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Psychological and neurophysiological effects of inhaled aromatherapy

Efeitos psicológicos e neurofisiológicos da aromaterapia inalatória

Efectos psicológicos y neurofisiológicos de la aromaterapia inhalada

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Nykole Nunes Passos
ORCID: https://orcid.org/0000-0002-3738-7697
Universidade Federal do Rio Grande do Norte, Brasil
E-mail: nykole.passos.846@ufrn.edu.br
Stephany Campanelli Esmaile
ORCID: https://orcid.org/0000-0003-3195-9663
Universidade Federal do Rio Grande do Norte, Brasil
E-mail: sce.neuroscience@gmail.com
Claudia Regina da Silva
ORCID: https://orcid.org/0000-0001-7361-567X
Universidade Federal do Rio Grande do Norte, Brasil
E-mail:claudiaregina261232@gmail.com
Raiane Caroline da Silva França
ORCID: https://orcid.org/0000-0003-1346-1554
Universidade do Estado do Rio Grande do Norte, Brasil
E-mail:raianecsf@gmail.com
Isabel Cristina Amaral de Sousa Rosso Nelson
ORCID: https://orcid.org/0000-0003-4840-6950
Universidade do Estado do Rio Grande do Norte, Brasil
E-mail: isabelrosso@uern.br

Abstract
Primary Study Objective: the aim of this review was to filter current research written in English from 2010 to 2020 to elucidate the following question: what are the psychological and neurophysiological effects of inhaled aromatherapy on human health? Papers were selected based on PRISMA recommendations from Pubmed, Science Direct and Virtual Health Library databases. PICO technique and PROSPERO registration were also considered during the elaboration of this Systematic Review. Setting: schools, hospitals, clinics and dental offices. Participants: children, adults and elderly. Intervention: Essential oil inhalation. Primary Outcome Measures: Psychological approaches (eg. psychometric scales and cognitive tasks) and neurophysiological approaches (eg. heart rate variability/HRV and salivary cortisol). Results: From 1.458 papers, 14 were selected for final analysis and displayed in a table containing the following information: Score based on credibility criteria, authors, country, group, sex, age, objective, procedure and outcome. Conclusion: Aromatherapy mainly modulates the autonomic nervous system, with a predominance of parasympathetic activation and contributes to reduce cortisol and to increase melatonin levels. In addition, it can alleviate anxiety, depression and insomnia.
Keywords: Aromatherapy; Neurophysiology; Essential oil; Systematic review.

Resumo
Objetivo principal do estudo: o objetivo desta revisão foi filtrar pesquisas atuais escritas em inglês de 2010 a 2020 para elucidar a seguinte questão: quais são os efeitos psicológicos e neurofisiológicos da aromaterapia inalatória na saúde humana? Os artigos foram selecionados com base nas recomendações PRISMA das bases de dados Pubmed, Science Direct e Virtual Health Library. Esta Revisão Sistemática foi registrada na PROSPERO e baseada na pergunta PICO. Ambiente: escolas, hospitais, clínicas e consultórios odontológicos. Participantes: crianças, adultos e idosos. Intervenção: Inalação de óleo essencial. Medidas de desfecho primário: Abordagens psicológicas (como escalas psicométricas e tarefas cognitivas) e abordagens neurofisiológicas (como variabilidade da frequência cardíaca/VFC e cortisol salivar). Resultados: Dos 1.458 artigos, 14 foram selecionados para análise final e apresentados em uma tabela contendo as seguintes informações: Escore baseado em critérios de credibilidade, autores, país, grupo, sexo, idade, objetivo, procedimento e desfecho. Conclusão: A aromaterapia modula principalmente o sistema nervoso autônomo, com predomínio da ativação parassimpática e contribui para a redução do cortisol e aumento dos níveis de melatonina. Além disso, pode aliviar a ansiedade, depressão e insônia.
Palavras-chave: Aromaterapia; Neurofisiologia; Óleo essencial; Revisão sistemática.

Resumen
Objetivo principal del estudio: el objetivo de esta revisión fue filtrar la investigación actual escrita en inglés de 2010 a 2020 para aclarar la siguiente pregunta: ¿cuáles son los efectos psicológicos y neurofisiológicos de la aromaterapia

inhalada en la salud humana? Los artículos se seleccionaron en base a las recomendaciones PRISMA de las bases de datos Pubmed, Science Direct y Virtual Health Library. Esta Revisión Sistemática fue registrada con PROSPERO y basada en la pregunta PICO. Lugar: escuelas, hospitales, clínicas y consultorios dentales. Participantes: niños, adultos y ancianos. Intervención: Inhalación de aceites esenciales. Medidas de resultado primarias: enfoques psicológicos (p. ej., escalas psicométricas y tareas cognitivas) y enfoques neurofisiológicos (p. ej., variabilidad de la frecuencia cardíaca/VFC y cortisol salival). Resultados: De 1.458 trabajos, 14 fueron seleccionados para el análisis final y presentados en una tabla que contiene la siguiente información: Puntuación basada en criterios de credibilidad, autores, país, grupo, sexo, edad, objetivo, procedimiento y resultado. Conclusión: La aromaterapia modula principalmente el sistema nervioso autónomo, con predominio de la activación parasimpática y contribuye a reducir el cortisol y aumentar los niveles de melatonina. Además, puede aliviar la ansiedad, la depresión y el insomnio.
Palabras clave: Aromaterapia; Neurofisiología; Aceite esencial; Revisión sistemática.

1. Introduction

The use of aromatic plants follows the history of mankind (Baudox, 2018; Festy, 2021; Lavabre, 2018). For instance, Egyptians recorded their knowledge of aromatic medicinal plants in the Ebers Papyrus around 2,800 years BC (Lavabre, 2018; Buckle, 2019), while in China (3,500 years BC) the first and oldest treatise of phytotherapy was found, as well as a very old rudimentary instrument made of clay, which possibly was used for the distillation of aromatic plants (Baudox, 2018; Festy, 2021). In ancient times, preparations with aromatic plants included not only the treatment of illnesses carried out by priest-physicians, but also the embalming of the dead, through the use of perfumed oils and resins impregnated in the fabrics and spiritual purification of houses, through fumigation (Baudox, 2018; Festy, 2021; Lavabre, 2018).

