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Analgesic Potential of Monoterpenes from Citrus Essential Oils

Ines Banjari, Jelena Balkić and Viduranga Yashasvi Waisundara

Abstract

Chronic pain is a noteworthy health issue with immense impact on global healthcare systems. Although this issue has not come into the limelight as other noncommunicable diseases, it should be highlighted that modern medicine still has no efficient treatment to curb chronic pain. In this aspect, essential oils have been used for the prevention of several disease conditions including pain management. These odorous products, obtained from botanically defined raw material, have a variable and complex composition. Their composition largely depends on the extraction technique used, from simple hydro-distillation, to supercritical or micro-wave-assisted extraction. Monoterpenoids are some of the most biologically active and highly researched compounds when it comes to antinociceptive effects. They are volatile oils, primarily composed of two isoprene units with highly distinctive aromas and flavors. More than 90% of the essential oils of medicinal plants consist of monoterpenoids like limonene, myrcene, α -terpineol, linalool, pinene, *p*-cymene, and nerol. Besides strong anti-inflammatory effect, all essential oils with high D-limonene content pose a significant free radical scavenging effect, predominantly disabling the production of reactive oxygen species. Further studies in humans are encouraged to determine the real long-term potential in treating chronic pain.

Keywords: chronic pain, essential oils, citruses, monoterpenes, limonene

1. Introduction

Chronic pain is defined as a long-term pain lasting 3–6 months after the normal healing period, and is described as continuous or recurrent [1]. The European Pain Federation (EFIC) in its Declaration on Pain identifies chronic pain as a distinct health issue, which has an immense financial impact on healthcare systems around the world [2]. In Europe, 20% of adults or one in five suffer from chronic pain, and about 34% of them describe their chronic pain as severe [3]. In the U.S., estimated prevalence among adults ranges from 11 to 40% [4]. Estimated total cost of the consequences of chronic pain across Europe is €300 billion [3], while the annual healthcare cost for back pain only was estimated to be £13.44 billion in Germany and £1 billion in UK [5].

Chronic pain alters all aspects of a patient's life inducing severe physical, psychological, and social impairments, while increasing consumption of opiates and analgesics. It eventually deteriorates an individual's quality of life [1, 3, 5].

The most common sites affected, according to a UK population study, are the lower back [30%], hip [25%], neck and shoulder (25%), and knee (24%) [6]. The underlying pathophysiology of chronic pain is usually complex, and can be explained by the presence of typical inflammation and neuropathy [7].

Modern medicine still has no efficient treatment to deal with chronic pain. Essential oils have been used to prevent and treat diseases for many centuries [8] and have been proven to pose antibacterial, antifungal, antiproliferative, anti-inflammatory, antioxidant, and anesthetic properties, although the exact mechanisms of action are still elusive [8, 9]. Recent meta-analysis by Lakhan et al. [10] found a significant positive effect of aromatherapy [compared with placebo or treatments as usual controls] in reducing pain intensity, with the strongest evidence for nociceptive and acute pain, unlike inflammatory and chronic pain. The aim of this chapter is to summarize the existing evidence on the effectiveness of Citrus essential oils, that is, their monoterpenes and especially limonene, for the treatment of chronic pain.

2. Essential oils


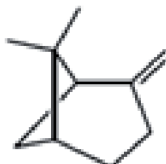
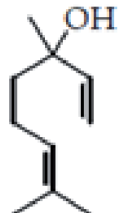
One of the modalities where plants have been put to use is aromatherapy, where they can be diffused aromatically, consumed internally, or applied topically to the skin [8, 11]. In general, the respiratory tract offers the most rapid way of entry of oils followed by the dermal pathway [12]. The main beneficial constituents present in essential oils are the monoterpenes, sesquiterpenes, and phenylpropanoids [9]. Citrus essential oils have been used for millennia to treat anxiety, agitation, stress, challenging behaviors, fatigue, and insomnia [11]. Composition of selected essential Citrus oils is given in **Table 1**, along with their beneficial health effects. The composition of a specific essential oil will vary significantly depending on the extraction technique used.

