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Effects of Aromatherapy Massage on Dry Eye Disease via the Autonomic Nervous System Regulation

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Abstract: Background: Dry eye syndrome (DES), also called as keratoconjunctivitis sicca (KCS), which is the condition of having dry eyes. Essential oils have drawn attention from researchers, practitioners, and therapists for their biological activities, due to pharmacological responses in the nervous system. Although there are limited reports regarding the effects of essential oils on dry eye disease, massaging clary sage and rosewood oils around the eyes, head, and neck may help alleviate dry eye. Purpose: In this study assessed the effects of an 8-week aromatherapy massage on tear secretion and autonomic nervous function adjustment in patients with dry eye symptoms. Methods: Sixty patients with dry eye symptoms aged 50–78 years were recruited and divided into three groups: massaged with a base (grapeseed) oil, essential (0.8% clary sage and rosewood) oils, and control (no treatment) groups. Ocular surface disease index, ocular surface analyzer, and heart rate variability were assessed. Overall, 8 cycles were performed over a period of 2 months. Results: Aromatherapy massage is using massage oil or lotion containing essential oils. These molecules will inhale or absorbed through the skin during the massage. The results showed that aromatherapy massage improved lipid layer quality, blinking quality, meniscus height, and noninvasive tear black-up time. Heart rate, standard deviation of heartbeat interval, low-frequency (LF) power, normalized LF power ratio (LF%), high-frequency (HF) power, and normalized HF power ratio (HF%) were altered in the aromatherapy massage group. Conclusion: The effects of aromatherapy massage on dry eye symptoms were improved through the lipid layer, blinking quality, meniscus height, and noninvasive tear black-up time. Aromatherapy massage using 0.8% clary sage and rosewood oils improved dry eye symptoms through autonomic activities.

Keywords: Dry Eye Disease, Essential Oil, Linalool, Ocular Surface Analyzer, Autonomic Nervous System

1. Introduction

Dry eye disease (DED) is a multifactorial disorder affecting approximately 5%–50% of individuals in different populations. Contributors to DED include, but are not limited to, lacrimal gland hypofunction, meibomian gland dysfunction (MGD), ocular surface inflammation, and corneal nerve dysfunction. Current DED treatments target specific aspects of the disease, such as inflammation of the ocular surface; however, not all individuals experience adequate relief from symptoms. [1] Systematic diagnosis and monitoring of dry eye can be accomplished using various validated measures of disease signs and symptoms. Commonly used subjective scales include the Ocular Surface Disease Index (OSDI) and the Symptom Assessment in Dry

Eye (SANDE). The OSDI is a 12-item questionnaire used to assess symptoms in the previous week. Scores range from 0–100, with higher scores indicating a more severe disease. SANDE uses a visual analog scale and asks patients to rate the severity and frequency of dry eye symptoms. [2] These can be used in conjunction with clinical findings such as corneal and conjunctival staining with fluorescein and/or lissamine green, tear break-up time, and Schirmer tests.

Traditional dry eye treatments include over-the-counter artificial tears, warm compresses, and eyelid cleansing with baby shampoo. [3] Topical 0.05% cyclosporine A (CsA), a fungal antimetabolite used as an anti-inflammatory agent for its ability to reduce IL-2 mediated T cell activation, was approved by the FDA in 2003 for the treatment of dry eye syndrome and has been used routinely in the clinic for the past 15 years. This is a standard offline dry eye treatment for people who have failed the aforementioned conservative measures. An estimated 48.2% of people with chronic DED are prescribed CsA, although doctors disagree on its efficacy. Several studies have reported improved symptoms, lower OSDI scores, and improved Schirmer test and tear break-up time (TBUT) results in CsA-treated patients. However, despite its long history and frequent use, active questions surrounding the use of topical CsA, including optimal concentration/dose, and the necessary duration of treatment, which patients are most likely to benefit from its use, remain. [4] In addition, ocular burning is a common side effect of topical CsA (occurring in up to 17% of patients) and the most common reason for treatment discontinuation [5] Other side effects include conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, and visual disturbances, such as blurred vision. [6].