Although the use of essential oils has been known since Antiquity, the term “aromatherapy” was first used by René Maurice Gattefossé in the early 20th century (Baudox, 2018; Buckle, 2019; Gnatta et al, 2016; Lakhan, Sheafer & Tepper, 2016) . In his 1937 book, *Aromatherapie*, Gattefossé claimed that herbal medicine could be used to treat any disease in the entire human body system (Lakhan, Sheafer & Tepper, 2016). Aromatherapy is considered nowadays a complementary practice that uses essential oils, classified as natural chemical compounds, extracted from vegetables, which are complex and highly volatile, produced as secondary metabolites of aromatic plants and characterized by their aromatic qualities (Baudox, 2018; Buckle, 2019; Gnatta et al, 2016; Igarashi, 2013; Lee et al, 2018; Sánchez-Vidaña, 2017).

In the United States, the Food and Drug Administration (FDA) guidelines classify essential oils as cosmetics and part of alternative and complementary medicine (ACM), but not as medicines for the treatment or prevention of disease (Farrar & Farrar, 2020). In France, it is considered a medical specialty, while in England it is an Integrative and Complementary Practice (ICP). Culturally, it is used in the East as part of Traditional Medicine (Gnatta et al, 2016). In Brazil, Aromatherapy is a ICP that is part of the National Policy on Integrative and Complementary Practices (PNPIC in Portuguese) of the Unified Health System (SUS) of this country. So far, the practice is not regulated as a profession and, therefore, it does not have any supervisory agencym (Gnatta et al, 2016; Brasil, 2018).

The clinical practice of aromatherapy integrates complementary and integrative care, used both in the hospital and outpatient settings, to control the symptoms of pain, nausea, muscle tension, decrease in anxiety, depression, stress and insomnia (Lakhan, Sheafer & Tepper, 2016; Lee, 2018; Farrar & Farrar, 2020). A frequently reported advantage compared to traditional medicines is that essential oils have fewer side effects, low cost and more diverse forms of application, including inhalation and massage (Lakhan, Sheafer & Tepper, 2016; Sánchez-Vidaña et al, 2017; Agatonovic-Kustrin et al, 2020; Lee et al, 2011; Zhang & Yao, 2019). Some studies also suggest that stimulation through the olfactory bulb can promote immediate pain reduction and changes in physiological parameters (Fakari et al, 2015; Shin & Lee, 2007) while others found no significant changes when offering olfactory stimulation (Martin, 2006).

Studies report that the inhalation of essential oils is capable of producing changes in physiological parameters [eg. blood pressure, heart rate, muscle tension, pupil dilation, body temperature, blood flow, electrodermal and cerebral activities] (Zhang & Yao, 2019; Es-Haghee et al, 2020; Zhang et al, 2016; Chen et al, 2015). Inhalation and oral administration were two common methods for essential oil manipulation in pre-clinical and clinical trials, while massage was used only in clinical trials with humans and intraperitoneal injection was only used in pre-clinical trials (Zhang N & Yao, 2019). In general, essential oils can be absorbed via smell, through the skin and ingestion. In this way, applications are divided into inhalation, topical and oral use (Lee et al, 2018).

The physiological activities of the human body are in constant adjustment in order to achieve and maintain homeostasis, which is the main function of the autonomic nervous system (ANS) (Chen et al, 2015). In stressful situations, the sympathetic ANS becomes more active, while the parasympathetic ANS reduces heart and respiratory rates in the absence of stressors (Liu , Lin & Chang, 2013). Heart rate variability (HRV), for example, reflects changes in the dominance of the autonomic nervous system, being a valuable, simple and non-invasive method to analyze the continuous changes in the sympathetic-parasympathetic balance of the nervous system. It is defined by the time interval between consecutive heartbeats (the RR interval), in which the variation at rest can be interpreted as a sign of healthy cardiac function. This analysis has been established over the past decades as a reliable tool to assess the state of cardiovascular autonomic function (Liu , Lin & Chang, 2013; Moreno et al, 2015; Baldwin & Chea, 2018).

An important aspect to be considered is the chemical composition of the essential oils used in the studies, since the combination of chemical components determines the mechanisms of action that produce the beneficial effects that support the clinical use of essential oils (Sánchez-Vidaña et al, 2017; Tadtong et al, 2015). The complete mechanism of action of essential oils is a challenge to be unraveled. One of the possible explanations is the involvement of analgesic components present in several essential oils, as well as their action in the parasympathetic nervous system (Buckle, 2019; Lee et al, 2018). However, some of the therapeutic effects of essential oils are still not sufficiently supported by scientific clinical studies (Lee et al, 2018). Therefore, more studies are needed in order to identify how essential oils and aromatherapy can contribute to human health. This systematic review aims to elucidate the following question: what are the psychological and neurophysiological effects of inhaled aromatherapy on human health?

2. Methodology

Articles were initially collected in PubMed, Science Direct and Virtual Health Library electronic databases using the predictor: "Aromatherapy”. Data extraction, analysis and selection of articles were performed in pairs (Table 1). The inclusion criteria was to select papers with the predictor “aromatherapy” in title (Identification). Then, duplicated papers were excluded (Screening) followed by a systematic filtering based on exclusion criteria (Eligibility). Subsequently, the final papers were read in full text for a critical analysis of the content (Included).

Table 1 - Databases and predictors used to collect eligible articles.

Database	Strategy
Pubmed	(aromatherapy[Title/Abstract]) Filters: only journal article, full text, 10 years and in English
Science Direct	Title, abstract, keywords: aromatherapy Filters: only 10 years and research articles
Virtual Health Library	(tw:(aromatherapy)) Filters: only completed text, 10 years, in English

Source: Authors.

