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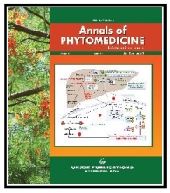

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The effects of ylang-ylang (*Cananga odorata* (Lam.) Hook.f. and Thomson) essential oil on behavioural symptoms and plasma biomarkers in long-term care residents with dementia

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Abstract

Behavioural and psychological symptoms of dementia (BPSD) including agitation, psychosis, depression, and apathy are very common among persons with dementia. Aromatherapy is one of the approaches used as a non-pharmacological management of BPSD. This study examines the effectiveness of diffused ylang-ylang essential oil based on dementia-related behavioural assessment tools and biochemical analysis on persons with BPSD. A pre-post quasi-experimental study was conducted over two months in three nursing homes with persons with dementia (n = 28). Ylang-ylang essential oil was diffused through an ultrasonic diffuser for 20 min twice a day during both intervention phase. Behavioural symptoms were documented, and blood was taken for biomarkers analysis. The scores of the Cohen-Mansfield Agitation Inventory (CMAI) and the Cornell Scale for Depression in Dementia (CSDD) decreased significantly following ylang-ylang aromatherapy. A significant reduction was seen in homocysteine, amyloid beta-42, interleukin-6 and interleukin-2 concentrations with inhalation of ylang-ylang essential oil. Overall, ylang-ylang aromatherapy helps to improve BPSD and is associated with reducing neurodegenerative and neuroinflammatory plasma biomarkers.

1. Introduction

Behavioral and psychological symptoms of dementia (BPSD) including agitation, psychosis, depression, and apathy are very common among persons with dementia. It refers to the range of non-cognitive and non-neurological symptoms of dementia (Tible *et al.,* 2017). BPSD contribute to caregiver burden and the escalating cost of care globally (Herrmann *et al.,* 2006). BPSD is generally managed through pharmacological and non-pharmacological interventions. Common medications prescribed for BPSD include antidepressants and antipsychotics (Ringman and Cummings, 2006). However, the use of antipsychotics is limited due to the risk of developing adverse effects such as cardiac arrhythmias, urinary retention, orthostatic hypotension, and extra-pyramidal symptoms (Duong *et al.,* 2017).

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Aromatherapy has recently acquired momentum as an alternative non-pharmacological approach for dealing with the symptoms of BPSD due to its minimal side effects (de Oliveira *et al.,* 2015). Essential oils such as lavender, lemon balm, lemon, orange, marjoram, patchouli, geranium, chamomile, tea tree, rosemary and thyme have been used in persons with dementia for the management of BPSD and cognition (Lillehei and Halcon, 2014). Among these oils, lavender was most studied in clinical trials (Fujii *et al.,* 2008; Holmes *et al.,* 2002; O'Connor *et al.,* 2013; Pamela Wan-ki *et al.,* 2007). Linalool, which is the main terpenoid found in lavender essential oil is associated with increased gamma-aminobutyric acid (GABA) which has a natural calming effect on the brain and helped in managing persons with BPSD (Wang and Heinbockel, 2018). Neurodegenerative, neuroinflammatory, and oxidative stress biomarkers are the common biomarkers used in the diagnosis of dementia (Park *et al.,* 2022). However, there is a lack of evidence on the effectiveness of aromatherapy-based intervention on blood biomarkers in persons with dementia.

Ylang-ylang (*Cananga odorata* (Lam). Hook.f. and Thomson) is a tropical tree found commonly in Southeast Asia and the ylang-ylang

flower also contains monoterpenes such as linalool that may help in the management of BPSD (Tan *et al.,* 2015). Several clinical studies have been conducted using ylang-ylang essential oil among healthy volunteers. Ylang-ylang essential oil reduces anxiety, stress, and blood pressure and shown to promote calmness (Bae *et al.,* 2018; Gnatta*et al.,* 2014; Hongratanaworakit and Buchbauer, 2006; Moss *et al.,* 2009). A recent study shows the promising impact of ylang-ylang aromatherapy by reducing the anxiety index and saliva alpha-amylase activity in inexperienced patients admitted for interventional neuroradiology procedures (Sriboonlert *et al.,* 2023). However, less is known about the effects of ylang-ylang essential oil on persons with dementia. Therefore, this study was undertaken to evaluate the effectiveness of ylang-ylang essential oil diffusion on BPSD and blood biomarkers amongst persons with dementia using two different approaches, through established behavioural assessment tools, and plasma biomarkers analysis.

