Effect of aromatherapy in patients with Alzheimer's disease: a randomised controlled clinical trial

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Abstract

Background: Aromatherapy is a complementary and alternative therapeutic method that has attracted much attention worldwide. Based on the lack of clinical research on the application of aromatherapy in the treatment of Alzheimer's disease (AD) in China, this study aimed to investigate the effect of aromatherapy in patients with AD.

Methods: 54 patients with AD were randomly allocated to aromatherapy groups and control groups in a 1:1 ratio. Eventually, 25 patients in the aromatherapy group (two participants discontinued midway) and 26 in the control group (one participant discontinued midway) completed the study. Both groups of patients received conventional treatment and nursing care, and the aromatherapy group received an hour of aromatic inhalation per day for 12 weeks,the control group inhaled only distilled water per day for 12 weeks. The Pittsburgh Sleep Quality Index, Neuropsychiatric Inventory–Brief Questionnaire form, Quality of Life-Alzheimer's Disease, and four kinds of biochemical indicators were evaluated as outcome measures.

Results: The Pittsburgh Sleep Quality Index and the Neuropsychiatric Inventory–Brief Questionnaire Form scores decreased, the Quality of Life-Alzheimer's Disease score improved ($P<0.05$), the malondialdehyde (MDA) content in serum was slightly reduced, superoxide dismutase (SOD) activity was enhanced ($P<0.05$), and TNF-α and IL-6 levels were significantly reduced ($P<0.05$) in the aromatherapy group, compared to those of the control group.

Conclusion: Aromatherapy can improve sleep, alleviate psychobehavioural symptoms and improve quality of life in patients with AD, which may be related to reducing the level of oxidative stress in patients and inhibiting inflammatory factors; it is a non-drug intervention that can be widely applied.

Trial registration: The trial was registered in the Chinese Clinical Trial Registry in 25/01/2022, ID: #ChiCTR2200055918.

Background

Alzheimer's disease (AD) is a neurodegenerative disorder that occurs more frequently in older adults and has an undetermined aetiology [1, 2]. It is generally believed that the pathogenesis of AD is related to excessive deposition of amyloid β protein (Aβ), neuroinflammation, and oxidative stress [3, 4, 5]. Scholars continue to research and develop new drugs to treat AD, but most have not been proven to be effective [12], and none have been shown to slow or prevent the damage and destruction of neurons [6].

AD is the most prevalent kind of dementia in older adults, accounting for 60–80% of all cases of dementia [7]. In 2015, it was estimated that there are approximately 47 million people living with dementia worldwide; the number of persons with dementia is also increasing as the population ages and life expectancy increases, and this number is expected to triple to 131.5 million by 2050 [1, 8]. Dementia has become a major and growing global health challenge for policymakers, healthcare professionals and family members. Without effective preventive measures, the number of patients with AD in China will rise significantly over the next 30 years [10] and is expected to match the total number of dementia sufferers in all developed countries [9].

The course of AD usually progresses over a period of years or even decades, which is undoubtedly a painful process for patients and their families, and also imposes a tremendous financial burden on society. At present, the total economic cost of care for patients with AD in the world has reached $1 trillion, and it is expected that this amount will increase to $2 trillion by 2030. The average survival period after AD diagnosis is less than 6 years, which seriously threatens the health of older adults [1, 3, 11]. Drug therapy usually does not reverse the pathological changes associated with AD, and there may be significant side effects, particularly in older individuals [13].

Aromatherapy refers to the use of plant-based essential oils to produce positive physiological, psychological, and spiritual effects, mainly through inhalation, massage, intestinal, and oral methods to successfully promote improved functioning of the internal nervous system [14]. Aromatherapy is a complementary and alternative therapeutic method that has attracted much attention worldwide in recent years. According to the National Center for Complementary and Integrative Health, Americans spend more than $3.02 billion annually on aromatherapy, and global spending is expected to grow to $5 trillion by 2050 [15]. Aromatherapy has the effect of alleviating individual negative emotions, providing sedative and analgesic effects, and improving cognition and sleep quality, among other benefits [15, 16]. Based on the lack of clinical research on the application of aromatherapy in patients

with AD in China, this study applied aromatherapy to patients at medical institutions with mild and moderate AD, and explored its effect by observing their sleep quality, mental behaviour, quality of life, and related biochemical indicators.