Dry eye symptoms are the most common complaints in ophthalmic practice, affecting people's quality of life and restricting their daily activities. Although various ocular and systemic conditions can determine the onset of dry eye, most cases originate from a deficient tear or excessive tear evaporation, leading to tear film instability. Essential oils have been recognized as therapeutic agents since ancient times, owing to their wide range of pharmacological and psychological properties. They are a complex mixture of volatile odor compounds consisting of benzenoids, phenylpropanoids, monoterpenoids, and sesquiterpenoids. Historical records show that essential oils were already in use for more than 2000 years in ancient India, Persia, Mesopotamia, Egypt, and China to relieve illnesses using their pleasant odors. [7] Currently, aromatherapy is used worldwide to alleviate insomnia, depression, anxiety, and cognitive disorders.

Essential oils have drawn attention from researchers, practitioners, and therapists for their biological activities, such as antibacterial, antiviral, anti-inflammatory, antifungal, antioxidant, anticancer, and antinociceptive properties. [8] An increasing number of studies in humans and animals have shown that several essential oils produce many pharmacological effects in the nervous system, resulting in anticonvulsant, analgesic, antidepressant, anxiolytic, and sedative effects. [9, 10] Therefore, it has been suggested that essential oils can effectively improve the symptoms of various mental illnesses, including depression, anxiety, and dementia. Nevertheless, there are limited reports regarding the effects of essential oils on DED. The use of essential oils in integrative medicine, such as aromatherapy massage, is widespread and involves the administration of essential oils by inhalation or skin absorption. Recent phytochemical studies have shown that medicinal herbs contain alkaloids, glycosides, saponins, methyl salicylate, mucilage, linalool, α-terpineol, geraniol, myrcene, and vitamin C, with anti-inflammatory, antipyretic, and antibacterial activities. Based on this background, essential oils were used as a new application to relieve DED symptoms. [11] To our knowledge, this is the first study of alternative medicine to develop alternative and complementary therapies and mechanisms in DED.

Clary sage essential oil is obtained mainly by hydrodistillation of the entire aerial part of Salvia sclarea. The main compounds in this essential oil include linalool, α-terpineol, geraniol, acetate derivative of geraniol, and myrcene. [12] Rosewood essential oil comprises d-linalool, β-terpineol, cis, trans-linalool oxides, and 1.8-cineole. The pharmacological effects of linalool include sedative, analgesic, anxiolytic, sedative, anti-inflammatory, antitumor, and antibacterial effects. [13] Neurochemical studies have shown that linalool exerts an inhibitory effect on glutamate receptors in the rat cortex. [14] Linalool also inhibited nitric oxide formation in vitro and blocked N-methyl-d-aspartate glutamate receptors. [15, 16] According to these reports, linalool affects neuronal activity. Therefore, in this study, we massaged clary sage and rosewood oils around the eye, head, and neck to alleviate dry eye.

2. Materials and Methods

2.1. Study Design and Participants

The participants were 50–75-year old people living in the Siangshan area, Hsinchu City, Taiwan, who did not work on rotating night shifts. The recruitment period lasted for 5 months (September 2019 to January 2020). Subsequently, we began the prescreening and intervention process when many potential participants were recruited. The data collection period was conducted between October 2019 and January 2020 (average temperature 21.47°C, relative humidity 3.17%). After the prescreening, the aim and detailed experimental procedure were explained to the participants. Figure 1 shows a flowchart of the experimental procedure and design. Then, the participants were allocated to one of three groups: the aromatic massage group (aromatic massage with 0.8% happy sage and rosewood essential oil), massage group (massage with basic essential oil), and no-treatment control group.