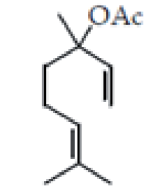
3. Extraction techniques of essential oils



There are several extraction techniques that are commonly used for the isolation and purification of bioactives from herbs used as pain medications. A summary of these techniques is shown in **Figure 1**. Most of these bioactives are extracted together with the essential oils of the herbs. It is important that the selected extraction technique is compatible with the bioactives as well as the herb, and is efficient in obtaining as much quantity as possible while preserving the functionality.

Techniques commonly employed for extracting essential oils include hydro-distillation, steam distillation, solvent extraction, head space analysis, and liquid CO₂ extraction [37]. Head space analysis is a potentially rapid method, which is used to extract essential oils and requires very little plant material, but a complete recovery may occur only for highly volatile materials. Conventional methods such as steam distillation and solvent extraction may result in severe losses of volatile materials because the liquid in which the oil is collected should be subsequently removed by evaporation. Application of heat in this instance is a disadvantage.

Ultrasound has been recently applied to improve the extraction of polysaccharides and essential oils from plant material that is used for pain medication, mainly through the phenomenon of cavitation [38–41]. Chemat et al. [41] prepared hexane extracts of two caraway seeds focusing on the carvone and limonene contents which were isolated in the process. The study demonstrated that the carvone yield and plant extract quality were better in ultrasound extraction compared with those obtained by conventional methodologies.

Essential oil		Main constituents	Health effects	Reference	Chemical structures of some key monoterpenes [13]
Common name	Latin name				
Sweet orange	<i>Citrus sinensis</i> L.	Limonene (66.8–80.9%), β -myrcene (3.76–6.28%), α -pinene (1.65–2.48%)	<ul style="list-style-type: none"> • High antioxidant activity in linoleic acid system 	[14–17]	 d-Limonene
Bitter orange	<i>Citrus aurantium</i> L.	Limonene (51.3–98.173%), α -pinene (0.476%), and β -pinene (0.176%)	<ul style="list-style-type: none"> • Mild sedative and hypnotic (calming) effect, motor relaxant effects, decreases the symptoms of anxiety • Gastroprotective properties • High free radical scavanging properties 	[13, 18–21]	
Neroli	<i>Citrus aurantium</i> L.	Linalool (29%), linalyl acetate (20%), β -pinene (3%), limonene (5%), nerolidol (9%), E-farnesol (5.14%)	<ul style="list-style-type: none"> • Decreases the symptoms of anxiety, improves mood, and creates a sense of well-being by regulating serotonin receptors • Anti-inflammatory activity against acute and chronic inflammation • Central and peripheral antinociceptive effects (due to high linalool content) • Decreases the abdominal constriction via inhibition of prostaglandin production 	[13, 21–23]	 β -Pinene
Orange Petitgrain	<i>Citrus aurantium</i> L.	Linalyl acetate (28.94–50.0%), linalool (36.10%), α -terpineol (6.80%)	<ul style="list-style-type: none"> • Free radical scavanging ability 	[13, 22, 24]	 Linalool

Essential oil		Main constituents	Health effects	Reference	Chemical structures of some key monoterpenes [13]
Common name	Latin name				
Mandarin	<i>Citrus reticulata</i> Blanco	Limonene (64–71%), β -myrcene (3.27–4.05%), decanal (2.33–7.71%), linalool (1.10–2.56%)	<ul style="list-style-type: none">Moderate radical scavenging activity	[13–15]	
Bergamot	<i>Citrus aurantium</i> subsp. <i>bergamia</i> (Risso & Poit.)	Limonene (25–53%), linalool (2–20%), linalyl acetate (15–40%), bergamottin (furanocoumarins)	<ul style="list-style-type: none">Good radical scavenging activity	[25–28]	
Lemon	<i>Citrus limon</i> (L.) Osbeck	D-Limonene and L-limonene (52.77%), β -pinene (10.80%), myrcene (10.16%)	<ul style="list-style-type: none">Significant antioxidant effect (preventing lipoperoxidation especially at a high dose)	[9, 11, 16, 29]	 <p>Linalyl acetate</p>
Key Lime	<i>Citrus aurantifolia</i>	Limonene (52.2%), γ -terpinene (17.0%), α -pinene (3.2%), and β -pinene (13.0%)	<ul style="list-style-type: none">Relieve common cold, flu, asthma, arthritisHigh radical scavenging activityAnti-inflammatory effects via reduced cell migration, cytokine production, and protein extravasation	[13, 30–32]	

