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Review article

A comprehensive review on clinically proven natural products in the management of nerve pain, with mechanistic insights

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ABSTRACT

Introduction: People are treating their neuropathic pain with several approved and licensed pharmacological drugs. But due to having existing limitations like low efficacy with some side effects, there needs to be a more effective alternative and complementary therapeutic options.
Purpose: s: The study was designed to discuss the mechanistic role of several clinically proven natural products that have been shown to play a significant role against different nerve pain or neuropathic pain.
Method: ology: Information for this review article was salvaged using several accessible searching databases like SciVerse Scopus ® (Elsevier Properties S. A, USA), Web of Science® (Thomson Reuters, USA), and PubMed® (U.S. National Library of Medicine, USA) considering some search items like - nerve pain, natural products in pain/nerve pain management, clinically proven natural products in pain management, pain-reducing agents and so on.
Result: Our study reported the therapeutic efficacy of natural products and their possible mechanism against neuropathic pain in the human body. Natural products widely used to treat neuropathic pain include comfrey root extract ointment, lavender oil, Rose Oil, aromatic essential oil, ginger oil, vitex agnus-castus, peganum oil, and ajwain 10%. Some common pathways are involved in pain relief through sensory stimulation, enzymatic, anti-inflammatory, and pain-related receptor regulation.
Conclusion: The present study suggests that the mentioned natural products can be an appropriate choice for the treatment and management of neuropathic pain.

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Abbreviations

NP	Neuropathic pain
LEO	Lavender essential oil
VAS	Visual Analogue Scale
TPPPS	Toddler Preschooler Postoperative Pain Scale
WOMAC	Western Ontario and McMaster Universities arthritis index
KOOS	Knee Injury and Osteoarthritis Outcome Score
NLC	Nanostructure lipid carrier
PGA	Patient Global Assessment
SODA	severity of the dyspepsia assessment
DOMS	Delayed-onset muscle soreness
SMGO	Swedish massage incorporated with ginger oil
TTM	Traditional Thai massage
ODQ	Oswestry Disability Questionnaire
RI	resistance index
PI	Pulsatility index
PMS	Premenstrual syndromes
SSRI	Selective serotonin reuptake inhibitor
PDSR	Penn daily symptom report
HAM-D	Hamilton depression rating scale
CGI-SI	Clinical global impression-severity of illness
MAO	Monoamine Oxidase

1. Introduction

Pain is an unpleasant sensory, emotional, and major health problem associated with quality of life, general and psychological health and social and economic wellbeing [1]. Nerve pain, also called neuropathic pain (NP), occurs when the somatosensory nervous system is damaged or dysfunctional [2]. This pain is different from other types of pain; NP causes abnormal sensation and increases response to painful stimuli that do not usually prove pain [3,4]. Around 7–8% of adults suffer from neuropathic pain [2]. Patients with nerve pain have to face numerous difficulties [5]. The management of nerve pain can be challenging due to its heterogeneous etiology and complex pathophysiology [6–8]. Although very few satisfactory pain relievers are prescribed and available in the local market, their existing limitation poses challenges for patients suffering from pain and discontinuing their therapies. Moreover, sometimes evaluation of pharmacotherapy in randomized clinical trials showed that clinically significant pain relief was experienced only by half of the patients, predominantly partial but not complete relief. However, the management of neuropathic pain depends on the types of pain and needs to consider the individual as a whole. Therefore, like other diseases, the medicinal plant can be an alternative and complementary treatment for nerve pain management, which will be novel and more effective therapy [9]. Medicinal plants and their isolated active components have significantly contributed to developing new therapeutic strategies against nerve pain through their secondary metabolites [10]. In this regard, essential oil may be a potent candidate for the management of nerve pain.

Essential oils are concentrated plant extracts, with highly complex compositions, and various functionalized chemical compounds that belong to different chemical classes [11]. Commercially and industrially significant essential oil crops are widely cultivated worldwide in various geographical regions [11]. Generally, essential oil is administered externally like topically, internally, inhalation or sometimes consumed orally [12]. A wide range of essential oil, including comfrey root extract ointment, lavender oil, rosa damascena (Rose) Oil, aromatic essential oil, vitex agnus-castus, peganum Oil, ajwain 10%. The use of essential oil for neuropathic benefit is not new and has become extremely popular due to its rare or mild side effects and availability to worldwide. The phytochemical screening of the essential oil revealed the presence of some secondary metabolites, including tannin, flavonoid, phenol, saponin, alkaloid, terpenoid, and steroid [13]. These phytoconstituents from essential oils work for many aspects of pain because they have multiple mechanisms to benefit our bodies. For instance, the essential oil may reduce the pro-inflammatory molecules like TNF-α, IL-1β, IL-6, NF-kB [14,15] and suppress enzymatic activities including cyclooxygenase (COX) 1 and 2 and lipooxygenase (LOX) pathways [14,15] leading to regulate prostaglandins (PG) E1, E2, F2α, and 6-keto PGF1α (PGI2) level [16]. Furthermore, the essential oil can decrease pain intensity by desensitizing peripheral and central TRPV1 receptors 16–19 and regulating neurotransmitters such as serotonin, endorphin and noradrenaline release in the brain [17].

So, phytochemicals and their derivatives found in essential oil are promising candidates for improving treatment efficacy and minimizing adverse reactions in patients suffering from nerve pain. The purpose of this review was to discuss all natural products clinically proven in the management of nerve pain.

2. Methodology

This review has been written based on a systematic search strategy and meta-analyses (PRISMA) guidelines [18]. SciVerse Scopus ®

(Elsevier Properties S. A, USA), Web of Science® (Thomson Reuters, USA), and PubMed® (U.S. National Library of Medicine, USA) are the general databases, we have used. Common searching keywords are nerve pain, natural products in pain/nerve pain management, clinically proven natural products in pain management, pain reducing agents and so on. A total of 271 non-duplicate articles have been identified in the initial phase and 181 relevant articles have been selected after initial screening. Finally, after 36 exclusions, only 145 more relevant articles have been selected. Non-English articles have been kept out of search. Only clinical and relevant scientific articles were considered as inclusion criteria for this study. The relevant articles' full manuscripts, including title, abstract and concluding remarks, have been thoroughly read to verify the expedience criterion.

3. Natural products widely used for nerve pain management

3.1. Comfrey root extracts

Comfrey root extracts (Symphyti radix) have been used as a medicinal plant for over 2000 years and are derived from *Symphytum officinale* L [18,19]. In the case of therapeutic properties, complete parts are used, but in particular, the root has a longstanding tradition. Comfrey root extract can mainly be used for topical nerve pain management, swelling in muscle, acute myalgia in the back, strain, contusion and distortion, epicondylitis, tendovaginitis, and periarthritis [19]. This wide range of therapeutics activities is due to containing numerous components, including allatonin (0.6–4.7%) [20], mucilage polysaccharides (29%) [21], phenolic ingredients like rosmarinic acids (0.2%), caffeic acid (0.004%), chlorogenic acid (0.012%) and others compound [22].

3.1.1. The mechanistic view in pain management

The main phytoconstituents of comfrey root extracts and molecular mechanisms have not been completely identified and remain elusive. But alcoholic extract of this root oil suppressed the pro-inflammatory scenario in primary human endothelial cells dose-dependent. The main point targeting pain is the NF-Ƙb. Alcoholic extract of this oil could suppress NF-κB pathways via signaling cascade, including regulation of IKK/IκBα complex activation and p65, transcription level leading to alter pro-inflammatory and suppress suppressed the further development of a pro-inflammatory scenario [23] [Fig. 1].

3.1.2. Clinical trial on pain management

A double-blind placebo-controlled trial with 60 patients with lower back pain is treated by Comfrey root extract at the dose of 3 times for five days. There were significant activities of comfrey root extract against lower back pain with a reduction of pain sensation ($p < 0.001$) [24]. Grube et al. conducted a randomized, bi-center, double-blind, placebo-controlled trial clinical study with 220 Osteoarthritis patients, and they found that comfrey root extract reduced pain, knee movement and life quality improved [25]. Comfrey root extract ointment is also active against uni-lateral ankle pain. Koll et al. performed a double-blinded placebo-controlled trial with 80 patients four times daily. They found that comfrey root extract ointment increases standardized pressure until pain reaction on the injured side versus healthy side as compared to baseline []. Furthermore, Predel et al. conducted a similar study with 82 patients four times daily for 7days and found a similar effect in uni-lateral ankle pain patients [26]. The same Comfrey root extract ointment was also evaluated in some clinical trials against osteoarthritis. Smith et al. investigated 43 patients suffering from osteoarthritis three times daily for six weeks and found that Comfrey root extract relieves pains, stiffness and improves physical functions

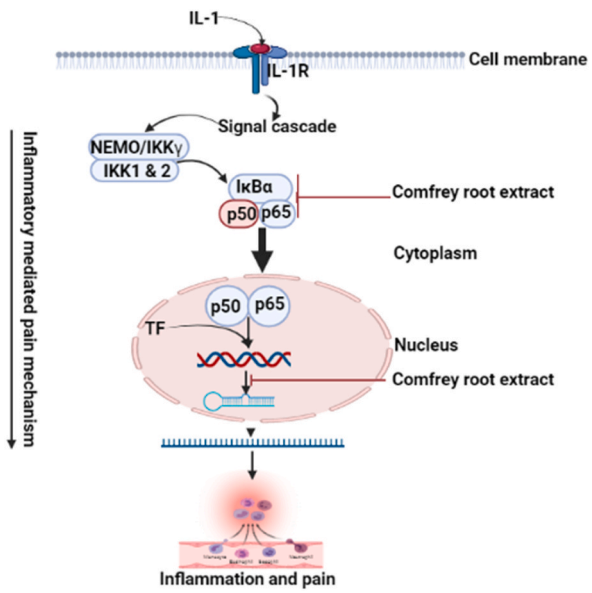

Fig. 1. Mechanistics insight of comfrey root extracts against nerve pain.

significantly [27]. Summary of anti-nerve pain of comfrey root extracts are summarised at Fig. 1.

3.2. Lavender oil

Lavender essential oil (LEO) is famous as a complementary medicine derived from the Lavender (Lavandula spp) [28]. Lavender comes in over 400 different varieties, each with its distinct aroma and features. Like all essential oils, it is not a pure substance; it is a complex mixture of phytochemicals. In all, more than 100 chemicals are found in lavender oil, albeit many of them are present in low concentrations. [29], but significant components are camphor, terpinene-4-ol, linalool, linalyl acetate, betaocimene, and 1,8-cineo [30]. Steam distillation is used to make pure lavender essential oil [31]. Lavender oil is used in massage therapy to help people relax by directly contacting their skin [32]. Although there is a few side effect of LEO [33], traditionally, this oil is used for numerous therapeutics and curative properties ranging from infectious diseases,e antibacterial [34], antifungal [35] to the non-infectious sedative, analgesic, and anticonvulsive [36], anti-depressive [37], neurological antioxidant and anti-inflammatory properties [38]. Moreover, according to emerging data, Lavender oil appears to be an effective and helpful medicinal treatment for acute, chronic, and intractable pain [39,40].

3.2.1. Lavender oil in nerve pain: in vivo study

Lavender essential oil acts as aromatherapy used in traditional medicine [36]. Maternal pains, fatigue, and mood are the major severe complications of the postpartum period. The treatment of this postpartum condition can be possible with lavender essential oil. In a randomized clinical trial conducted by F. Vaziri (2017), it has been shown that lavender oil aromatherapy in 56 women at the first hours of the postpartum period resulted in better physical and mood status compared to the nonaromatic group [41]. For the determination of the effect of lavender oil on pain in preterm infants during heel lancing. C. Usta designed A double-blind, randomized controlled clinical study with 61 premature infants and found that lavender scent effectively reduces pain control in premature infants [42]. However, lavender essential oil inhalation does not reduce pain in open-heart surgery patients [40]. The lavender essential oil reduces pain associated with dialysis needle insertion, proved by A. A. Ghods with 36 patients in A randomized clinical trial study [43]. They found that Lavender's topical application reduces moderate strengths of pain during the insertion of dialysis needles. Likewise, dialysis needles, Lavender essential oil also reduced pain in patients after coronary artery bypass surgery. Z. Seifi et al. summarised that inhaling lavender aroma oil in 60 patients could suppress the pain of bypass surgery patients [44]. To determine lavender oil efficacy on pain during vascular access among patients undergoing hemodialysis in a hospital-based trial with 60 patients, E. Taşan et al.

Table 1
Summary of nerve pain management by lavender oil.

