BPSD and/or cognitive function. There are some reports of the effects of aromatherapy on the central features of dementia. Jimbo and his colleagues<sup>9</sup> showed that aromatherapy improved cognitive function significantly on both the Japanese version of the Goofries, Barene, Steen scale and Touch Panel-type Dementia Assessment Scale in patients with Alzheimer's disease.

Table 1: Baseline characteristic of mild cognitive impairment in Prasat Neurological Institute

Parameter	Total N=35 (%)
Sex (M:F)	4:6
Median age (years)	61.06 (56.00-65.00)
Marriage status (%)	
- Married	34 (97.1)
- Window	1 (2.9)
Education (%)	
- Elementary	2 (5.7)
- Secondary education	25 (71.4)
- Bachelor's degree	8 (22.9)
Occupation (%)	
- Specific occupation	4 (11.4)
- Basic occupation	29 (82.9)
- Unemployment	2 (5.7)
Age of diagnosis (%)	
- 51-60 years	11 (29.4)
- 61-70years	24 (70.6)
First presentation (%)	
- Memory impairment	35 (100)
Current medication (%)	
- ACEI	18 (51.4)
- CCB	2 (5.7)
- CCB, Statin	5 (14.4)
- Metformin, Statin	1 (2.9)
- Metformin, Statin, CCB	1 (2.9)
- Station	2 (5.7)
- ACEI, Statin	2 (5.7)
Underlying disease (%)	
- Hypertension	20 (57.1)
- Diabetic mellitus	2 (5.7)
- Hyperlipidemia	15 (42.9)
Alcohol drinking (%)	
- No	35 (100)
Hearing problems (%)	
- No	35 (100)
Visual problems (%)	
- No	35 (100)

Table 2: Primary and secondary outcomes

	Before	After	P-value
Primary outcomes			
<b>MOCA</b>	22.0 ( 21.00-23.00)	22.00 (21.00-24.00)	0.001
- Visuospatial and executive functions	4( 3.00-4.00)	4( 3.00-4.00)	0.083
- Naming	2( 2.00-3.00)	2( 2.00-3.00)	1.000
- Attention	5( 4.00-5.00)	5( 4.00-5.00)	0.317
- Language repetition	2(1.00-2.00)	2(1.00-2.00)	0.317
- Language fluency	1(1.00-1.00)	1(1.00-1.00)	1.000
- Abstract	1( 1.00-2.00)	1( 1.00-2.00)	1.000
- Delay recall	2( 2.00-3.00)	3( 2.00-3.00)	0.007
- Orientation	5(5.00-5.00)	5(5.00-5.00)	0.157
Secondary outcomes			
<b>NPI-Q (median) severity</b>	0(0.0-2.0)	0(0.0-0.0)	0.001
- Delusions	0(0.0-0.0)	0(0.0-0.0)	1.000
- Hallucination	0(0.0-0.0)	0(0.0-0.0)	1.000
- Agitation or aggressive	0(0.0-0.0)	0(0.0-0.0)	1.000
- Depression or dysphoria	0(0.0-0.0)	0(0.0-0.0)	0.317
- Anxiety	0(0.0-0.0)	0(0.0-0.0)	0.317
- Elation or euphoria	0(0.0-0.0)	0(0.0-0.0)	1.000
- Apathy or indifference	0(0.0-0.0)	0(0.0-0.0)	0.157
- Disinhibition	0(0.0-0.0)	0(0.0-0.0)	1.000
- Irritability or lability	0(0.0-0.0)	0(0.0-0.0)	0.083
- Motor disturbance	0(0.0-1.0)	0(0.0-0.0)	0.001
- Nighttime behaviors	0(0.0-1.0)	0(0.0-0.0)	0.002
- Appetite and eating	0(0.0-0.0)	0(0.0-0.0)	1.000
<b>NPI-Q (median) distress</b>	3(2.0-4.0)	0(0.0-1.0)	0.001
- Delusions	0(0.0-0.0)	0(0.0-0.0)	1.000
- Hallucination	0(0.0-0.0)	0(0.0-0.0)	1.000
- Agitation or aggressive	0(0.0-0.0)	0(0.0-0.0)	1.000
- Depression or dysphoria	0(0.0-0.0)	0(0.0-0.0)	1.000
- Anxiety	0(0.0-0.0)	0(0.0-0.0)	0.046
- Elation or euphoria	0(0.0-0.0)	0(0.0-0.0)	1.000
- Apathy or indifference	0(0.0-0.0)	0(0.0-0.0)	0.157
- Disinhibition	0(0.0-0.0)	0(0.0-0.0)	1.000
- Irritability or lability	0(0.0-0.0)	0(0.0-0.0)	0.005
- Motor disturbance	1(1.0-2.0)	0(0.0-1.0)	0.001
- Nighttime behaviors	1(1.0-2.0)	0(0.0-0.0)	0.001
- Appetite and eating	0(0.0-0.0)	0(0.0-0.0)	0.046
<b>HAM-A</b>	4(3.0-4.0)	1(0.0-1.0)	0.001
- Anxious mood	0(0.0-1.0)	0(0.0-0.0)	0.005
- Tension	0(0.0-0.0)	0(0.0-0.0)	0.025
- Fears	0(0.0-0.0)	0(0.0-0.0)	0.317
- Insomnia	1(1.0-2.0)	0(0.0-1.0)	0.001
- Intellectual	1(1.0-2.0)	1(0.0-1.0)	0.001
- Depress mood	1(1.0-1.0)	0(0.0-0.0)	0.001
- Somatic muscular	0(0.0-0.0)	0(0.0-0.0)	1.000
- Somatic sensory	0(0.0-0.0)	0(0.0-0.0)	1.000
- Cardiovascular symptoms	0(0.0-0.0)	0(0.0-0.0)	1.000
- Respiratory symptoms	0(0.0-0.0)	0(0.0-0.0)	1.000
- GI symptoms	0(0.0-0.0)	0(0.0-0.0)	1.000
- GU symptoms	0(0.0-0.0)	0(0.0-0.0)	1.000
- Autonomic symptoms	0(0.0-0.0)	0(0.0-0.0)	1.000
- Behavior at interview	0(0.0-0.0)	0(0.0-0.0)	1.000