2. Material and Methods

2.1 Study design and ethical consideration

A pre-post quasi-experimental study was conducted in persons with dementia at three nursing homes across Klang Valley, Selangor, Malaysia over two months. The study protocol was approved by the Human Ethics Committee of the University Research Ethics Committee of Universiti Teknologi MARA (Approval Code: REC/02/2020 (FB/31)). Informed consent was obtained from the participants' next-of-kin or caregiver before the commencement of the study. This study has been registered on clinicaltrial.gov (NCT05034107).

2.2 Participant recruitment

Paired t-test was used to calculate the sample size required for this study using the effect size of 0.53 (Ballard *et al.,* 2002). A minimum of 28 people with dementia needed to be recruited based on the paired t-test sample size calculation. A universal sampling method was used to recruit participants. Persons with confirmed diagnosis of dementia with at least one symptom of BPSD and living in nursing homes at Klang Valley, Selangor, were included in this study. Nursing home managers were contacted *via* telephone and email to explain the study. Nursing homes keen to participate were approached, and further information about this study was provided. The nursing home managers selected eligible residents based on inclusion and exclusion criteria. Baseline Mini-Mental State Examination (MMSE) and Clinical Frailty Scale (CFS) were assessed by the researchers to estimate the severity of dementia.

2.3 Intervention

A ylang-ylang essential oil that is readily available on the market was used for the aromatherapy intervention. Based on the manufacturer's safety information, a particular brand of ylang-ylang essential oil was chosen (Young Living Essential Oils/Essential Oil and Aromatherapy, 2022). An ultrasonic diffuser was used to diffuse water in the pre-intervention phase and ylang-ylang essential oil during the intervention phase. The ultrasonic diffuser was used for 20 min twice daily for 1 month, and it has the capacity to cover an area of up to 300 square feet (Comparison Chart, 2021). Figure 1 shows an overall flowchart of this study. Caregivers of nursing homes were trained on essential oil handling and diffusing techniques before the commencement of the study. Caregivers were informed to observe and document the changes in the BPSD of each participant in a data collecting from daily. The caregivers were also trained to record any adverse events observed or complained by participants during or after the intervention.

The behavioural assessment tools include the Cohen-Mansfield Agitation Inventory (CMAI), (Cohen-Mansfield Agitation Inventory, 2020), the Cornell Scale for Depression in Dementia (CSDD)(George Alexopoulos, 1998) and the Neuropsychiatric Inventory- Brief Questionnaire Form (NPI-Q) (Cummings, 1994) were assessed during the pre-and post-intervention phases by interviewing the caregivers. Furthermore, 10 ml of blood sample was taken from the peripheral vein of participants after an overnight fast (between 7 p.m. and 8 a.m.) for biochemical analyses at pre and post intervention. For plasma, blood was collected in vacutainer blood collection tubes that contain anticoagulants. The tubes were centrifuged at 1,000 xg for 10 min using a refrigerated centrifuge. Blood analysis for neuroinflammatory, neurodegenerative, stress hormone and oxidative stress biomarkers were assessed using an enzyme-linked immunosorbent assay (ELISA) kit and colorimetry assay kit from Elabscience Biotechnology Inc® (Houston, Texas, USA).

