Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science

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Background.—Comprehensive literature reviews of historical perspectives and evidence supporting cannabis/cannabinoids in the treatment of pain, including migraine and headache, with associated neurobiological mechanisms of pain modulation have been well described. Most of the existing literature reports on the cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), or cannabis in general. There are many cannabis strains that vary widely in the composition of cannabinoids, terpenes, flavonoids, and other compounds. These components work synergistically to produce wide variations in benefits, side effects, and strain characteristics. Knowledge of the individual medicinal properties of the cannabinoids, terpenes, and flavonoids is necessary to cross-breed strains to obtain optimal standardized synergistic compositions. This will enable targeting individual symptoms and/or diseases, including migraine, headache, and pain.

Objective.—Review the medical literature for the use of cannabis/cannabinoids in the treatment of migraine, headache, facial pain, and other chronic pain syndromes, and for supporting evidence of a potential role in combatting the opioid epidemic. Review the medical literature involving major and minor cannabinoids, primary and secondary terpenes, and flavonoids that underlie the synergistic entourage effects of cannabis. Summarize the individual medicinal benefits of these substances, including analgesic and anti-inflammatory properties.

Conclusion.—There is accumulating evidence for various therapeutic benefits of cannabis/cannabinoids, especially in the treatment of pain, which may also apply to the treatment of migraine and headache. There is also supporting evidence that cannabis may assist in opioid detoxification and weaning, thus making it a potential weapon in battling the opioid epidemic. Cannabis science is a rapidly evolving medical sector and industry with increasingly regulated production standards. Further research is anticipated to optimize breeding of strain-specific synergistic ratios of cannabinoids, terpenes, and other phytochemicals for predictable user effects, characteristics, and improved symptom and disease-targeted therapies.

Key words: cannabis, cannabinoids, marijuana, CBD, cannabidiol, THC, Δ9-tetrahydrocannabinol, migraine, headache, terpenes, flavonoids

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INTRODUCTION

Migraine affects approximately 18% of women and 6% of men in the United States (US) and Europe, and more than 10% of the world's population, accounting for approximately 700 million migraineurs worldwide.[1] It is estimated that there are 38 million migraineurs in the United States, accounting for 12% of the US population, and that 1in 4 households have someone with migraine. In 2016, migraine was determined to be the 2nd leading cause of all global disability, and the 2nd leading cause of all neurological disease burden.[2] These estimates have increased from prior estimates of migraine as the 6th leading cause of all global disability, and headache disorders as the 3rd leading cause of disability worldwide.[3] Migraine accounts for 50% of all neurologic disability and costs more than $20 billion per year with 113 million lost workdays annually.[4] Furthermore, chronic pain in general is the largest contributor to years lived with disability globally,[5] and is associated with tremendous negative impacts on social, economic, and personal function.

Migraine treatment is divided into acute and preventive therapy. Most existing preventive therapies are adopted from anti-epileptic, antidepressant, and antihypertensive medications. However, many of these medications are not well tolerated, resulting in poor compliance. OnabotulinumtoxinA is currently available for treatment of chronic migraine, and calcitonin gene related peptide (CGRP) antagonists, and neuromodulation devices are either available or in late-stage development for both acute and preventive migraine therapies. The most frequently used acute migraine medications include analgesics such as nonsteroidal anti-inflammatories (NSAIDs) and triptans.[6,7] Unfortunately, although the only medication class developed solely for migraine, 25% of patients do not respond to triptans.[8] Furthermore, only one-third of patients taking a triptan are pain-free at 2 hours, and only 17%-25% remain pain-free over

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the next 24 hours.[9,10] This confers a large unmet need for additional migraine specific medications in both the acute and preventive treatment of migraine.

New migraine specific medications are desperately needed. Data have shown that cannabinoids appear to work uniquely and synergistically within the inherent pathways of migraine and pain, including triptan mechanism of action pathways.[11–17] Comprehensive literature reviews of historical perspectives and neurobiological mechanisms of action of cannabis/cannabinoids in the treatment of pain, including migraine and headache, have been performed.[11–14,18,19] This paper should be considered an extension of those publications.