2.2. Ethics Statement

The study was approved by the Institutional Review Board of Yuanpei University Medical and Technology (YPU-IRB-1080729) and was conducted in accordance with the principles of the Declaration of Helsinki. The process

details were explained to the contributors and written informed consent was obtained from each participant.

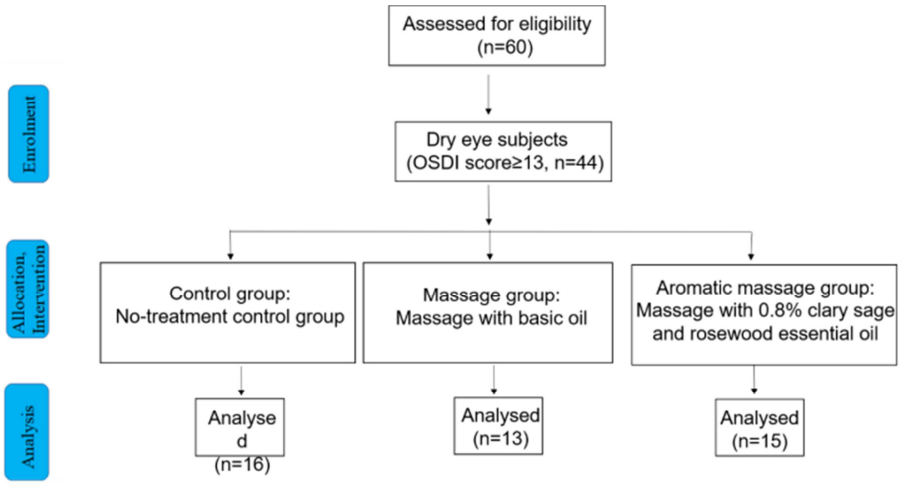

Figure 1. *Flowchart of the experimental procedure and design.*

2.3. Materials of Aromatherapy

We selected clary sage (Salvia sclarea) and rosewood (Aniba rosaeodora var. amazonica Ducke) oils as the intervention medium for essential oil treatment, while the control group used grapeseed oil. We mixed the treatment with 0.8% clary sage and 0.8% rosewood essential oil for the mixed essential oil treatment. This dosage was based on the test of cultured human retinal cells and the absorption efficiency of the skin (approximately 25%). All oils used in this study were commercially available (Triton Essential Oil Company, Miaoli, Taiwan). We also performed aromatherapy following the instructions provided by Hsiu-Yin Kuo. The aromatherapy massage developed by Hsiu-Yin Kuo is an extension of classical massage based on the autonomic plexus around the eye, head, and neck.

2.4. Biocompatibility of Essential Oil

The biocompatibility of the essential oil was evaluated using the water-soluble tetrazolium (WST-1) assay in the L929 cell lines from BCRC, Taiwan. The biocompatibility of the as-prepared composite was tested according to the ISO 10993-5 standard. An extract medium was prepared by adding 0.2 g/mL specimen to high-glucose DMEM (Sigma, USA), followed by incubation at 37°C for 24 h. The cells were subsequently seeded in 96-well plates at a density of 5×10^3 cells/well and incubated at 37°C for 1 day. The culture medium was replaced with the extract medium, and the samples and cells were incubated for 1 to 3 days. Before the assay, 10 µL of WST-1 reagent was added to each well and incubated for 4 h. After incubation, the plate was placed in a spectrophotometric plate reader (ELISA reader, Tecan Sunrise, Switzerland) set to read the absorbance at 450 nm (with a reference filter at 600 nm) for determining the amount of formazan formed, which directly correlates to the number of metabolically active cells. The percentage of cell viability was calculated using the following equation (1):

$$\text{Cell viability (\%)} = ([\text{OD experiment} - \text{OD background}] \times 100)/ ([\text{OD control} - \text{OD background}]) \quad (1)$$

2.5 Aromatic Massage Interventions

The participants were divided into three groups: Group A/control group, received no treatment; Group B/massage group, received essential supplements around the eyes; and Group C/aromatic massage group, massaged with 0.8% clary sage and rosewood essential oils around the eyes. The massage lasted for 5–6 min and was performed twice a week for 8 weeks. Physiological measurements were performed before and 8 weeks after the massage intervention.