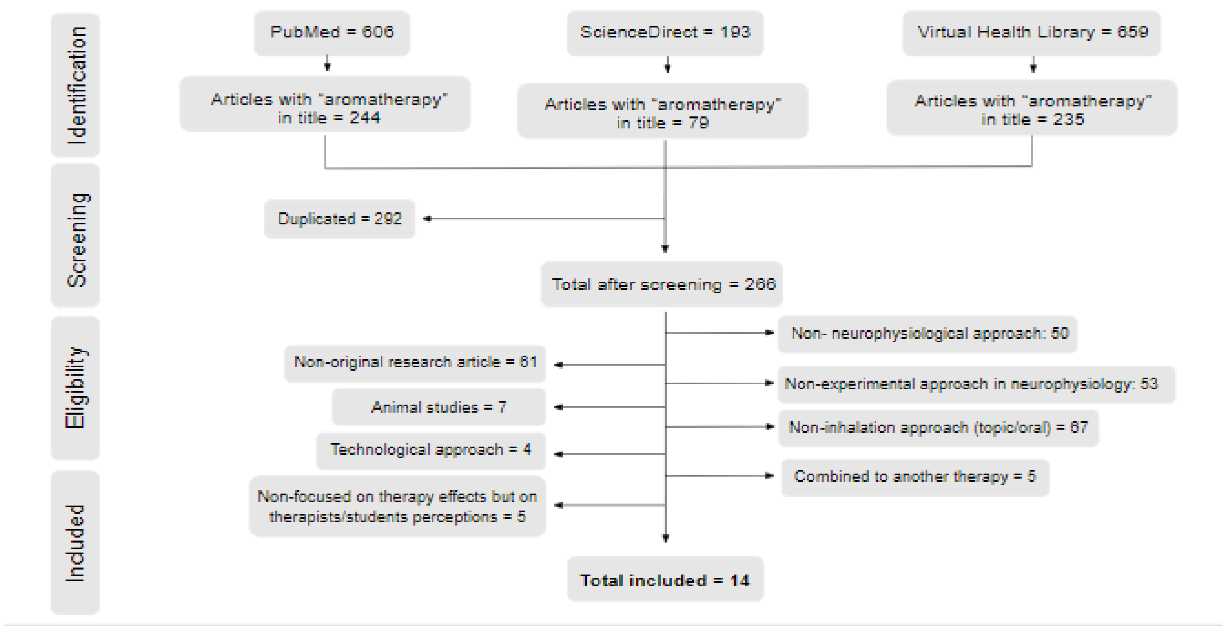
In Table 1, note that the search strategies were customized according to the filters available in each database.

Exclusion criteria were: non-original research article; technological approach; non-focused on therapy but on therapists' perception on the effects of essential oils; non-neurophysiological approach; non-experimental approach on neurophysiology; non-inhalatory approach (topic/oral); combined to another therapy; animal studies. This study filtered papers from 2010 to 2020 and followed recommendations described by PRISMA (Liberati et al, 2009). To provide transparency and best-quality evidence, the protocol for this systematic review was registered on PROSPERO (Unique ID number: CRD42021271736). Credibility criteria were also considered to better analyze the quality of the selected papers (Galvão & Ricarti, 2019).

3. Results

After filtering, 14 of 1.458 papers selected for final analysis (Figure 1**)** and displayed in a table containing the following information: Score based on credibility criteria (Table 2).

Figure 1. Selection of articles.



Source: Authors.

In Figure 1, note that the filtering of articles occurred according to the exclusion and inclusion criteria adopted.

From the 14 selected articles nine analyzed both genders and five articles analyzed only female participants. Two analyzed children, one elderly and one pregnant patients. Twelve articles are from Asia, while two are from North and Central America. Beyond HRV, other physiological parameters were analysed such as electroencephalogram (EEG), salivary s-IgA (immunoglobulin), salivary cortisol (stress hormone), serum melatonin (sleep hormone) and noradrenaline tests. Cognitive tasks were Simple Reaction Time (SRT) and Go/No-Go Task (GNG). Psychometric scales were Beck Anxiety Inventory (BAI), State-Trait Anxiety Inventory (STAI), Profile of Mood States (POMS), Chinese version of the Pittsburgh Sleep Quality Index (CPSQI), Center for Epidemiologic Studies Depression scale-Revised (CESD-R), General Comfort Questionnaire (GCQ), Perceived Stress Scale (PSS), Perceived Stress and Sleep Quality evaluated through numerical rating scale (NRS), Expectancy of Aromatherapy Effects, Pain and Stress through Visual Analogue Scale (VAS), Outcher Pain Scale, Children Fear Scale and Fatigue Self Checklist.

Table 2 - Summary of selected papers published between January/2010 and February/2020.

Score - Author (Country)	**Group: ♀/♂ (age)**	**Objective**	**Procedure**	**Outcome**
E - Chang and Shen, 2011 (Taiwan).	Test group: 29 ♀ and 25 ♂ (below 34, between 35 and 44, above 45 years old). No control group.	To evaluate the performance of aromatherapy in reducing stress.	The test group inhaled 2% of bergamot (*Citrus bergamia*) through an ultrasonic diffuser for 10 minutes. BP and HRV were recorded 5 minutes before and after the application of aromatherapy.	Low BP and high HRV after the application of aromatherapy (activation of parasympathetic system).
B - Chien et al, 2012 (Taiwan).	Test group:29 ♀. Control group: 31 ♀ (45-55 years old).	To determine the effects of lavender E.O (*Lavandula angustifolia*) on self-reported sleep and HRV in middle-aged women with insomnia.	The test group received 0,25 mL E.O for 50 mL of water in the ultrasonic diffuser for 20 minutes, twice per week during 12 weeks. The control group received a health education program for sleep hygiene.	Inhalation of lavender may have a short-term persistent effect on HRV with an increase in parasympathetic modulation. Women had significant improvement in sleep quality after the 12-week intervention. However, aromatherapy does not appear to modulate HRV in the long term.
C - Jaafarzadeh et al, 2013 (Iran).	Test and control group: 20 ♀ and 10 ♂ (6-9 years old).	To investigate the effect of aromatherapy with sweet orange E.O (*Citrus sinensis*) in childhood anxiety during dental treatment.	Crossover study. Each child underwent 2 dental procedures, one with and one without the E.O (control). Salivary cortisol and pulse rate before and after treatment at each visit were measured.	The use of sweet orange E.O can reduce salivary cortisol and pulse rate, indicating an attenuation of the childhood anxiety state.
C - Matsumoto et al, 2013 (Japan).	Test and control group: 17 ♀ (20,6 ± 0,2 years old).	To examine the calming effects of aromatherapy with E.O of lavender (*Lavandula angustifolia*) on premenstrual symptoms, from the perspective of the autonomic nervous system function.	Crossover study. Women were examined twice (with and without the E.O) in the late luteal phases. Test: 10 µl of E.O was used in the diffuser pad. Control: water in the diffuser pad. HRV and POMS were applied before and after intervention.	Lavender aromatherapy is a potential therapeutic modality that could alleviate premenstrual emotional symptoms, which is attributable to the dominance of the parasympathetic nervous system.
B - Igarashi et al, 2013 (Japan).	Test group: 7 ♀. Control group: 6 ♀ (27-29 years old).	To clarify the physical and psychological effects of	Women chose 1 of 3 E.O: Lavender (*Lavandula angustifolia*), Petitgrain	Inhalation of E.O containing linalyl acetate and linalool improved the POMS score

