Clinical efficacy of olfactory training using aromatic traditional Chinese medicine in managing olfactory dysfunction induced by SARS-CoV-2

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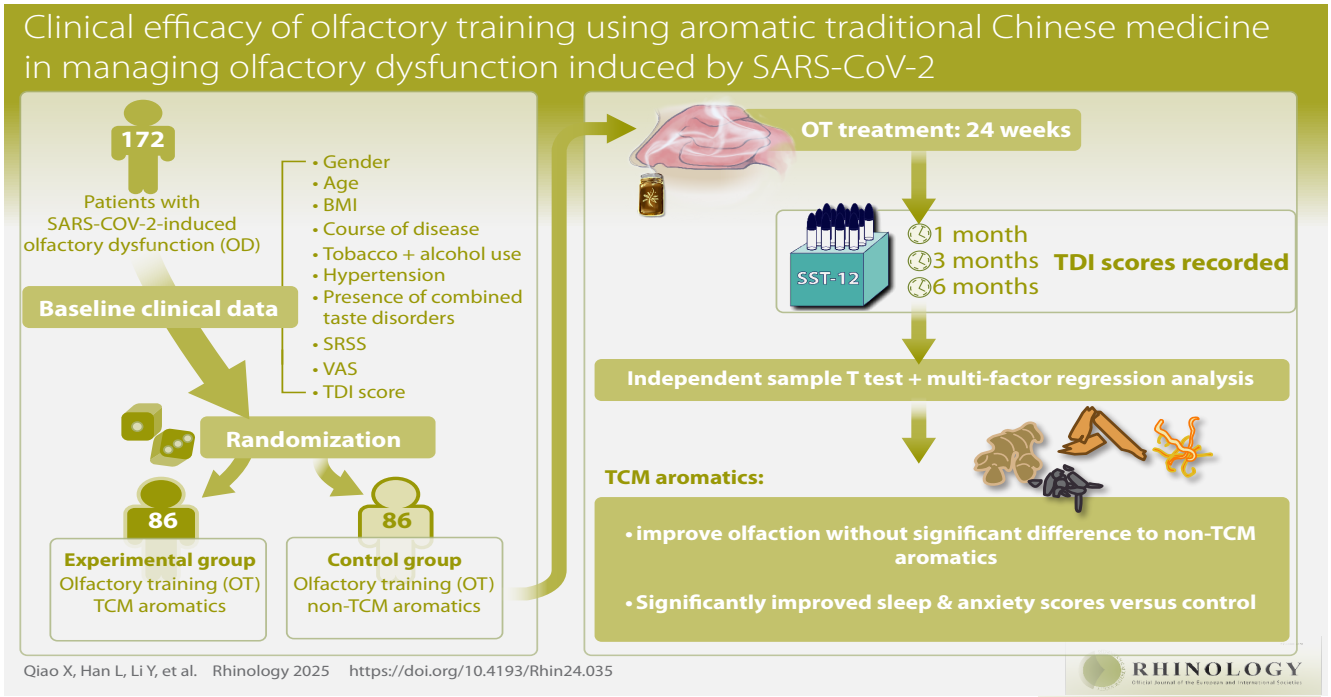

Abstract

Objective: The aim of this study is to assess the clinical efficacy of olfactory training using aromatic traditional Chinese medicine (TCM) for addressing severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-induced olfactory dysfunction, while also exploring the factors that influence the observed efficacy. **Methods**: 172 outpatients with SARS-CoV-2-related olfactory dysfunction were randomized into two groups. The experimental group received olfactory training with TCM aromatics (ginger, Pericarpium Citri Reticulatae, Santali Albi Lignum, Styrax), while the control group used non-TCM aromatics (phenyl ethanol-rose, menthol-mint, citronellal-lemon, eugenol-clove) for 24 weeks. Olfactory function was assessed using the Sniffin' Sticks test and TDI (threshold-discrimination-identification) scores at baseline, 1, 3, and 6 months post-treatment. **Results**: Response rates at 1, 3, and 6 months post-treatment were 3.66%, 25.61%, and 43.90% in the experimental group, and 4.94%, 23.46%, and 43.21% in the control group. The TDI scores of the experimental group and the control group were statistically different before and after treatment. At 3 and 6 months post-treatment, TDI scores increased significantly, with enhanced odor discrimination and identification capabilities in both groups compared to pre-treatment, while the odor detection threshold was not improved compared with that before treatment. At the 3- and 6-month follow-ups, experimental group showed significantly higher self-rated sleep and anxiety scores than controls, indicating notable improvement in both after treatment. **Conclusion**: Olfactory training with aromatic TCM offers an effective treatment for SARS-CoV-2-induced olfactory dysfunction, improving odor discrimination, identification without significant differences compared to conventional aromatics, besides, it may also improve anxiety and sleep quality.