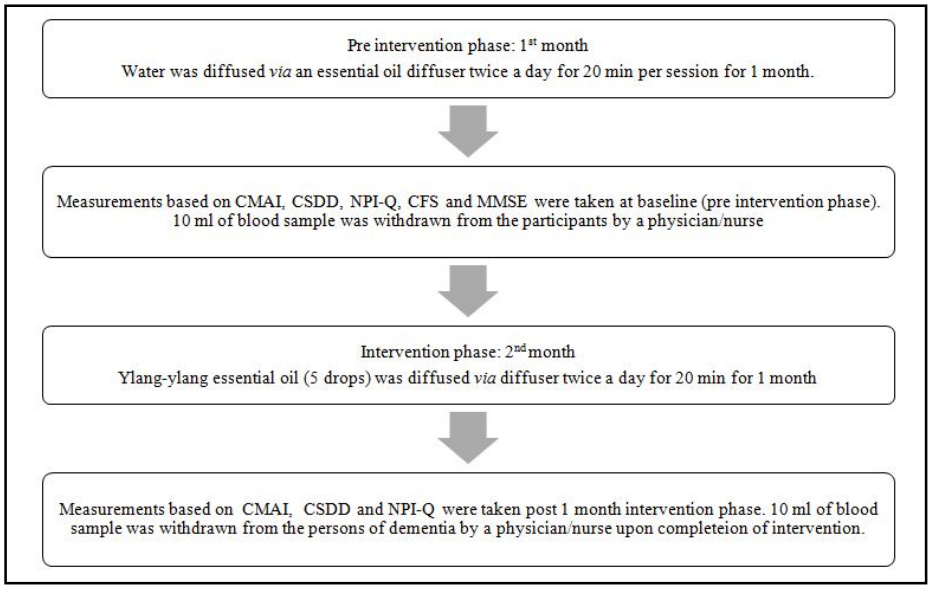

Figure 1: Overview of the study protocol.

2.4 Statistical analysis

The results are expressed as median and mean ± SD for quantitative variables and percentages for categorical variables. A Wilcoxon Signed-rank test was used to analyze the differences in median and mean of the observed outcomes from CSDD, CMAI and NPI-Q scores and changes in blood biomarkers in both pre-and post-intervention phases. A p-value of < 0.05 is considered statistically significant. Statistical package for the social sciences (SPSS) version 26 were used to perform all analyses in this study.

3. Results

The demographic information of the study participants is listed in Table 1. Most participants were female (64.3%), with a mean age of 65. Most of them were Indians (42.9%). Even though more than half of the participants had at least a basic education level, 43% of the participants' educational background was unknown.

Table 1: Demographic data of participants in this study

Variable	Item	Number (n=28)	Percentage (%)
Sex	Male	10	35.7
	Female	18	64.3
Age	Less than 64 years old	13	46.43
	65 or more years old	15	53.57
Race	Malay	6	21.4
	Chinese	9	32.1
	Indian	12	42.9
	Others	1	3.6
Education background	No formal education	2	7.1
	Primary education	8	28.6
	Secondary education	4	14.3
	Tertiary education	2	7.1
	Unknown	12	42.9
Marital status	Single	9	32.1
	Married	11	39.3
	Widow	5	17.9
	Widower	3	10.7

Incidence of behavioural issues including agitation, depression and neuropsychiatric symptoms were assessed based on CMAI, CSDD and NPI-Q scores upon interviewing the caregiver's pre and post aromatherapy. A significant reduction in agitation was observed based on median changes in CMAI overall score pre- and post-intervention (Figure 2A). In terms of depression level, the overall CSDD score decreased significantly upon ylang-ylang aromatherapy (Figure 2B). Based on the NPI-Q score, no significant association was observed between ylang-ylang aromatherapy and the reduction in neuropsychiatric symptoms of participants (p=0.144) as well as caregivers' distress (p=0.361) (Figure 2C).