Methods

Participants

A total of 138 patients with AD residing at the dementia ward in a hospital in ChengDu, China in March 2021 were recruited for this randomised controlled clinical trial. Participants were enrolled according to the following inclusion criteria: (1) patients with AD diagnosed by clinicians according to the 10th Revision of the International Classification of Diseases and Related Health Problems (ICD-10); (2) Clinical Dementia Rating (CDR) score of 1 or 2 points; (3) education level of primary school and above, and age ≥ 60 years; (4) ability to understand the content of the questionnaire and respond; (5) participant voluntarily signed the informed consent form. Exclusion criteria were as follows: (1) patients with complete loss of self-care ability; (2) terminally ill patients; (3) patients with severe mental illness, drug and alcohol dependence, (4) those with complex and unpredictable conditions, and (5) living in the ward for < 12 weeks after study initiation. After the exclusion criteria were applied, 54 patients with AD were included in the study.

The study adheres to CONSORT guidelines and was reviewed and approved by the Ethics Committee of Chengdu Eighth People's Hospital. All subjects or their guardians signed an informed consent form after the purpose of the study and the process of its implementation were explained to them.

Figure 1 illustrates the flow of the study. The trial was registered in the Chinese Clinical Trial Registry (#ChiCTR2200055918).

Randomization and blinding procedures

The 54 patients were assigned random numbers generated using a random number table. The numbers were sorted by size and patients were distributed to groups in a 1:1 ratio. Patients assigned odd numbers were placed in the aromatherapy group, and patients with even numbers into the control group. The trial blinded patients' group information, the same group of patients lived in the same ward, and both groups of patients used the nebulizer every night. The operation of the nebulizer and the addition of essential oils were carried out by the caregiver, so the patients were blinded to their interventions. Scale evaluators, venous blood collectors, and data analysts were blinded the study.

Intervention

Both groups of patients received routine interventions, namely conventional treatment and nursing care, mainly including symptomatic treatment involving the use of anti-inflammatory, sedative, hypoglycaemic, and antihypertensive drugs. Other activities such as listening to music, watching film and television programs, puzzle games, and other recreational activities were also performed. The aromatherapy group received aromatherapy based on the following protocol: (1) an aromatherapy machine from Midea company (Foshan, Guangdong, SC-3E25) was placed in each ward (10–15 m^2) with 3 patients; (2) aromatherapy mentioned in the literature usually includes a mixture of two or more essential oils [15]; we selected lavender, sweet orange, and bergamot essential oils, mixed in a ratio of 1:1:1; (3) trained caregivers were responsible for pouring essential oils and water in the appropriate proportion (6 drops of essential oil mixed with 200 mL distilled water) into the machine at 9:00 pm every night for 1 h. Aromatherapy was administered for a total of 12 weeks, and the control group was administered distilled water over the same time period.

Outcome measures

Evaluations for this study were assessed and collated by trained team members who were not involved in implementing the study. Both groups of participants were assessed before initiation of the study and at the end of weeks 8 and 12 of the intervention. The

following indicators were included in the study:

Pittsburgh Sleep Quality Index (PQSI) [17]: This scale comprises seven components and 18 entries. Components 1 to 7 involve overall sleep quality, sleep time, sleep latency, duration of sleep, sleep efficiency, sleep disturbance, if medicines are required to sleep, and dysfunction during the day due to sleepiness, with a total score of 0–21 points. A lower score indicates better sleep status, and a PQSI score of ≥ 8 points indicates sleep problems.

Neuropsychiatric Inventory-Questionnaire (NPI-Q) [18]: This tool evaluates 12 neuropsychiatric behavioural disorders that are common in dementia. The NPI-Q first confirms if each symptom is present (yes = 1, no = 0) and subsequently determines the frequency and severity of symptoms in patients exhibiting symptoms. The score for each symptom is a product of frequency and severity, and the total NPI score for all symptoms is 0–144 points. Higher scores indicate greater severity of behavioural psychosocial disorder.

Quality of Life-Alzheimer's Disease (QOL-AD) [19]: This scale evaluates the quality of life of patients with AD in the form of patient self-assessment or caregiver evaluation, consisting of 13 entries. Each entry has four options that correspond to 1 to 4 points; the total score ranges between 13 and 52 points, with a higher score indicating a better quality of life.