Key words: aromatic traditional Chinese medicine, olfactory agent, olfactory dysfunction, olfactory training, SARS-CoV-2

Introduction

Since late 2019, the global outbreak of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has given rise to the coronavirus disease 2019 (COVID-19) pandemic. Recent clinical trials have brought to light a prevalence of olfactory dysfunction, including hyposmia and anosmia, in patients diagnosed with COVID-19 [1]. Historically, olfactory disorders have been linked to viral upper respiratory tract infections associated with common colds, influenza, parainfluenza viruses, rhinoviruses, and other endemic coronaviruses [2]. Notably, olfactory dysfunction induced by viral infections is reported to constitute a considerable proportion, ranging from 11%–45%, of all cases of olfactory dysfunction [3]. Furthermore, it is estimated that COVID-19-related olfactory dysfunction may account for 5% to 85% of total cases of olfactory dysfunction [4]. On May 13, 2020, global health entities such as the World Health Organization, the European Centre for Disease Prevention and Control, and various national health authorities officially recognized olfactory dysfunction as a symptom of COVID-19.

The standard clinical interventions for olfactory dysfunction resulting from SARS-CoV-2 primarily involve pharmacological approaches. Additionally, there has been a growing emphasis on olfactory training, an innovative therapeutic modality for addressing olfactory dysfunction, by experts and scholars worldwide in recent years. Olfactory training involves the systematic and repetitive exposure to various everyday odors to facilitate the recovery of olfactory function. Numerous clinical trials have underscored the positive impact of olfactory training on patients with olfactory dysfunction [5-8]. Traditionally, olfactory training was performed with standardized agents from professional manufacturers, necessitating purchase and presenting inconveniences in terms of usability and portability. In this study, olfactory training incorporated traditional Chinese medicine (TCM) olfactory agents due to two key considerations. First, it is proposed that aromatic TCMs may yield effects comparable to conventional olfactory agents in terms of olfactory stimulation. Second, aromatic TCMs, through direct stimulation of the brain and modulation of mood and nervous systems via their inherent plant aroma, offer comprehensive therapeutic effects that surpass those of conventional olfactory training. The aim of this prospective study was to analyze the efficacy of olfactory training using TCM olfactory agents in the management of SARS-CoV-2-induced olfactory dysfunction while exploring factors influencing its effectiveness.

Materials and methods

Clinical information

A cohort of 172 patients experiencing olfactory dysfunction attributed to SARS-CoV-2, who were diagnosed and treated at the outpatient facilities of the Department of Otolaryngology at the Shaanxi Provincial People's Hospital between August 2021 and August 2023, were enrolled in this study. The investigators used a quasi-randomization method, which is that the investigators assigned patients to an experimental group and a control group in an alternate manner. The experimental group was treated with olfactory agents containing four different kinds of traditional Chinese medicine aromatics including ginger, Pericarpium Citri Reticulatae, Santali Albi Lignum and Styrax, while the control group was treated with olfactory agents containing four kinds of aromatics including phenyl ethanol-rose, menthol-mint, citronellal-lemon, eugenol-clove. This study was reviewed and approved by the Ethics Committee of the Shaanxi Provincial People's Hospital. Furthermore, all enrolled patients signed a consent form.