Country of study	Object	Research unit	Result	*P value*	Tools used	Ref
Iran	Determining the effect of lavender on episiotomy wound healing and pain relief	56 women patients	Lavender was effective in episiotomy pain relief	$P < 0.001$	VAS score	[41]
Turkey	Determining the effect of lavender oil on pain in preterm infants during heel lancing	61 premature infants	lavender scent was effective in pain control in premature infants	$p > 0.05$	PIPP-R scores	[42]
Egypt	Determining the effect of lavender on episiotomy wound healing and pain relief	69 women patients	Lavender sitz bath twice daily was effective in episiotomy wound healing and pain relief	$P = 0.011$	REEDA scale VAS score	[136]
Iran	Determining effect on open-heart surgery	40 women patients	Lavender essential oil inhalation has no effect on reducing the pain of open-heart surgery	$P > 0.05$	Pain scores	[40]
Iran	Determination of the effect of lavender essential oil on pain during the insertion of dialysis needles	36 women patients	lavender decreases moderate intensities of pain during the insertion of dialysis needle	$p = 0.001$		[43]
NA	Investigating the effects of inhalation with lavender essential oil on pain severity of patients after coronary artery bypass surgery	60 women patients	Inhalational aromatherapy with lavender essential oil could relief pain of patients	$p = 0.001$	VAS score	[44]
Tukey	Evaluating the effect of lavender oil on pain during vascular access among patients undergoing hemodialysis.	60 women patients	Dcrease pain level during vascular access without negative effects.		VAS, pain score	[45]
Iran	Evaluating the effects on the pain resulting from the vaccination.	99 infants	lavender oil could reduce the pain and improve soothing in the infants with the pentavalent vaccine injection.		NIPS scores	[46]
Iran	Valuating the effect of lavender oil on pain and comfort in cardiac patients after injection of enoxaparin	50 heart patients	Decreased pain and increasing the level comfort	$P < 0.001$	VAS visual scale	[47]
	Pain perception during dental injection in children	24 children, 7–9 years	Effective on reducing pain perception during dental injection in children	$P < 0.001$	FRS	[48]
Iran	Investigating the effect of Lavender oil in labor pain	60 primiparous women	Lavender oil massage was helpful, providing pain relief and psychological support during labor		VAS	[49]
Turkey	Investigating the effect of Lavender oil on dysmenorrhea related pain	438 midwifery and nursing students.	Lavender oil massage was effective in reducing dysmenorrhea.	$P < 0.001$	VAS score	[50]

discovered that inhaling this aromatic oil reduced pain levels during vascular access without causing any side effects [45]. Pentavalent vaccine injection sometimes causes pain in infants. So, preventing such pain, F. Vaziri et al. tested lavender oil effects on the pain resulting from the vaccination with 42 infants and found that a low dose of this oil can suppress pain in infants with the pentavalent vaccine injection [46]. Enoxaparin used in cardiac patient's causes pain and discomfort to the injection site. The lavender essential oil can prevent this symptom. T. Badri et al. summarised that lavender oil has a significant effect on pain, decreasing and increasing the comfort level of patients taking enoxaparin, so it can be used to relieve pain and increase the comfort of patients taking enoxaparin [47]. Dental pain is a common problem from children to adults. So reducing dental anxiety with pain by lavender oil can be an alternative treatment instead of conventional treatment. A randomized clinical trial by F. Ghaderi and N with 24 children, aged 7–9, proved that in a dental context, lavender Aromatherapy had been shown to reduce dental anxiety and pain [48]. Midwives face a difficult task regarding labor pain, but Aromatherapy is a non-pharmacological technique for reducing labour pain. A. Zahra (2013) states that aromatherapy massage was effective in managing pain relief and psychological sustenance during labour [49]. Dysmenorrhea is a medical condition for painful menstrual periods which are caused by uterine contractions. The Aromatherapy of lavender oil by S. E. Apay et al. showed that massage effectively reduced dysmenorrhea. In addition, this study showed that the effect of aromatherapy massage on pain was higher than that of placebo massage [50]. Sometimes lavender essential oil has a combined effect on controlling pain. Y. B summarised that aromatic lavender oil with acupressure was an effective method for short-term low back pain relief [51]. Summary of nerve pain management by lavender oil are tabulated in Table 1. [Table: 01].

3.3. Rose oil

Damask rose (flower's king), bearing the scientific name *Rosa damascene,* is one of the Rosaceae family species cultivated worldwide, especially in Iran. They are mainly grown for being used in the perfume and food industry [52]. It is a decorative and valuable herb containing modern pharmacological characteristics of astringent, antioxidant, antimicrobial, analgesic, and anti-inflammatory [53]. Almost 18,000 cultivars and more than 200 species of rosa have been identified all over the world so far. Rose water and essential oil are ordinarily used for treating stomachache, fever, sore throat, chest pain, ophthalmic difficulties, menstrual bleeding, breast tenderness, constipation, and other digestive complications [54]. Various extracts and separated components from fruits, flowers, petals, and hips (seed-pot) of this plant have been investigated in several studies and have been proved to have anti-convulsive, anti-hypnotic, anti-diabetic, *anti*-HIV, and cardiovascular regulating activity [52–56]. This review assembles up-to-date and absolute information on *R. damascena* extract in alleviating various nerve pains with the possible mechanism of action.

3.3.1. Nerve pain management by rose oil

Several investigations were conducted on humans to evaluate the effectiveness of various extracts of *R. damascena* on several nerve pains. A double-blind cross-over clinical trial by Bani et al. was done to investigate the performance of fruit extract of R. damascene as capsules in treating primary dysmenorrhea, cyclic pain during menstruation [52]. 18–24 years old 90 students with pain intensity scores of 5–8 in the Visual Analogue Scale (VAS) were irregularly categorized and divided into two groups of 46 persons each. The participants were provided with two capsules of Mefenamic Acid and *Rosa damascene* fruit extract with identical physical characteristics in two repetitive cycles per 6 h for 3 days in a cross-over form. The data were collated through the questionnaire of demographic characteristics and checklist of VAS. A considerable difference had been found in each group in average pain intensity at different hours of measurement after cessation of the first and second cycle ($P < 0.001$), although average pain intensity was not statistically significant between first ($P = 0.35$) and second cycle ($P = 0.22$) in two groups. The study concluded that Rosa damascene fruit extract has a similar pain-lowering effect as that of synthetic drug Mefenamic acid. Rose oil extracted in carrier oil was utilized topically without a massage to manage low back pain during pregnancy and Hot- and Cold-type migraine headaches and analyzed for its pain reduction performance [55,56]. Before and after the intervention, pain intensity was measured using a visual analogue scale (VAS), the Roland-Morris Disability Questionnaires [56] and applying syndrome differentiation model [55], respectively. Results concluded that rose oil extracts caused a significant reduction in pain intensity in all cases, irrespective of different experimental conditions. Interestingly, the intensity of migraine headaches was found to be considerably lower in patients with "hot" migraine syndrome than "cold" types.

A randomized clinical trial by Hamdamian et al. on the inhalation effect of rose oil essence in reducing pain at three stages of cervical dilation (4–5, 6–7, and 8–10 cm) during the first stage of labor was carried out applying numerical pain rating scale, demographic and obstetric questionnaire [57] for analysis. Pain severity of the aromatherapy receiving group was found considerably lower as compared to the control group after treatment. Rose essential oil aromatherapy response on renal colic pain was studied by Ayan et al. where it was used as supplementary and additional therapy to conventional treatment [58]. Results indicated that the VAS values after 10 or 30 min of therapy were found to be statistically lower in the group where conventional treatment along with aromatherapy was administered. Bastani et al. conducted a non-randomized clinical trial to evaluate the efficacy of inhalation aromatherapy with *R. damascena* against the acute pain of older people after knee arthroplasty [59]. Eighty elderly patients were separated into control and experimental groups. Inhalation therapies with Damask Rose (three-four drops of rose essence with 5 cc normal saline) were performed after 24 h of surgery, and there were four sessions within 2 h with 30 min intervals. The Control group received the same treatment only with distilled water. Comparing the differences in VAS pain scores before and after the intervention, a lower score of experimental group was observed after the intervention than control group as well as before intervention ($P < 0.001$). In a similar study by Bikmoradi et al. damask rose inhalation therapy was investigated for its response towards pain management after dressing in 50 patients who had second- and third-degree burn injuries [60]. Five drops of 40% damask rose essence in distilled water and five drops of distilled water was given for inhalation by experimental and control group respectively. VAS scores at 30 min before

entering and at 15 and 30 min after leaving the dressing room were measured and compared to check the changes in pain severity. Results revealed significant pain reduction in the experimental group was observed before and after the therapeutic intervention ($P < 0.05$). Sadeghi et al. carried out a trial to check the effect of self-aromatherapy massage with rose oil on the abdomen in treating primary dysmenorrhea among 75 students [61]. Subjects were randomly categorized into three different groups: rose oil aromatherapy massage group ($n = 25$); an unscented almond oil massage group ($n = 25$), and a control group ($n = 25$) where massage was applied by the participants themselves on the first day of menstruation for two subsequent cycles. Self-report of the participants disclosed that, rose oil aromatherapy massage decreases the pain severity of primary dysmenorrhea more than only-massage therapy. Gharabaghi et al. utilized *Rosa damascene* hip extracts as capsules for postoperative pain in voluntary surgical delivery [62]. In this study, 87% women were randomly divided into two groups where group A patients were given rose hip extracts capsules, whereas group B was provided with a placebo. Capsules were given 15 min before anaesthesia to both groups (A and B), and the pain score was measured in the VAS scale at various intervals after surgery. Results revealed that the severity of pain in group A was better than group B at every measured time. The effect of *Rosa damascena* inhalation therapy on the postoperative pain intensity in 64 children of 3–6 years of age by Marofi et al. [63]. Participants were randomly divided into two groups in this double-blind placebo-controlled clinical trial. Patients were given inhalation aromatherapy with rose and almond oil in groups A and B. Inhalation aromatherapy was given on arrival, 3, 6, 9, and 12 h afterward. Both the groups were given common palliative treatments to alleviate pain. The postoperative pain in children was evaluated with the Toddler Preschooler Postoperative Pain Scale (TPPPS) after 30 min of treatment. Results concluded that, after each time of aromatherapy and at the end of treatment, the pain score was considerably lowered in the rose aromatherapy intervention group compared to the placebo group. All the reports had concluded that rose extract possesses pain-alleviating properties. Generally, the medicinal performances of *R. damascena* were assigned to numerous pharmacologically active substances such as flavonoids (e.g. kaempferol and quercetin), terpene, myrecene, carboxylic acids, and vitamin C. Among all these, nonadecane, beta-citronellol, henicosane, geraniol, and docosane were thought to relieve pain effectively. Topical application of rose oil on the skin, forehead, and temporal zones can ascertain quick transport due to the axonal arborization in the cutaneous layers and close target organ (i.e. brain) [64]. It is assumed that the neurological sensitization of the afferent pathway for olfaction and reduced action of the sympathetic nervous system, elevated activity of the parasympathetic nervous system, and liberation of endorphin by *Rosa damascene* essential oil can influence the central nervous system resulting in an improvement in pain threshold [55,56]. But, a report of a similar reaction with cutaneous absorption of rose oil without olfactory sensitization has illustrated that rose oil molecules can also enter the bloodstream through dermal absorption [65]. And inhalation aromatherapy involves the stimulation of neurotransmitters to transmit a signal to limbic and hypothalamus parts of the cerebrum via the olfactory bulb [17,57]. Also, 2-phenylethyl alcohol found in *R. damascena* has been observed to be an antinociceptor lowering pain intensity [57]. Therefore, it can be perceived that *R. damascena* is effective against pains originating in the uterus, such as dysmenorrhea, labour pain, and the central nervous system, such as migraine and pregnancy-related low back pain.

3.4. Blended oil

Intake of essential oils through dermal absorption or olfactory inhalation to assert healing or therapeutic effect is generally termed aromatherapy [66]. Highly concentrated oils, typically extracted from fruits, flowers, stalks, leaves, roots, or sometimes distilled from resins, are used to cure disease and improve physical and psychological health. These plant-derived oils are so powerful and thickened that they act on pressure areas and revive. They can be administered in a small quantity in several ways like inhalation, massage, or topical application onto the dermis and are seldom ingested [17]. Inspiration and the topical administration of these plant-derived oils for the ailment of the mental and physical statute are the basis of aromatherapy. Olfactory nerves from the nose to the brain are the action area for these essential oils. Single essential oil or sometimes blended with others reduces the intensity of various types of pains through aromatherapy in some investigations. Among them, topical application of rose oil without massage in low back pain [56], inhalation of lavender oil in postoperative pain of inguinal hernia [67], application of lavender, clary sage, and marjoram blend with massage in primary dysmenorrhea [68], topical application with abdominal massage of lavender, clary sage and rose blend in painful periods and dysmenorrhea [69], lavender, clary sage, ginger and geranium oil blend with effleurage massage for menstrual pain [70], have shown considerable reduction in pain intensity in the aromatherapy intervention groups in contrast to no intervention groups.

