

AROMATHERAPY – A NON-PHARMACOLOGICAL APPROACH IN PAIN CONTROL

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Abstract: Pain represents an unpleasant sensory and emotional experience and one of the most frequent symptoms in clinical practice. Pain control is crucial not only for the physical, but also for the emotional and psychological support of the patient. Pain treatment includes pharmacological and non-pharmacological methods. Integrating the non-pharmacological methods in pain management provide a holistic approach of the patient, addressing both the physical symptoms, and the psycho-emotional aspects of the patient's suffering. Aromatherapy is an important non-pharmacological method that involves the use of essential oils extracted from plants to promote relaxation and reduce stress, contributing to pain relief. Certain scents were demonstrated to have analgesic and calming effects. This article presents the most important components of the essential oils and the mechanisms explaining their effects in pain, mood, and behaviour modulation, in promoting relaxation and stress management, improving wellbeing and life quality in individuals dealing with pain, as demonstrated by evidence-based studies meeting the criteria of aromachology, the science analysing the olfactory effects on mood, physiology and behaviour. A lot of published data show positive outcomes about therapeutical effects of essential oils in pain control, but there is still a large individual variability in responsivity to aromatherapy, so that the effectiveness of aromatherapy in pain management cannot be yet conclusive to establish standard protocols for the use of aromatherapy in pain modulation.

Key words: pain modulation and management, control, aromatherapy, aromachology, essential oils, non-pharmacological treatment.

1. Introduction

Pain is an unpleasant sensation and experience, representing one of the most

frequent symptoms that addresses patients to the medical services.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional

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experience associated with, or resembling that, associated with actual or potential tissue damage" [1].

This definition emphasizes that pain is not merely a sensation but also includes an emotional component. It acknowledges that pain can be linked to actual or potential tissue damage but also recognizes that pain perception is influenced by emotional and psychological factors. The IASP's definition reflects a multidimensional understanding of pain, considering both the sensory and emotional aspects of the experience.

Pain control encompasses pharmacological and non-pharmacological treatment. Non-pharmacological methods can represent a crucial role in pain management, providing a complementary approach to traditional pharmacological interventions. These methods are often used alone or in combination with medication to address various types of pain.

The integration of non-pharmacological methods into pain management plans offers a holistic and patient-centered approach, addressing not only the physical symptoms but also the psychological and emotional aspects of pain. It's essential for healthcare providers to tailor interventions to individual needs and preferences. Additionally, combining non-pharmacological methods with pharmacological approaches can enhance overall pain control and improve the quality of life for individuals dealing with pain.

2. Definition of terms. Aromatherapy.

Aromachology

Aromatherapy represents a non-pharmacological method used for

physical, psychological, and emotional wellbeing, and also for symptom control by concentrated aromatic essences extracted from plants, including essential oils (EOs).

Odors and fragrances were proved to affect mood and behavior. Scientific research for exploring and interpreting these effects, and also physiological, pharmacological, and psychological mechanisms involved, led to the development of a new interdisciplinary scientific field – **aromachology**, defined by the Sense of Smell Institute in 1982 as the science analysing the olfactory effects on mood, physiology and behaviour [2]. As a science, in the era of evidence-based medicine, aromachology research must meet rigorous criteria as: 1) theory guided goals and clear hypothesis testing, 2) fragrances testing by appropriate clinical and experimental methodology, 3) data demonstrated in sufficient and representative subject populations and appropriate contrasting control groups, and analysed using suitable statistical methods, and 4) results thoroughly investigated and analyzed by scientific peers and accepted for publication in reputable journals [2]. *Id est*, not all the published data claiming to demonstrate the effects of various aromatic compounds on mood, behaviour, mental state, in controlling different symptoms or clinical conditions are however scientifically meaningful. Methodological problems regarding dependent measures and stimuli, data collecting and statistical interpretation led to inconsistencies in the data, such as mediating variables of culture, experience, sex differences, and personality.

The data presented in this article are based on well documented studies, meeting the criteria of aromachology.

Aromachology-based aromatherapy represents a holistic complementary therapy involving inhaling or applying concentrated plant extracts to the skin, often through methods such as diffusers, massage, or bath immersion.

Some EOs can also be conditioned for internal use (*per os*) for even further antiviral or antibacterial properties, alone or as a complementary therapy to potentate the effect of pharmacological antiviral or antibacterial molecules.

EOs were proved to have therapeutic properties that can positively influence the body and mind, offering relaxation, stress relief, and various health benefits in controlling pain, anxiety, insomnia and also respiratory and urinary tract infections.

3. Essential oils

Essential oils, the aromatic elixirs derived from plants, have enchanted humanity for centuries with their captivating scents and therapeutic potential.