Essential oil		Main constituents	Health effects	Reference	Chemical structures of some key monoterpenes [13]
Common name	Latin name				
Sweet lime	<i>Citrus limetta</i>	Limonene (85–95%), camphene (1.78%), p-cymene (0.38%), geraniol (0.36%), α-terpinene (0.33%), α-terpineol (0.31%), neral (0.29%), β-bisabolene (0.12%)	<ul style="list-style-type: none"> Strong antioxidant, antibacterial, and antifungal activity 	[33]	 γ-Terpinene
Grapefruit	<i>Citrus paradisi</i> Macfady	Limonene (50.8–86.27%), β-myrcene (3.51–6.20%), α-terpinene (2.11%), linalool oxide (2.29–6.52%), nootkatone (8.47–25.4%)	<ul style="list-style-type: none"> Moderate antioxidant activity in linoleic acid system 	[14–16, 34]	 α-Terpineol
Yuzu or Yuja	<i>Citrus junos</i> Sieb. ex Tanaka	Limonene (63.1–68.1%), γ-terpinene (11.4–12.5%), β-phellandrene (4.6–5.4%), myrcene (3.0–3.2%), and α-pinene (2.3–2.7%)	<ul style="list-style-type: none"> Anti-inflammatory properties (ability to inhibit the production of cytokines and ROS and reduces eosinophil migration) Decreases total mood disturbance and tension-anxiety 	[13, 35]	

Essential oil		Main constituents	Health effects	Reference	Chemical structures of some key monoterpenes [13]
Common name	Latin name				
Palestinian or Indian sweet lime	<i>Citrus limettoides</i> Tanaka	D-Limonene (89.089%), β -myrcene (2.933%), (\pm)-linalool (2.927%), α -pinene (0.865%), (E)-citral (0.749%)	<ul style="list-style-type: none">• Antibacterial and antifungal activity• For acne control, for the treatment of various infectious diseases (e.g., typhoid fever), food poisoning, inflammation, sepsis, endocarditis, bladder, prostate, and epididymal infections	[36]	

Table 1.
Composition of selected essential Citrus oils and observed health effects.

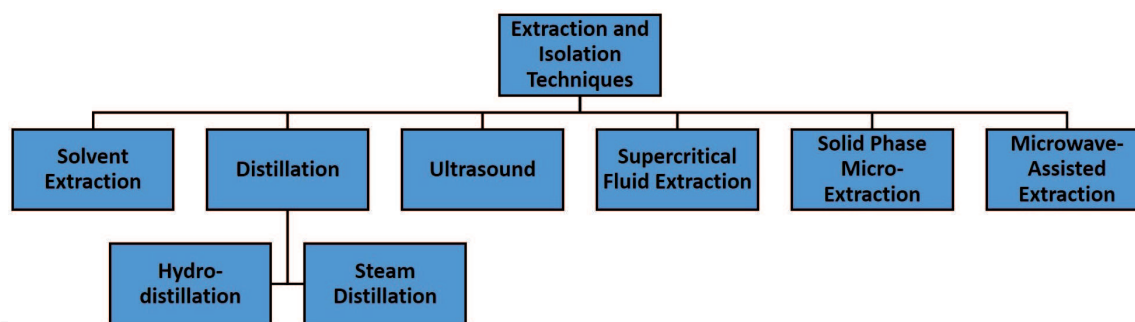


Figure 1.
 Common extraction techniques used for the preparation of essential oils and their bioactives.

Supercritical extraction (SFE) of the compounds responsible for the mitigating pain contained in herbs is another favorable technique that can be used for industrial-scale yielding of the responsible bioactives [42, 43]. Microwave-assisted extraction (MAE) is another method that is typically used for the extraction of bioactives for pain medication [44]. This technique offers a rapid delivery of energy to a total volume of solvent and solid herb matrix with subsequent heating of the solvent and solid matrix, efficiently and homogeneously [40]. Accelerated solvent extraction (ASE) is a solid-liquid extraction process performed to isolate bioactives for pain medication at elevated temperatures, usually between 50 and 200°C and at pressures between 10 and 15 MPa [40]. Solvent-free microwave extraction (SFME) is considered as a green method for the extraction of essential oils from herbs for pain medication. The methodology is a combination of microwave heating and dry distillation performed at atmospheric pressure without any added solvent or water [45].