Biochemical indices:

Fasting venous blood (5 mL) was drawn and centrifuged (3000 rpm for 10 min) was collected before and 12 weeks after the intervention at the hospital laboratory for the general collection of noncoagulants in the blood vessel without anticoagulant. The serum was transferred to a microcentrifuge tube, labelled, and preserved at -80°C for subsequent analysis. All patient specimens were sent to the CAMILO BIOLOGICAL company to determine the content of superoxide dismutase (SOD), malondialdehyde (MDA), interleukin 6 (IL-6), and tumour necrosis factor alpha (TNF-α) using the double antibody sandwich ELISA method.

Data analysis

The collected data were analysed using SPSS software version 25 (IBM Corp. Armonk, NY). The data were analysed using descriptive statistics (mean, standard deviation, median, frequency, and ratio). For dependent groups, a t-test and Mann–Whitney U test were utilised. All statistical tests were two-sided, with an inspection level of $\alpha = 0.05$. Statistical significance was set at $P < 0.05$.

Results

Twenty-five patients with AD in the aroma group (two participants discontinued midway) and 26 in the control group (one participant discontinued midway) completed the study (Table 1). There were no statistically significant differences between the two groups regarding baseline participant characteristics. There were no statistical differences in the total PQSI, NPI-Q, and QOL-AD scores between the two groups before the intervention ($P > 0.05$); however, at week 8, the PQSI score of the aromatherapy group was significantly lower than that of the control group ($P = 0.003$), and the QOL-AD score was significantly improved compared to that of the control group ($P = 0.009$); the NPI-Q score of the aromatherapy group was slightly lower than that of the control group, but the distinction was insignificant ($P = 0.077$). At the end of the 12-week intervention, the PQSI and NPI-Q scores of the two groups were reduced compared with before the intervention. Furthermore, the QOL-AD score was improved compared to before the intervention, and the difference in the scores between the two groups was statistically significant ($P < 0.05$) (Table 2).

Table 1
Characteristics of the participants (n = 51)

	Age mean ± SD	Male n (%)	MMSE	ADL	Course
Aromatherapy group (n = 25)	85.04 ± 4.51	13 (52.0%)	13.24 ± 3.53	50.80 ± 11.43	5.96 ± 2.86
control group (n = 26)	83.11 ± 6.27	8 (34.6%)	11.73 ± 3.80	47.50 ± 8.97	6.08 ± 2.95
Statistical value	t = 1.255	χ^2 = 0.942	t = 1.466	t = 1.150	t=-0.143
P-value	0.215	0.210	0.149	0.256	0.887

Table 2
Comparison of PQSI, NPI-Q and QOL-AD scores at pre-intervention, post-8-weeks, and post-12-weeks

Group	PQSI (mean ± SD)			NPI-Q (median)			QOL-AD (mean ± SD)		
	Pre-intervention	Post-8-weeks	Post-12-weeks	Pre-intervention	Post-8-weeks	Post-12-weeks	Pre-intervention	Post-8-weeks	Post-12-weeks
Aromatherapy group (n = 25)	10.80 ± 4.32	7.80 ± 2.90	5.16 ± 2.43	4 (1.5, 14)	6 (1.5, 10)	1 (0, 5)	30.68 ± 3.16	32.08 ± 3.03	34.96 ± 2.94
control group (n = 26)	11.23 ± 4.10	10.46 ± 3.20	8.07 ± 3.06	4.5 (1, 9.25)	6.5 (1.75, 10.5)	7.5 (0, 14.25)	31.27 ± 2.51	30.00 ± 2.42	33.00 ± 2.80
Statistical value	t=-0.365	t=-3.106	t=-3.763	z=-0.435	z=-0.284	z=-2.522	t=-0.739	t= 2.720	t= 2.440
P-**value**	0.716	0.003	0.000	0.664	0.777	0.012	0.463	0.009	0.018

Figures 2 and 3 show a comparison of the measured serum indices. A statistically meaningful difference could not be found in oxidative stress levels between the two groups before the intervention (P > 0.05). After the 12-week intervention, patients in the aromatherapy group had lower serum MDA content than the control group, but the difference was not significant (P > 0.05); SOD activity was higher (P < 0.05) (Figs. 2a, 2b). No significant differences were noted in inflammatory factor levels in the two groups before the intervention (P > 0.05). However, after the 12-week intervention, the levels of TNF and IL-6 levels in the aromatherapy group were lower than those in the control group, and the results were statistically significant (P < 0.05) (Figs. 3a, 3b).