3.1. Definition

Essential oils are highly concentrated volatile aromatic liquids extracted from flowers, leaves, seeds, peels, branches, bark, wood, roots, underground stems, gums or oily resin of plants by physical methods such as pressing or distillation [3]. These oils carry the distinctive

fragrance and therapeutic properties of the plants from which they are derived – a complex mixture of alcohols, esters, aldehydes, oxides, phenols, coumarins, ethers, ketones, acids and other ingredients, and may also contain secondary metabolites involved in plants growth-control and interaction with other plants or species [3], [4], [5]. EOs are often referred to as the “essence” of a plant, encapsulating its unique aroma and medicinal characteristics.

3.2. Extraction Methods

Several methods are used to extract EOs, each tailored to the specific plant material. Steam distillation is a common technique, involving the passage of steam through plant material to release and collect the essential oil. Cold pressing is utilized for citrus fruits, where mechanical pressure extracts the oil from the peel. Solvent extraction, enfleurage, and expression are additional methods employed, each preserving the delicate aromatic compounds of the plants.

Table 1 encompasses some common methods of essential oil extraction.

The choice of extraction method depends on factors such as the plant material, the desired quality of the essential oil, and the properties of the specific compounds being targeted. Each method has its advantages and disadvantages, and the resulting essential oil may vary in terms of fragrance, purity, and chemical composition.

EOs can also be obtained by chemical synthesis.

Methods used for essential oils extraction Adapted from [3])

Table 1

Extraction Method	Process	Examples
Steam Distillation / Step-by-Step Distillation	Steam is passed through the plant material, causing the volatile compounds in the plant to evaporate. The steam carrying these aromatic molecules is then condensed back into liquid form, resulting in a mixture of water and essential oil. - the most common method of essential oil extraction	Lavender Peppermint Eucalyptus
Hydro-distillation	Similar to steam distillation, but with water as the extracting agent. The plant material is immersed in water, and steam is passed through it to extract the essential oil	Clove Cinnamon
Cold Pressing (Expression)	The oil-containing glands in the peel of the fruit are ruptured through mechanical pressure, releasing the essential oil. The oil is then separated from the fruit juice. - method primarily used for citrus fruits	Lemon Orange Bergamot
Solvent Extraction	Solvents (such as hexane) are used to dissolve essential oil from the plant material. The solvent is then evaporated, leaving behind the essential oil - method often used for delicate flowers that may not withstand the high heat of steam distillation	Jasmine Rose
CO ₂ Extraction (Supercritical Fluid Extraction)	CO ₂ is used as a solvent under high pressure and low temperature, creating a supercritical fluid. This fluid extracts the essential oil without the use of heat, resulting in a high-quality product	Rosemary Ginger
SFE (Supercritical Fluid Extraction)	Similar to CO ₂ extraction but using other supercritical fluids like propane or ethylene. This method can extract a wide range of compounds, including essential oils, with high selectivity	Various herbs and spices
Enfleurage	This traditional method involves placing plant material on a layer of fat, which absorbs the essential oils from the plant. The fat is then washed with alcohol to separate the essential oil from the fat	Jasmine Tuberose
Maceration	Plant material is soaked in a carrier oil to absorb its essential oil. The mixture is then filtered to obtain the oil	Vanilla Calendula

3.3. Composition

The chemical constituents of essential oils can vary widely depending on the plant species, the plant part from which

the oil is extracted, the growing conditions, and the extraction method.

However, some common classes of chemical compounds found in essential oils are shown in Table 2.

Chemical compounds of the Eos and their demonstrated effects

Table 2

Chemical Class	Chemical Compounds	Examples	Properties	Pharmacological effects	Other effects and usage
Terpenes	• pinene (pine terpene) [6]	Turpentine	✓ often responsible for the characteristic aromas of EOs	- anxiolytic - anticonvulsant - neuroprotective - gastroprotective - cytoprotective	- alpha-pinene is used as an antioxidant - the main industrial use of β -pinene is thermal cracking to myrcene
	• limonene [6]	Tangerine Oil Lemon Oil Orange Oil Camphor White Oil Peppermint Oil Neroli Oil	✓ diverse biological activities and contribute to the therapeutic effects of EOs	- anti-dementia - anti-cancer - antioxidant	- raw materials for preparing artificial orange blossom, sweet flower, lemon, and bergamot oil - raw materials for synthetic rubber
	• myrcene				
Monoterpene alcohols	• monoterpenes alcohol camphene (camphor terpene) [7]	Camphor Fir oil Herbs Orange blossom	✓ contribute to the floral and sweet notes in essential oils	- control of neuropathic pain - inhibition of inflammation - lowering of blood lipids	- used in the synthesis of spices, pesticides, camphor
	• linalool (galolol) [8]	Linalam oil Linalool oil Galago oil Rosewood oil Lavender oil Bergamot oil Green tea	✓ can have antimicrobial and soothing properties	- sedative - analgesic - antibacterial - anti-dementia	- fragrances - deodorants - anti-caries - insecticides
	• menthol [9]	Peppermint Peppermint EO		- local analgesia	- used as a flavoring agent (in toothpaste, perfume, beverages and candy)