3.4.1. Reduction of nerve pain by blended oil

The usefulness of the three most popular essential oils' synergistic blend in treating painful menstruation and dysmenorrhea was investigated in a control trial study [69]. Subjects were classified as an experimental group receiving aromatherapy (group 1), a placebo group (group 2) and a control group (group 3). The experimental group was given massage on the surface of the abdomen using an oil blend of lavender (*Lavandula officinalis*), clary sage (*Salvia sclarea*), and rose (*Rosa centifolia*) at 2:1:1 ratio in almond oil, while the placebo group was given almond oil massage alongside the control group having no such treatment. Assessment of pain intensity and severity using a visual analogue scale (VAS) and a verbal multidimensional scoring system respectively showed significantly lowered scores in the aromatherapy group compared to the other two groups. Menstrual pains plummeted from 7.40 to 4.26 on receiving aromatherapy on the first day of the cycle in the experimental group indicating that aromatherapy can impart pain relief at the starting days of menstruation. Results concluded that topically applied synergistic blends of lavender, clary sage, and rose with massage effectively alleviate the pain of menstrual cramps. The report suggested that lavender's analgesic, sedative, and anticonvulsant behaviour; anticonvulsant, menstruation regulating and estrogen activity supporting nature of clary sage; and uterine problem-solving property of rose may bring the combined actions into effect to reduce menstrual cramps of dysmenorrhea. A similar study by Ou *et al.* marjoram (*Origanum majorana*) was used instead of rose with lavender and clary sage oil blend and investigated

against pain in primary dysmenorrhea [68]. Lavender (*Lavandula officinalis*), clary sage (*Salvia sclarea*) and marjoram (*Origanum majorana*) in a 2:1:1 ratio was mixed to jojoba cream at 3% concentration and applied daily with massage in the lower abdomen of the experimental group. The duration of pain was considerably low after aromatherapy intervention was observed in both the numeric and verbal rating scales. Gas chromatography-mass spectrometry (GC-MS) analysis illustrated that the blended essential oils contain four prominent analgesic elements that amount to around 79.29%, constituting linalyl acetate, linalool eucalyptol and b-caryophyllene, which may act together to give pain reduction action. The secretion of prostaglandins (PGs) gets effectively restricted by Linalool that causing uterine muscle contraction in PD. Because when the release of PGs is high, there is higher myometrial contraction, uterine ischemia, and cramping followed by pelvic pain. A terpene oxide generated from marjoram oil, Eucalyptol (1.8-cineole), can inhibit the metabolism of arachidonic acid, which helps to release PGs with inflammatory effects tested on human blood monocytes. Several researchers have also studied some other synergistic essential oil blends. A study on the effectiveness of an oil blend consisting of lavender, clary sage, ginger, geranium with a ratio of 1: 1: 1: 1 mixed with almond oil for menstrual pain reduction through massage effleurage concluded that a significant fall in the pain intensity was observed in the group given four essential oils blend aromatherapy than the group treated with one essential oil [70]. Massage effleurage is dermal stimulation in the form of gentle flowing strokes. Through massage effleurage by aromatherapy oils, hypoxia that happens in the tissue will be suppressed because the oxygen content in the tissue rises so that the pain experienced is lessened. In addition, it can also increase blood circulation, minimize stress and relax stiff muscles. After being given a massage, there will be endorphin secretion, increasing the pain threshold to reduce the pain. A review analysis included studies conducted by Hur and Park, where an aromatherapy massage with blended oils of rosa damascena, clary sage, geranium, and jasmine [71] was administered on the experimental group while clary sage was used along with citrus aurantium, frankincense and lavender to treat pain and anxiety during the active phase of labor in the study by Kyoung and Haeng [71]. Although a decrease in pain intensity had been found by analyzing responses from experimental groups in both studies, the anxiety level was not significantly different between the intervention and non-intervention groups. To sum up, aromatherapy, either using a single essential oil or blending some oils applied with acupressure, taper, compress, footbath, massage or inhalation, can give pain reduction performances irrespective of pain types, experimental conditions, and essential oils oil types. The activation characteristics of such oils rest in their chemical structure identical with real hormones [17]. One of the key characteristics of this therapy is the penetration ability of these oils to reach hypodermic tissues. The possible method of their action lies in assimilating these oils into a biological message by the receptor cells when inhaled. The message in the form of a signal is transmitted to limbic and hypothalamus parts of the cerebrum through the olfactory bulb. These messages may stimulate the brain to liberate neurotransmitters like serotonin, endorphin etc. to link our neural tissues to other bodily systems, confirming expected changes and giving relaxation. To give desired action on health, serotonin, endorphin and noradrenalin are liberated from soothing oil, aromatic and stimulating oil respectively [17]. But any studies have not confirmed whether the pain reduction activity is achieved by the massage or by the essential oils themselves as the effectiveness of the essential oils blends without massage has not been studied separately. A probable reason can be contentment with pain management has rare connection to pain alleviation rather depends on sharing, staff behaviour, and empathy [72]. This requirement is satisfied by applying aromatherapy to some extent. The connection and recognition associated with aromatherapy intervention can be fruitful for one. By secreting endorphins in the plasma, increasing parasympathetic stimulation and raising release of the neuro messenger serotonin to impart antinociception, massage can decrease stress induced hormone release. Massage may provide worthwhile effects on managing pain [68] when standard pain control procedure is associated with aromatherapy. It is cost-effective and has lesser adverse events than conventional pain control drugs. [Flow chart: 01].

3.5. Ginger oil

This review analysis summarizes the reported clinical trial interventions that evaluated the therapeutic effect of one of the most widely used medicinal plants, ginger, on several pain management and its possible mechanism of action. Ginger (*Zingiber officinales*) which belongs to the family of Zingiberaceae, is a perennial climbing plant indigenous to southeastern Asia [73]. In Ayurvedic and Chinese medicine, it had been applied as an anti-inflammatory and anti-rheumatic for musculoskeletal troubles for more than 2500 years [74]. More than 400 pharmacological and active constituents are separated and identified from ginger rhizomes extracts [73]. Gingerols, shogaols, zingerones, gingerdiols, gingerdione, and paradols play a prominent function in several pharmacological activities. Many clinical interventions have been conducted so far using various preparations of ginger either alone or blended with some other plant extracts to give a synergistic effect on pain relief.

3.5.1. Ginger oil to ease different types of pain

I. Osteoarthritis (OA) pain

Total 13 clinical trials have been conducted so far on humans to check the effectiveness of ginger in treating moderate-to-severe pain of osteoarthritis among aged citizens. Fifty-nine older persons from a senior citizens center of Hong Kong were randomized into an experimental group receiving aromatherapy, a placebo group and a control group, respectively, in a trial conducted by Yip and Tam [74]. A session of aroma massage on both lower limbs of participants of the experimental and placebo groups was given six times within 2–3 weeks. 30–35 min massages with ginger essential oil (1% ginger and 0.5% orange oil in olive oil) and olive oil were given to the intervention group, and placebo group, respectively, along with conventional treatment, and the control group encountered no massage but conventional treatment throughout the study. Knee pain severity, stiffness level, and bodily movement was investigated by Western Ontario and McMaster Universities arthritis index (WOMAC) and VAS, and quality of life by the Short Form 36 item general

health questionnaire (SF-36), respectively. Results exhibited that the betterment of bodily movement and pain was higher in the intervention group than the other two groups at the beginning but not retained till the end. Also, there were no considerable differences between the baseline and the end of evaluation in seven dimensions for all groups in the ultimate quality of living. The participants have reported no adverse effects during the study period.

In a randomized clinical trial to evaluate the effects of ginger extract on knee osteoarthritis patient's difficulties and pain by Zakeri et al., out of 204 enrolled patients, 103 patients received ginger extract while the rest received placebo [75]. Ginger was administered as zintoma capsules containing 250 mg of powdered ginger (*Zingiber officinale*), and the placebo capsules contained starch. After six weeks of intervention, a positive response was characterized by a reduction in pain of >15 mm on VAS or a 20% reduction in WOMAC index score. Results disclosed that the pain reduction score of VAS and WOMAC was higher in ginger than in the placebo group. Also, drop-in morning difficulties were more excellent in the ginger than placebo. Ginger extract was compared to placebo and Ibuprofen in patients with hip or knee osteoarthritis in a controlled, double-blind, cross-over 3-week study by Bliddal et al. where 56 patients were eventually categorized into three different treatment groups given either 170 mg EV. ext-33 ginger extract, 400 mg ibuprofen or placebo [76]. From the result, the efficacy was found as Ibuprofen > ginger extract > placebo for pain score (Friedman test: 24.65, $P < 0.00001$) with no adverse effects. No significant difference has been observed between the placebo and ginger extract groups (Siegel-Castellan test). Paramdeep G. carried out a study incorporating 60 OA patients into three groups where the group I was given 50 mg Diclofenac tablet and placebo; group II received 750 mg ginger with Placebo capsule, and group III received ginger 750 mg capsule alongside diclofenac 50 mg tablet [77]. All groups showed significant betterment in WOMAC and VAS score in pain relief after the intervention period, although the highest relief was imparted by a combination of ginger and Diclofenac in group III. But in a controlled trial on knee OA patients using 1 g powdered ginger as a capsule per day instead of placebo conducted by Niempoog et al. showed no improvement in pain relief even after eight weeks of intervention [78]. Thirty participants enrolled in each group. Knee Injury and Osteoarthritis Outcome Score (KOOS) characterized the drug's efficacy. Altman and Marcussen conducted 6 weeks on 247 knee OA patients to check the efficiency of a standardized preparation of 2 ginger species *Zingiber officinale* and *Alpinia galangal* (EV. EXT 77) [79]. The WOMAC and VAS score analysis showed statistically superior pain relief in the intervention group than the control group (63% against 50%), although patients receiving ginger extract reported more gastrointestinal (GI) side effects. A pilot study by Rondanelli et al. focused on treating chronic pain of 15 knee OA patients using *Zingiber officinale* and *Echinacea angustifolia* root extract supplementation for 30 days [80]. After 30 days of supplementation, a significant improvement was observed for Tegner Lysholm scale score ($p < 0.05$), SF-36 ($p < 0.05$) and a drop in knee circumference. In a double-blind and controlled clinical trial study by Zahmatkash et al. on 92 knee osteoarthritis patients, an ointment containing ginger, cinnamon, mastic, and sesame oil combination was administered topically 2 times a day for six weeks in the experimental group while the control group was given Salicylate ointment [81]. The intensity of pain and movement restrictions were analyzed through VAS. No statistical difference was observed between the two groups in the case of pain intensity and bodily motion, but in repeated measurements, in the following weeks, such indexes showed significant downward trends. Ginger (*Zingiber officinale*) and plai (*Zingiber cassumunar*) blended gel to relieve knee OA pain against 1% diclofenac gel was investigated in a study by Niempoog et al. [82]. 100 patients were randomly categorized into plygersic gel group and the Diclofenac gel group. The plygersic group received 1 g m ointment solution quarterly a day for two months, whereas the diclofenac group received the same treatment with 1% Diclofenac sodium gel. The KOOS score revealed that both the gel asserted improvement in all assessments after cessation of six weeks of active medications. A similar study by Amorndoljai et al. focused on comparing the performance of ginger (*Zingiber officinale* Roscoe) extracts in nanostructure lipid carrier (NLC) for managing knee OA pain against 1% diclofenac gel [83]. The two types treated 120 OA patients with an age range of 50–75 years of gel for 12 weeks, and the performance was monitored every four weeks using the WOMAC and the Patient Global Assessment (PGA). Results revealed that both the treatment options were able to impart pain relief and easier body function after the treatment period and no considerable differences in the result between these two groups were observed. Ginger extract (Zintona EC) performance at treating symptomatic gonarthritis was investigated for six months' period by researcher Wigler et al. [84]. Twenty patients completed the whole treatment protocol. 250 mg of *Zingiberis Rhizoma* in the form of a capsule was given to the experimental group while the similar-looking same number of capsules were given to the placebo group per day. After 24 weeks of active medication, the VAS score of pain showed statistically significant improvement in both groups. The aim of research by Drozdov et al. was to investigate the change in pain intensity and gastropathy conditions of OA patients receiving ginger or diclofenac for treatment [16]. 43 knee and hip OA patients were investigated for four weeks where 21 patients (17 women, 4 men) received 340 mg EV. EXT 35 *Zingiber officinale* extract, while 22 patients (18 women, 4 men) took Diclofenac 100 mg tablet daily. Arthritic pain was evaluated using VAS on standing and moving. The severity of the dyspepsia assessment (SODA) form was utilized for GI pain and dyspepsia assessment. Esophagogastroduodenoscopy (EGDS) before and after the active medications was also carried out alongside serum gastrin-17 levels and stomach mucosa prostaglandins (PGs) E1, E2, F2α, and 6-keto PGF1α (PGI2) evaluation. Though the VAS pain score of both groups on both conditions (standing and moving) was found to be lowered, the ginger group gave lessened SODA score for GI pain only with no reduction in dyspepsia, while EGDS showed potentially soared levels of PGE1, PGE2, and PGF2α in the mucous membrane layer of the stomach. The increase in PGs levels of the mucous membrane of the stomach is connected to a rise in serum gastrin-17. In contrast, higher SODA pain and dyspepsia values with a considerable drop in stomach mucosa prostaglandins and degeneration of mucous membrane of the stomach was observed in the diclofenac group. Two other clinical trials had been carried out on knee or hip OA patients utilizing ginger extract not to measure pain relief efficacy but to evaluate ginger extract performance on pro-inflammatory cytokine concentrations [14] and nitric oxide and *C*-reactive protein [15] respectively [14,15]. These studies focused on determining the mechanism of action of active anti-inflammatory compounds of ginger that give pain relief effects in OA. They were conducted by the same researchers' team of Khosravi and Naderi et al., where 120 participants were divided into either ginger group (GG) or placebo group (PG). In both investigations, participants in the experimental group received 500 mg ginger capsules, while the placebo group received 500 mg

starch capsules. Serum levels of tumor necrosis factor-α (TNF-α) and interleukin- 1β (IL-1β) [14] and nitric oxide (NO) and hs-C reactive protein (hs-CRP) using enzyme-linked immunosorbent assay kits [15] were evaluated at baseline and after three months of the experiment from collected serum samples. Although, at baseline, pro-inflammatory markers (cytokine, NO and hs-CRP) concentrations did not differ between the two groups, after the active medication period, both cytokines and NO and hs-CRP concentration decreased more significantly in the GG as compared to PG. The results concluded that ginger supplementation might significantly benefit knee osteoarthritis [14,15].

II. Menstrual pain/Dysmenorrhoea

A placebo-controlled clinical trial was carried out by Kim et al. on 63 female nurses to check the efficacy of five essential oil blends to manage pain and anxiety during menstruation [85]. 26 participants belonging to the experimental group performed self-abdomen massage with blended oil, and other two groups were placebo (N = 18) and control or no treatment group (N = 19). Results were evaluated using the VAS score. The experimental group gave themselves self-abdomen massage for 10 min with an oil blend of ginger (*Zingiber officinale*), rose absolute (*Rosa centifolia*), rose otto (*Rosa damascena*), clary sage (*Salvia sclarea*), and rose geranium (*Pelargonium graveolens*) in a 1:0.5:0.1:1:1 ratio that was diluted in almond oil, jojoba oil, and evening primrose oil in an 8:1:1 ratio maintaining a final concentration of 3% of essential oil. Self-abdomen massage with almond oil was the intervention for the placebo group. After 24 h, menstrual pain relief was higher in the essential oil group compared to the other two groups.