MCI = mild cognitive impairment, MOCA = Montreal Cognitive assessment, NPI-Q = Neuropsychiatric Inventory Questionnaire, Hamilton Anxiety Rating Scale (HAM-A)

Rosemary contains an essential oil (0.6-2%) of varying components.<sup>12</sup> Major constituents of essential oil are 1,8-cineole,  $\alpha$ -pinene, camphor, borneol and carvacrol but the one being most potent is 1,8-cineole. Recent studies found that rosmarinic acid has potent effect on inhibition towards Butyrylcholinesterase (BuChE) and Acetylcholinesterase (AChE) which are the important enzymes used for degradation of Acetylcholine. Studies of Orhan et al. found that rosmary essential oil had inhibition effect on BuChE than AChE. Rosemary extracts also acts as potent radical scavenger. Carnosol and carnosic acid are thought to be the major antioxidant components.

Jimbo<sup>9</sup> used rosemary and lemon essential oils in the morning and lavender and orange in the evening. A number of clinical trials of aromatherapy, principally using either lavender or lemon balm demonstrated a significant impact on behavioral problems in patients with dementia. Holmes and Ballard<sup>13</sup> stated that as mechanisms of action of aromatic essential oils, the individual's perception of the pleasantness of an odor and the individual's past association with an odor were considered from psychological aspects, and that inhibition of glutamate binding, GABA augmentation, and acetylcholine receptor binding were focused from petrochemical effects

From previous studies,<sup>14-17</sup> rosemary aromatherapy used to address behavior and psychological symptoms in dementia. Most commonly delivered through electric diffusers and vaporizers and stimulates the olfactory sense. The emotional significance of an odor is provided by the role of amygdala in the cerebral analysis. There was study that also be found that the olfactory sense may be linked with implicit memory.<sup>2</sup>

In our study, all patients were amnesic MCI and MOCA scores was improved especially in domain of delayed recall significantly in statistic that correlated with previous studies. We hypothesized that the improvement may be from the action mechanism of inhibition of cholinesterase especially BuChE enzyme. For the other domains which scores were not improved significantly, this may be from our small sample size study and we also found that some domains hadn't have any impairment at baseline such as attention and language domains or have very mild impairment such as visuospatial/executive, naming domains before intervention.

Median NPI-Q distress score was improved statistically significant after intervention. In subgroup analysis, domain of nighttime behavior and motor disturbance improved significantly in statistic. Most of patients reported the improvement of insomnia problem, these may be from the action mechanism on modulation of GABA-A receptor. Many recent studies shown that rosemary also effected on depressive mood that correlated in our study in HAM-A scores which improved both insomnia and depressive mood significantly. About NPI-Q severity, median score was not different before and after intervention, however most patients had severity scored 0 in all domains at baseline before intervention.

We concluded in our study that rosemary essential oil may have benefit on improvement cognitive function in MCI patients especially domain of delayed recall from MOCA test and also improved insomnia, anxiety and depressive mood. However, potential bias in statistically may be occurred due to our small sample size study. Further large-scale randomized controlled trials should be investigated in this group.

### Limitation

1) Small sample size; some participants denied joining this activities as they must visit at OPD for assessment earlier within 6 weeks.

2) Too short duration for follow up and assess the outcomes of cognitive function and mood that learning effect of neuropsychology test may be occurred when patients are required to repeat the test before three months.

### Conclusions

Our finding was correlated with previous studies of benefit of rosemary in Alzheimer's disease. However, only few studies investigated the effect of rosemary in MCI. We focus in MCI group which is the pre-clinical stage of dementia that is the point of no return. We proposed from our results that Aromatherapy of Rosemary essential oil seems to be safe and effective for improvement cognition of memory domain and behavioral problems in people with MCI.

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