Chemical Class	Chemical Compounds	Examples	Properties	Pharmacological effects	Other effects and usage
	<ul style="list-style-type: none"> citronellol (vanillyl alcohol) [10] 	D-citronellol: Citronella oil Rue oil Lemon oil Eucalyptus oil L-citronellol: Rose oil Geranium plants oil		<ul style="list-style-type: none"> anti-dementia antibiotic and antifungal (in vitro) 	<ul style="list-style-type: none"> indispensable raw material for the preparation of various rose flower fragrances used in a variety of cosmetic fragrances
	<ul style="list-style-type: none"> borneol [11], [12] 			<ul style="list-style-type: none"> inhibits nociception anti-inflammatory 	
	<ul style="list-style-type: none"> geraniol 				
Sesquiterpene lactone	<ul style="list-style-type: none"> myrrh alcohol β-caryophyllene farnesene tea matzolin genistein 		✓ larger molecules contributing to the woody and earthy scents in EOs	<ul style="list-style-type: none"> anti-inflammatory 	
Sesquiterpene alcohols	<ul style="list-style-type: none"> patchouli alcohol [13] 	Patchouli		<ul style="list-style-type: none"> brain protection antibacterial anti-inflammatory 	<ul style="list-style-type: none"> Patchouli oil, determination of Patchouli alcohol Gas chromatography
	<ul style="list-style-type: none"> nerol [14] 	Rutaceae plant Sweet orange Bergamot Honeysuckle plant		<ul style="list-style-type: none"> antibacterial 	<ul style="list-style-type: none"> valuable spice (preparation of rose and orange blossom and other floral fragrances)
Sesquiterpenes cerulean	<ul style="list-style-type: none"> variant allen [15] 	Asteraceae EOs		<ul style="list-style-type: none"> anti-allergic effect on skin 	
Phenols	<ul style="list-style-type: none"> eugenol [16] 	Clove Oil Purple Galangal Camphor	✓ strong antimicrobial properties	<ul style="list-style-type: none"> anesthetic neuroprotective anti-inflammatory antioxidant 	<ul style="list-style-type: none"> can be used as a soap fragrance unilateral EO of many flowers

Chemical Class	Chemical Compounds	Examples	Properties	Pharmacological effects	Other effects and usage
			✓ can contribute to the spicy and warming aspects of EO		which can be used to prepare gypsophila-shaped spices - can be used to prepare strong fragrance of dried fruits
	• thymol (5-methyl-2-isopropylphenol) [17]	Thyme Labiata thyme Vanilla Umbelliferous parsley seeds		- antioxidant - antiseptic - antiproliferative	- cigarette additives - preservative
Aldehydes	• citral [18]	Maple cod oil Pine oil	✓ contribute to the fresh, citrusy, or fruity scents in essential oils	- analgesic - anti-inflammatory - antioxidant - antibacterial - antitumoral - antidiabetic	- flavoring agent to formulate lemon-flavored products (lemon essence)
	• citronellal [18]	Citronella Oil Eucalyptus Oil	✓ some have antimicrobial properties	- anticonvulsant - antipyramidal - wound healing - antidiabetic	- used to prepare citrus and cherry flavors, low-grade soap flavors - raw material for other flavors - used to synthesize menthol
	• benzaldehyde				
Ketones	• camphor (1,7,7-trimethylbicyclo [2.2.1]heptan-2-one) [19]	Natural mint Miscanthus	✓ mucolytic and expectorant effects ✓ some can have cooling or warming sensations	- used as a traditional Chinese medicine	- mostly used in the manufacture of mothballs
	• menthone (mentholone, mendonone) [20]			- analgesic effect with peppermint	- spice for preparing geranium oil (a raw