For safety, after the 12-week intervention, the two groups of patients and nurses did not complain about serious adverse reactions caused by spray or aroma inhalation, such as allergies, dizziness and other discomforts, indicating that the safety of aromatherapy was more reliable in this research process.

Discussion

About 90% of patients with AD will develop psychobehavioural symptoms such as agitation, apathy, anxiety, sleep disorders, and depression as the disease progresses, particularly in the middle and late stages of the disease; patients often exhibit more than one symptom [20], which can cause great pain to the patient and family and exert a heavy economic burden on society. The results of this study showed that the PQSI scores of patients in the aromatherapy group decreased at the end of the 8-week and 12-week interventions and the 12-week score was lower than the 8-week score, suggesting that aromatherapy had a positive effect on sleep quality in patients with AD, which was consistent with the findings of Takeda et al. [21]. Fujii et al. [22] reported that

aromatherapy was effective for psychobehavioural symptoms in patients with AD, and their findings were consistent with our results. Aromatherapy could alleviate the psychobehavioural symptoms of patients with AD, but there were no significant differences in the NPI-Q scores of the two groups of patients in this study at the end of the 8-week intervention. However, there was a difference in the scores of the two groups after 12 weeks of intervention, and the results showed that the NPI-Q score of the aromatherapy group was lower than that of the control group, which suggested that our aromatherapy implementation needed to be prolonged.

There are many complex factors influencing the quality of life of older adults with dementia, and improving their quality of life has always been a primary focus of medical care [23]. An increasing number of dementia-related research focuses on methods or interventions to improve the quality of life; results of the present study reveal that aromatherapy can improve the quality of life of patients with AD. The QOL-AD score of this study was mainly evaluated by the caregivers, and its intervention was improved; the caregivers believed that they could clearly feel the increase in nocturnal sleep time and the reduction of agitated behaviour in some patients with AD, which was reflected from the fact that aromatherapy was not only beneficial to patients, but also reduced the burden on caregivers.

Oxidative stress is an important factor in the development of AD. When the body is adversely stimulated, excessive production of highly active molecules, such as reactive oxygen species, can lead to an imbalance between oxidative and antioxidant defences, leading to oxidative stress [24]. Excess reactive oxygen species can cause protein damage, leading to oxidative stress and ultimately cell death [25]. Stringfellow et al. [26] suggested that reactive oxygen species can also accelerate apoptosis. In this study, MDA levels increased after oxidative stress and decreased compared to the levels in controls after aromatherapy, but the difference was not statistically significant. SOD is a catalytic enzyme that reduces O_2 to H_2O_2, and therefore, has antioxidant activity [27]. We observed an increase in SOD activity after aromatherapy compared with that in the control group, suggesting that aromatherapy has the potential to repair brain tissue damage. These findings are consistent with those of a previous study by Ruperto and Barata [28] that showed that the active ingredients in essential oils, thymol and carvacrol, have higher antioxidant capacity for lipid peroxidation. Although the underlying pathophysiology of AD is unclear, excessive cytokine-mediated inflammation is believed to play a leading role in the progression of AD. Long-term activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines and chemokines, creating a neurotoxic environment that exacerbates the progression of AD [29]. Aromatherapy reduces the concentration of pro-inflammatory mediators such as TNF-α and IL-6 in the serum, and our results are consistent with those of previous studies, demonstrating the anti-inflammatory effect of aromatherapy on the disease. For example, D-borneol is a major chemical component present in lavender oil, and oral or intrathecal administration of D-borneol inhibits the expression of inflammatory factors TNF-α, IL-1β, and COX-2 in rat models of ischaemic stroke [30].

The study, which was affected by COVID-19, avoided cross-infection and was not conducted in multiple centres. Although the ratio of essential oils to water was quantified in this study, the composition of essential oils and the combinations of different dosages were not analysed. Future studies should use double-blind randomised controlled trials while applying the same aromatherapy in homes, communities, and long-term care facilities and comparing effects to yield more convincing results.