2.6. Ocular Surface Disease Index (OSDI) Testing

The validated OSDI questionnaire was used to investigate dry eye-related syndromes in participants whose scores were >13 and enrolled in the intervention. The total OSDI score for each participant was calculated using Equation (2):

$$\text{OSDI} = [(\Sigma\text{scores on domain} \times 25) / (\#\text{ of answered questions})] \quad (2)$$

2.7. Ocular Surface Analysis

All ocular surface examinations were performed using an ocular surface analyzer (SBM Sistemi, Turin, Italy). This all-in-one device allows automated measurement of lipid layer thickness, blinking quality, tear meniscus height, noninvasive breakup time (NIBUT), and infrared meibography. The lipid layer thickness was estimated by observing the interference pattern and color of the moving lipid tear film. The scale of lipid layer thickness was 1: <15 mm, 2: ~15 mm, 3: ~30 mm, 4:

30~80 mm, 5: ~80 mm, 6: 80~120 mm, and 7: 120~160 mm. NIBUT was measured without fluorescein dye after the participants were asked to blink three consecutive times and then hold their eyes open. The measurement was repeated thrice, and the mean value was recorded. The tear meniscus height was measured along the lower lid margin immediately below the pupil. Infrared meibography was performed after everting the inferior eyelid, and meibomian gland loss was defined as the percentage of gland loss relative to the total tarsal area of the lid. The blinking analysis was performed by recording a 30-s video. Simultaneously, the patient was asked to blink naturally by avoiding forced blinking, and the percentage closure of the maximal palpebral fissure opening was noted.

2.8. Measurement of Heart Rate Variability (HRV)

This experiment measured the HRV, which reflects autonomic nervous system activity, before and after the intervention. The HRV instrument (WG-101) was obtained from Vicon Healthcare International Inc. (Taiwan). HRV-related parameters, standards, and clinical uses were obtained from the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. [17].

2.9. Statistical Analysis

The obtained data were analyzed using SPSS 20 software. The measurements for both eyes of the same individual are presented as mean ± SD. Within-group differences were compared before and after treatment using a paired sample t-test. In addition, the effects of the control, massage, and aromatic massage groups were analyzed using analysis of covariance (ANCOVA). If there was a significant difference, a post-hoc analysis was performed using the Scheffé or Tukey test. Statistical significance was set at $p < 0.05$.

3. Results

3.1. The Evaluation of Cell Viability of Essential Oil

The biocompatibility of the essential oil was determined using WST-1 assay. Figure 2 indicates cell viability according to the WST-1 assay. There was no significant difference in cell viability for the groups of rosewood, clary sage and control. On the basis of ISO-10993, we believe that the essential oil would produce no toxicity.

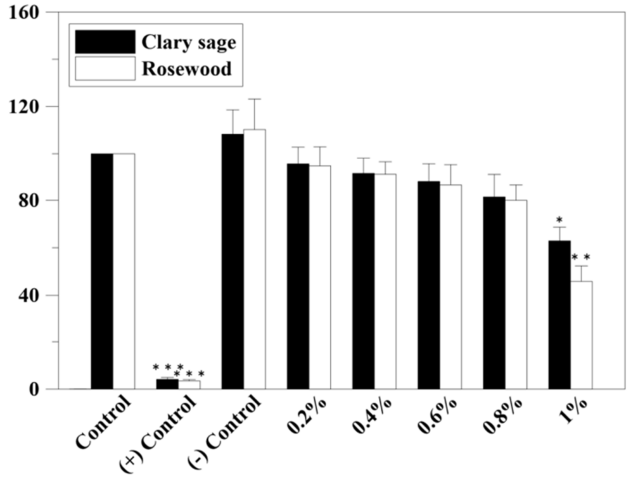

Figure 2. *The cell viability of rosewood, clary sage and control group by WST-1. (n = 12, * p < 0.05 compared with control).*