Chemical Class	Chemical Compounds	Examples	Properties	Pharmacological effects	Other effects and usage
					material for edible cooling flavors, a good spice for toothpaste)
Esters	<ul style="list-style-type: none"> • linalyl acetate [21] • agaryl acetate 	Natural bergamot Lavender fragrance	✓ contribute to the	<ul style="list-style-type: none"> - treatment of insomnia - analgesic - antihypertensive 	- main component of jasmine, ylang-ylang, sweet-scented osmanthus, lilac and other floral fragrances
	<ul style="list-style-type: none"> • methyl phthalate [22] • methyl salicylate [22] 	Calgrass oil Wintergreen oil Birch oil Green tea seed oil Clove oil Oak tree oil Tuberose oil	fruity and floral scents in essential oils ✓ often calming and sedative effects	<ul style="list-style-type: none"> - toxicity 	- often used as a flavoring agent for cavity medicines and pharmaceutical preparations
	<ul style="list-style-type: none"> • methyl benzoate 			<ul style="list-style-type: none"> - insecticide 	- preparation of fragrances and artificial essential oils
	<ul style="list-style-type: none"> • bornyl acetate [11], [12] 			<ul style="list-style-type: none"> - Inhibits nociception - anti-inflammatory 	
Oxides	<ul style="list-style-type: none"> • 1,8-cineole (eucalyptol) [24] 	Eucalyptus Aromatic wolf leaf Galangal Camphor Rosa white Cardamon	✓ oxides can have expectorant and respiratory-supporting properties ✓ contributes to the cooling sensation in some EO	<ul style="list-style-type: none"> - inhibits pain - anti-inflammatory - antioxidant (for the treatment of respiratory and cardiovascular diseases) 	- manufacture of pharmaceutical products - flavor and spice blending
Coumarin	<ul style="list-style-type: none"> • coumarine (oxynaphthalen) [25] 	Black bean Fragrant snake		<ul style="list-style-type: none"> - antiproliferative 	<ul style="list-style-type: none"> - generally not for food - smoking and

Chemical Class	Chemical Compounds	Examples	Properties	Pharmacological effects	Other effects and usage
		chrysanthemum Wild vanilla Orchid			external use are allowed
Acids	• lauric acid (dodecanoic acid) [26]	Coconut oil Palm seed oil Babassu oil		- antiproliferative	- flavors - food additives
	• cinnamic acid (β -phenylacrylic acid) [27]	Cinnamon bark Benzoin		- antibacterial - antidiabetic - antiproliferative	- raw material for the production of soaps, detergents, cosmetic surfactants and chemical fiber oils
	• isovaleric acid (3-methylbutyric acid) [28]	Apples Valerian Lemon leaf Lemongrass Spearmint Melaleuca		- antidepressive	- commonly used in baked goods, meat products - used in the manufacture of medicines, spices, condiments
	• bay leaf [29]	Bay leaves Tobacco leaves		- melanin inhibition	- used in spices, cigarettes

Some chemical constituents are found in a variety of plant EOs, such as camphene and linalool. Some substances are unique to some EOs, such as menthol and camphor [19], [27], [28].

Understanding the specific compounds present in an essential oil is essential for assessing its potential therapeutic effects. Additionally, the interaction of these compounds within the overall chemical profile of an essential oil can influence its aroma and efficacy. Essential oils should be used with care, following proper dilution and safety guidelines, as the

effects of essential oils can vary, and individual responses may differ.

3.4. Administration

A variety of methods can be used for EOs administration in medical purposes, including inhalation, oil massage or even oral administration, techniques which can be collectively referred to as aromatherapy [29].

Moreover, EOs are frequently components of a variety of products for applications such as sterilization, virus killing, fungicidal, anti-parasitic,

insecticidal, pharmaceutical, and cosmetic [3], [29].

Different components of the EOs were proved to have specific effects.

However, for medical purposes, EOs should be used with caution and under the guidance of a qualified healthcare professional or aromatherapist. While some essential oils have demonstrated potential therapeutic properties, their application for medical purposes requires proper knowledge, adherence to safety guidelines, and consideration of individual health conditions.

Here are several ways in which EOs may be administered for potential medical benefits:

Inhalation. Inhalation can be achieved through direct inhalation from the bottle, using a personal inhaler, or by diffusing oils into the air. Inhalation allows the aromatic compounds of essential oils to enter the respiratory system, potentially influencing the limbic system and emotional wellbeing. It may also have respiratory benefits.

Topical application by diluting EOs in a carrier oil before being applied to the skin. Common carrier oils include jojoba, coconut, and sweet almond oil. Topical application allows the absorption of EO compounds through the skin. It may be used for localized effects, such as pain relief, skin conditions, or muscle relaxation.

Massage. EOs are diluted in a carrier oil and applied during massage sessions. Massage with essential oils combines the benefits of aromatherapy with the physical effects of massage. It may

enhance relaxation, reduce muscle tension, and promote overall wellbeing.

Baths. A few drops of EOs are added to a carrier oil or bath salts before being dispersed in bathwater. Aromatic baths can provide relaxation, alleviate stress, and address skin conditions. However, caution is advised to avoid skin irritation, and proper dilution is essential.

Compresses. A few drops of EOs are added to warm or cold water and soaked into a cloth, which is then applied to a specific area of the body. Compresses can be used for localized effects, such as reducing inflammation, soothing sore muscles, or addressing skin conditions.

Oral ingestion. Some EOs are considered safe for ingestion, but this should only be done under the guidance of a qualified professional. Oils may be diluted in water, added to capsules, or incorporated into culinary preparations. Ingestion is believed to support various health concerns, such as digestive issues, immune support, and overall wellbeing.