Conclusion

Aromatherapy improves sleep quality in patients with AD, alleviates psychobehavioural symptoms, and improves quality of life. This effect of aromatherapy is probably caused by regulating oxidative stress damage in the brain and inhibiting the expression of inflammatory factors to delay the deterioration of AD. In fact, the method of stimulating the olfactory nerve through scent exposure is easy to implement because of its low invasiveness and is suitable not only for patients with AD, but also for caregivers [31]. Our research confirms the effectiveness of aromatherapy as a non-pharmacological intervention for the treatment of patients with AD, and its potential as a valuable option is worthy of widespread application at healthcare facilities, communities, and homes in the future.

Abbreviations

AD: Alzheimer's disease

PQSI: Pittsburgh sleep quality index,

NPI-Q: Neuropsychiatric Inventory–Brief Questionnaire form,

QOL-AD: Quality of Life-Alzheimer's Disease

MDA: Malondialdehyde

SOD: Superoxide dismutase

IL: Interleukin

CDR:

Declarations

The authors have no conflict of interest to disclose.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Chengdu Eighth People's Hospital (2021-CBYEC-040) and registered with the China Clinical Trials Registration Center (ChiCTR2200055918). The entire research process followed the requirements of the Declaration of Helsinki. Prior to implementation, this study signed an informed consent form with all subjects or dependents and explained to them the purpose of the study and the process of implementation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

LL, DR: designed the experiments and wrote the first draft of the manuscript; YQH, LTT, ZH: assisted in completing the experiment and analysed the data; HJX, ZH: assisted in completing the experiment and modifying the manuscript. All authors read and approved the final manuscript.