The inclusion criteria for participant selection encompassed the following parameters: 1) Patients with a documented history of SARS-CoV-2 infection and onset of olfactory dysfunction attributable to viral infection within a duration of ≤ 12 months; with the method of that samples of upper respiratory tract (pharyngeal swab, nasal swab, nasopharyngeal extract) or lower respiratory tract (sputum, airway extract, alveolar lavage fluid), blood, feces, urine and conjunctival secretions were taken for nucleic acid detection, and positive results were diagnosed as SARS-CoV-2 positive infection patients; 2) Patients possessing comprehensive medical histories, devoid of any instances of trauma, Alzheimer's disease, Parkinson's disease, psychiatric disorders, or immune disorders; 3) Patients undergoing nasal endoscopy to eliminate the presence of nasal conditions such as nasal cavity neoformation, rhinosinusitis, allergic rhinitis, and olfactory cleft edema; 4) Patients undergoing both sinus computed tomography and brain magnetic resonance imaging to exclude the existence of nasal, sinus, or intracranial space-occupying lesions, as well as neurodegenerative diseases; 5) Patients demonstrating insufficient response to medications (for over 1 month), including glucocorticoids, Ginkgo biloba extracts, and vitamin A. The experimental time of admission was from 1 month to 12 months after the occurrence of olfactory disorder.

The exclusion criteria for participants included the following: patients presenting contraindications to therapeutic methodologies or pharmacological agents; patients discontinuing treatment due to intolerance or adverse reactions; and patients with concurrent afflictions or requiring medications that could potentially interfere with the anticipated therapeutic outcomes.

Experimental methods

Medical history acquisition

Comprehensive patient information was collected at the time of enrollment utilizing a structured questionnaire. The data collected included demographic details such as gender, age, body mass index (BMI), duration of the disease, history of smoking

and alcohol consumption, presence or absence of diabetes mellitus, history of hypertension, whether taste dysfunction was concurrently experienced, self-rating scale of sleep (SRSS) scores, and Visual Analogue Scale for Anxiety (VAS-A) scores [9, 10].

Olfactory function test

The Sniffin' Sticks test, using the odorous "Sniffin' Sticks" pens manufactured by Burghart in Wedel, Germany, was administered prior to the treatment and at intervals of 1 month, 3 months, and 6 months post-treatment. The test comprised three distinct subtests: (i) Odor threshold (T) test, wherein scores ranged from 16 points (indicating perception at the lowest concentration) to 0 points (indicating inability to perception at the highest concentration); (ii) Odor discrimination (D) test, where a score of 16 indicated successful discrimination of all presented odors; and (iii) Odor identification (I) test, where a score of 16 indicated accurate identification of all presented odors. Subsequently, the scores obtained from the T, D, and I tests were aggregated, yielding the total threshold-discrimination-identification (TDI) score, which served as a comprehensive metric for assessing olfactory function.

Treatment protocol

12 TCM olfactory agents in the pre-experiment, including cinnamon, gladiolus acorus, agarwood, orange peel, patchouli, Angelica angelica, sandalwood, ginger, borneol, wormwood, Suhexiang, and alacacia bark. 3-MI was used to make the olfactory disorder model by intraperitoneal injection of animal experiment. The Buried food pellets (BFT) test evaluated the olfactory function of mice, and finally selected four of the 12 Chinese medicinal materials as the most effective olfactory agents for experimental use. Participants assigned to the experimental group underwent olfactory training using an aromatic olfactory blend derived from four distinct TCMs: ginger, Pericarpium Citri Reticulatae, Santali Albi Lignum, and Styrax. Conversely, patients in the control group engaged in olfactory training with four distinct odors, such as phenyl ethanol-rose, menthol-mint, citronellal-lemon, and eugenol-clove (obtained from Sigma-Aldrich, St Louis, MO, USA). The patients tried to smell each olfactory agent for 10-seconds duration during the treatment, with a 10-second interval between the two olfactory agents. The olfactory training session extended for a duration of 5 minutes, and this regimen was implemented twice daily, specifically before breakfast and before sleep [11]. Assessment of olfactory function was conducted at intervals of 1, 3, and 6 months post-treatment.