However, not all essential oils are safe for internal use, and proper dosage is crucial.

Individual responses to essential oils can vary, and not all oils are suitable for every person or condition. Additionally, some essential oils may interact with medications or exacerbate certain health conditions.

That is why following recommended dilution ratios, adhere to safety guidelines, and being aware of any contraindications associated with specific EOs are crucial in a proper utilization of EOs in medical practice, as a complementary method to

enhance the effects of pharmacological interventions.

4. Aromatherapy – mechanisms of action in pain control

Several theories and factors may contribute to the analgesic effects reported by some individuals.

• Limbic system activation by inhalation and olfactory pathways

When essential oils are inhaled, the olfactory system is activated. The olfactory system is closely linked to the limbic system in the brain, which plays a role in emotions and mood. Inhalation of certain essential oils may trigger the release of neurotransmitters and endorphins, contributing to a sense of wellbeing and potentially influencing pain perception.

The limbic system is represented by a set of brain structures involved in emotions, memory, and arousal. It includes the amygdala, hippocampus, thalamus, hypothalamus, and other interconnected regions. The limbic system plays a crucial role in processing emotions and can influence the perception and modulation of pain.

The limbic system is connected with the opioid interneuron system in the spinal cord through complex neural networks that contribute to the modulation of pain perception. While the limbic system and the opioid system operate in different regions of the central nervous system, they interact to influence emotional and sensory aspects of pain.

On the other hand, the opioid system involves the release of endogenous opioids (opioid peptides produced naturally in the body, such as endorphins) and their interaction with opioid receptors

in the central nervous system, including the spinal cord. Opioid interneurons in the spinal cord are part of this system and play a role in inhibiting pain signals.

The connection between the limbic system and the opioid system is complex and involves various pathways:

✓ Endorphin release

Emotions, stress, and mood, which are modulated by the limbic system, can influence the release of endogenous opioids, including endorphins. These opioids act on receptors in the spinal cord to modulate pain signals.

✓ Descending Modulation

The limbic system has connections with brain regions (periaqueductal gray matter of the midbrain – PAG, raphe nuclei in the brainstem) that send descending pathways to the spinal cord. These descending pathways can modulate the activity of spinal interneurons, including those involved in the opioid system, to influence pain transmission [30], [31].

Enkephalin-releasing neurons from the periaqueductal gray matter of the midbrain project to the raphe nuclei in the brainstem. Neurons in the raphe nuclei release pain inhibitory modulators as noradrenalin and serotonin (5-hydroxytryptamine, 5-HT) and descend to the dorsal horn of the spinal cord, stimulating opioid interneurons located in substantia gelatinosa (Laminae II). When activated, these interneurons release endogenous opioid peptides (enkephalin or dynorphin). By binding specific opioid receptors, mu (μ) and kappa (κ), the pain signals transmitted from peripheral nociceptors by A-delta and C fibers are inhibited / attenuated before reaching the cortical areas that interpret the signal as pain (the anterior cingulate gyrus), as the

activation of the opioid receptors inhibits the release of substance P from the presynaptic membrane of the incoming first-order neurons, inhibiting thus the activation of the second-order neuron responsible for transmitting the pain signal up the spinothalamic tract to the ventral posterolateral nucleus (VPL) of the thalamus [32].

This is referred to as the *gate control theory of pain* and is supported by the fact that electrical stimulation of the PAG results in immediate and profound analgesia [32].

Viewing distressing images associated with pain can also activate the periaqueductal gray [33].

Emotional responses to pain, perceived social or emotional pain seem to be connected with the anterior cingulate, not only by reducing nociceptive signaling, but also by reducing sensitivity to pain. Moreover, an “analgesic” effect for emotional pain was demonstrated by activation of mu-opioid receptors [33], [34].

✓ *Stress Response*

The limbic system is involved in modulating stress body's stress response, leading to the release of endogenous opioids, reducing temporarily the perception of pain (stress-induced analgesia).

While there is a connection between the limbic system and the opioid system, the relationship is intricate and involves multiple neural pathways. The modulation of pain is a complex process influenced by sensory, emotional, and cognitive factors. Understanding these interactions is crucial for developing comprehensive pain management strategies.

• **Modulation of neurotransmitters**

Some EOs may interact with neurotransmitters in the brain, such as

serotonin and dopamine, which are involved in mood regulation and pain processing. For example, lavender essential oil has been studied for its potential to modulate serotonin receptors (serotonin being an inhibitory synaptic mediator of pain transmission). Moreover, lavender EO was demonstrated to exert an inhibitory action on N-methyl-D-aspartic acid (NMDA) receptors [35].