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Figures

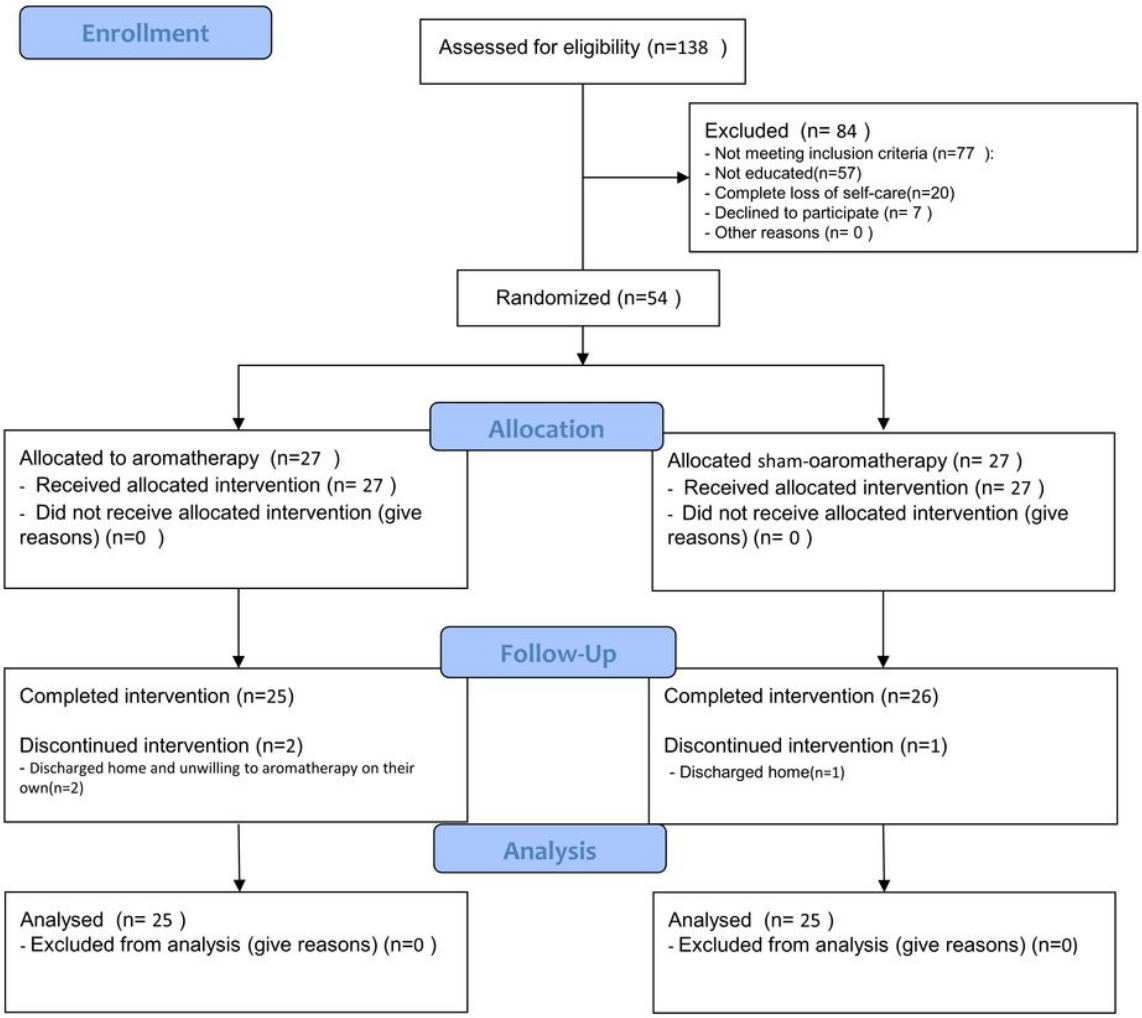

Figure 1

Schema illustrating study flow

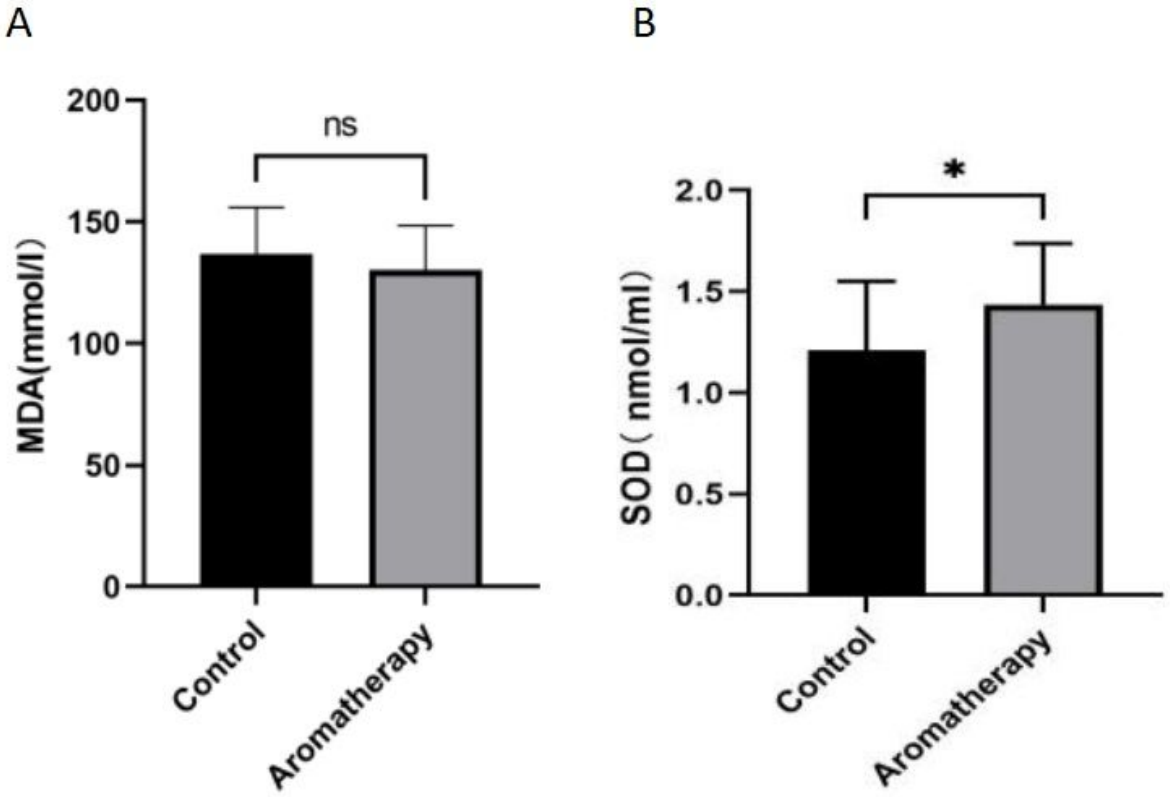

Figure 2

Effect of aromatherapy on oxidative stress levels in patients with AD

a: MDA levels in the control and aromatherapy groups; b: SOD levels in the control and aromatherapy groups. Aromatherapy groups were treated with aromatherapy once daily for 8 weeks. Data are presented as the mean ± SD (n=51) *P<0.05, ****P<0.001 compared with the control group.