Efficacy assessment

The assessment of efficacy centered on the alteration in mean TDI scores post-treatment. A discernible improvement was deemed "effective" when TDI scores exhibited an increase > 6 points [12].

Sample size

Using the following formula, standard deviation was set as 3, and for TDI score, 1 was used as the acceptable equivalence threshold in order to obtain a larger sample size, with $\alpha = 0.05$ (bilateral) and $\beta = 0.2$.

$$n = 2\left[\frac{(\mu_{1-\alpha} + \mu_{1-\beta})\ S}{\delta}\right]$$

Based on the calculation, 67 effective cases is necessary in each group, taking into account factors such as lost follow-up and the actual number of clinical patients, 172 subjects were enrolled in this experiment, and 86 were enrolled in the experimental group and 86 in the control group. See the Graphical Abstract for more details.

Statistical analysis

Statistical analyses were conducted using SPSS version 20 software. Logistic regression analyses were conducted wherein clinical efficacy served as the dependent variable, while gender, age, BMI, duration of disease, history of smoking and alcohol consumption, history of diabetes mellitus, history of hypertension, and the presence or absence of taste dysfunction were considered as independent variables. Additionally, the TDI scores, SRSS scores, and VAS-A scores within each group were compared before and after the treatment phases using repeated measure analysis of variance (RM-ANOVA) and the paired t-test.

Results

Basic information of patients

A total of 172 patients were initially enrolled, and 86 patients were assigned to the experimental and control group each. All enrolled patients were tested positive for SARS-CoV-2. A total of 9 patients experienced treatment interruptions or were lost to follow-up for various reasons, including 2 patients who were lost to follow-up and 7 patients with interrupted treatments due to business trips, distributed across both groups (5 patients in the control group and 4 patients in the experimental group). Eventually, 82 cases were analyzed in the experimental group, and 81 cases were examined in the control group.

In the experimental group, the demographic composition comprised 39 males and 43 females, with ages ranging from 16 to 72 years and a mean age of 49.1 ± 15.2 years. The duration of disease spanned from 4 to 10 months, with a mean duration of 6.6 ± 1.3 months. Notably, there were 25 patients with BMI ≥ 24 (30.5%), 15 patients reported a history of alcohol consumption (18.3%), 14 patients had diabetes mellitus (17.1%), 20 patients exhibited hypertension (24.4%), and 30 patients presented with concurrent taste dysfunction (36.6%). The experimental group recorded VAS-A scores of 8.83 ± 1.04 and SRSS scores of 39.36 ± 5.41. The control group comprised of 33 males and 48 females, with ages ranging from 15 to 75 years and a mean age of 51.4 ±

Table 1. Comparisons of TDI scores within the two groups prior to and at various time intervals following treatment.

Time points	Control group				Experimental group			
	T	D	I	TDI	T	D	I	TDI
Before treatment [a]	6.67±1.67	7.08±1.66	2.79±1.61	15.91±2.67	6.60±2.07	7.17±1.25	2.93±1.28	16.31±2.38
At 1 month post-treatment [b]	6.78±2.55	7.23±1.78	2.66±1.99	17.41±2.96	6.68±2.45	7.31±1.22	296±1.47	16.74±2.12
At 3 months post- treatment [c]	6.82±2.34	8.61±1.99	4.83±1.26	20.64±3.01	6.69±3.00	8.75±1.42	5.11±1.02	20.51±3.04
At 6 months-post treatment [d]	6.77±2.27	9.39±3.01	6.04±1.42	22.33±3.73	7.08±2.38	9.75±2.06	6.55±1.53	22.27±3.99
F values (p value)	22.63	32.16	28.17	19.33	21.36	18.77	19.98	18.24
	p<0.05	p <0.05	p <0.05	p <0.05	p <0.05	p <0.05	p <0.05	p <0.05
P_{a-b} values	0.386	0.285	0.186	0.698	0.248	0.543	0.330	0.641
P_{a-c} values	0.412	0.011	0.004	0.010	0.342	0.007	0.000	0.001
P_{a-d} values	0.145	0.001	0.011	0.004	0.619	0.000	0.019	0.003
P_{b-c} values	0.104	0.000	0.006	0.010	0.343	0.005	0.000	0.001
P_{b-d} values	0.100	0.001	0.004	0.011	0.646	0.009	0.011	0.009
P_{c-d} values	0.151	0.000	0.011	0.001	0.416	0.000	0.000	0.001