The efficacy of ginger root extract in alleviating pain severity in primary dysmenorrhea patients was investigated by Jehnabi E [86]. First 3 days of the first menstruation cycle, 70 female students were given three capsules of either placebo or 500 mg ginger root extract every day. After one menstruation, a five-factor Likert scale (worst; worse; same; better; lot better) was utilized to evaluate reaction to treatment. The Ginger group showed a significant reduction in VAS score after the intervention period compared to the placebo group. Another similar study by Rahnama et al. utilizing *Zingiber officinale* R. rhizome extract for treating the pain of primary dysmenorrhea in 120 students investigated ginger root powder effect using two different research protocols [87]. Both investigations were done on the same participants (ginger and placebo group) with one-month intervals. Three times per day, both groups received 500 mg capsules of either ginger root powder or placebo in both procedures. In the first experiment, ginger and placebo were administered two days before the menstrual period until the first three days. Medication was given on the first 3 days of menstruation in the second one. A verbal multidimensional scoring system and VAS was used to analyze the pain severity result. Results revealed that for both protocols (protocol one $P = 0.015$, and protocol two $P = 0.029$), pain relief was better in the experimental group against placebo. Ozgoli et al. tried to compare the pain-relieving performances among ginger, mefenamic acid, and ibuprofen in a comparative study including 150 students suffering from primary dysmenorrhea [88]. Participants were categorized into three equal groups and received 250 mg ginger rhizome powder, 250 mg mefenamic acid or 400 mg ibuprofen capsules a quarter times a day during first 3 days of menstruation, respectively. In all groups, menstrual pain severity was down just after one cycle.

To sum up, ginger was as effective as two other synthetic drugs to treat dysmenorrheal pain. On the other hand, Kashefi et al. recruited 150 high school students and divided them into three groups to compare ginger and zinc sulfate performance [89]. Ginger, zinc sulfate, and placebo capsules were given to three groups from one day before the starting of menstruation till the first three days of the cycle. The intensity of pain was evaluated every 24 h by VAS. The pain intensity was considerably different throughout the active medication period in both the intervention groups ($p < 0.001$). Also, both intervention groups showed higher pain relief than the placebo group ($p < 0.05$). Shirvani et al. conducted a randomized trial to compare the efficacy of ginger against stretching exercises in treating primary dysmenorrhea [90]. Sixty-one students with menstrual pain and without having regular exercise were enrolled in each of two groups and were evaluated. From the first day of menstruation, the ginger group received 250 mg ginger as capsules and a 10 min stretching exercise of belly and pelvic three times a week. VAS measured the pain after the first and second months. The report concluded that exercise was considerably more effective than ginger for pain relief ($P = 0.02$), the intensity of menstrual pain ($P = 0.02$), and a drop in menstrual duration ($P = 0.006$) compared to the first cycle.

III. Muscle pain

Five clinical trials have evaluated ginger's activity in reducing muscle pain originated from various sources. The objective of the research by Black et al. was to determine the performance of raw (study 1) and heat-treated (study 2) ginger supplementation (2 gms) on muscle ache for 11 days, enrolling 34 and 40 participants for both studies, respectively [91]. Pain and inflammation were induced by doing 18 intense actions of the elbow flexors by the participants. Some physical parameters were evaluated, including pain severity levels before and after three days of exercise. Results showed similar pain relief by raw and heat-treated ginger 24 h after eccentric exercise instead of placebo. Ginger reduced muscle pain, but heat treatment did not affect ginger performance. Performance of 2-g oral dose of ginger against placebo on quadriceps muscle pain during and after medium level cycling exercise was investigated by the same researchers' team, Black and O'Connor, in 25 participants [92]. In every 5 min of exercise, quadriceps muscle pain, heart rate (HR), work rate, RPE, and oxygen uptake (VO_2) were measured, while HR and VO_2 were evaluated 20 min after exercise. Results showed that placebo and ginger had no significant differences in performance on measured parameters during or after cycling activity [92]. They also investigated a single, large dose of ginger performance on muscle pain, swelling, and disability induced by intense exercise [93]. Twenty-four eccentric actions of non-dominant elbow flexors were done by 28 participants who later received ginger or placebo after one day and two days of exercise. Results exhibited that ginger ingestion did not decrease VAS scores of pain severity compared to placebo at 24 h or 48 h after exercise. Therefore, intense exercise-induced muscle pain can not be managed by a single 2-g dose of ginger even after 45 min of oral intake. On the other hand, a similar study on 20 participants giving oral administration of 4 g ginger

against placebo for five day period in treating muscle damage initiated by elbow flexor intense exercise conducted by Matsumura et al. found the opposite result [94]. Although the pain was substantially lifted but didn't get affected by ginger. Reports suggested that ginger supplementation can be adopted to assert quick recovery of muscle power after intense physical activity but not for treating muscle damage. A similar investigation using two different concentrations (7% and 14%) of another ginger species, *Zingiber cassumunar* (Plai cream), on delayed-onset muscle soreness (DOMS) from intense exercises were conducted by Manimmanakorn et al. where four sets of 25 eccentric exercise concerning quadriceps muscle were performed by 75 volunteers (28 males and 47 females) on an isokinetic dynamometry machine [95]. Participants were then divided into three categories (14% Plai, 7% Plai and placebo cream). All participants were given 2 g of the cream to be applied smoothly onto the quadriceps muscles for 5 min instantly after the intense action and at every 8 h after that for seven days. VAS analysis showed that 14% Plai cream significantly decreased muscle pain over the seven days ($P = 0.03$) while 7% Plai cream showed non-significant reduction compared to the placebo cream.

IV. Other kinds of pain

Performance of Swedish massage incorporated with ginger oil (SMGO) aromatherapy as opposed to a traditional Thai massage (TTM) on treating chronic low back pain of elderly persons was investigated by Sritoomma et al. [96]. 140 participants were randomly categorized into two groups where Group I (treatment) was given 2% ginger oil with a Swedish massage and Group II (usual massage) received TTM with no oil for 30 min for 15 weeks period. Massage efficacy on pain was determined on a short-term (six weeks) and long-term (15 weeks) basis through VAS analysis using McGill Pain Questionnaire (MPQ), while Oswestry Disability Questionnaire (ODQ) was used for disability improvement analysis. Results revealed that both types of massage (SMGO and TTM) showed substantial betterment in pain alleviation ($p < 0.05$) and disability improvement ($p < 0.05$) throughout assessments, and SMGO showed slightly better performance than TTM in all cases ($p = 0.04$). Cady et al. carried out a multicenter pilot study where 60 patients were randomized at 3:1 and received supplementation of sublingual feverfew/ginger against placebo to treat 221 attacks of migraine over a 1-month duration [97]. In just 2 h, feverfew/ginger supplementation imparted pain relief effect on 63% of subjects whereas it was 39% for placebo. Feverfew/ginger showed better performance as compared to placebo. The purpose of a community trial study by Nieman et al. was to evaluate the result of 8-weeks consumption of a commercialized dietary supplement against placebo in treating joint pain difficulty in adults [98]. The Supplement contained ginger root concentrate, glucosamine sulfate, methyl-sufonlylmethane (MSM), white willow bark extract (15% salicin), boswella serrata extract (65% boswellic acid), turmeric root extract, cayenne, and hyaluronic acid named as Instaflex™. One hundred people aged 50–75 years received either Instaflex™ or placebo capsules per day for eight weeks. The primary and secondary outcome was assessed by WOMAC and SF-36, respectively, systemic inflammation by serum *C*-reactive protein and nine plasma cytokines, and physical function by a 6-min walk test. A 12-point Likert visual scale (12-VS) was utilized bi-weekly to check joint pain severity. Results showed that Instaflex™ reduced joint pain severity more effectively than placebo ($P = 0.025$), and improvements in performing daily chores were observed in 74% of participants who received Instaflex™ supplement. And only one study on ginger performance at reducing pain associated with PMS was conducted by Khayat et al. [99]. Daily 2 ginger capsules were administered to 70 participants of intervention and control groups from 1 week before the onset of menstruation continuing to the first three days of menstruation for three consecutive cycles. The intensity of PMS was measured using three items, including mood symptoms, physical symptoms, and behavioral characteristics from the participants' self-reports. Baseline data were compared to the data taken after 1, 2, and 3 months of ginger supplementation. Although there were no substantial differences regarding PMS symptoms before treatment, significant differences were found after the intervention between the two groups ($p < 0.0001$). Substantial proof supports that ginger possesses hypoalgesic functions. Many reports recommended that the pain-reducing effect of ginger was linked to blocking of both the cyclooxygenase (COX) 1 and 2 enzymes and lipooxygenase (LOX) routes, followed by the reduction in prostaglandin and leukotriene generation and secretion of pro-inflammatory cytokines in vitro by the active ingredients of ginger, 6-gingerols and 6-shogaol [74,77,80,82,88,89]. This perceived idea recommends that consumed ginger could reduce hypersensitivity of muscle-fiber stretching via restricting stimulation of type III and type IV afferent nerve fibres using compounds like bradykinin and blunt sensory nerve fibers by prostaglandins and cytokines such as IL-1 and IL-6. Ginger, additionally, may act both peripherally and centrally. Gingerols, shogaols and zingerone are recognized as TRPV1 mediator binders [80,91]. TRPV1 mediators who are found in both peripheral and central nervous tissue, are thought to act in pain reception and processing [91]. Stimulation of TRPV1 mediators by binders such as capsaicin/6-shogaol can primarily be aching. However, single high doses or prolonged supplementation may attribute antinociception to mechanical and chemical stimuli clearly through prohibiting the secretion of the neuro-peptide, substance P [74,85,91]. Thus, ginger supplementation can decrease joint and muscle-pain intensity in the mentioned literature to some extent by inhibiting stimulation of TRPV1 mediators peripherally and centrally [74,80,85,91]. Furthermore, ginger can reduce inflammation in patients with OA by ginger can be explained from the ginger response on inflammation-causing factors. Two crucial cytokines TNF-α and IL-1β, which may cause inflammation and degenerative joint disease through activation of synovial cells of the joints, can also influence NF-kB, an indifferent eukaryotic transcription factor to initiate inflammation [14,15]. And inflammation is imparted by this nuclear factor by activating iNOS, LOX and COX-2 routes and by influencing the liberation of inflammatory cytokines. Gingerols and shogaols of ginger may act to reduce the two pro-inflammatory factors TNF-α and IL-1β in rheumatoid cartilage. In synoviocytes, these pharmacologically active elements reduce the IL-1β- or TNF-α-influenced expression of TNF-α mRNA and protein, the TNF-α-propagated release of COX2, and the TNFα-triggered stimulation of the NF-kB [14,15]. In addition to inhibiting COX and LOX pathways, this way, they can cease the inflammation. Soared release of prostaglandins from the endometrial tissue may attribute to primary dysmenorrhea, which in 80% of cases can be treated by prostaglandin inhibitors [86,88]. PGs are generated in cyclooxygenase and lipooxygenase routes from arachidonic acid. Studies showed that two PGs—PGE2 and PGF2α are more prominent in the menstrual blood of women suffering from dysmenorrhea. The menstrual

pain results from myometrial contractions propagated by PGs (mainly PGF2α) secreted in endometrium [88]. Reports suggested that gingerols and shogaols of *Zingiber officinale* work against TRPV1 receptors and show suppressive action on arachidonic acid (prostaglandins, thromboxanes) metabolism via the COX2 [80]. Thus, ginger's dual inhibition of COX and LOX pathways was attributed to the reason behind ginger's pain alleviation action. Also, some symptoms of PMS, like pain, are common with dysmenorrhea (such as backache and abdominal pain) [99]. Thus, a similar mechanism for PMS pain management [99]. Besides, the betterment in physical activities found may also be linked to pain management by these pharmacologically active constituents. A narrative review on the efficacy of ginger in lowering various types of pain in animals and human also stated that ginger might impart pain relief through different mechanisms: blocking COX and LOX pathways to inhibit prostaglandins activity, restraining oxidative chain reactions, inhibition of the transcription factor NF–kB, or working against vanilloid nociception [73]. Also, studies suggested some pharmacological elements of the respective essential oils, which may give a synergistic effect [85,96]. For pain alleviation alongside ginger essential oil in the studies mentioned above.

3.6. A shrub - vitex agnus castus

Vitex agnus castus (VAC), typically named monk pepper or chaste tree, is a deciduous shrub belonging to the Lamiaceae family [100]. According to ethnomedicinal evidence of several nations, this plant has been used to alleviate menstrual difficulties, eye problems, spasmodic dysmenorrhea, inadequate lactation, treatment of acne, snakebites, and scorpion sting stomachache, and also as antispasmodic, anaphrodisiac, and emmenagogue agent [101]. Evidences of clinical trials on using various VAC extracts to treat different types of nerve pain are as bellows.