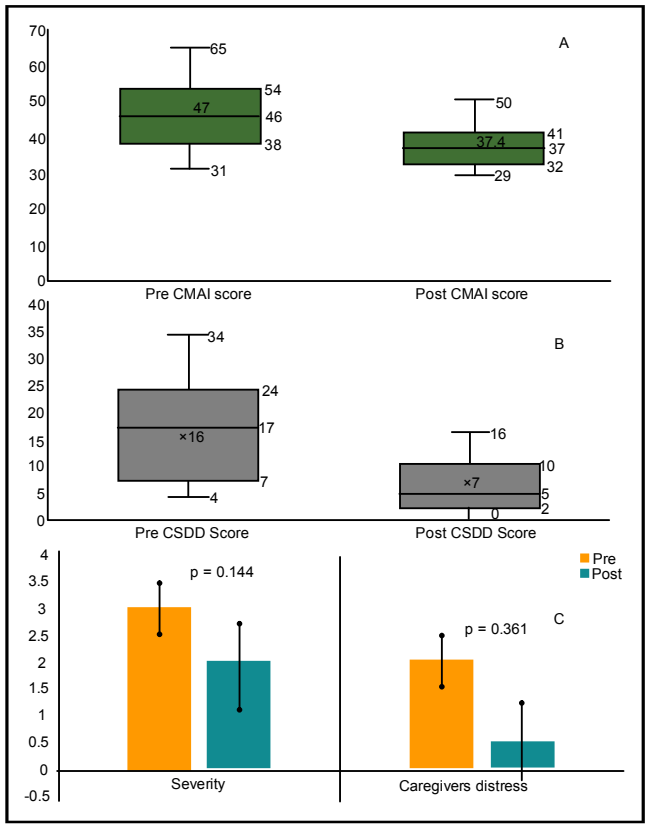

Figure 2: The changes in the CMAI, CSDD and NPI-Q score pre- and post-ylang-ylang aromatherapy. (A) shows the boxplot for CMAI score on pre-and post-ylang-ylang aromatherapy; p-value = 0.002, (B) shows the boxplot for CSDD score, pre-and post-ylang-ylang aromatherapy; p-value < 0.001, and (C) shows the bar chart of the NPI-Q score on the severity of neuropsychiatric symptoms and caregivers' burden. Data are presented in the form of a median (interquartile range). The Wilcoxon signed-rank test was used to compare the changes in the median between pre- and post-aromatherapy.

Secondary outcome measures aim to determine the effects of ylang-ylang aromatherapy on blood biomarkers related to the pathology of dementia in persons with BPSD. In this study, 12 biomarkers were assessed from plasma samples pre and post-ylang-ylang aromatherapy. Blood analysis for neurodegeneration (*i.e.,* $A\beta_{1-40}$, $A\beta_{1-42}$, $A\beta_{42}/A\beta_{40}$ ratio, homocysteine, folate and BDNF), neuroinflammatory (*i.e.*, interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α)), stress hormone (*i.e.*, cortisol and ACTH) and oxidative stress (*i.e.,* TBARS and MDA) biomarkers were assessed in this study. Data obtained from these secondary outcome measures are presented as mean ± SD. Table 2 summarizes the changes in blood biomarkers pre and post-ylang-ylang aromatherapy.

Table 2: Changes in blood biomarkers pre and post aromatherapy

Parameters	Biomarkers	Pre concentration (mean ± SD)	Post concentration (mean ± SD)	p-value
Neurodegenerative	Homocysteine (µmol/l)	23.25 ± 8.3	20.08 ± 8.7	**0.001**
	Folate (ng/ml)	06.29 ± 3.9	5.74 ± 3.2	0.524
	BDNF (pg/ml)	02.04 ± 0.9	1.62 ± 0.9	0.279
	Aβ1-40 (pg/ml)	0.27 ± 0.06	0.29 ± 0.08	0.210
	Aβ1-42 (pg/ml)	0.22 ± 0.16	0.18 ± 0.2	**0.020**
Neuroinflammatory	IL-6 (pg/ml)	13.41 ± 6.9	10.92 ± 6.4	**0.023**
	IL-2 (pg/ml)	12.55 ± 12.8	10.74 ± 12.1	**0.050**
	TNF-α (pg/ml)	19.59 ± 28.2	20.22 ± 31.8	0.859
Stress hormones	Cortisol (ng/ml)	0.62 ± 0.13	0.58 ± 0.15	0.274
	ACTH (pg/ml)	0.82 ± 0.16	0.97 ± 0.13	**<0.001**
Oxidative stress	TBARS (µmol/l)	1.05 ± 0.2	1.43 ± 0.9	**0.016**
	MDA (ng/ml)	0.70 ± 0.2	0.75 ± 0.2	**0.014**