		inhaled aromatherapy in 28-week pregnant women.	(*Citrus aurantium*), Bergamot (*Citrus aurantium L. ssp. Bergamia*) and received inhalation with 5 drops in the diffuser for 5 minutes. The type of control performed was not specified. POMS and heart parameters (low and high frequency domain for autonomic nervous system evaluation) were used.	and promoted parasympathetic activity, based on an intragroup comparison. Nonetheless, in the comparison between groups, no substantial difference was observed.
B - Liu et al, 2013 (Taiwan).	Test and placebo groups: 26 ♀ and 3 ♂ (41.4 ± 4 years old in average).	To elucidate the beneficial effect of aromatherapy in relieving work-related stress for teachers with different hours.	Placebo group: Inhalation with synthetic essence with aroma similar to bergamot E.O in ultrasonic diffuser for 15 minutes Test group: Inhalation with bergamot E.O diluted to 2% in ultrasonic diffuser for 15 minutes. BAI and HRV were measured.	Natural bergamot E.O reduced the stress effects of elementary school teachers.
B - Chamine and Oken, 2015 (EUA).	Test group: 27. Placebo groups: 54. 79% ♀ 21% ♂ (58,2 years old on average).	To evaluate the stress-reducing effects of aromatherapy on cognitive tasks and the stress- sensitive ERP components.	Test group: 1 drop of Lavender (*Lavandula angustifolia*) in 15 ml of grape seed oil. Detectable placebo group: 1 tablespoon of coconut oil diluted in 15ml of grape seed oil. Undetectable placebo group: water only. PSS, VAS, EEG, salivary cortisol, SRT and go/no-go task were used.	Regardless of the experienced aroma, people who received the suggestion of stress-reducing effects showed better cognitive performance than people who did not receive this information, highlighting a placebo effect.
C - Watanabe et al, 2015 (Japan).	Test group: 41 ♀ (21.3 ± 1.02 years old). No control group.	To obtain clinical evidence of bergamot E.O use on stress and anxiety.	Crossover study. The setup was rest, rest + water vapor, rest + water vapor + Bergamot for 15 minutes each. Six permutations in this order were made to exclude an influence of this experimental sequence. POMS, STAI and Fatigue Self Checklist were applied and HRV and salivary cortisol was measured.	Salivary cortisol, HRV, negative emotions and tiredness parameters were better after the intervention with inhaled bergamot.
B - Huang and Capdevila, 2016 (China).	Test group: 20 80% ♀ and 20% ♂. Control group: 68,4% ♀ and 31,6% ♂ (42.21 years old on average).	To analyze the effectiveness of aromatherapy in improving work performance and reducing stress in the workplace.	Test group: 2% Petitgrain (*Citrus aurantium*) inhalation. Control group: sweet almond fatty oil. TAI-State and POMS were applied before and after each session and HRV recorded during each session.	Aromatherapy can improve performance in the workplace by a combination of reduced stress levels and increased levels of attention and alertness.
A - Lee et al, 2017 (South Korea).	Test group: 30 ♀ (37.3 years old in average). Control group: 30 ♀ (35.8 years old in average).	To examine the effects of E.O inhalation on perceived stress, depression, sleep quality, and immune function.	Inhalation of a blend with Lemon, Eucalyptus, Tea tree and Peppermint (ratio of 4: 2: 2: 1) 24h/day for 4 weeks. HbA1c and IgG, perceived stress and sleep quality were measured. CES-D was also used.	Inhaling the E.O blend resulted in less perceived stress and depression, as well as better sleep quality, but it did not influence physiological parameters such as stress index or immune status.

A - Alemdar e Aktas, 2019 (Turkey).	Aroma group: 39. Lidocaine group: 39 Bubble- blowing group: 39 Buzzy group: 39 Control group: 39, 46,2% ♀ and 53,8% ♂ (5-10 years old).	To investigate the effects of inhalation of lavender (*Lavandula angustifolia*) on pain, stress and fear in children undergoing phlebotomy.	For the aroma group, 5ml of Lavender dilution (1 drop in 20ml of distilled water) was heated and inhaled for 10 minutes. Outcher pain scale, Children's Fear Scale and salivary cortisol were measured.	A significant difference was found between the intervention and control groups in terms of pain levels during and after phlebotomy, specially the Buzzy and Bubble- blowing groups.
D - Velasco-Rodríguez et al, 2019 (Mexico).	Test group: 37 ♀ and 30 ♂ (≥ 60 years old). No control group.	To analyze the effect of aromatherapy with Lavender on serum melatonin levels in non-institutionalized elderly.	Inhalation of 5 drops of Lavender in 20ml of water in the diffuser for 30 minutes, twice a week for 4 weeks. Serum melatonin was measured.	The use of lavender E.O increases melatonin levels in the elderly.
B - Takagi et al., 2019 (Japan).	Test group 1: 41 ♀ and 40 ♂ (24.0 ± 2.4 years old). Test group 2: 9 ♀ and 13 ♂ 22.4 ± 0.9 years old). From test group 1, 16 volunteers were allocated to the control group.	To evaluate the application of aromatherapy as a complementary and alternative medicine and its influence on the autonomic nervous and immune systems.	Test group 1 was divided into 5 subgroups: Grapefruit, Lavender. Rosemary, Tea tree and control. Serum noradrenaline and s-IgA were measured. Test group 2 was only to examine s-IgA secretion related to Lavender (Lavandula angustifolia) intervention.	Aromatherapy with Lavender and Grapefruit significantly increased the level of s-IgA and decreased norepinephrine release.
B - Kasar et al, 2020 (Turkey).	Aroma group: 16 ♀ and 6 ♂ (48.6 ± 12.0 years old). Placebo group: 19 ♀ and 3 ♂ (48.1 ± 11.9 years old). Control group: 17 ♀ e 5 ♂ (49.7 ± 10.6 years old).	Examine the effects of inhaling lavender on levels of pain, comfort and anxiety, as well as measuring cortisol during trigger point injection in individuals with myofascial pain syndrome.	Aroma group: Inhalation with 5 drops of Lavender in 100ml of water in the diffuser; Placebo group: odorless oil inhalation. Control group: no intervention. Pain assessment by VAS, GCQ, STAI and salivary cortisol were measured.	The results showed that patients in the aroma group had lower anxiety levels than those in the placebo and control groups after the intervention.