I. Cyclic Mastalgia

Quite several clinical trials have been reported so far on VAC application in treating cyclic mastalgia (a diffuse, periodic, and bilateral breast pain). In an investigation by Kilicdag et al., two groups of women (each containing 40) suffering from cyclic mastalgia and mild hyperprolactinemia were included in the study of finding the response of *V. agnus-castus* in treating these above two symptoms. The findings were cross-checked to bromocriptine (dopamine agonist) therapy [102]. The patients were given randomly to a continued 3-month intervention of either bromocriptine (2.5 mg twice daily) or *V. agnus-castus* (40 mg daily). Pre- and post-treatment findings were compared to evaluate the intervention efficacy by measuring serum prolactin levels on 5–8 days of the menstrual cycle and breast pain (assessed by VAS). Both groups had considerably lower breast pain after active medications in the mastalgia cases. There was no adverse event reported for *V. agnus-castus* during the experimental period, while 12.5% of the patients who received bromocriptine complained about nausea and vomiting. Comparison analysis on fructus agni casti (fruit extract of VAC) and flurbiprofen in treating cyclic mastalgia in premenopausal women was conducted by Dinç and Coşkun [103]. One hundred fourteen premenopausal patients aged less than 40 years were separated into two groups and treated with fruit extract (40 mg tablet daily) and flurbiprofen (200 mg daily in two portions) for three months. VAS scores revealed that both medications could considerably reduce the pain intensity, although they had some side effects. But there was no evidence of surpassing each other's performance between the medications. Halaska et al. carried out a study to evaluate the performance of a VAC extract solution (VACS) in patients experiencing cyclic mastalgia [104]. For three cycles, two × 30 drops/day (32.4 mg extract of the VAC drug) were administered and pain severity was measured using a VAS once a cycle. VACS gave a significantly higher VAS value compared to placebo in all three cycles. Alleviating the typical symptoms of PMS, including mastalgia by VAC had been studied in an investigation by Schellenberg experimenting on 170 women, some of whom received oral contraceptive pills [105]. They received either 20 mg VAC fruit extract or placebo daily for three consecutive menstrual cycles. Significant relief in all typical symptoms, including headache and breast pain, was observed in women of the VAC group. The author suggested that mastalgia was found to be improved in the experimental group as compared to the placebo group (52% vs 24%).

II. Dysmonnerhoea

Aksoy et al. investigated the efficacy of VAC extract against ethinyl estradiol/drospirenone in women with severe primary dysmenorrhea utilizing Doppler ultrasonography to evaluate uterine artery blood flow [106]. For three menstrual cycles, 30 patients were given 0.03 mg/drospirenone while VAC extract was given to other 30. Pre- and post-treatment uterine artery resistance index (RI), pulsatility index (PI) and VAS were recorded for three months. Results indicated that the VAS score was lower in post-treatment analysis than pre-treatment evaluation.

III. Migraine

A clinical observation study tried to check the performance of VAC extract in treating headaches in migrainous women suffering from premenstrual syndrome (PMS) [107]. One hundred seven enrolled women were subjected to VAC (40 mg/day) for PMS treatment for 3 months. In the case of migraine, 42% of patients faced a 50% lower recurrence of monthly migraine attacks, while the number of headache days per month was halved for 57% of patients. The uptake of this herb by migrainous women affected by PMS was safe and compliant and could effectively reduce migraine recurrence and time of attacks.

IV. Pain associated with premenstrual syndromes (PMS)

Many clinical trials had been carried out by using various preparations of VAC in treating PMS, and few of them included pain assessment as part of the PMS management. Premenstrual syndrome (PMS) is a pervasive cycle-dependent disorder. Although a lot of symptoms have been observed widely, the most commons are fatigue, tension, irritability, mood swings, anxiety, depression, tenderness and fullness of breasts, change in appetite, abdominal bloating, swelling of extremities, headache, chest pain, slight pelvic pain, backache, itching, etc. [108,109]. In a prospective randomized study by Ma et al., the VAC extract (BNO 1095) was given orally to 33 patients of the treatment group that contained 40 mg of the herbal drug while 34 patients of the placebo group received similar tablets without drugs once per day [108]. To identify and observe moderate to severe PMS, a premenstrual syndrome diary (PMSD) was used a questionnaire to record self-response. A 4-point rating scale from absent (0) to severe (3) and factor scales incorporating 17 items were included in the questionnaire. After 3rd medication cessation, the PMSD sum score was lower for the VAC group than the placebo. Also, positive impacts on the scores of negative affect and water retention (factor 1 and 2) between the two groups at cycle 3 were observed though for food cravings (factor 3) and pains (factor 4) scores were unaffected. Loch et al., in a multicentric non-interventional trial, administered a drug from VAC fruit extract to 1634 patients suffering from PMS [109]. A new questionnaire was developed to measure the effect of VAC on psychic (depression, anxiety, sleeping problems, mood swings, etc.) and somatic (craving, headache, tachycardia, back and joint pain, etc.) complaints. After three menstrual cycles of active medications, PMS complaints, including all kinds of pain, were reduced in 93% of patients. 20 mg V. *agnus-castus* extract (Ze 440) was investigated for three menstrual cycles by Berger et al. on 50 patients suffering from PMS [110]. 13 patients received related oral contraceptives. The MMDQ (Moos RH, 1968) questionnaire was utilized for self-assessment. Patients were asked about 47 symptoms of their premenstrual phase measured on a 6-grade scale. The MMDQ was completed at the pretreatment phase, after three cycles' treatment and after three cycles of cessation of the treatment period. Results concluded that the intervention reduced PMS-related symptoms, although symptoms slowly returned after treatment cessation. And intake of oral contraceptives showed no effect on results. Forty-one patients were randomly categorized into fluoxetine, a selective serotonin reuptake inhibitor (SSRI), or VAC group in a trial by Atmaca et al. and given 20–40 mg/day drugs for two months [111]. The outcome assessment included the Penn daily symptom report (PDSR), the Hamilton depression rating scale (HAM-D), and the clinical global impression-severity of illness (CGI-SI) and improvement (CGI-I) scales. The result disclosed that both VAC and fluoxetine treatments were effective and close to the expected outcomes for patients with PMDD. Fluoxetine treated psychological symptoms, while the VAC extract managed physical symptoms. Prilepskaya et al. investigated extract of VAC (VAC, BNO 1095) incorporating PMSD and PMTS score [112]. For three consecutive cycles, 120 patients received Agnucaston® tablet (40 mg herbal drug) orally once per day. Throughout the study period, the patients self-assessed 18 PM S symptoms and filled in standardized PMSD. It was observed that 67.8% of patients gave positive response to treatment during the third cycle. The objective of another phytotherapeutic intervention study on perimenopausal women by Die et al. was to investigate the impact of a blend of *Hypericum perforatum* (St. John's wort) and VAC in relieving PMS-like symptoms [113]. In this 16 weeks trial, patients received tablets containing a blend of 1000 mg VAC dry fruit and 5400 mg dry *Hypericum perforatum* flowering top or placebo tablets twice daily to measure the relief of PMS-like symptoms. The evaluation was based on Abraham's Menstrual Symptoms Questionnaire, consisting of four clusters. The trial concluded that the herbal formulation positively responded in managing PMS-like scores compared to control group. Similar results were found by Zamani et al. when 40 drops of VAC extract or matching placebo was applied on 128 women six days before the onset of menstruation and continued to next six consecutive cycles to treat PMS like symptoms [114]. All participants filled in a self-assessment tool before and after the study period which included questions on the premenstrual period. Each item was measured using a visual analogue scale (VAS). Although both groups exhibited a considerable change before and after the intervention to alleviate mild and moderate PMS, VAC extract gives better VAS values than placebo ($P < 0.0001$). Schellenberg et al. included 162 women suffering from PMS (18–45 years) and were given VAC fruit extract (Ze 440) at three different doses (8, 20 and 30 mg) or matching placebo for three consecutive menstrual cycles [115]. PMS symptom score improved against 20 mg intervention in coparison with the other two groups and placebo. 20 mg of chaste tree extract (Prefemin®) was effective in managing PMS symptoms without imparting any adverse effects when administered once daily for three menstrual cycles in a trial by Momoeda et al. [116]. 69 Japanese women aged 18–44 years participated in this phase 3 investigations and self-assessed ten PMS symptoms via a VAS. A significant reduction in VAS score was observed just after one menstrual cycle ($P < 0.001$), which continued to plummet till the third menstrual cycle. The study suggested VAC extract as a potential candidate to eliminate PMS symptoms in Japanese patients without potential side effects. Kaplanoglu and Aban researched 120 women suffering from PMS treated with ethinyl estradiol-drospirenone (EE-Drs), VAC extract and placebo for three consecutive cycles to treat PMS [117]. Fifteen symptom scores documented in PMSD was used to analyze the efficacy result at luteal phase after the third medication period. After active medication, both EE-Drs and VAC extract showed considerable positive response towards PMS treatment and related breast pain. VAC was more effective for reduced coordination, while EE-Drs was more effective for crying attacks. Khalilzadeh et al. carried out a study on rats in order to determine the possible peripheral and central impacts of VAC essential oil (EOVAC) utilizing nociceptive tests like formalin test, acetic acid-induced writhing response and tail immersion test. Report concluded that, antinociceptive effects in the rats might occur through endogenous opioidergic system as well as muscarinergic receptors of cholinergic system in these models of pain in rats after injecting EOVAC hypodermically (88). Rat's response was similar to that of human. Possible mechanism of action of VAC for relieving PMS symptoms have not been identified so far in any literature. As the cause of PMS is not well clarified, PMS are typically symptomatically handled. Therefore, it is beneficial to opt for wide spread therapeutic agents from different pharmacological compounds of VAC to treat PMS. The fruits of VAC consists of chemical constituents like essential oils, flavonoids, iridoid glycosides, and diterpenoids such as agnuside, isoflavonoids, and phenolic compounds [101]. Flavonoids that contain casticin, apigenin, vitexin, isovitexin, luteolin, orientin, isoorientin, santin, etc., are known to be the principal active compounds of the plants [101]. Mastalgia, a pain of breast, is the most common physical symptoms of PMS. This distress has been identified to be caused of latent hyperprolactinemia, i.e. stress induced stimulated mammary glands that gives soared release of pituitary prolactin. Generally, prolactin

release is controlled by hypothalamic dopamine. Therefore, inhibition of prolactin release by the activation of dopamine D2 receptors may play a prominent role to manage mastalgia with other PMS complaints [106,111,115]. Additionally, an increased prolactin plasma level can also be a vital sign of PMS. Therefore, a dopaminergic agonistic response of the extract may play a role in alleviating PMS symptoms in treated subjects [105,107,112,114]. Also, some pharmacological compounds of VAC are identical to sex hormones. Thus, their activity may also be connected to the cessation of stress generated prolactin release through dopamine activation without disturbing LH and FSH. For its selective affinity, molecular weight and retention time, Linoleic acid has been acknowledged as an estrogen receptor ligand, can be obtained from VAC fruit extract [101]. In vitro studies revealed that linoleic acid and other active compounds could bind to μ-opioid receptors, β-estrogen receptors (ERs), endorphins, and neuroactive flavonoids and induce specific estrogen-inducible genes to produce relief from PMS symptoms [101,105,107,112,115]. Apart from that, dopamine blocking activity may not affect PMS symptoms related to fluid retention. In that case, some pharmacological compounds may play via opioid receptors or attribute to mood change through the GABA system and influence the overall performance of the extract [110].

3.7. Peganum oil

Peganum harmala (L.) belongs to the family Zygophyllaceae, widely known as 'Harmal', grows commonly in semiarid and deserted areas of south-east Morocco and is dispersed in North Africa and the Middle East [118]. In Moroccan and Iranian history, various extracts from seeds of *Peganum harmala* were adopted as a treatment for arthritic pain, joint pain, and stomachache [118,119]. One of these extracts is massaging oil called Roghan-e-Espand (Peganum oil). Seeds of *Peganum harmala* are abundant in alkaloids, flavonoids, saponin, terpenes, sterols, and quinones, which possess various pharmacological actions and are used to treat various diseases [119–121]. Here, we will try to summarize the up-to-date information on *Peganum harmala* L oil extract in alleviating various nerve pain with the possible mechanisms of action.

3.7.1. Peganum oil in pain management

Only two studies have been carried out on humans utilizing two different forms of *peganum harmala L* plant seed to verify its pain-alleviating activity. Abolhassanzadeh et al. researched to evaluate the efficacy of peganum oil in treating knee osteoarthritis of people of age ranging from 40 to 70 years [119]. Fifty-four patients were divided into an experimental group given peganum oil extracted in olive oil massage and a control group given only olive oil massage on the knee four drops three times each day until four weeks. Responses to WOMAC and VAS questionnaires between 0 and 4 weeks were analyzed to measure the improvement of the pain, stiffness and activity symptoms. The measured outcomes revealed that trouble with activity and pain intensity was considerably lower in the experimental group after four weeks of intervention. VAS score revealed that peganum oil reduced knee pain three times higher (52.56%) than the control group (17.00%). Besides, Peganum oil showed a good reaction to stiffness and movement pain with no side effects. Results concluded that the alkaloid elements, which possess analgesic properties, may impart antinociceptive activities peripherally and centrally via opioid receptors, giving the ultimate pain reduction performance. Shakeri et al., in a randomized clinical trial, utilized *Peganum harmala* seed orally on pain alleviation and removal of kidney and ureteral stones and compared its efficiency against tamsulosin (a synthetic drug) [120]. 80 patients (>18 years) having kidney and ureteral stones of size 4–10 mm were randomly categorized into two groups where group 1 was prescribed with 0.4 mg tamsulosin capsules, and group 2 was given 50 mg/kg harmala seed extract in the form of the capsule after the meal every night for two weeks. Patients were re-tested to determine the change in stone sizes, and residual stones sizes were measured after 2 weeks of intervention. Although VAS score of pain reduced exponentially in both groups, *P. harmala* group showed notable improvement. The efficiency of both treatment options was more than 77%, with no visible side effects throughout the period. The study concluded that both drugs showed reduced urinary stone size and numbers, although *P. harmala* gave more pain relief. Although the specific compound and reason behind the pain reduction mechanism were not identified or discussed in the report, researchers argued that the well-established analgesic performance of harmala seed gave that pain reduction effect. Generally, the therapeutic agents of harmala seeds are known to be many alkaloids incorporating β-carbolines, such as harmine, harmaline, harmalol, harman and quinazoline derivatives, and vasicine (peganine) and vasicinone [121]. And, research proved that among all these compounds, the harmaline of the harmala alkaloid extract was able to provide antinociception to induce pain reduction effect [121]. The mechanism of action has been concerned, either by blocking the LOX and COX pathway or by stimulating the release of cytokines such as TNF-α, interleukin-1β and interleukin-8; by resident peritoneal macrophages and mast cells, or by both mechanisms, alkaloid may impart analgesic response [118]. The pain alleviation effect of hydroalcoholic extract of the plant as rubbing oil was studied on male rats using formalin test [122]. The result was similar to that of humans. Researchers claimed that one element that has a prominent role in the body in generating pain and inflammation is prostaglandins. And the analgesic effect of the plant was supposed to mediate through an agonist mechanism on the surface of benzodiazepine receptors. β-carboline of harmala plant regulates Monoamine Oxidase (MAO) action and raises the concentration of norepinephrine, serotonin and dopamine in the neural synapses linked to thoughts, emotions, memory and controlling few activities of the rat's body with the liberation of serotonin and catecholamine. Thus, rats' pain was suppressed by serotonin, which is liberated in neurons of the spine [122]. Farouk et al. investigated ethyl acetate (EAE), butanolic (BE) and aqueous (AqE) extracts of seeds of *Peganum harmala* for their analgesic performance utilizing writhing, formalin, tail-flick and hot plate tests of mice [123]. All the extracts showed a significant reduction in acetic acid-generated writhings in mice with the highest impact by BE extract. EAE and BE extracts showed analgesic effect centrally during hot plate and tail flick tests. Also, the Analgesic behaviour of crude alkaloids of 6 different medicinal plants including *Peganum harmala* seed, was studied by Shoaib et al., investigating writhing, formalin and tail immersion tests in mice [124]. Among the six extracts, peganum oil gave the second-highest analgesic performance. Both results suggested that various extracts of *Peganum harmala* impart antinociception via opioid receptors acting both peripherally and centrally [123,124].