3.2. Ocular Surface Analysis

The mean ocular surface recordings before and after the investigation in the three groups are presented in Table 1. There was no significant difference in the control group after the 8-week intervention. The results of both eyes in the lipid layer thickness, blinking quality, meniscus height, and NIBUT after the intervention showed a significant improvement in the aromatic massage groups compared to the massage group using the paired samples *t*-test. A comparison of the essential oil effect of the trial (two eyes between massage and aromatic massage groups) using ANCOVA and Tukey's post hoc analysis showed a significant change in the lipid layer thickness of the right eye between the control and aromatic massage groups. This change was not significant in MGD (%) after the intervention among the three groups.

Table 1. *Ocular surface analysis in control, massage and aromatic massage group before and after 16th intervention.*

Test	Treatment	Control (n = 16)		Massage (n = 13)		Aromatic Massage (n = 15)	
		Right	Left	Right	Left	Right	Left
Lipid layer thickness (scale)	Before	1.69 ± 0.20	1.81 ± 0.21	1.77 ± 0.28	2.92 ± 0.29	1.93 ± 0.21	2.33 ± 0.25
	After	2.13 ± 0.22	2.19 ± 0.21	2.85 ± 0.27**	2.77 ± 0.28	3.00 ± 0.26***†	3.13 ± 0.32*
Blinking quality (%)	Before	89.38 ± 3.30	81.56 ± 4.84	74.62 ± 4.80	80.38 ± 4.70	70.93 ± 4.63	73.40 ± 4.91
	After	81.81 ± 5.17	83.00 ± 5.46	91.23 ± 3.36**	86.31 ± 3.64	86.64 ± 4.14*	87.43 ± 3.91**
Meniscus height (mm)	Before	0.30 ± 0.03	0.30 ± 0.03	0.32 ± 0.04	0.32 ± 0.04	0.28 ± 0.02	0.30 ± 0.02
	After	0.33 ± 0.03	0.37 ± 0.05	0.36 ± 0.04	0.33 ± 0.03	0.34 ± 0.03*	0.37 ± 0.03*
NIBUT (sec)	Before	11.76 ± 1.71	11.66 ± 1.59	12.37 ± 1.86	11.20 ± 2.01	9.83 ± 1.24	9.27 ± 1.28
	After	11.54 ± 1.76	12.77 ± 1.87	14.72 ± 1.96	14.40 ± 2.06	15.12 ± 1.38**	14.67 ± 1.39***
Meibomian gland dysfunction (%)	Before	34.75 ± 4.06	39.31 ± 4.23	37.46 ± 5.16	38.77 ± 3.33	35.07 ± 5.52	34.60 ± 3.70
	After	28.25 ± 2.93	36.63 ± 3.04	33.15 ± 1.91	41.62 ± 4.37	33.13 ± 4.11	34.87 ± 2.97

1. All data presented as Mean ± SE.
2. Paired samples t-test, * $p < 0.05$.
3. Analysis of covariance using the Tukey test, † $p < 0.05$ comparison between control group and aromatic massage group.
4. NIBUT: Noninvasive Black-Up Time.
5. Lipid layer thickness scale 1: <15 mm, 2: ~15 mm, 3: ~30 mm, 4: 30~80 mm, 5: ~80 mm, 6: 80~120 mm, and 7: 120~160 mm.

3.3. HRV Analysis

HR, standard deviation of heartbeat interval (SD), low-frequency (LF) power, normalized LF power ratio (LF%), high-frequency (HF) power, and normalized HF power ratio (HF%) were collected from HRV before and after the test at the first and sixteenth massages in the three groups (Table 2). The results indicated that the aromatic massage group differed after the aromatic treatment between the first and sixteenth massages in HR, SD, LF, HF, and HF%. In addition, there were significantly better parameters after the intervention (the eighth week) than in the control and massage groups. Most importantly, the significant differences in HF% after aromatic massage intervention of eight weeks, which represented the improvement of parasympathetic nervous activity was better than the other two groups.