BP: blood pressure; HRV: heart rate variability; E.O: essential oil; POMS: Profile of Mood States; BAI: the Beck Anxiety Inventory; ERP: event-related potentials; PSS: Perceived Stress Scale; VAS: Visual Analog Scale; EEG: electroencephalogram; SRT: Simple Reaction Time; TAI-Scale: Trait Anxiety Inventory-Scale; HbA1c: Glycated hemoglobin A1c; IgG: immunoglobulin G; CES-D: The Korean version of the Center for Epidemiologic Studies Depression Scale; s-IgA: salivary immunoglobulin A; GCQ: General Comfort Questionnaire; STAI: State Anxiety Index. Source: Authors.

In Table 2, note Score based on credibility criteria: Authors (Country), Group, Sex, Age, Objective, Procedure and Outcome.

To facilitate the analysis of selected articles, credibility criteria were adopted. The final 14 articles were scored based on their methodology (Table 3), with the ideal sample number ($n \geq 30$) being considered one of the prerequisites for quantitative analysis. This is because 30 or more volunteers per group are needed to have an approximately normal statistical sampling distribution (Fink, 2003; Wisz et al, 2008; Wolf et al, 2013). The essential oils mentioned in the articles were: Lavender (Lavandula angustifolia), Sweet orange (Citrus sinensis), Bergamot (Citrus aurantium L. ssp. Bergamia), Grapefruit (Citrus paradisi), Petitgrain (Citrus aurantium), Peppermint, Melaleuca, Eucalyptus and Lemon - which species were not mentioned.

Table 3 - Credibility criteria.

Score	Criteria	Quantity
A	- Randomized with a control group; - With 30 or more volunteers per group; - Use of validated psychometric scales and/or neurophysiological data.	02
B	- Randomized with control group; - Less than 30 volunteers per group; - Use of validated psychometric scales and/or neurophysiological data.	07
C	- Randomized (crossover trial); - Less than 30 volunteers per group; - Use of validated psychometric scales and/or neurophysiological data.	3
D	- Non-randomized and no control group; - With 30 or more volunteers per group; - Use of validated psychometric scales and/or neurophysiological data.	1
E	- Non-randomized and no control group; - Less than 30 volunteers per group; - Use of validated psychometric scales and/or neurophysiological data.	1

Source: Authors.

In Table 3, note that a significant part of the articles correspond to score B: Randomized with control group; Less than 30 volunteers per group; Use of validated psychometric scales and/or neurophysiological data.

Two randomized clinical trials were scored as “A”: Lee et al (2017) used a blend containing essential oils of Lemon, Tea tree, Eucalyptus and Peppermint (Lee et al, 2017), while Alemdar and Aktas (2019) used exclusively the essential oil of lavender for the intervention with aromatherapy (Alemdar & Aktaş, 2019) . The seven articles classified as “B” make up the majority of the sample. Of these, three used lavender essential oils exclusively (Chien, Cheng & Liu, 2012; Chamine & Oken, 2015; Kasar et al, 2020); one compared the effects of lavender, petitgrain and bergamot essential oils separately (Igarashi, 2013); one studied only the effects of bergamot essential oil (Liu, Lin & Chang, 2013); one analyzed only petitgrain essential oil (Huang & Capdevila, 2017); and one separately compared the essential oils of grapefruit, lavender, rosemary and tea tree (Takagi et al, 2019). The “C” articles used only sweet orange essential oil (Jafarzadeh, Arman & Pour, 2013); only Lavender essential oil (Matsumoto T, Asakura H, Hayashi, 2013); and only bergamot essential oil (Watanabe et al, 2015). In category “D” is the article by Velasco-Rodriguez et al (2019) who used lavender essential oil (Velasco-Rodríguez et al, 2019) while in category “E” is the article by Chang and Shen (2011) with their studies on the Bergamot essential oil (Chang & Shen, 2019).

The most frequent form of use was inhalation through an ultrasonic diffuser, present in 10 studies (Igarashi, 2013; Liu, Lin &Chang, 2013; Chien, Cheng & Liu, 2012; Kasar, 2020; Huang & Capdevila, 2017; Jafarzadeh, Arman & Pour, 2013; Matsumoto , Asakura & Hayashi, 2013; Watanabe et al, 2015;Velasco-Rodríguez et al, 2019; Chang & Shen, 2011). The device disperses the essential oil into the atmosphere through an ultrasonic process that produces a cold mist, a necessary condition so that the active principle of the essential oil is not altered (Velasco-Rodríguez et al, 2019). In Chamine and Oken (2015), participants received essential oil diluted in fatty oil for inhalation whereas in Lee et al (2017) participants wore a pendant during the day and a scent stone at night (Lee et al, 2017; Chamine & Oken, 2015). Alemdar and Aktas (2019) asked participants to inhale an essential oil dilution in warm water, directly from the bottle while Takagi et al. (2019) used essential oils in a cotton ball (Alemdar & Aktaş, 2019; Takagi et al, 2019).

The assessment of heart rate variability (HRV) was present in several articles (Liu, Lin & Chang, 2013; Alemdar & Aktas, 2019; Chien, Cheng & Liu, 2012; Huang & Capdevila, 2017; Matsumoto, Asakura & Hayashi, 2013; Watanabe et al, 2015; Chang & Shen, 2011), as well as the measurement of salivary cortisol (Igarashi, 2013; Lee et al, 2017; Alemdar & Aktas, 2019; Chamine & Oken, 2015; Kasar et al, 2020; Takagi et al, 2019; Jafarzadeh, Arman & Pour, 2013; Matsumoto , Asakura & Hayashi, 2013; Watanabe et al, 2015). Melatonin was also quantified in one study. The sleep hormone is responsible for regulating the circadian cycle and is associated with light and dark periods that directly affect sleep induction. Because of this, blood samples were collected to quantify the level of melatonin and the results indicated that the use of lavender essential oil in the elderly increases the secretion of melatonin, which means better sleep quality (Velasco-Rodríguez et al, 2019). Several factors disrupt sleep, but depression has been specifically correlated with sleep disorders in many studies. Due to this, researchers have examined whether a blend with Lemon, Eucalyptus, Tea tree and Peppermint could alleviate perceived stress, depression, sleep quality and immune function. The psychological results were promising but no significant physiological result was found (Lee et al, 2017).