3.8. Ajwain 10% (Trachyspermum ammi sprague) topical cream

Trachyspermum ammi (L.) Sprague is Ajwain, carom, or bishop weeds is a herbaceous plant and have included in the essential medicinal family, Apiaceae, (Gersbach and Reddy 2002). Ajwain plant is usually found in Iran (Persia), Asia, and Turkey. In some parts of India, Ajwain cultivation is found. Ajwain is also found in the Middle East and North Africa. Several chemical constituents have been reported for this herb, mainly thymol, terpenoids, *p*-cymene, gamma-terpinene, and essential oil [125–128]; therefore, it has some medicinal importance. This medicinal plant is widely used for several biological activities, including anti-inflammatory, antimicrobial, immunomodulatory, antioxidant, anti-filarial, anthelmintic, hypolipidaemic, gastro-protective, and nematicidal activity [128]. However, this plant is widely used against numerous pain-related treatments, including nerve pain, stomach pain.

3.8.1. Mechanism of action of ajwain 10% topical cream

The actual mechanism of Ajwain 10% (*Trachyspermum ammi* Sprague) topical cream in analgesia or pain relief is relatively unknown. However, in an *in vivo* study on male adult rate (200–250 g), Al-Khazraji et al. found that *Trachyspermum ammi* seed extract could decrease nerve pain may be due to having dopaminergic and cholinergic muscarinic activities of the extract [129]. Further study needs more confirmation results.

3.8.2. Clinical trial on pain management by ajwain 10% topical cream

Although numerous studies are available against several diseases, clinical trials for nerve pain are limited. Petramfar et al. conducted a double-blind. A randomized placebo-controlled trial with 92 adults with moderate to severe neuropathic pain patients two times daily for 28 days. They found that, the mean change in absolute pain score for feet burning (−3.55 vs-0.76), numbness (-0.58 vs-0,11), allodynia (0.64 vs.06) and tingling (−1.69 vs-0.16) were significantly greater in the Ajwin group versus placebo respectively ($P < 0.001$,$P = 0011$,$P = 0.023$,$P < 0.001$ respectively) [130].

4. Limitations and recommendations

The essential oil has a wide range of pharmacological mechanisms that could alleviate nerve-related pain. Some of these mechanisms pay to essential oil as a powerful anti-nerve agent. However, in addition to the pharmaceutical benefits, there are also significant limitations to predicting the true potentiality of this essential oil against nerve pain. Pure essential oils are very concentrated, and some can be toxic, so people should not ingest them directly. One should use them by other means of administration in skin or other ways. Applying undiluted essential oil to the skin can cause irritation and inflammation, so concentrated oil needs to dilute oils in a carrier oil before using them directly [131] and it is advisable to perform a patch test before using new oil. Essential oils may interact with certain medications, such as antidepressants and stimulants [132]. People taking prescription medications should seek advice from their doctor before using essential oil. As with herbal supplements, The US Food and Drug Administration does not regulate essential oils [133,134]. So, before using essential oil, one should read all labels to ensure that getting pure essential oil rather than mixed with other ingredients. Pregnant women should discuss with their doctor before using essential oil. As a result, before adding essential oil to the medicine cabinet as a natural therapeutic agent or medication, consider it must first be approved by testing *in vivo,* and clinical trials with post-marketing surveillance reports. Moreover, still more original research is required to find out the drug interaction, convenient nano-formulation, and pharmacodynamics and pharmacokinetics of each of these essential oils to confirm their safety to humans.

5. Concluding remarks

People with nerve pain are frequently extremely sensitive to some severe cases in the body and sometimes cause death. This moribund condition demands an alternative therapy that has minimum side effects and promoting researchers to confer new drugs from a natural product. As far as our knowledge, this is the first review related to clinical natural product against nerve pain and this review suggest that natural products are alternative options to relieve and manage nerve pain. According to our findings, most pathways implicated in pain management are sensory stimulation, enzymatic, anti-inflammatory, and pain-related receptor regulation. More specially, the molecular mechanism involved in nerve pain management is the inhibition of inflammatory molecules including cytokines like IL-1, IL-6, TNF-α, NF-ƘB, prostaglandins, COX-2, and TRPV1. Although our targeted clinically natural product has been effective in treating nerve pain, there are still some limitations that must be overcome, necessitating further research. However, until the specific medication for nerve pain is available in pharma markets, authors suggest using these natural products and oils tropically or in other suitable ways.

To sum up, our review indicates that, due to several therapeutic benefits, our targeted natural compounds might be an additional and alternative treatment option for nerve pain.

Author contributions

MNA contributed in designing the project. SD and MS were involved in manuscript writing. MSH, FA and MTI retrieved information from databases. MS, AAM, and MMI have handled all figures and table rearrangements. Finally, MNA critically revised all important intellectual contents.

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The authors declare no conflict of interest.

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References

[1] National Institute for Health and Care Excellence, Neuropathic Pain in Adults : Pharmacological Management in Non- Specialist Settings, NICE Guidel., 2013.
[2] B.P. Murnion, Neuropathic pain: current definition and review of drug treatment, Aust. Prescr. (2018), https://doi.org/10.18773/austprescr.2018.022.
[3] T.S. Jensen, et al., A new definition of neuropathic pain, Pain (2011), https://doi.org/10.1016/j.pain.2011.06.017.
[4] N.B. Finnerup, et al., Neuropathic pain: an updated grading system for research and clinical practice, Pain (2016), https://doi.org/10.1097/j.pain.0000000000000492.
[5] M. Dueñas, B. Ojeda, A. Salazar, J.A. Mico, I. Failde, A review of chronic pain impact on patients, their social environment and the health care system, J. Pain Res. (2016), https://doi.org/10.2147/JPR.S105892.
[6] B. Amin, H. Hosseinzadeh, Evaluation of aqueous and ethanolic extracts of saffron, Crocus sativus L., and its constituents, safranal and crocin in allodynia and hyperalgesia induced by chronic constriction injury model of neuropathic pain in rats, Fitoterapia (2012), https://doi.org/10.1016/j.fitote.2012.03.022.
[7] M. Zimmermann, Pathobiology of neuropathic pain, Eur. J. Pharmacol. (2001), https://doi.org/10.1016/S0014-2999(01)01303-6.
[8] C.J. Woolf, R.J. Mannion, Neuropathic pain: aetiology, symptoms, mechanisms, and management, Lancet (1999), https://doi.org/10.1016/S0140-6736(99)01307-0.
[9] G. Garg, J.D. Adams, Treatment of neuropathic pain with plant medicines, Chin. J. Integr. Med. (2012), https://doi.org/10.1007/s11655-012-1188-6.
[10] J.B. Calixto, A. Beirith, J. Ferreira, A.R.S. Santos, V.C. Filho, R.A. Yunes, Naturally occurring antinociceptive substances from plants, Phytother Res. 14 (6) (2000) 401–418, https://doi.org/10.1002/1099-1573(200009)14:6<401::aid-ptr762>3.0.co;2-h.
[11] N.S. Sangwan, A.H.A. Farooqi, F. Shabih, R.S. Sangwan, Regulation of essential oil production in plants, Plant Growth Regul. (2001), https://doi.org/10.1023/A:1013386921596.
[12] S. Koyama, T. Heinbockel, The effects of essential oils and terpenes in relation to their routes of intake and application, Int. J. Mol. Sci. (2020), https://doi.org/10.3390/ijms21051558.
[13] M. Djellouli, H. Benmehdi, S. Mammeri, A. Moussaoui, L. Ziane, N. Hamidi, Chemical constituents in the essential oil of the endemic plant Cotula cinerea (Del.) from the southwest of Algeria, Asian Pac. J. Trop. Biomed. (2015), https://doi.org/10.1016/j.apjtb.2015.06.007.
[14] H. Mozaffari-Khosravi, Z. Naderi, A. Dehghan, A. Nadjarzadeh, H. Fallah Huseini, Effect of ginger supplementation on proinflammatory cytokines in older patients with osteoarthritis: outcomes of a randomized controlled clinical trial, J. Nutr. Gerontol. Geriatr. 35 (3) (2016) 209–218, https://doi.org/10.1080/21551197.2016.1206762.
[15] Z. Naderi, H. Mozaffari-Khosravi, A. Dehghan, A. Nadjarzadeh, H.F. Huseini, Effect of ginger powder supplementation on nitric oxide and C-reactive protein in elderly knee osteoarthritis patients: a 12-week double-blind randomized placebo-controlled clinical trial, J. Tradit. Complement. Med. 6 (3) (2016) 199–203, https://doi.org/10.1016/j.jtcme.2014.12.007.
[16] V.N. Drozdov, V.A. Kim, E.V. Tkachenko, G.G. Varvanina, Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip, J. Alternative Compl. Med. 18 (6) (2012) 583–588, https://doi.org/10.1089/acm.2011.0202.
[17] B. Ali, N.A. Al-wabel, S. Shams, A. Ahamad, S.A. Khan, F. Anwar, Asian paci fi c journal of tropical biomedicine, Asian Pac. J. Trop. Biomed. (–11) (2015) 1, https://doi.org/10.1016/j.apjtb.2015.05.007.
[18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097.
[19] C. Staiger, Comfrey root: from tradition to modern clinical trials, Wien Med. Wochenschr. 163 (3–4) (2013) 58–64, https://doi.org/10.1007/s10354-012-0162-4.
[20] R. Dennis, C. Dezelak, J. Grime, Studies on symphytum species - HPLC determination of allantoin, Acta Pharm Hung 57 (6) (1987) 267–274.
[21] G. Franz, Studies on the mucopolysaccharides of Tussilago farfara L., Symphytum officinalis L., Borago officinalis L. and Viola tricolor L, Planta Med. (1969), https://doi.org/10.1055/s-0028-1099849.
[22] C. Staiger, Comfrey: a clinical overview, Phytother Res. (2012), https://doi.org/10.1002/ptr.4612.
[23] J. Seigner, et al., A symphytum officinale root extract exerts anti-inflammatory properties by affecting two distinct steps of NF-κB signaling, Front. Pharmacol. (2019), https://doi.org/10.3389/fphar.2019.00289.
[24] B.M. Giannetti, C. Staiger, M. Bulitta, H.G. Predel, Efficacy and safety of comfrey root extract ointment in the treatment of acute upper or lower back pain: results of a double-blind, randomised, placebo controlled, multicentre trial, Br. J. Sports Med. 44 (9) (2010) 637–641, https://doi.org/10.1136/bjsm.2009.058677.
[25] B. Grube, J. Grünwald, L. Krug, C. Staiger, Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial, Phytomedicine 14 (1) (2007) 2–10, https://doi.org/10.1016/j.phymed.2006.11.006.
[26] H.G. Predel, B. Giannetti, R. Koll, M. Bulitta, C. Staiger, Efficacy of a Comfrey root extract ointment in comparison to a Diclofenac gel in the treatment of ankle distortions: results of an observer-blind, randomized, multicenter study, Phytomedicine 12 (10) (2005) 707–714, https://doi.org/10.1016/j.phymed.2005.06.001.
[27] D.B. Smith, B.H. Jacobson, Effect of a blend of comfrey root extract (Symphytum officinale L.) and tannic acid creams in the treatment of osteoarthritis of the knee: randomized, placebo-controlled, double-blind, multiclinical trials, J. Chiropr. Med. (2011), https://doi.org/10.1016/j.jcm.2011.01.003.
[28] H.M.A. Cavanagh, J.M. Wilkinson, Lavender essential oil: a review, Aust. Infect. Control 10 (1) (2005) 35–37, https://doi.org/10.1071/hi05035.