T, odor threshold; D, odor discrimination; I, odor identification; [a] = before treatment; [b] = at 1 month after treatment; [c] = at 3 months after treatment; [d] = at 6 months after treatment.

Table 2. Comparison of the TDI scores during the same time periods in the two groups.

Parameters	Before treatment			At 1 month after treatment			At 3 months after treatment			At 6 months after treatment		
	Experimental group	Control group	P	Experimental group	Control group	P	Experimental group	Control group	P	Experimental group	Control group	P
T	6.40±2.04	6.67±1.06	>0.05	6.48±2.25	6.70±3.01	>0.05	6.49±2.88	6.82±2.53	>0.05	6.65±2.33	6.77±2.12	>0.05
D	6.97±1.21	7.08±1.77	>0.05	7.11±1.27	7.38±2.15	>0.05	8.54±1.27	8.61±1.67	>0.05	9.57±3.26	9.39±2.54	>0.05
I	2.73±1.09	2.79±1.21	>0.05	2.79±1.46	2.57±1.97	>0.05	4.91±1.16	4.83±1.12	>0.05	6.49±2.05	6.04±1.90	>0.05
TDI scores	16.20±2.93	16.73±2.75	>0.05	16.56±2.89	17.82±1.66	>0.05	20.35±2.44	20.44±3.40	>0.05	22.79±3.48	22.37±3.41	>0.05

T, odor threshold; D, odor discrimination; I, odor identification.

10.1 years. The duration of disease in this group varied from 3 to 11 months, with a mean duration of 7.4 ± 2.0 months. Furthermore, 22 patients had a BMI ≥ 24 (27.2%), 19 patients reported a history of alcohol consumption (23.5%), 18 patients had diabetes mellitus (22.2%), 20 patients exhibited hypertension (24.7%), and 28 patients presented with concurrent taste dysfunction (34.6%). The control group recorded a VAS-A score of 8.33 ± 1.39 and an SRSS score of 39.20 ± 4.72. Additionally, olfactory dysfunction in the enrolled patients predominantly manifested as hyposmia, with 59 cases of hyposmia and 23 cases of anosmia in the experimental group, and 55 cases of hyposmia and 26 cases of anosmia in the control group. Notably, a more pronounced reduction in Identification (I) scores was observed within the context of TDI scores, and an increased prevalence of anxiety and sleep disorders was noted among patients [13].

Clinical efficacy

At 1, 3, and 6 months post-treatment, the response rates to olfactory training were observed to be 3.66%, 25.61%, and 43.90% in the experimental group and 4.94%, 23.46%, and 43.21% in the control group, respectively. RM-ANOVA showed that the TDI scores of the experimental group and the control group were statistically different before and after treatment (p<0.05). Further multiple comparison showed that the change in the TDI score of 1 month after treatment was not statistically significant compared with that before treatment (p>0.05). At 3 months and 6 months after treatment, TDI scores of the two groups were higher than those before treatment, with statistical significance (p<0.05), and the odor discrimination ability and odor recognition ability of the two groups at 3 months and 6 months after treatment were improved compared with those before treatment

Table 3. A comparison of the VAS-A and SRSS scores during the same time period in the two groups.

Parameters	Before treatment			At 1 month after treatment			At 3 months after treatment			At 6 months after treatment		
	Experimental group	Control group	P	Experimental group	Control group	P	Experimental group	Control group	P	Experimental group	Control group	P
VAS-A scores	8.83±1.04	8.33±1.39	>0.05	7.07±245	7.21±3.57	>0.05	4.99±3.04	7.02±3.03	<0.05	2.95±5.73	6.97±3.89	<0.05
SRSS scores	39.36±5.41	39.20±4.72	>0.05	40.11±2.35	41.08±1.52	>0.05	27.44±2.67	39.00±2.82	<0.05	20.57±3.26	37.39±2.54	<0.05

Table 4. Regression analysis of factors affecting clinical efficacy.