4. Bioactive components in essential oils

One of the most biologically active and best studied herbal compounds are monoterpenoids, which consist of two isoprene units, but contain a wide variety of structures. They are volatile oils with highly distinctive aromas and flavors. More than 90% of the essential oils of medicinal plants consist of monoterpenoids [46]. Most studies analyzing analgesic potential of essential oils were tested on animal models [47].

Out of all terpenoid compounds, limonene and carvone have shown to be effective in several tumors (stomach, pulmonary, and mammary) [48]. D-limonene and/or its metabolites have been found in serum, liver, lung, kidney, and other tissues such as adipose tissue and mammary glands, which may explain its positive effect on mammary gland carcinoma [49]. D-limonene is also an excellent solvent of cholesterol; so, it is used clinically to dissolve cholesterol-containing gallstones [49]. Because of its gastric acid neutralizing effect and its support of normal gastrointestinal motility, it has also been used for relief of heartburn [49].

5. Essential oils monoterpenes

5.1 Limonene

Limonene is a colorless liquid hydrocarbon classified as a monocyclic terpene [30], one of the main constituents found in essential oils extracted from citrus peels [50]. Out of the two isomers, D- and L-limonene, D-isomer is more common and possesses a strong orange odor [30, 50, 51], which is the reason for its wide application as a flavor and fragrance additive [49]. Health benefits of limonene include

antioxidant, anti-inflammatory, vasorelaxant, anticarcinogenic, chemopreventive, and chemotherapeutic potentials [13, 52–54].

The analgesic effect is helpful in relieving headaches and stomach ache, relaxing the muscles, and preventing muscle stiffness. It also helps to overcome fatigue and it plays a vital role in relaxing and stabilizing the nervous system and, therefore, is used as a sedative [50, 52].

Yoon et al. [55] carried out a study to verify the pharmacological and biological effects of limonene on the production of pro-inflammatory cytokines and inflammatory mediators in RAW 264.7 macrophages and concluded that limonene effectively inhibited lipopolysaccharide-induced nitric oxide (NO) and prostaglandin E₂ production that included dose-dependent decreases in the expression of inducible nitric synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins. The same study also showed inhibition of macrophage-cytokine production [55]. A beneficial antioxidant effect via increased iNOS and COX-2 protein expression was found in ulcerative colitis rat models [53]. Moreover, systemic application of limonene reduced nociceptive behaviors via H₂O₂-induced TRPA1 activation, and this effect is related to the inflammatory pain [51]. Myrcene and limonene inhibit IL-1 β -induced responses found in osteoarthritis [56].

In conclusion, D-Limonene presented significant antinociception in different models of nociception without opioid receptor stimulation [57]. Instead, it is more likely related to the appreciable anti-inflammatory activity of this compound [58].

5.2 Myrcene

Myrcene or β -myrcene is a monoterpene polyunsaturated acyclic found in nature, originally isolated from lemon grass oil (*Cymbopogon citratus*) [58]. Besides its effect on both central and peripheral sites through endogenous opioids and α 2-adrenoreceptors, it was also shown to inhibit lipopolysaccharide [LPS]-induced inflammation including cell migration and production of NO, along with significant inhibition of c-interferon and IL-4 production [58, 59].

5.3 α -Terpineol

α -Terpineol is a volatile monoterpene alcohol, relatively nontoxic, and one of the major components of the essential oils of various plant species, being a nonirritant at 1–15%, and non-phototoxic [13]. There are three isomers, α -, β -, and γ -terpene, with the latter two differing only by the location of the double bond [51]. It is the third most representative monoterpene in citrus species [60]. It has insecticidal, antimicrobial, antispasmodic, anticonvulsant [47], antinociceptive, and immunostimulant properties, and it increases the skin's permeability to soluble compounds [60].

Studies have found that α -terpineol possesses peripheral and central analgesic properties [7]. A research conducted on mice, using carrageenan and TNF- α induced hypernociception, showed increase of the mechanical threshold of hypernociceptive behavior by α -terpineol, probably by the inhibition of inflammatory mediators (inhibiting the release of substance P and other inflammatory molecules such as serotonin, histamine, bradykinin, and prostaglandins) [60]. α -Terpineol showed an antioxidant activity as it was able to suppress the superoxide production by agonist-stimulated monocytes [7]. Moreover, α -terpineol showed higher COX-2 activity inhibition than aspirin, the most popular NSAID, and most potently inhibited the expression of pro-inflammatory cytokines and NF- κ B activation [7, 61]. α -Terpineol also showed antinociceptive effect in the capsaicin (neurogenic origin), glutamate, and formalin-induced orofacial nociception tests [51, 62, 63].