[29] R. Shellie, L. Mondello, P. Marriott, G. Dugo, Characterisation of lavender essential oils by using gas chromatography-mass spectrometry with correlation of linear retention indices and comparison with comprehensive two-dimensional gas chromatography, J. Chromatogr. A 970 (1–2) (2002) 225–234, https://doi.org/10.1016/S0021-9673(02)00653-2.

[30] S. Price, The Aromatherapy Workbook : Understanding Essential Oils from Plant to User, HarperCollins UK, 2000.

[31] V.D. Zheljazkov, C.L. Cantrell, T. Astatkie, E. Jeliazkova, Distillation time effect on lavender essential oil yield and composition, J. Oleo Sci. 62 (4) (2013) 195–199, https://doi.org/10.5650/jos.62.195.

[32] A. Sarkic, I. Stappen, Essential oils and their single compounds in cosmetics-a critical review, Cosmetics 5 (2018), https://doi.org/10.3390/cosmetics5010011, 1.

[33] K.A.Y.R. Lee, J.E. Harnett, R. Cairns, Essential oil exposures in Australia: analysis of cases reported to the NSW Poisons Information Centre, Med. J. Aust. 212 (3) (2020) 132–133, https://doi.org/10.5694/mja2.50403.

[34] P. Kwiatkowski, et al., The antibacterial activity of lavender essential oil alone and in combination with octenidine Dihydrochloride against MRSA strains, Molecules 25 (1) (2020), https://doi.org/10.3390/molecules25010095.

[35] F. Behmanesh, et al., Antifungal effect of lavender essential oil (lavandula angustifolia) and clotrimazole on Candida albicans : an in vitro study, Sci. Tech. Rep. 2015 (2015) 1–5, https://doi.org/10.1155/2015/261397.

[36] P.H. Koulivand, M. Khaleghi Ghadiri, A. Gorji, Lavender and the nervous system, Evid. base Compl. Alternative Med. 2013 (2013), https://doi.org/10.1155/2013/681304.

[37] K. Ogata, et al., Lavender oil reduces depressive mood in healthy individuals and enhances the activity of single oxytocin neurons of the hypothalamus isolated from mice: a preliminary study, Evid. base Compl. Alternative Med. (2020) 2020, https://doi.org/10.1155/2020/5418586.

[38] G.L. da Silva, et al., Antioxidant, analgesic and anti-inflammatory effects of lavender essential oil, An. Acad. Bras. Cienc. 87 (2) (2015) 1397–1408, https://doi.org/10.1590/0001-3765201520150056.

[39] M. Ching, Contemporary therapy: aromatherapy in the management of acute pain? Contemp. nurse a J. Aust. Nurs. Prof. 8 (4) (1999) 146–151, https://doi.org/10.5172/conu.1999.8.4.146.

[40] A. Salamati, S. Mashouf, F. Sahbaei, F. Mojab, F. Mojab, Effects of inhalation of lavender essential oil on Open-Heart surgery pain, Iran. J. Pharm. Res. (IJPR) 13 (4) (2014) 1257–1261, https://doi.org/10.22037/ijpr.2014.1575.

[41] F. Vaziri, M. Shiravani, F.S. Najib, S. Pourahmad, A. Salehi, Z. Yazdanpanahi, Effect of lavender oil aroma in the early hours of postpartum period on maternal pains, fatigue, and mood: a randomized clinical trial, Int. J. Prev. Med. 8 (2017), https://doi.org/10.4103/ijpvm.IJPVM_137_16.

[42] C. Usta, B. Tanyeri-Bayraktar, S. Bayraktar, Pain control with lavender oil in premature infants: a double-blind randomized controlled study, J. Alternative Compl. Med. 27 (2) (2021) 136–141, https://doi.org/10.1089/acm.2020.0327.

[43] A.A. Ghods, N.H. Abforosh, R. Ghorbani, M.R. Asgari, The effect of topical application of lavender essential oil on the intensity of pain caused by the insertion of dialysis needles in hemodialysis patients: a randomized clinical trial, Compl. Ther. Med. 23 (3) (2015) 325–330, https://doi.org/10.1016/j.ctim.2015.03.001.

[44] Z. Seifi, et al., The effect of inhalation aromatherapy with lavender essential oil on pain severity of patients after coronary artery bypass surgery: a single-blind randomised clinical trial, J. Clin. Diagn. Res. 12 (7) (2018) LC01–LC05, https://doi.org/10.7860/JCDR/2018/34865.11721.

[45] E. Taşan, O. Ovayolu, N. Ovayolu, The effect of diluted lavender oil inhalation on pain development during vascular access among patients undergoing haemodialysis, Compl. Ther. Clin. Pract. 35 (2019) 177–182, https://doi.org/10.1016/j.ctcp.2019.02.010.

[46] F. Vaziri, M. khosropoor, M. Hidari, S. Pourahmad, B. Morshed Behbahani, F. Saki, The effect of aromatherapy by lavender oil on infant vaccination pain: a double blind randomized controlled trial, J. Caring Sci. 8 (1) (2019) 17–21, https://doi.org/10.15171/jcs.2019.003.

[47] T. Badri, T.F. Iman, A.Q. Ali, T. Fakhry, T. Mohsen, The effect of lavender oil on pain and comfort in cardiac patients after injection of enoxaparin, Iran. J. Nat. Resour. 14 (4) (2019) 21–26. Accessed: Jun. 11, 2021. [Online]. Available: https://www.sid.ir/en/journal/ViewPaper.aspx?id=800024.

[48] F. Ghaderi, N. Solhjou, The effects of lavender aromatherapy on stress and pain perception in children during dental treatment: a randomized clinical trial, Compl. Ther. Clin. Pract. 40 (2020), https://doi.org/10.1016/j.ctcp.2020.101182.

[49] A. Zahra, Lavender aromatherapy massages in reducing labor pain and duration of labor: a randomized controlled trial, African J. Pharm. Pharmacol. 7 (8) (2013) 456, https://doi.org/10.5897/ajpp12.391, 430.

[50] S.E. Apay, S. Arslan, R.B. Akpinar, A. Celebioglu, Effect of aromatherapy massage on dysmenorrhea in Turkish students, Pain Manag. Nurs. 13 (4) (2012) 236–240, https://doi.org/10.1016/j.pmn.2010.04.002.

[51] Y.B. Yip, S.H.M. Tse, The effectiveness of relaxation acupoint stimulation and acupressure with aromatic lavender essential oil for non-specific low back pain in Hong Kong: a randomised controlled trial, Compl. Ther. Med. 12 (1) (2004) 28–37, https://doi.org/10.1016/j.ctim.2003.12.003.

[52] S. Bani, S. Hasanpour, Z. Mousavi, P. Mostafa Garehbaghi, M. Gojazadeh, The effect of rosa damascena extract on primary dysmenorrhea: a double-blind cross-over clinical trial, Iran. Red Crescent Med. J. 16 (1) (2014) 1–6, https://doi.org/10.5812/ircmj.14643.

[53] M. Akram, et al., Chemical constituents, experimental and clinical pharmacology of Rosa damascena: a literature review, J. Pharm. Pharmacol. 72 (2) (2020) 161–174, https://doi.org/10.1111/jphp.13185.

[54] M. Homayoun, M. Seghatoleslam, M. Pourzaki, R. Shafieian, M. Hosseini, A. Ebrahimzadeh Bideskan, Anticonvulsant and neuroprotective effects of Rosa damascena hydro-alcoholic extract on rat hippocampus, Avicenna J. phytomedicine 5 (3) (2015) 260–270, https://doi.org/10.22038/ajp.2015.4138.

[55] M. Niazi, M.H. Hashempur, M. Taghizadeh, M. Heydari, A. Shariat, Efficacy of topical Rose (Rosa damascena Mill.) oil for migraine headache: a randomized double-blinded placebo-controlled cross-over trial, Compl. Ther. Med. 34 (2017) 35–41, https://doi.org/10.1016/j.ctim.2017.07.009.

[56] M. Shirazi, et al., The effect of topical rosa damascena (rose) oil on pregnancy-related low back pain: a randomized controlled clinical trial, J. Evidence-Based Complement. Altern. Med. 22 (1) (2017) 120–126, https://doi.org/10.1177/2156587216654601.

[57] S. Hamdamian, S. Nazarpour, M. Simbar, S. Hajian, F. Mojab, A. Talebi, Effects of aromatherapy with Rosa damascena on nulliparous women's pain and anxiety of labor during first stage of labor, J. Integr. Med. 16 (2) (2018) 120–125, https://doi.org/10.1016/j.joim.2018.02.005.

[58] M. Ayan, U. Tas, E. Sogut, M. Suren, L. Gurbuzler, F. Koyuncu, Investigating the Effect of Aromatherapy in Patients 19 (4) (2013) 329–333, https://doi.org/10.1089/acm.2011.0941.

[59] C.N. Care, Research paper: the effect of inhalation, Aromatherapy With Damask Rose 3 (2) (2017) 153–160.

[60] A. Bikmoradi, M. Harorani, G. Roshanaei, S. Moradkhani, G.H. Falahinia, The Effect of Inhalation Aromatherapy with Damask Rose, 2016, https://doi.org/10.4103/1735-9066.180380.

[61] H.S.A. Shahr, M. Saadat, M. Kheirkhah, E. Saadat, The Eff Ect of Self-Aromatherapy Massage of the Abdomen on the Primary Dysmenorrhoea, 2015, pp. 382–385, https://doi.org/10.3109/01443615.2014.958449.

[62] P. Mostafa-Gharabaghi, A. Delazar, M.M. Gharabaghi, M.J. Shobeiri, The View of Cesarean Pain after Preemptive Use of Rosa Damascena Extract in Women with Elective Cesarean Section, 2013, pp. 226–235.

[63] M. Sirousfard, M. Moeini, A. Ghanadi, Evaluation of the effect of aromatherapy with 20 (2) (2015) 247–254.

[64] S.R. Sancho, V. Merino, Development of Antimigraine Transdermal Delivery Systems of Pizotifen Malate, Elsevier B.V., 2015, https://doi.org/10.1016/j.ijpharm.2015.07.033.

[65] T. Hongratanaworakit, Relaxing effect of rose oil on humans, Nat. Prod. Commun. 4 (2) (2009) 291–296, https://doi.org/10.1177/1934578x0900400226.

[66] D. Lakhan, S.E. Sheafer, H. Tepper, The effectiveness of aromatherapy in the management of labor pain and anxiety: a systematic review, Pain Res. Treat. 2016 (2016) 1–13.

[67] H. Bagheri, et al., The effects of inhalation aromatherapy using lavender essential oil on postoperative pain of inguinal hernia: a randomized controlled trial, J. PeriAnesthesia Nurs. 35 (6) (2020) 642–648, https://doi.org/10.1016/j.jopan.2020.03.003.

[68] M.C. Ou, T.F. Hsu, A.C. Lai, Y.T. Lin, C.C. Lin, Pain relief assessment by aromatic essential oil massage on outpatients with primary dysmenorrhea: a randomized, double-blind clinical trial, J. Obstet. Gynaecol. Res. 38 (5) (2012) 817–822, https://doi.org/10.1111/j.1447-0756.2011.01802.x.