Influencing factors	Control group			Experimental group		
	OR value	95%CI value	p value	OR value	95%CI value	p value
Gender	0.561	0.101~2.306	0.323	1.784	0.452~7.999	0.314
Age	0.868	0.279~1.304	0.502	1.100	0.847~1.236	0.476
Body mass index (BMI)	1.843	0.545~7.112	0.403	0.328	0.088~1.218	0.348
Course of disease	0.794	0.634~0.959	0.003	1.437	1.213~1.766	0.001
History of smoking and alcohol	2.509	0.542~14.160	0.301	0.432	0.105~1.871	0.502
Whether to merge dysgeusia	1.974	0.722~6.094	0.339	0.086	0.321~3.651	0.0738
VAS-A scores	0.902	0.682~1.438	0.921	1.106	0.871~1.659	0.072
SRSS scores	1,002	0.871~14.228	0.866	1.211	1.034~1.683	0.094
Diabetes	2.710	0.691~13.567	0.108	1.438	0.325~7.656	0.807
Hypertension	1.381	0.386~6.287	0.658	0.546	0.211~2.014	0.369
TDI scores before treatment	1.055	0.8075~1.465	0.564	1.105	0.924~1.435	0.774

(p<0.05), while the odor detection threshold was not improved compared with that before treatment, as shown in Table 1. The paired t-test was used to compare the TDI scores between the experimental group and the control group at different periods before and after treatment, and there was no statistical difference (p>0.05), as shown in Table 2.

VAS-A and SRSS scores in the two groups

At the 3-month and 6-month post-treatment assessments, a discernible improvement in anxiety and sleep parameters was evident in the experimental group when compared to the control group (p<0.05), as illustrated in Table 3.

Analysis of influencing factors for clinical efficacy

The results of the Logistic regression analysis revealed that in both groups, the duration of the disease emerged as a significant factor influencing efficacy. Patients with a shorter duration of disease, defined as the time interval between the onset of initial symptoms and the initiation of olfactory training, demonstrated better efficacy following olfactory training when compared to those with a longer duration of disease. For the experimental group, the odds ratio (OR) was 1.437 with a confidence interval (CI) of 1.213–1.766, and p = 0.001. Similarly, in the control group, OR= 0.794 with a confidence interval = 0.634–0.959, p=0.003, as outlined in Table 4.

Discussion

SARS-CoV-2 is the coronavirus responsible for the COVID-19 pandemic. COVID-19 manifests clinically with a spectrum of symptoms ranging from upper respiratory tract infections to severe respiratory distress, acute cardiac injury, and, in severe cases, death. This coronavirus shares considerable genetic similarities with other β-coronaviruses, including SARS-CoV and Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV), responsible for the SARS and MERS pandemics, respectively. Findings from studies conducted on individuals with COVID-19 consistently indicate a substantial decline in olfactory function post-infection, with hyposmia emerging as a noteworthy symptom independent of nasal obstruction [14]. Several studies have substantiated the correlation between COVID-19 and anosmia, with hyposmia and anosmia, often accompanied by taste dysfunction, emerging as distinctive indicators of CO-

VID-19 infections and potential markers for diagnosis. Data from a study conducted at Guy's Hospital in London, UK, indicated that approximately 67% of patients with COVID-19 experienced loss of taste or olfactory senses either prior or after diagnosis [15]. Similarly, in Germany, over two-thirds of diagnosed cases exhibited olfactory dysfunction [16]. Olfactory dysfunction after SARS-CoV-2 infection has also been documented in China [17]. The impact of olfactory dysfunction extends beyond its symptomatic manifestation, affecting the quality of life, social interactions, and nutrient intake of patients, potentially leading to depression and other psychological issues [18,19]. The mechanistic underpinnings of SARS-CoV-2 infections and their association with olfactory dysfunction involve various factors, including a reduction in the number of olfactory receptors in the olfactory tract, the absence of olfactory receptor cilia resulting from viral infections, and the replacement of the olfactory epithelium by the respiratory epithelium with extensive scarring [20]. It was also found that SARS-CoV-2 entry receptor ACE2 is more highly expressed (and co-expressed with viral entry-associated protease TMPRSS2) in nasal epithelial cells, specifically goblet and ciliated cells [21].