The immunoglobulin A (s-IgA) has been reported as a biomarker of mental stress associated with the autonomic nervous system and the immune system. Based on this, one of the studies reported that the use of lavender or grapefruit essential oil can increase salivary s-IgA secretion, reducing stress and enhancing the immune system in healthy adults (Takagi et al, 2019). Since many studies on the physiological effects of lavender have been conducted in short periods, another research evaluated the effectiveness of lavender essential oil aromatherapy on HRV before and after 12 weeks of treatment in middle-aged women with insomnia. Inhalation of lavender seems to have only a short-term persistent effect on HRV with an increase in parasympathetic modulation but it was not significant in the long term (Chien, Cheng & Liu, 2012). Additionally, when evaluating blood pressure and parameters of the autonomic nervous system 5 minutes before and after application of the aromatherapy spray with essential oil of Bergamot, a significant reduction in blood pressure, heart rate, with increases in HRV after the intervention was noticed, indicating parasympathetic dominance (Chang & Shen, 2011).

Regarding the effect of aromatherapy on work stress in teachers, a study compared the test group (bergamot essential oil) with the placebo group (artificial essence) and, based on measures such as HRV, it was concluded that only the test group obtained a reduction in stress levels (Liu, Lin & Chang, 2013). Similarly, another study investigated the effectiveness of aromatherapy in improving the performance of administrative university workers, noting a reduction in stress due to an increase in HRV. At the same time, attention and alertness levels increased, suggesting a balance between the parasympathetic and the sympathetic autonomic nervous systems (Huang & Capdevila, 2017). In contrast, expectancy is related to the undesirable placebo effect. By analyzing the performance of volunteers in cognitive tasks (such as go/no-go) and their components of stress-sensitive event-related potentials (ERP), scientists found that, independently of the type of aroma, people who received the suggestion of stress-reducing aroma effects had better responses than the other groups (Chamine & Oken, 2015) . The psychological effect of aromatherapy was also noticed in a study with patients with myofascial pain syndrome during trigger point injection. Although Lavender essential oil was probably able to reduce anxiety and improve comfort, the physiological parameter (salivary cortisol) had no significant reduction among the test, placebo and control groups (Kasar et al, 2020).

Parallelly, while one group of research measured and found the lavender relaxing effect (*Lavandula angustifolia*) in premenstrual symptoms through the POMS scale and HRV (Matsumoto, Asakura & Hayashi, 2013), another group used the low frequency of R-R interval parameter from the electrocardiogram as an indication of the dominance of the parasympathetic autonomic nervous system in pregnant women. The Mood States Profile (POMS) scale was also applied. Participants were randomly assigned to an aromatherapy group (high linalool and linalyl acetate) and a control group. There was a significant intragroup change (before and after intervention) but not between the two groups (Igarashi, 2013). The psychological and physiological effects of aromatherapy were also analyzed in women in a different context. The intervention consisted of rest, rest + water vapor, rest + water vapor + bergamot essential oil for 15 minutes each. The 41 volunteers were divided into 6 groups that had the order of this protocol different from each other. Salivary cortisol sample analysis, Mood State Profile, State-Trait

Anxiety Inventory and Fatigue Self-Check List, in addition to heart rate values, as an indicator of the activity of the parasympathetic nervous system, evidenced a positive effect of inhalation of bergamot with water vapor in a relatively short time (Watanabe et al, 2015).

Considering the use of aromatherapy in children, two articles had different results: one of them analyzed the level of pain and fear in children submitted to phlebotomy, using the Outcher pain scale, Children's Fear Scale, and salivary cortisol measurement. Although there were no significant improvements in the aromatherapy group, the group that used the bubble-blower and the Buzzy (a small vibrating device with an ice pack) showed to be promising (Alemdar & Aktas, 2019. The other article evaluated children submitted to two dental treatment consultations: one with aromatherapy (intervention) and one without aromatherapy (control). From the analysis of salivary cortisol and pulse rate before and after treatment at each visit, a significant difference was noted between the two groups, thus favoring the use of sweet orange essential oil to reduce anxiety (Jafarzadeh, Arman & Pour, 2013).

4. Discussion

Different essential oils are used daily all over the world. Most selected studies used lavender essential oil, followed by citrus. The results showed that these essential oils influenced the nervous system, promoting modulation of the central nervous system, parasympathetic ANS dominance activated by an increase in the release of melatonin, endorphins and a decrease in cortisol. It is known that the composition of essential oils varies depending on the species of the aromatic plants. Therefore, the studies were divided into sections, according to the type of essential oil used or combinations.

LAVENDER (*Lavandula angustifolia*)

In Chien et al. (2012), intervention with lavender essential oil increased parasympathetic modulation, verified by increasing HRV, in middle-aged women, reducing the symptom of insomnia, while in Velasco-Rodríguez et al. (2019), there was an increase in melatonin production in elderly men and women (Chien, Cheng & Liu, 2012; Velasco-Rodríguez et al, 2019). Both findings are in agreement with the literature regarding the direct and indirect effects of lavender essential oil on sleep quality (Hudson, 1996; Roozbeh et al, 2019; Sayorwan et al, 2012). The main compounds of lavender are linalool, linalyl acetate, followed by components of a smaller proportion, such as lavandulol, coumarin and terpinen-4-ol, which justifies its sedative potential (Moussi et al, 2017).

One study compared the effects of lavender and bitter orange essential oils on sleep quality in postmenopausal women. Among the mechanisms of action of lavender to improve sleep disorders are the blocking of acetylcholine secretion and the linalool interaction with gamma-aminobutyric acid (GABA) receptors in the central nervous system (CNS) (Kamalifard et al, 2018). Another double-blind crossover clinical trial included 100 menopausal women, aged 45 to 55 years, divided into two intervention (lavender) and control (diluted milk) groups. The authors identified that the mechanism of action of lavender can also be attributed to a decrease in cortisol and stimulation of beta-endorphin secretion (Kazemzadeh et al, 2016).