[69] S.H. Han, M.H. Hur, J. Buckle, J. Choi, M.S. Lee, Effect of aromatherapy on symptoms of dysmenorrhea in college students: a randomized placebo-controlled clinical trial, J. Alternative Compl. Med. 12 (6) (2006) 535–541, https://doi.org/10.1089/acm.2006.12.535.
[70] W. Pujiati, Y. Siagian, C. Hardivianty, Application of essential oils: lavender, clary sage, ginger and Geranium as aromatherapy through effleurage massage for menstrual pain, Int. J. Sci. Res. 8 (10) (2019) 1476–1480.
[71] A. Ghiasi, L. Bagheri, A. Haseli, A systematic review on the anxiolytic effect of aromatherapy during the first stage of labor, J. Caring Sci. 8 (1) (2019) 51–60, https://doi.org/10.15171/jcs.2019.008.
[72] A.D. Quinlan-colwell, jhn (2015) 177–182.
[73] M. Rondanelli, et al., Clinical trials on pain lowering effect of ginger: a narrative review, Phyther. Res. 34 (11) (2020) 2843–2856, https://doi.org/10.1002/ptr.6730.
[74] Y.B. Yip, A.C.Y. Tam, An experimental study on the effectiveness of massage with aromatic ginger and orange essential oil for moderate-to-severe knee pain among the elderly in Hong Kong, Compl. Ther. Med. 16 (3) (2008) 131–138, https://doi.org/10.1016/j.ctim.2007.12.003.
[75] Z. Zakeri, S. Izadi, Z. Bari, F. Soltani, B. Narouie, M. Ghasemi-Rad, Evaluating the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis, J. Med. Plants Res. 5 (15) (2011) 3375–3379.
[76] H. Bliddal, et al., A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis, Osteoarthritis Cartilage 8 (1) (2000) 9–12, https://doi.org/10.1053/joca.1999.0264.
[77] G. Paramdeep, Efficacy and tolerability of ginger (Zingiber Officinale) in patients of osteoarthritis of knee, Indian J. Physiol. Pharmacol. 57 (2) (2013) 177–183.
[78] S. Niempoog, K.K. Pawa, C. Amatyakul, The efficacy of powdered ginger in osteoarthritis of the knee, J. Med. Assoc. Thai. 95 (Suppl 1) (2012) 59–64.
[79] R.D. Altman, K.C. Marcussen, Effects of a ginger extract on knee pain in patients with osteoarthritis, Arthritis Rheum. 44 (11) (2001) 2531–2538, 10.1002/1529-0131(200111)44:11<2531::AID-ART433>3.0.CO;2-J.
[80] M. Rondanelli, et al., The effect and safety of highly standardized Ginger (Zingiber officinale) and Echinacea (Echinacea angustifolia) extract supplementation on inflammation and chronic pain in NSAIDs poor responders. A pilot study in subjects with knee arthrosis, Nat. Prod. Res. 31 (11) (2017) 1309–1313, https://doi.org/10.1080/14786419.2016.1236097.
[81] ref 4.pdf." .
[82] K. Injury, The Efficacy of Plygersic Gel for Use in the Treatment of Osteoarthritis of the Knee, vol. 95, 2012, pp. 113–119.
[83] P. Amorndoljai, S. Taneepanichskul, S. Niempoog, U. Nimmannit, A comparative of ginger extract in nanostructure lipid carrier (NLC) and 1% diclofenac gel for treatment of knee osteoarthritis (OA), J. Med. Assoc. Thail. 100 (4) (2017) 447–456.
[84] I. Wigler, I. Grotto, D. Caspi, M. Yaron, The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis, Osteoarthritis Cartilage 11 (11) (2003) 783–789, https://doi.org/10.1016/S1063-4584(03)00169-9.
[85] Y. Kim, M. Soo, Y. Seok, M. Hur, Self-aromatherapy Massage of the Abdomen for the Reduction of Menstrual Pain and Anxiety during Menstruation in Nurses : A Placebo-Controlled Clinical Trial, vol. 3, 2011, pp. 3–6, https://doi.org/10.1016/j.eujim.2011.08.007.
[86] E. Jenabi, "B7E19a460Ed6B4D0Aaadf69F7Bae0830C6D8," pp. 14–16.
[87] P. Rahnama, A. Montazeri, H.F. Huseini, S. Kianbakht, M. Naseri, Effect of Zingiber officinale R. Rhizomes (ginger) on pain relief in primary dysmenorrhea: a placebo randomized trial, BMC Compl. Alternative Med. 12 (2012), https://doi.org/10.1186/1472-6882-12-92.
[88] G. Ozgoli, M. Goli, F. Moattar, Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea, J. Alternative Compl. Med. 15 (2) (2009) 129–132, https://doi.org/10.1089/acm.2008.0311.
[89] F. Kashefi, M. Khajehei, M. Tabatabaeichehr, M. Alavinia, J. Asili, Comparison of the effect of ginger and zinc sulfate on primary dysmenorrhea: a placebo-controlled randomized trial, Pain Manag. Nurs. 15 (4) (2014) 826–833, https://doi.org/10.1016/j.pmn.2013.09.001.
[90] M.A. Shirvani, N. Motahari-Tabari, A. Alipour, Use of ginger versus stretching exercises for the treatment of primary dysmenorrhea: a randomized controlled trial, J. Integr. Med. 15 (4) (2017) 295–301, https://doi.org/10.1016/S2095-4964(17)60348-0.
[91] C.D. Black, M.P. Herring, D.J. Hurley, P.J. O'Connor, Ginger (Zingiber officinale) reduces muscle pain caused by eccentric exercise, J. Pain 11 (9) (2010) 894–903, https://doi.org/10.1016/j.jpain.2009.12.013.
[92] C.D. Black, P.J. O'Connor, Acute effects of dietary ginger on muscle pain induced by eccentric exercise, Phyther. Res. 24 (11) (2010) 1620–1626, https://doi.org/10.1002/ptr.3148.
[93] J. Caldwell, C. Green, and M. Health, "Abstracts (196) A Longitudinal Examination of Cancer Pain : the Role of Gender and Breakthrough Pain Folk Medicine/Herbal Remedies," no. vol. 196, p. 196.
[94] M.D. Matsumura, G.S. Zavorsky, J.M. Smoliga, The effects of pre-exercise ginger supplementation on muscle damage and delayed onset muscle soreness, Phyther. Res. 29 (6) (2015) 887–893, https://doi.org/10.1002/ptr.5328.
[95] N. Manimmanakorn, A. Manimmanakorn, D. Boobphachart, W. Thuwakum, W. Laupattarakasem, M.J. Hamlin, Effects of Zingiber cassumunar (Plai cream) in the treatment of delayed onset muscle soreness, J. Integr. Med. 14 (2) (2016) 114–120, https://doi.org/10.1016/S2095-4964(16)60243-1.
[96] N. Sritoomma, W. Moyle, M. Cooke, S.O. Dwyer, The effectiveness of Swedish massage with aromatic ginger oil in treating chronic low back pain in older adults : a randomized controlled trial, Compl. Ther. Med. 22 (1) (2014) 26–33, https://doi.org/10.1016/j.ctim.2013.11.002.
[97] R.K. Cady, J. Goldstein, R. Nett, R. Mitchell, M.E. Beach, R. Browning, A double-blind placebo-controlled pilot study of sublingual feverfew and ginger (LipiGesic™M) in the treatment of migraine, Headache 51 (7) (2011) 1078–1086, https://doi.org/10.1111/j.1526-4610.2011.01910.x.
[98] D.C. Nieman, R.A. Shanely, B. Luo, D. Dew, M.P. Meaney, W. Sha, A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial, Nutr. J. 12 (1) (2013) 1–9, https://doi.org/10.1186/1475-2891-12-154.
[99] S. Khayat, M. Kheirkhah, Z. Behboodi Moghadam, H. Fanaei, A. Kasaeian, M. Javadimehr, Effect of treatment with ginger on the severity of premenstrual syndrome symptoms, ISRN Obstet. Gynecol. 2014 (2014) 1–5, https://doi.org/10.1155/2014/792708.
[100] E. Khalilzadeh, et al., Antinociceptive Effects , Acute Toxicity and Chemical Composition of Vitex Agnus-Castus Essential Oil, vol. 5, 2015, pp. 218–230, 3.
[101] F. Heydarpour, M.H. Farzaei, Pharmacognosy Reviews, 2018, https://doi.org/10.4103/phrev.phrev.
[102] E. Aslan and M. Abdelaleem, "Fructus Agni Casti and Bromocriptine for Treatment of Hyperprolactinemia and Mastalgia," doi: 10.1016/j.ijgo.2004.01.001.
[103] T. Dinç, F. Coşkun, Comparison of Fructus Agni Casti and Flurbiprofen in the Treatment of Cyclic Mastalgia in Premenopausal Women, 2014, pp. 34–38, https://doi.org/10.5152/UCD.2014.2409.
[104] M. Halas, Treatment of Cyclical Mastalgia with a Solution Containing a Vitex Agnus Castus Extract : Results of a Placebo-Controlled Double-Blind Study, 1999, pp. 175–181.
[105] R. Schellenberg, Treatment for the Premenstrual Syndrome with Agnus Castus Fruit Extract : Prospective , Randomised , Placebo Controlled Study, vol. 322, 2001, pp. 134–137.
[106] A.N. Aksoy, I. Gözükara, S.K. Kucur, Evaluation of the efficacy of Fructus agni casti in women with severe primary dysmenorrhea, A prospective comparative Doppler study 40 (3) (2014) 779–784, https://doi.org/10.1111/jog.12221.
[107] A. Ambrosini, C. Di, G. Coppola, F. Pierelli, C. Di Lorenzo, Use of Vitex Agnus-Castus in Migrainous Women with Premenstrual Syndrome : an Open-Label Clinical Observation, 2013, pp. 25–29, https://doi.org/10.1007/s13760-012-0111-4.
[108] L. Ma, S. Lin, R. Chen, X. Wang, Treatment of Moderate to Severe Premenstrual Syndrome with Vitex Agnus Castus (BNO 1095) in Chinese Women, vol. 26, 2010, pp. 612–616, https://doi.org/10.3109/09513591003632126.
[109] N. Boblitz, Treatment of Premenstrual Syndrome with a, vol. 9, 2000 no. 3.
[110] D.B.W. Schaffner, E.S.B. Meier, Efficacy of Vitex Agnus Castus L . Extract Ze 440 in Patients with Pre-menstrual Syndrome (PMS), 2000, pp. 150–153.
[111] M. Atmaca, S. Kumru, E. Tezcan, Fluoxetine versus Vitex Agnus Castus Extract in the Treatment of Premenstrual Dysphoric Disorder, 2003, pp. 191–195. November 2002.
[112] V.N. Prilepskaya, A. V Ledina, A. V Tagiyeva, F.S. Revazova, Vitex Agnus Castus : Successful Treatment of Moderate to Severe Premenstrual Syndrome, 2006, pp. 55–63, https://doi.org/10.1016/j.maturitas.2006.06.017.

[113] H.J. Teede, Short Report and Vitex Agnus-Castus on PMS-like Symptoms in Late-Perimenopausal Women : Findings from a Subpopulation Analysis, vol. 15, 2009, pp. 1045–1048, 9.
[114] O. Report, "c r v i h o e f.".
[115] R. Schellenberg, C. Zimmermann, J. Drewe, G. Hoexter, C. Zahner, Phytomedicine Dose-dependent efficacy of the Vitex agnus castus extract Ze 440 in patients suffering from premenstrual syndrome, Eur. J. Integr. Med. 19 (14) (2012) 1325–1331, https://doi.org/10.1016/j.phymed.2012.08.006.
[116] M. Momoeda, H. Sasaki, E. Tagashira, Efficacy and Safety of Vitex Agnus - Castus Extract for Treatment of Premenstrual Syndrome in Japanese Patients : A Prospective , Open-Label Study, 2014, pp. 362–373, https://doi.org/10.1007/s12325-014-0106-z.
[117] M. Kaplanoglu, Ethinyl Estradiol-Drospirenon versus Vitex Agnus-Castus Extract in Efficacy of the Treatment of Premenstrual Syndrome Ethinyl Estradiol-Drospirenon versus Vitex Agnus-Castus Extract in Efficacy of the Treatment of Premenstrual Syndrome Premenstruel Sendro, 2015, https://doi.org/10.4328/JCAM.3297.
[118] L. Farouk, A. Laroubi, R. Aboufatima, A. Benharref, A. Chait, Evaluation of the analgesic effect of alkaloid extract of Peganum harmala L, Possible mechanisms involved 115 (2008) 449–454, https://doi.org/10.1016/j.jep.2007.10.014.
[119] Z. Abolhassanzadeh, E. Aflaki, G. Yousefi, A. Mohagheghzadeh, Randomized Clinical Trial of Peganum Oil for Knee Osteoarthritis, 2015, pp. 1–6, https://doi.org/10.1177/2156587214566867.
[120] N. Shakeri, S. Mehrabi, A. Mehrabi, H.M. Jahanabad, Journal of Nephropathology Tamsulosin on Pain Relief and Expulsion of Renal and Ureteral Stones ; a Randomized Clinical Trial, vol. 9, 2020, https://doi.org/10.34172/jnp.2020.40, 4.
[121] P. Potential, Medicinal and Pharmacological Potential of Harmala (Peganum Harmala L .) Seeds, 2011, https://doi.org/10.1016/B978-0-12-375688-6.10070-2.
[122] S. Moradi, N. Yousofvand, Rubbing Oil Effect on Pain in Small Male Mice, vol. 13, 2016, pp. 821–826.
[123] Antinociceptive Activity of Various Extracts of Peganum Harmala L . And Possible Mechanism of.".
[124] M. Shoaib, et al., Scientific investigation of crude alkaloids from medicinal plants for the management of pain, BMC Compl. Alternative Med. (2016) 1–8, https://doi.org/10.1186/s12906-016-1157-2.
[125] B. Ranjan, S. Manmohan, S.R. Singh, R.B. Singh, Medicinal uses of trachyspermum ammi: a review, The Pharma Research 5 (2011) 247–258.
[126] A. Qureshi, K. Eswar, Phytochemical constituents and pharmacological activities of Trachyspermum ammi, Plant Arch 10 (2010) 955–959.
[127] J.A. Duke, Handbook of phytochemical constituents of GRAS herbs and other economic plants, in: Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2018.
[128] M.M. Zarshenas, M. Moein, S.M. Samani, P. Petramfar, An overview on Ajwain (Trachyspermum ammi) pharmacological effects; modern and traditional, J. Nat. Remedies (2014), https://doi.org/10.18311/jnr/2014/96.
[129] S.M. Al-Khazraji, The pain decreasing effect of the alcoholic extract of Trachyspermum ammi (L.)(Ajwain) in experimental animals, J. Pharmaceut. Sci. Res. 11 (3) (2019) 1087–1091.
[130] P. Petramfar, M. Moein, S.M. Samani, S.H. Tabatabaei, M.M. Zarshenas, Trachyspermum ammi 10 % topical cream versus placebo on neuropathic pain, a randomized, double-blind, placebo-controlled trial, Neurol. Sci. (2016), https://doi.org/10.1007/s10072-016-2600-3.
[131] Carrier Oil: Types, Use, and More." https://www.healthline.com/health/carrier-oil#black-seed-oil (accessed Mar. 29, 2022).
[132] Can Essential Oils Interfere With the Prescriptions You're Writing? | ThriveAP." https://thriveap.com/blog/can-essential-oils-interfere-prescriptions-youre-writing (accessed Mar. 29, 2022).
[133] FDA Guidelines | Registrar." https://www.registrarcorp.com/fda-guidelines/?lead_source=GoogleAd&utm_source=google&utm_medium=cpc&utm_term=fda regulations&utm_content=114954786954&utm_campaign=11453632249&matchtype=p&device=c&gclid=Cj0KCQjw3IqSBhCoARIsAMBkTb2m18tM6FIERoOHi4kqrgEwTdVUEKfVZ4m3hwRYFVXpgQzVQvkzjhUaAvCrEALw_wcB (accessed Mar. 29, 2022).
[134] P.V. Gersbach, N. Reddy, Non-invasive localization of thymol accumulation in Carum copticum (Apiaceae) fruits by chemical shift selective magnetic resonance imaging, Ann. Bot. (2002), https://doi.org/10.1093/aob/mcf179.