In this study, the psychophysical olfactory examination results from the analysis of 163 patients revealed that 114 patients, constituting 69.9% of the cases, experienced hyposmia. The TDI scores further indicated that the reduction in odor identification was more prominent, aligning with findings from previous studies. Recently, olfactory training has gained increasing prominence as a therapeutic approach for SARS-CoV-2-induced olfactory dysfunction in clinical practice. The effectiveness of olfactory training, a treatment for olfactory dysfunction, is closely tied to the specific olfactory agents used. However, further research is required to broaden and enhance the medical evidence in this regard. Traditionally, olfactory agents were predominantly standardized preparations from specialized companies. These agents, housed in glass bottles designed for liquid containment, posed challenges for portability over long distances, leading to potential treatment interruptions. Moreover, these agents were not cost-effective and did not facilitate the symptomatic treatment of secondary symptoms arising from olfactory dysfunction, limiting their utility. Existing research bring in light the fact that the complexity or sequence of olfactory agents has no impact on efficacy [22]. Therefore, there is a need for olfactory training approaches that reduce treatment costs and streamline the treatment process [23]. Olfactory training can enhance patient compliance and achieve therapeutic effects when it is specific and individualized to the diverse etiologies and clinical manifestations of patients. Considering this, in the present study, we opted for an aromatic olfactory agent comprising four different TCMs that are readily available: ginger, Pericarpium Citri Reticulatae, Santali Albi Lignum, and Styrax.

Aroma inhalation therapy, using different combinations of medicines for various populations, physiques, symptoms, and diseases, aligns with the principles of TCM, emphasizing syndrome differentiation, individualized treatment, and adapting treatment to the patient, season, and locality. Aromatic TCMs, characterized by pungency, warmth, fragrance, and dryness, produce aromatic substances when burned using an aromatherapy furnace. They contain volatile oils that, due to their small, highly liposoluble and absorbable nature, can be inhaled and absorbed through the nasal mucosa. These substances are then distributed systemically, imparting regulatory effects on the body. Modern pharmacological studies indicate that aromatic substances possess antibacterial and antiviral properties, enhance immune function, induce tranquility, aid sleep, regulate mood, exhibit anti-depressive effects, offer antioxidant properties, enhance brain tissue ischemia, and protect nerves [24]. Aromatic TCMs are generally safe, well-tolerated, and cost-effective. The use of TCMs in olfactory training not only stimulates olfactory function through odor exposure but also provides tailored training programs for patients with olfactory dysfunction based on diverse etiologies and clinical presentations. Consequently, olfactory training with aromatic TCMs is anticipated to offer superior efficacy compared to conventional olfactory training, particularly in addressing accompanying symptoms of olfactory dysfunction. In this study, the selection of ginger, Pericarpium Citri Reticulatae, Santali Albi Lignum, and Styrax for olfactory training is based on the varying aromatic properties of these medicinal Chinese herbs. These properties contribute to balancing the yin and yang of the human body by regulating qi and blood circulation. Specifically, ginger eliminates pathogens and strengthens vital qi, Pericarpium Citri Reticulatae resolves dampness and relieves depression, Santali Albi Lignum calms the heart and tranquilizes the mind, and Styrax benefits intelligence and induces resuscitation.