• **Gate control theory of pain modulation**

The gate control theory of pain modulation suggests that non-painful input (transmitted by myelinated A-alpha and A-beta fibers) can close neural gates to painful input (transmitted by A-delta and C fibers). The non-painful signals activate the inhibitory (opioid) intercalary neuron in the dorsal horn of the spinal cord, closing the gate for the pain signals transmission and reducing the perception of pain. Pleasant scents and sensory stimulation by EOs used in aromatherapy may influence this gating mechanism and alter the perception of pain.

• **Anti-Inflammatory effects**

EOs like frankincense or ginger may contribute to pain relief by anti-inflammatory effects, as chronic pain is often associated with inflammation.

• **Distraction and relaxation**

Aromatherapy may serve as a distraction from pain, shifting focus to pleasant sensory experiences. Additionally, the relaxation induced by certain essential oils, such as lavender or chamomile, can contribute to overall pain relief by reducing stress and tension.

5. Evidence-based studies supporting the effect of EUs in pain control

In medical practice, EOs find applications in various domains due to their diverse properties and potential therapeutic benefits.

Lavender EO was demonstrated to have an analgesic effect using a formalin-induced pain model test. Researchers reported that lavender EO proved analgesic effects similar to those of indomethacin or tramadol by targeting G-protein coupled receptors [36].

Similar reports were published for *Bergamot EO* in alleviating formalin-induced or capsaicin-induced pain [37], [38], [39].

Limonene, a terpene compound of *Tangerine oil*, *Lemon oil*, *Orange oil*, *Camphor white oil*, *Peppermint oil*, *Neroli oil* was reported to have antihyperalgetic effects in an experimental neuropathic pain model [40].

Some studies reported *bornyl alcohol EO* (a bicyclic monoterpene alcohol) to exert a significant reduction in the perception of pain induced by intraperitoneal injection of acetic acid the pain, by modulating TRPM8 ion channels [11], [12], [41], [42].

Cis-basil and -pinene compounds of *Pod EO* have been discovered to be the main analgesic constituents exerting dose-dependent antinociceptive effects in acetic acid-induced writhing test and hot plate test [43].

Thymol, an active component of *Ophiopogon EO*, was reported to attenuate acetic acid-induced pain behavior by blocking voltage-gated sodium channels and inhibiting interferon- γ (IFN- γ) production [17], [44].

6. Conclusions

A body of scientific evidence demonstrate therapeutic effects of certain compounds in the essential oils extracted from plants as lavender (*Lavandula officinalis*), sage (*Salvia sclarea*), chamomile (*Matricaria recutita* L.), rosemary (*Rosmarinus officinalis* L.), lemon (*Citrus limon*), orange (*Citrus sinensis*), bergamot (*Citrus bergamia*), ginger (*Zingiber officinale Roscoe*) in pain control, completing the action of pharmacological molecules in the treatment of pain.

Although a lot of published data show positive outcomes of essential oils' therapeutic effects in pain control, a lot of individual variability in responsivity to aromatherapy is also reported.

Therefore, the effectiveness of aromatherapy for pain control is not conclusive and no standard protocols for the use of aromatherapy in pain management can be established so far, more scientific evidence and better understanding of specific mechanisms being needed.

Aromatherapy is for sure a complementary approach to be considered in pain management, but should not replace conventional medical treatments, especially in severe or chronic pain conditions.

References

1. Raja SN. IASP revised definition of pain. 2020, July 16. Available at: <https://www.iasp-pain.org/publications/iasp-news/iasp-announces-revised-definition-of-pain/>. Accessed on November 28, 2023.
2. Herz RS. Aromatherapy facts and fictions: a scientific analysis of olfactory