Table 2. *The parameters of heart rate variability in control, massage, aromatic massage groups in the first and 8th wks' measurement.*

Parameters	Measurement	Control (n = 16)		Massage (n = 13)		Aromatic massage (n = 15)	
		Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
HR (bpm)	1st	70.55 ± 2.45	70.25 ± 2.44	67.42 ± 1.78	67.44 ± 1.96	72.56 ± 2.60	69.71 ± 2.28
	8th	72.07 ± 2.58	71.74 ± 2.41	76.95 ± 2.87	72.83 ± 2.50***	74.63 ± 2.73	70.26 ± 2.71***
SD (ms)	1st	25.27 ± 2.43	25.64 ± 3.75	35.15 ± 5.77	32.92 ± 3.08	30.74 ± 4.11	26.79 ± 2.71
	8th	27.16 ± 2.46	26.71 ± 2.46	23.26 ± 2.67	23.41 ± 2.20	25.43 ± 4.04	32.80 ± 3.49*
LF [ln (ms2)]	1st	4.40 ± 0.22	4.35 ± 0.22	4.92 ± 0.25	4.75 ± 0.19	4.63 ± 0.25	4.59 ± 0.24
	8th	4.42 ± 0.16	4.38 ± 0.15	4.33 ± 0.22	4.03 ± 0.19	4.19 ± 0.33	4.83 ± 0.23*
HF [ln (ms2)]	1st	4.19 ± 0.25	4.17 ± 0.25	4.65 ± 0.24	4.73 ± 0.26	4.66 ± 0.31	4.36 ± 0.32
	8th	3.85 ± 0.27	3.91 ± 0.27	4.17 ± 0.23	4.23 ± 0.25	3.67 ± 0.34	4.68 ± 0.31***
LF% (n.u.)	1st	50.36 ± 4.15	50.13 ± 4.20	48.82 ± 4.65	49.58 ± 4.69	42.04 ± 4.21	48.35 ± 4.25
	8th	55.09 ± 4.01	54.96 ± 3.99	47.44 ± 4.42	38.37 ± 2.39	49.15 ± 5.04	49.66 ± 3.87
HF% (n.u.)	1st	38.79 ± 3.50	38.68 ± 3.49	37.72 ± 3.85	42.22 ± 4.52	41.87 ± 2.77	38.89 ± 3.75
	8th	32.84 ± 3.61	32.47 ± 3.46	39.79 ± 3.53	46.70 ± 2.85	32.13 ± 2.69	43.45 ± 2.43***

1. All data presented as Mean ± SE.
2. Paired samples t-test, pretest vs. posttest, $^{*}p<0.05$.
3. HR: Heart Rate, SD: Standard Derivation of Average Normal to Intervals, HF: High-Frequency Power, LF: Low-Frequency Power, LF%: Normalized LF, HF%: Normalized HF.

4. Discussion

Aromatherapy massage is a Swedish massage therapy using massage oil or lotion containing essential oils. These essential oil molecules are inhaled or absorbed through the skin during an aromatherapy massage. They are believed to promote beneficial changes in the mind and body by affecting the brain involved in emotions. The primary purpose of this study was to explore improvements in tear secretion and autonomic nervous function adjustment in patients with DED.

Aromatherapy massage appears to reduce pain and discomfort associated with menstrual cramps and ease menopausal symptoms. [18] Previous studies suggested that aromatherapy massage may or may not relieve cancer-related stress. [19, 20] When comparing aromatherapy massage with no massage, they found that "there was some indication of benefit in the aromatherapy-massage group, but this benefit is unlikely to translate into clinical benefit." A review of previously published studies concluded that there were no differences in the effects of massage on depression, mood disturbance, psychological distress, nausea, fatigue, physical symptom distress, or quality of life compared with no massage [20, 21]. However, no studies have reported the effects of aromatherapy massage on dry eye symptoms.