Olfactory training, a new therapeutic approach, involves regular stimulation of the olfactory sensation in patients with olfactory dysfunction using specific odors to facilitate the recovery of olfactory function [25,26]. A comprehensive review of existing research revealed that olfactory training could be a promising and effective intervention for patients experiencing olfactory dysfunction, with response rates ranging from 28% to 63% [27]. Moreover, the mammalian olfactory system exhibits regenerative potential throughout life, with robust regenerative abilities observed in the olfactory epithelium and olfactory bulb, along with certain plasticity in advanced olfactory centers. This regenerative capacity provides a theoretical foundation for treating olfactory dysfunction through olfactory training [28]. Recent studies have demonstrated that repeated olfactory stimulation can enhance electroantennogram responses in the olfactory epithelium, suggesting that olfactory training may directly contribute to the remodeling of the olfactory epithelium by increasing the

number of human olfactory neurons [29]. Additionally, olfactory training significantly increases the volume of the olfactory bulb and enhances network connections in olfactory-related cerebral cortex regions, underscoring its crucial role in central system remodeling [30].

In the current study, there was no statistically significant difference in efficacy between the two groups before treatment and at different treatment periods ($p > 0.05$), suggesting that the diverse olfactory agents used in the two groups demonstrated comparable efficacy in treating SARS-CoV-2-induced olfactory dysfunction. TDI scores remained unchanged in both groups after 1 month of treatment ($p > 0.05$) but revealed statistically significant elevation after 3 and 6 months of treatment ($p < 0.05$). This disparity in efficacy can be attributed to the fact that the regeneration of the olfactory system requires a longer timeframe. Logistic regression analysis identified the duration of the disease as the principal factor influencing the prognosis of patients in both groups, consistent with previous research [31]. In both groups, improvements in odor discrimination and identification capabilities were observed after 3 and 6 months of treatment ($p < 0.05$), while the odor threshold remained unaltered ($p > 0.05$). This indicated that the enhancement in TDI scores in patients with SARS-CoV-2-induced olfactory dysfunction following olfactory training primarily stems from changes in odor discrimination and identification capabilities rather than changes in the odor threshold. Based on these findings, it is postulated that different olfactory agents may be functionally equivalent in stimulating the olfactory system and nasal trigeminal system. However, this hypothesis warrants confirmation through further relevant studies.

Olfactory training using aromatic olfactory agents derived from TCMs emerges as an effective intervention for patients with SARS-CoV-2-induced olfactory dysfunction, notably enhancing olfactory discrimination and identification capabilities [32]. Aromatic olfactory agents of TCMs offer distinct advantages compared to conventional olfactory agents. Firstly, the diverse properties of aromas from various Chinese medicinal herbs not only stimulate the olfactory system but also leverage their unique aromas to regulate qi, balance yin and yang in the human body, providing additional therapeutic benefits [33]. Notably, we observed a superior improvement in anxiety and sleep among patients in the experimental group than in the control group, attributed to the distinctive therapeutic effects of aromatic TCMs. Secondly, aromatic olfactory agents of TCMs are readily accessible, cost-effective, and portable in daily life.

Conclusion

Olfactory training with aromatic TCM is a recommended therapeutic approach for patients with SARS-CoV-2-induced olfactory dysfunction. Additionally, emphasizing prolonged olfactory training and initiating it at the earliest opportunity is crucial for optimal recovery of olfactory function in patients.

It is worth noting that this study lacks an in-depth analysis of syndrome differentiation and treatment for patients with SARS-CoV-2-induced olfactory dysfunction. Consequently, more targeted and individualized training programs were not developed, representing a direction for future research.

Authorship contribution

Conception and design of the research: XFQ, LYH, YC; Acquisition of data: LYH, YFI, XL; Analysis and interpretation of the data: HMZ, HRD, XL; Statistical analysis: LYH, HMZ, HRD, YC; Obtaining financing:XFQ; Writing of the manuscript: XFQ, HL; Critical revision of the manuscript for intellectual content: XFQ, YFL, HL; All authors read and approved the final draft.

Conflict of interest

The authors declare no competing financial interests.

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Ethics Committee of the Shanxi Provincial People's Hospital Affiliated to Shanxi Medical University (No.2021-51). Written informed consent was obtained from all participants.

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