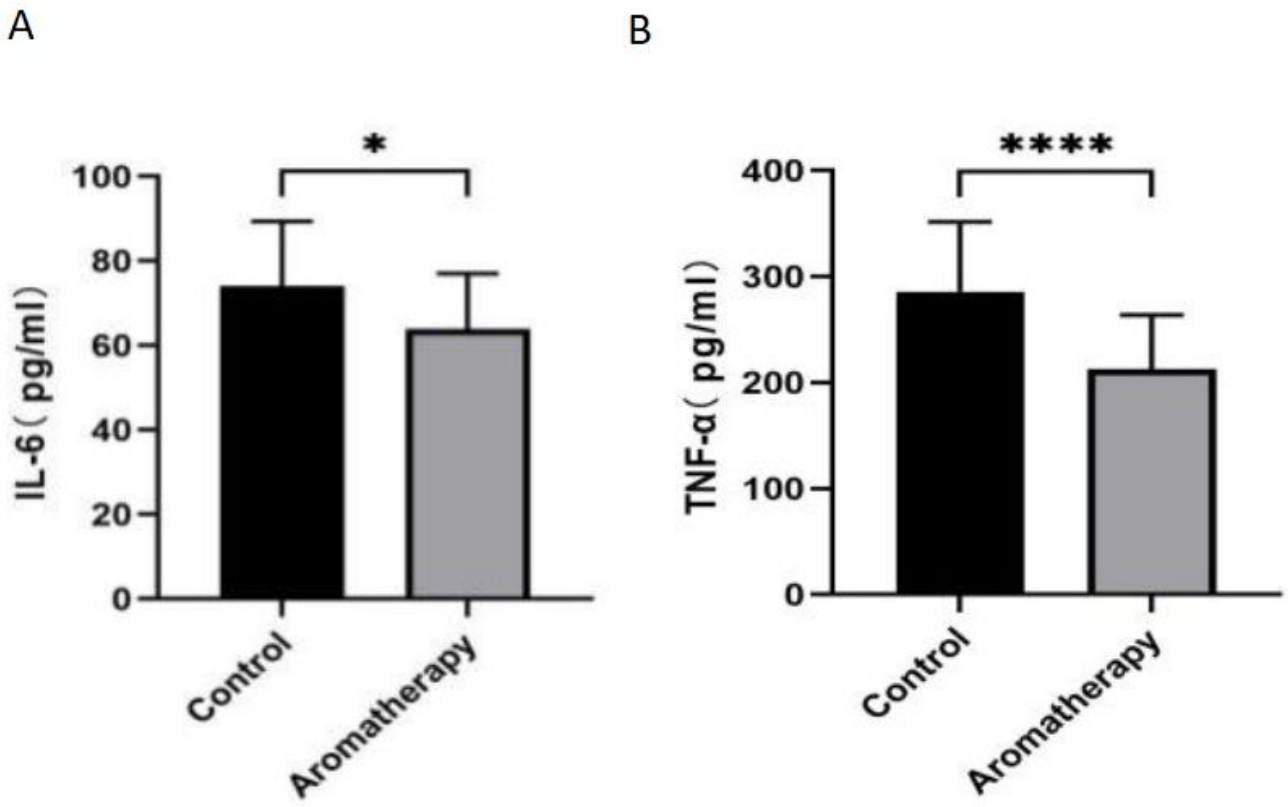

Figure 3

Effect of aromatherapy on inflammatory response in patients with AD

a: IL-6 levels in the control group and aromatherapy group; b: TNF-α levels in the control and aromatherapy groups; aromatherapy groups were treated with aromatherapy once daily for 8 weeks. Data are presented as the mean ± SD (n=51) *P<0.05, ****P<0.001 compared with the control group.