Anti-inflammatory effects that α -terpineol from orange juice demonstrated *in vitro* (suppressed IL-6 and increased IL-10) were further analyzed by *ex vivo* experiments, and results have shown anti-inflammatory action in macrophages after incubation of human blood with α -terpineol [61]. Described effects were attributed to α -terpineol, while linalool and limonene had no significant action [61]. On the other hand, a research conducted on morphine-tolerant mice showed inhibitory effect of α -terpineol in low dosages on the induction of dependence on morphine and attenuated the signs of withdrawal syndrome without antinociceptive effect [46].

5.4 Linalool

Linalool is an acyclic oxygenated monoterpene reported to be the major volatile component of the essential oils of several aromatic species, including the Rutaceae family, with sedative, antidepressant, anticancer, antifungal, and pesticidal properties [13]. It is the most studied monoterpene in various painful conditions [58]. A research on adult female Swiss mice treated with a single intraperitoneal injection of (-)-linalool (50 or 200 mg/kg) or multiple treatments given chronically (twice daily for 10 days; 50 mg/kg, i.p.) showed that (-)-linalool significantly reduced CFA-induced mechanical hypersensitivity (complete Freund's adjuvant) and produced effective reduction in CFA-induced paw edema following the acute treatment [61, 64]. Following intraperitoneal administration in mice, linalool was found to produce antinociceptive and antihyperalgesic effects in different animal models in addition to its anti-inflammatory properties [65]. (-)-Linalool acts as analgesic on several receptors, including opioids, adenosine A1 and A2, cholinergic M2, and produces changes in K⁺ channels, thus exerting analgesic-like activity [58, 66].

Some recent studies demonstrate that (-)-linalool inhibits transient receptor potential A1 (TRPA1) and N-Methyl-D-aspartate (NMDA) channels and decreases the nociception induced by cinnamaldehyde or capsaicin [58, 67].

It is neither toxic nor irritable to skin and presents an extremely low risk of skin sensitization [13]. However, due to poor oral availability, despite the biological properties of (-)-linalool, its use in the treatment of painful and inflammatory disorders is still limited [51]. Nascimento et al. [68] used pure 95% linalool, complexed and noncomplexed in β -cyclodextrin (used to increase aqueous solubility and bioavailability of monoterpenes), in an animal model of fibromyalgia. They found that both formulations had an anti-hyperalgesic effect, with the complexed form being more effective and producing a longer lasting effect (for 24 h after administration) [68]. Analgesic effect of linalool on acute central nociception (hot plate), visceral (acetic acid), and chronic pain models of neuropathic origin, and the opioid and glutamatergic systems are probably involved in this action [51, 62, 67, 69]. One preclinical trial showed that linalool from rosewood was able to reduce the action potential amplitude assessed using an isolated nerve in the single sucrose gap technique, showing it blocked neuronal excitability [70].

5.5 Pinene

α -Pinene is an organic compound of the terpene class, one of two isomers of pinene, the other being β [30]. The effects of *Ugni myricoides* (Kunth) O. Berg essential oil and its major constituent, α -pinene [52.1%], were analyzed in inflammatory and neuropathic models of hypernociception in mice, and the results showed that the oil significantly prevented mechanical hypernociception induced by carrageenan or complete Freund's adjuvant (CFA), and those effects were attributed to α -pinene, which clearly has a potential role for the management of

inflammatory and neuropathic pain [61]. Furthermore, the effect on inflammatory processes were observed in studies performed *in vivo*, in which repeated treatments with α -pinene [5–50 mg/kg, p. o.] were able to abolish the mechanical sensitization induced by CFA or by the partial ligation of the sciatic nerve [58]. In addition, it has been shown that α -pinene has anti-inflammatory and anti-catabolic activities in human chondrocytes [56].