- effects on mood, physiology and behavior. *International Journal of Neuroscience*. 2009; 119: 263–290. doi: 10.1080/00207450802333953.
3. Liang J, Zhang Y, Chi P, et al. Essential oils: Chemical constituents, potential neuropharmacological effects and aromatherapy – A review. *Pharmacological Research – Modern Chinese Medicine*. 2023; 6: 100210. doi: <https://doi.org/10.1016/j.prmcm.2022.100210>.
 4. Soliman SA, Hafez EE, Al-Kolaibe A. Biochemical characterization, antifungal activity, and relative gene expression of two *Mentha* essential oils controlling *Fusarium oxysporum*, the causal agent of *Lycopersicon esculentum* root rot. *Plants*. 2022; 11 (2): 11020189. doi: 10.3390/plants11020189.
 5. Camele I, Grulova D, Elshafie HS. Chemical composition and antimicrobial properties of *Mentha x piperita* cv. 'Kristinka' (Peppermint) essential oil. *Plants*. 2021; 10 (8): 10081567. doi: 10.3390/plants10081567.
 6. Salehi B, Upadhyay S, Erdogan Orhan I. Therapeutic potential of α - and β -pinene: a miracle gift of nature. *Biomolecules*. 2015; 9(11): 738. doi: 10.3390/biom9110738.
 7. Vallianou I, Hadzopoulou-Cladaras M. Camphene, a plant derived monoterpene, exerts its hypolipidemic action by affecting srebp-1 and mtp expression. *PLoS One*. 2006; 11(1): e147117. doi: 10.1371/journal.pone.0147117.
 8. An Q, Ren J, Li X. Recent updates on bioactive properties of linalool. *Food Funct*. 2021; 12(21): 10370–10389. doi: 10.1039/D1FO02120F.
 9. Pergolizzi JV, Taylor R, Lequang JA. The role and mechanism of action of menthol in topical analgesic products. *J. Clin. Pharm. Thera*. 2018; 43(3): 313–319. doi: 10.1111/jcpt.12679.
 10. Santos PL, Matos JPSC, Picot L. Citronellol, a monoterpene alcohol with promising pharmacological activities - a systematic review. *Food Chem. Toxicol*. 2019: 123459–123469. doi: 10.1016/j.fct.2018.11.030.
 11. Almeida JRGD, Souza GR, Silva JC. Borneol, a bicyclic monoterpene alcohol, reduces nociceptive behavior and inflammatory response in mice. *Sci. World J*. 2013: 20131-20135. doi: 10.1155/2013/808460.
 12. Wang S, Zhang D, Hu J. A clinical and mechanistic study of topical borneol-induced analgesia. *EMBO Mol. Med*. 2017; 9(6): 802-815. doi: 10.15252/emmm.201607300.
 13. Bhatia SP, Letizia CS, Api AM. Fragrance material review on patchouli alcohol. *Food Chem. Toxicol*. 2008; 46(11) (Suppl): S255–S256. doi: 10.1016/j.fct.2008.06.069.
 14. Wang Z, Yang K, Chen L. Activities of nerol, a natural plant active ingredient, against candida albicans in vitro and in vivo. *Appl. Microbiol. Biotechnol*. 2020; 104(11): 5039–5052. doi: 10.1007/s00253-020-10559-2.
 15. Mckay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (*Matricaria recutita* L.). *Phytother. Res*. 2006; 20(7): 519–530. doi: 10.1002/ptr.1900.
 16. Barboza J, Da Silva Maia Bezerra Filho C, Silva RO. An overview on the anti-inflammatory potential and antioxidant profile of eugenol. *Oxid. Med. Cell. Longev*. 2018: 20181–

20189. doi: 10.1155/2018/3957262.
17. Elbe H, Yigitturk G, Cavusoglu T. Apoptotic effects of thymol, a novel monoterpene phenol, on different types of cancer. *Bratisl. Med. J.* 2021; 121(02): 122–128. doi: 10.4149/BLL_2020_016.
 18. Siegel E, Wason S. Camphor toxicity. *Pediatr. Clin. N. Am.* 1986; 33(2): 375–379. doi: 10.1016/s0031-3955(16)35008-8.
 19. Bethesda. Peppermint. *Drugs and lactation database (LactMed®)*. 2022; 03. PMID:30000911. Available at: <https://pubmed.ncbi.nlm.nih.gov/30000911/>. Accessed on November 30, 2023.
 20. Hsieh YS, Kwon S, Lee HS. Linalyl acetate prevents hypertension-related ischemic injury. *PLoS One*. 2018; 13(5): e198082. doi: 10.1371/journal.pone.0198082.
 21. Cai Z, Peng J, Chen Y. 1,8-cineole: a review of source, biological activities, and application. *J. Asian Nat. Prod. Res.* 2021; 23(10): 938–954. doi: 10.1080/10286020.2020.1839432.
 22. Al-Warhi T, Sabt A, Elkaeed EB. Recent advancements of coumarin-based anticancer agents: an up-to-date review. *Bioorg. Chem.* 2020; 103104163. doi: 10.1016/j.bioorg.2020.104163.
 23. Verma P, Ghosh A, Ray M. Lauric acid modulates cancer-associated microRNA expression and inhibits the growth of the cancer cell. *Anticancer. Agents Med. Chem.* 2020; 20(7): 834–844. doi: 10.2174/1871520620666200310091719.
 24. Ruwizhi N, Aderibigbe BA. Cinnamic acid derivatives and their biological efficacy. *Int. J. Mol. Sci.* 2020; 21(16): 5712. doi: 10.3390/ijms21165712.
 25. Szczesniak O, Hestad KA, Hanssen JF. Isovaleric acid in stool correlates with human depression. *Nutr. Neurosci.* 2016; 19(7): 279–283. doi: 10.1179/1476830515Y.0000000007.
 26. Choi SY. Inhibitory effects of geranic acid derivatives on melanin biosynthesis. *J. Cosmet. Sci.* 2012; 63(6): 351–358.
 27. Bethesda. Chamomile. *Drugs and Lactation Databaset.* 2021; (02). PMID:30000867. Available at: <https://pubmed.ncbi.nlm.nih.gov/30000867/>, Accessed on November 28, 2023.
 28. Bethesda. Lavender. *Drugs and Lactation Databaset.* 2022; (02). PMID:30000925. Available at: <https://pubmed.ncbi.nlm.nih.gov/30000925/>. Accessed on November 28, 2023.
 29. Sharmeen JB, Mahomoodally FM, Zengin G. Essential oils as natural sources of fragrance compounds for cosmetics and cosmeceuticals. *Molecules.* 2017; 26(3): 666. doi: 10.3390/molecules26030666.
 30. Faull OK, Subramanian HH, Ezra M, Pattinson KTS. The midbrain periaqueductal gray as an integrative and interoceptive neural structure for breathing. *Neuroscience and Biobehavioral Reviews.* 2019; 98: 135–144. PMID 30611797. doi:10.1016/j.neubiorev.2018.12.020.
 31. Silva C, McNaughton N. Are periaqueductal grey and dorsal raphe the foundation of appetitive and aversive control? A comprehensive review. *Progress in Neurobiology.* 2019; 177: 33–72. PMID 30786258. doi:10.1016/j.pneurobio.2019.02.001.
 32. Basbaum A, Fields HL. Endogenous pain control mechanisms: review and