In this study, aromatherapy massage improved dry symptoms through the quality of blink, lipid layer thickness, and break-up time in ocular surface analysis, and increased the parasympathetic activities through the HF value and normalized HF (HF%) value in HRV. The essential oils included rosewood and clary sage, which are rich in linalool and are known to have anxiolytic, sedative, and anticonvulsant effects. Linalool could inhibit the increase in cAMP levels that protects against seizures in a diversity of models of epilepsy. In addition, rosewood oil, R(-)-linalool, and (±)-linalool exclusively inhibited cAMP accumulation stimulated by forskolin, even when adenosine receptors were blocked with the non-selective adenosine receptor antagonist 3-isobutyl-methyl-xanthine (IBMX). However, the compounds presented different relative efficacies in the chicken retina. [22] These results extend the range of subcellular mechanisms underlying the relaxant action of linalool in the central nervous system.

Previous reports have suggested that linalool has moderate sedative effects. [23, 24] Lis-Balchin and Hart showed that spasmolysis or relaxation of the smooth muscle of the ileum in vitro correlates with this holistic relaxant effect in humans. [25] They also reported that the spasmolytic effect of essential oils is most likely mediated via cAMP and not via cGMP, and they suggested that the mode of action of linalool reflects that of the whole oil. [26] Furthermore, linalool has been reported to suppress caffeine-induced over agitation of the central nervous system (CNS). [23, 24] Elisabetsky and Souza also showed that linalool reduced motor activity in mice and exhibited dose-dependent binding to glutamate, a primary excitatory neurotransmitter in the CNS. [14] In addition, Buchbauer et al. showed that linalool can be detected in mice at a high concentration in blood samples from the retrobulbar venous plexus after inhalation. [24] These reports suggest that

linalool might be absorbed by inhalation and elicit sedative effects in the CNS. Therefore, the sedative effects on both autonomic nerve activities and mood states, activation of parasympathetic nerves, and regulation of autonomic nerves after inhalation of the essential oil relieved DED, at least partly, by these pharmacological effects. However, the pharmacological pathway and optimal dosage remain unclear. Therefore, in vitro and in vivo studies should be performed to clarify the pharmacological pathway and optimal dosage of linalool.

5. Conclusion

To the best of our knowledge, this is the first study to investigate the effects of essential oils on DED treatment and their probable mechanism of pharmacological effects. In this study, these essential oil molecules are inhaled or absorbed through the skin during an aromatherapy massage. We founded that the effects of aromatherapy massage on dry eye symptoms were improved through the lipid layer, blinking quality, meniscus height, and noninvasive tear black-up time. The mechanism may activate parasympathetic nerves and regulate autonomic nerves after inhalation of R(-)-linalool in essential oil. However, the pharmacological pathway and optimal dosage remain unclear. Therefore, essential oils are a potential alternative and complementary therapy for DED alleviation, it still need to investigate the pharmacokinetics and signal pathway in the animal study in the future.

Statement of Ethics

The study was approved by the Institutional Review Board of Yuanpei University Medical and Technology (YPU-IRB-1080729); and was conducted in accordance with the principles of the Declaration of Helsinki. The process details were explained to the contributors and written informed consent was obtained from each participant.

Conflict of Interest Statement

The authors have declared that no competing interest exists.

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Author Contributions

HYK collected the data, executed most of the experiments, and drafted the manuscript. CTH and CCH contributed to the active discussion of experimental design and performing of the study. CKC and HCW supervised the study, assisted with study conceptualization, and made a substantial contribution to the revision of the manuscript. All authors have read and approved the final submitted manuscript. Hsiao-Chuan Wen and Chao-Kai Chang contributed equally to the writing of this article.

Data Availability Statement

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

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