β -Pinene is present in high amounts [5.1–13.1%] in lime citrus oil [32]. In animal models, β -pinene showed to be effective only on acute central nociception, yet, it was able to reverse the antinociceptive effect of morphine in tests equivalent to the effect of naloxone [58].

5.6 p-cymene

Biological precursor of carvacrol, p-cymene occurs in oranges and tangerines [51, 71]. Different behavioral tests of nociception in animal models showed that it exerted both peripheral and central antinociceptive action [51]. A study investigated the antinociceptive potential of p-cymene in mice models of orofacial nociception induced by formalin, capsaicin, and glutamate, and results showed that the treatment with p-cymene at all doses reduced the nociceptive behavior in all nociception tests, suggesting an action in both neurogenic and inflammatory pain [71]. Moreover, tests conducted on Swiss mice showed decreased mechanical hypernociception, reduced leukocyte and neutrophils migration, and reduced TNF- α level [51]. Like other previously mentioned terpenic compounds, p-cymene has a relatively short pharmacological half-life and bioavailability; so, complexation with β -cyclodextrin has shown to improve its analgesic and anti-inflammatory effects through improved bioavailability [72].

5.7 Nerol

This acyclic monoterpene alcohol is found in many essential oils, *Citrus aurantium* among them [51]. In the oxazolone-induced colitis model, González-Ramírez et al. [73], observed antinociceptive effect of nerol [30 mg/kg], which led to a significant reduction on expression of some pro-inflammatory cytokines, like IL-13 and TNF- α , which are highly characteristic for gastrointestinal tract disorders [51].

6. Analgesic potential of some essential oils

All essential oils with high D-limonene content pose significant free radical scavenging effect, predominantly disabling production of reactive oxygen species (ROS) [13]. Essential oils of sweet orange, lemon, and bergamot are most widely used to test analgesic effects in animal models. More recently, some essential oil blends were tested in various human cell models and showed significant positive effects on inflammation, immune modulation, cell cycle regulation, and other cellular functions [8].

7. Safety

Bioactive compounds found in essential oils are quickly absorbed after dermal, oral, or pulmonary administration, and are excreted by the kidneys in the form of phase-II conjugates [66]. Only a small fraction is eliminated unchanged by the lungs [66]. Generally speaking, Citrus essential oils are nontoxic, non-mutagenic,

and noncarcinogenic, meaning that sweet orange, bitter orange, neroli, petitgrain, lemon, lime (both distilled and expressed), bergamot, and grapefruit oils have GRAS status [74].

However, a mixture of two optic isomers of limonene present in the essential oils of citrus fruits was shown to be hepatotoxic, have a sedative muscular relaxing effect in mice and be nephrotoxic only in male rats, cause small-scale irritation in rabbits, and be carcinogenic and teratogenic [75].

The fast metabolism and short half-life of active compounds have led to the belief that there is a minimum risk of accumulation in body tissues [12]. In humans, ingestion of D-limonene resulted in an excretion of 52–83% of the dose in the urine within 48 hours [49]. However, limonene at 20 g caused diarrhea and transient proteinuria in healthy volunteers [75]. Vapor inhalation caused respiratory disorders coupled with a decrease in vital capacity [75]. No neurological disorders occurred, but chronic exposure can induce irritation and allergy; therefore, it must be mentioned in the list of “ingredients” of cosmetics [75]. It is not acutely toxic, nephrotoxic, or carcinogenic for humans, but the oxidized D-limonene may carry some toxicity, hence, citrus oils should be stored in dark at 4°C [13]. Nevertheless, unoxidized D-limonene is listed as an allergen by the EU, and moderately allergenic in Germany [13].

8. Conclusions

All phytochemicals present in essential oils presented here may simultaneously target multiple mechanisms involved in chronic pain. Despite long history of therapeutic applications of essential oils for the treatment of pain, only recently more attention was given to their components and elucidating mechanisms behind their antioxidant, anti-inflammatory, and antinociceptive potential. Monoterpenes are key holders of analgesic potential in Citrus essential oils, especially D-limonene and linalool. Essential oils are generally considered as safe; however, due to low bioavailability and stability, monoterpenes are complexed with β -cyclodextrin to improve their analgesic activity [62, 69]. Further studies are encouraged to determine the analgesic potential of Citrus essential oils in managing daily activities of people with a long-term history of chronic pain.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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