By analyzing the effect of lavender essential oil aromatherapy on serum melatonin levels in non-institutionalized elderly people, the researchers point out that the anxiolytic effect of lavender may be related to the inhibition of voltage-dependent calcium channels, especially in neurons in the hippocampus region, while there is evidence that the sympathetic autonomic activation is suppressed with the use of lavender, in addition to favoring the excretion of endorphins in the plasma and decrease of the stress hormone, factors related to the release of melatonin (Velasco-Rodríguez et al, 2019).

When investigating the effects of reducing stress and pain in children, an article classified as B showed a significant difference between the control group and the test group (Kasar et al, 2020), while an article scored as A did not obtain promising results after the intervention with aromatherapy (Alemdar & Aktas, 2019). This is possibly due to the limitations of the second study, especially in relation to the low concentration of this essential oil, diluted in the proportion of 1 drop of essential oil for every 20ml of water, of which 5ml were offered for inhalation during the intervention. Another study compared the pain intensity among children during venipuncture. They inhaled 5 drops of lavender diluted in 2% alcohol, which was embedded in a sticker on the shirt collar for 20 minutes before entering the venipuncture room and were tested using the Oucher Scale ten minutes after the procedure, showing that the aromatherapy intervention with Lavender essential oil helped to reduce the intensity of pain during the insertion of the intravenous catheter in children (Bikmoradi et al, 2017).

Chamine and Oken 2015 recruited 81 adults and evaluated the effects of lavender essential oil on stress reduction, cognitive function and the importance of expectation in aromatherapy actions. Overall, while not detecting aromatherapy-specific effects on stress, the study provides evidence that manipulating expectancy by verbal suggestion of aromatherapy effectiveness might underlie some changes in behavior and brain function after exposure to aromatherapy. The results indicate that enhancing beliefs in a positive effect of an intervention might be beneficial for performance (Chamine & Oken, 2015).

The HRV was also analyzed in junior university students after intervention with lavender essential oil combined with sandalwood essential oil. Aromatherapy intervention appears to reduce stress among adolescents, however, participants with a low level of stress appeared to respond better to combination therapy with essential oil, while those with medium to high levels of stress appeared to respond poorly to aromatherapy compared to the control group (Lin et al, 2021). Pain reduction during the premenstrual period was also observed in young women (Matsumoto, Asakura & Hayashi, 2013). In general, lavender can have a short-term relaxing effect on the autonomic nervous system. A study with twenty healthy volunteers assessed autonomic parameters such as blood pressure, heart rate, respiratory rate, and skin temperature to determine the arousal level of the autonomic nervous system. Inhalation of lavender increases heart rate variability and parasympathetic tone, possibly due to its main components, which are rapidly absorbed by the body through inhalation, with the plasma level reaching a peak a few minutes after administration. Linalyl acetate has narcotic action and linalool acts as a sedative of the nervous system (Sayorwan et al, 2012).

BERGAMOT (*Citrus bergamia*)

Through the analysis of HRV, salivary cortisol and questionnaires applied to 41 healthy female volunteers, the researchers found that inhaling bergamot essential oil in water vapor exerts psychological and physiological effects in a relatively short time (Watanabe et al, 2015). By analyzing a group of fifty-four elementary school teachers, it was found that inhaling bergamot essential oil reduces anxiety between the groups with moderate and severe anxiety, but not in the group with mild anxiety, which remained stable (Chang & Shen, 2011). Furthermore, bergamot seems to reduce work stress among elementary school teachers in a study by conducting 2 blind tests (Liu, Lin & Chang, 2013). The major compounds of the essential oil of bergamot are the monoterpenes limonene, γ-terpinene and β-pinene, the monoterpene alcohol, linalool and the monoterpenic ester, linalyl acetate, which make up more than 90% of the entire oil (Corasaniti et al, 2007).

Under this experimental setting of *in vivo* and *in vitro* studies, recently data have been gathered demonstrating that bergamot essential oil is endowed with specific and reproducible effects on the CNS of rat, indicating that the combination of volatile components appears to modulate synaptic plasticity, in addition to exerting a neuroprotective effect observed in the course of cerebral ischemia and pain. Effects on alertness and relaxation have been noted in EEG patterns (Bagetta et al, 2010). This neuroprotective effect is corroborated by Corasaniti et al. (2007), who, in their in vitro study with human SH-SY5Y neuroblastoma cells exposed to N-methyl-D-aspartate (NMDA), point to the reduction of neuronal damage caused by excitotoxic stimuli, due to the prevention of the involvement of critical pathways of injury-induced death (Corasaniti et al, 2007). Additionally, Amantea et al. (2009) investigated the effects of bergamot essential oil on brain damage caused in rats and showed, through microdialysis experiments, the significant reduction of excitatory amino acids, aspartate and glutamate, efflux in the frontoparietal cortex typically observed after occlusion of the middle cerebral artery, in addition to significantly increasing the phosphorylation of the harmful downstream kinase, GSK-3β, whose activity is down-regulated through phosphorylation by Akt, thus promoting neuroprotection (Mannucci et al, 2018).

PETITGRAIN (*Citrus aurantium*)

The main components of petitgrain (linalyl acetate, linalool and myrcene) seem to promote an autonomic balance between the sympathetic and parasympathetic system, resulting in an improvement in the mental and emotional condition due to a reduction in the level of stress and an increase in the level of excitement of the participants in terms of attention and alertness (Huang & Capdevila, 2017). The results are consistent with lavender studies since Lavender major components are also linalool and linalyl acetate. The bioactivities of petitgrain essential oil are a potential to be explored, since several articles mention petitgrain of different species or essential oils obtained from different parts of the *Citrus aurantium* plant, which makes it difficult to correctly filter evidence in relation to the essential oil of petitgrain from *Citrus aurantium* specifically (Liu, Lin & Chang, 2013; Chang & Shen, 2011).

The composition of essential oils is significantly different in flowers, leaves and bark. Linalyl acetate (50%) is the main constituent of the oil of leaves (petitgrain), and linalool (35%) of the essential oil of flowers (neroli), while the bark contains an essential oil composed of d-limonene and d-linalool (Roozbeh et al, 2019). Many studies show the neurophysiological effects of essential oils of *Citrus aurantium* obtained from different parts of plants: Pultrini et al (2006) mention the anxiolytic and sedative effects of the essential oil obtained from the bark (bitter orange oil), evidenced on mice tests while the results of Namazi et al (2014) confirmed the reduction of anxiety of women during labor after using the essential oil obtained from the flower (known as neroli). Fayed (2009) points out the antioxidant and anticancer effects of petitgrain essential oil in NB4 cell line and in HL-60 cell line, however, in this study the species *Citrus reticulata* was used, which has, among the main components, γ-terpinene (47.89%), methyl N-methyl anthranilate (13.17%), α-terpinene (7.40%), β-phellandrene (6.26%) and trans-isolimonene (5.87%) (Pultrini et al, 2006; Namazi et al, 2014; Fayed, 2009).