4. Discussion

Agitation is a symptom of the physical changes in the brain caused by dementia. Agitation is observed to be more frequent among persons with dementia living in nursing homes (Carrarini *et al.,* 2021; Kongpakwattana *et al*., 2018). Previously ylang-ylang was tested on animal models and proved to reduce agitation in ICR mice (Nan *et al*., 2016). In this study, ylang-ylang aromatherapy was effective in reducing agitated behaviour based on the CMAI score significantly. However, no human study was conducted previously to verify the reduction of agitation using ylang-ylang essential oil. Correspondingly, depression symptoms have shown reduction upon inhalation of ylang-ylang essential oil based on the CSDD score. Depression has been proposed to be a risk factor for dementia and half of the patients with late-onset depression have been diagnosed with dementia (Muliyala and Varghese, 2010). The usage of ylang-ylang essential oil had reduced stress scores among healthy volunteers (Bae *et al*., 2018; Jung *et al*., 2013; Pujiarti *et al*., 2017). The reduction of depression reported in this present study suggests that ylang-ylang essential oil also tends to reduce depression among persons with dementia. With regards to NPI-Q results, no significant reduction was found in this study. To support this finding, a previous lavender aromatherapy study with a similar number of participants as this study, also showed no significant reduction of NPI (Fujii *et al.*, 2008). A negative correlation was observed in the NPI-Q with respect to the severity of dementia and caregivers' burden in this study. This finding could be influenced by the differences in caregivers' experiences in dealing with persons with dementia as there were multiple trial sites in this study.

The effects of ylang-ylang aromatherapy on the blood biomarkers of persons with BPSD are analyzed in this study based on 5 neuropathological hallmarks. On the neurodegeneration biomarker, the concentration of $A\beta_{1-40}$ increases while $A\beta_{1-42}$ declined significantly upon ylang-ylang aromatherapy in persons with dementia. Accumulation of amyloid beta (Aβ) is the known neuropathological hallmark of Alzheimer's disease and dementia. In the human brain, the foremost Aβ variants detected are $A\beta_{1-40}$ and $A\beta_{1-42}$ and higher concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ cause neurodegeneration (Hernández-Zimbrón *et al*., 2016). A study by Okuda and colleagues revealed that after two months of exposure to a combination of lavender and orange essential oils during the day and a combination of lemon and rosemary essential oils at night, AD mice exhibited significantly reduced levels of Aβ in their brains as well as abnormal tau protein (Okuda *et al*., 2020). Linalool which is one of the main components of ylang-ylang essential oil and other essential oil has the potential to exert a protective effect against amyloid-β neurotoxicity (Hancianu *et al*., 2013). In this study, $A\beta_{1-42}$ formation showed a significant decline in ylang-ylang aromatherapy in persons with dementia. This finding suggests that diffusion of ylang-ylang inhibits and/or lowers the formation of new $A\beta_{1-42}$ plaques captured in the plasma of persons with dementia.

A higher homocysteine level can cause vascular damage and increase oxidative stress (Chia *et al*., 2007). Homocysteine levels were significantly decreased after using nine essential oils, including oils from peppermint, ginger, and caraway using blood analysis (Han *et al*., 2017). Conversely, *Lavandula angustifolia, Salvia sclarea, Santalum album* and *Citrus sinensis* essential oils were diffused to 52 female volunteers. The homocysteine level in urine samples was high as compared to before being exposed to essential oil inhalation (Zhang *et al*., 2013). In the present study, homocysteine levels showed reduction after the inhalation of ylang-ylang aromatherapy among persons with dementia. Significant reduction of homocysteine ($p<0.001$) suggests that ylang-ylang essential oil may reduce oxidative stress associated with reduced risk of dementia. Contrarily, there was a non-significant reduction in folate concentration and BDNF concentration post-ylang-ylang aromatherapy.