- hypothesis. *Ann. Neurol.* 1978; 4(5): 451–62. PMID 216303. doi:10.1002/ana.410040511.
33. Eisenberger NI, Lieberman MD, Williams KD. (October 2003). Does rejection hurt? An fMRI study of social exclusion. *Science.* 2003; 302(5643): 290–292. PMID 14551436. doi:10.1126/science.1089134.
34. Gorka SM, Fitzgerald DA, de Wit H, Angstadt M, Phan KL. Opioid modulation of resting-state anterior cingulate cortex functional connectivity. *J Psychopharmacol.* 2014; 28(12): 1115–24. PMID 25237122. doi:10.1177/0269881114548436.
35. López V, Nielsen B, Solas M. Exploring pharmacological mechanisms of lavender (*Lavandula angustifolia*) essential oil on central nervous system targets. *Front. Pharmacol.* 2017: 8280. doi: 10.3389/fphar.2017.00280.
36. Silva GI, Luft C, Lunardelli A. Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil. *An. Acad. Bras. Cienc.* 2015; 87(2): 1397-1408. doi: 10.1590/0001-3765201520150056.
37. Scuteri D, Rombolá L, Tridico L. Neuropharmacological properties of the essential oil of bergamot for the clinical management of pain-related BPSDs. *Curr. Med. Chem.* 2019; 26(20): 3764-3774. doi: 10.2174/0929867325666180307115546.
38. Bagetta G, Morrone LA, Rombolà L. Neuropharmacology of the essential oil of bergamot. *Fitoterapia.* 2010; 81(6): 453-461. doi: 10.1016/j.fitote.2010.01.013.
39. Katsuyama S, Otowa A, Kamio S. Effect of plantar subcutaneous administration of bergamot essential oil and linalool on formalin-induced nociceptive behavior in mice. *Biomed. Res.* 2015; 36(1): 47-54. doi: 10.2220/biomedres.36.47.
40. Piccinelli AC, Santos JA, E.C. Konkiewitz EC. Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, α -phellandrene, and essential oil from *Schinus terebinthifolius* fruits in a neuropathic pain model. *Nutr. Neurosci.* 2014; 18(5): 217-224. doi: 10.1179/1476830514Y.0000000119.
41. Khalilzadeh E, Vafaei SG, Hasannejad H. Antinociceptive effects, acute toxicity and chemical composition of *Vitex agnus-castus* essential oil. *Avicenna J. Phytomed.* 2015; 5(3): 218-230.
42. Anaya-Eugenio GD, Rivero-Cruz I, Bye R. Antinociceptive activity of the essential oil from *Artemisia ludoviciana*. *J. Ethnopharmacol.* 2016: 179403-179411. doi: 10.1016/j.jep.2016.01.008.
43. Shafaroodi H, Roozbahani S, Asgarpanah J. The essential oil from *Ferulago angulata (schltdl.) boiss. fruits* exerting potent analgesic and anti-inflammatory effects. *J. Physiol. Pharmacol.* 2021; 72 (1). doi: 10.26402/jpp.2021.1.08.
44. Mendes SS, Bomfim RR, Jesus HCR. Evaluation of the analgesic and anti-inflammatory effects of the essential oil of *Lippia gracilis* leaves. *J. Ethnopharmacol.* 2010; 129(3): 391-397. doi: 10.1016/j.jep.2010.04.005.