SWEET ORANGE (*Citrus sinensis*)

The use of sweet orange essential oil among kids before dental treatment is promising since it reduces salivary cortisol concentration and heart rates (Jafarzadeh, Arman & Pour, 2013). This is in line with a recently published meta-analysis that claims aromatherapy is effective in reducing dental anxiety in patients (Purohit et al, 2021). The authors claim that aromas affect the limbic system, which is related to heart rate, blood pressure, breathing, memory, stress, emotions and hormonal balance, as they enter the brain, promoting a subtle but integral impact. In another study with Swiss male mice tests, the essential oil of C. sinensis exerted an anxiolytic-like effect without altering locomotor activity. The researchers found that pre-treatment with L-arginine prevented this anxiolytic-like effect in animals and concluded that nitrergic neurotransmission plays a relevant role in the anxiolytic effect of C. sinensis essential oil (Hocayen et al, 2019). A clinical trial tested the effects of orange essential oil compared to fluoxetine in 150 individuals with major depressive disorder - evaluated using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The researchers concluded that orange essential oil has an effective antidepressant effect especially at the dose of 10 drops three times a day (Sargolzaee et al, 2004).

ESSENTIAL OILS COMPARISON AND SYNERGIES

Mood and ANS activity of pregnant women were evaluated under Lavender (*Lavandula angustifolia*), Petitgrain (*Citrus aurantium*) and Bergamot (*Citrus aurantium* L. SSP. *Bergamia*) interventions. The three groups were compared and showed improvements in mood states and ANS balance, however they did not differ significantly between each other, probably because they all contain linalyl acetate and linalool in their composition (Igarashi, 2013). Comparing Lavender (*Lavandula angustifolia*), Grapefruit (*Citrus paradisi)*, Rosemary (*Rosmarinus officinalis*) and Tea tree (*Melaleuca alternifolia*), authors concluded that Grapefruit and Lavender were able to reduce stress and improve immune system through analysis of salivary and serum secretory immunoglobulin A (sIgA), in addition to serum norepinephrine levels (Takagi et al, 2019).

A synergy composed of Lemon (*Citrus* sp.), Eucalyptus (*Eucalyptus* sp.), Tea tree (*Melaleuca alternifolia*) and Peppermint (*Mentha piperita*) in a ratio of 4:2:2:1, 24 hours a day, for 4 weeks was able to reduce stress perception and depression and increase sleep quality in adults, based on psychometric scales. However, no changes in physiological parameters were found. In this study, stress was divided into perceived stress and physiological stress (ie. stress index, LF, HF, HbA1c) and immunity was measured based on immunological indices (ie IgG, CD4, CD8, CD16 + 56). Parameters were evaluated before treatment and after the second and fourth weeks of treatment. Intervention with aromatherapy proved to be effective in relieving psychological stress and anxiety. However, there were no significant differences between the aromatherapy groups and in objective stress indicators, including the stress index, SNA activation and HbA1c levels (Lee et al, 2017).

Another study investigated the effects of aromatherapy on blood pressure and stress responses in hypertensive people. Participants used a synergy of lavender, ylang ylang and bergamot, via inhalation, once daily for four weeks. The intervention promoted a reduction in cortisol levels, psychological stress and blood pressure. The results suggest that the inhalation method with essential oils can be considered an effective intervention in the improvement of stress and hypertension conditions (Hwang, 2006).

4.1 Perspectives

There is evidence of physiological effects of aromatherapy applied through inhalation through measurement of parameters such as heart rate variability, blood pressure, respiratory rate, serum cortisol levels and immunological factors, in addition to the application of cognitive tests. Similar to conventional psychotropic drugs, the natural aromas of essential oils are able to interact and modulate different mechanisms, possibly facilitating neurotransmission and promoting neuroprotection. The action of essential oils on different neural pathways without having the side effects commonly present in treatments with synthetic drugs represents a valuable resource for comprehensive health care, which enables the complementary use of aromatherapy in the treatments of depression, anxiety and dementia, for example. Due to the complexity of the chemical composition of essential oils and their wide interaction with different receptors, more research is needed in order to elucidate the different mechanisms of action. The inclusion of placebo groups and the comparison between inhalation of essential oils versus synthetic essences in controlled studies are crucial, as well. In studies with essential oil blends, it is recommended to make 3 isolated groups, an intervention group with synergy, a placebo group with artificial aroma and a negative control, with undetectable aroma, such as water in the diffuser, for example.

One should also consider that different contexts may promote distinct responses to aromatic stimuli: the use of essential oils during sleep or wakefulness; time, frequency and total duration of the aromatherapy intervention; the concentration of essential oils and the dispersion method; the use of standardized dilution protocols, in previously tested devices or through validated techniques. The listed aspects will certainly provide more consistent and comparable data among studies of inhaled aromatherapy.

According to the results, it is suggested that essential oils can be useful as complementary resources to be used not only in clinics and hospitals, but also in offices and schools, providing safe and efficient reduction of stress and anxiety, especially the lavender essential oil, the most cited in selected studies and complementary articles in this review. Due to the broad scientific basis, it is suggested that the use of lavender essential oil can be integrated into the public health system.

5. Conclusion

The included studies mainly used lavender and citrus essential oil. Aromatherapy modulates the autonomic nervous system, with a predominance of parasympathetic activation, decrease in cortisol, increase in melatonin and improvement in the state of anxiety, depression and insomnia. Some limitations were observed: limited sample sizes and heterogeneity of forms of use and concentrations of essential oils in interventions, which may have caused changes in the results.

For future studies, the use of previously validated protocols is suggested. Even so, the results were favorable to the use of aromatherapy, as there were psychological and neurophysiological effects, with no adverse reactions reported. Therefore, more studies to prove the effects of inhaled aromatherapy in different populations, differentiating its effects from the placebo effect are suggested to be carried out.

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