Brain inflammation plays a role in dementia. In dementia, cleavage of the amyloid precursor protein (APP) causes IL-6 production in immune cells, which upregulates APP and hyperphosphorylated tau in neurons (Hampel *et al*., 2005). In another study, IL-2 secretion was higher in vascular and moderately severe AD groups as a result of increased neuronal damage. According to another study by

Huberman and his co-researchers, the severity of dementia may be correlated with elevated levels of IL-2 secretion (Huberman *et al*., 1995). Reduction in IL-6 and IL-2 levels reported in this study suggests that ylang-ylang aromatherapy reduced $A\beta_{1-42}$ aggregation and thus, reduce the inflammation of the brain. With regards to TNF-α concentrations, previous longitudinal studies have found higher levels of TNF-α, in peripheral blood samples of patients with AD compared to a control group (Lai *et al*., 2017). However, in this study, the TNF-α concentrations in blood were not affected by ylang-ylang aromatherapy.

Oxidative stress is commonly linked with ageing. In this study, TBARS and MDA parameters were considered as biomarkers of the oxidative stress of persons with dementia pre and post-aromatherapy. Ylang-ylang aromatherapy did not show any significant finding upon inhalation among persons with dementia on oxidative stress. Several animal and human studies have shown a higher oxidative stress level in dementia subjects tested using TBARS and MDA (Biotechnology 2006; Kamsler *et al*., 2006; Keller *et al*., 2005; Serrano and Klann, 2004). As dementia worsens, lipid peroxidation increases as the chain of reactions of oxidative degradation of lipids produces more TBARS and MDA (Kandlur *et al*., 2020). Increased concentrations of TBARS and MDA in plasma participants in this study indicated that ylang-ylang did not affect the progression of oxidative damage in persons with dementia.

Comprehensively, ylang-ylang essential oil has been proven to reduce BPSD among persons with dementia by reducing agitation and depression. Hence, the present study suggests that inhalation of ylang-ylang essential oil may be a promising non-pharmacological approach to reducing BPSD in persons with dementia. The blood analysis on neurodegenerative biomarkers suggests that ylang-ylang has the potential to lessen the production of new $A\beta_{1-42}$and elevation of homocysteine levels which reduces neuronal damage in the brain. However, the mechanism of this impact is still not clear. Reduction in depressive behaviour may also be due to lesser neuronal damage in the brain (Dong and Jacob, 2016). Correspondingly, a lower level of $A\beta_{1-42}$ is a factor to reduce the growth of pro-inflammatory cytokines IL-6 and IL-2 suggesting ylang-ylang aromatherapy reduces the inflammation of the brain. Reduction in pro-inflammatory cytokines in the brain may alleviate neurotoxic effects implicated in each anxiety disorder. Therefore, the association between reduction in neuroinflammation and agitation is seen in this study. However, further studies are integral to having a deeper understanding of the mechanism of ylang-ylang aromatherapy on behavioural and blood biomarker changes.

5. Conclusion

In conclusion, this study is the first to report the effects of ylang-ylang essential oil aromatherapy in persons with BPSD. Ylang-ylang essential oil significantly lowered agitation and depression based on total CMAI and CSDD scores. Several neurodegenerative biomarkers, including homocysteine levels and $A\beta_{1-42}$, were reduced significantly post-ylang-ylang aromatherapy. Similarly, pro-inflammatory biomarkers IL-6 and IL-2 were also significantly reduced. Overall, ylang-ylang essential oil has provided some beneficial effects on persons with dementia, especially in managing BPSD.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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