This paper has 3 primary goals. The first is to summarize the most recent evidence for the use of cannabis/cannabinoids in migraine and headache treatment. Second, to review the current literature regarding the use of cannabis/cannabinoids in chronic pain disorders, since these data likely extrapolate to headache disorders given overlapping neurobiological pathways of pain. Third, to explore the growing evidence for the use of cannabis to help with the opioid epidemic, as cannabis use has been associated with lowering opioid mortality and has shown benefit in detoxification from opioids.

Cannabis science is a rapidly evolving science with accumulating evidence for various therapeutic purposes. This science no longer revolves around use of generic unspecified cannabis strains with undefined content of Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and other phytochemicals. There are now strict and sterile production procedures with the goal of optimizing the breeding of cannabis strains and strain standardization with specific compositions of the major cannabinoids, THC and CBD, as well as minor cannabinoids and other important phytochemicals, particularly terpenes and flavonoids. Although most of the existing cannabis science literature focuses primarily on the major cannabinoids, THC and CBD, the minor cannabinoids, terpenes, and flavonoids have generally been ignored. Evidence suggests that these constituents, especially cannabinoids and terpenes, play significant roles in influencing one another and working synergistically. This results in a wide range of user effects, benefits, and side effects between strains with varying ratios of these components. The synergy and interactions between these cannabis compounds are referred to as the "cannabis entourage effects."[20,21] This paper will review the literature regarding the analgesic, anti-inflammatory, and other medicinal benefits of major and minor cannabinoids, primary and secondary terpenes, and flavonoids found in cannabis.

Because of the increasing evidence of cannabinoid efficacy in the treatment of pain and a combined number needed to treat (NNT) of 3.4, the Canadian Pain Society revised their consensus statement in 2014 to recommend cannabinoids as a third-level therapy for chronic neuropathic pain.[22] In 2017, The US National Academies of Sciences, Engineering, and Medicine published a statement that the use of cannabis for the treatment of pain is supported by well-controlled clinical trials and that there is substantial evidence that cannabis is an effective treatment for chronic pain in adults.[23]

In most medicinal cannabis registries, the most commonly reported reason for cannabis use by patients is chronic pain of some form. The first study using objective data for assessing national medicinal cannabis consumption came from data from a nationwide registry of all patients with a medical cannabis prescription in the Netherlands between 2003 and 2010.[24] The registry monitored 5540 patients use of 4 different cannabis strains of varying THC and CBD content and their use of co-medications. Notably, 53.6% of all users across each strain were also using some form of pain medication (nonopioid 40.5%, weak opioid 21.8%, strong opioid 21.2%) as the most common type of co-medication. It is likely that these people were using medicinal cannabis for some form of pain.

Another study evaluated the reasons why 348 patients in the waiting area of a Michigan medicinal cannabis certification clinic were seeking medicinal cannabis. Of all patients (recertification and 1st time applicants), 87% were using medicinal cannabis for severe or chronic pain relief (91% in 1st time applicants).[25] Chronic pain was observed as the most common reason for the use of medicinal cannabis across most other registries as well.[26–34]

THE ENDOCANNABINOID SYSTEM AND PAIN

The neurobiological pathways of cannabinoids and pain, including migraine, were detailed and summarized previously.[11–17] The endocannabinoid system involves the central and peripheral nervous system. It is involved in inflammatory and pain processes, and plays a role in a multitude of regulatory physiological processes across virtually every organ system.[35–40] The endocannabinoid system appears to work both independently and synergistically, binding other molecular targets within major endogenous pain circuitry systems, including inflammatory, endorphin/enkephalin, vanilloid/transient receptor potential cation channel subfamily V (TRPV), subfamily A (TRPA), subfamily M (TRPM), and a class of nuclear receptors/transcription factors called the peroxisome proliferator-activated receptors (PPAR).[41] The efficacy of cannabinoids in the treatment of chronic neuropathic pain is partly attributed to the endocannabinoid system modulation of the descending supraspinal inhibitory pathways. These pathways are often impaired in chronic pain syndromes.

The activities of the endocannabinoid system revolve around the presynaptic G protein-coupled cannabinoid 1 (CB1) and 2 (CB2) receptors, which inhibit adenylate cyclase activity.[42] There is a presumed third cannabinoid receptor, G protein-coupled receptor 55 (GPR55), termed CB3.[43] The primary endogenous cannabinoid receptor ligands (endogenous cannabinoids; endocannabinoids) are arachidonic acid derivatives synthesized "on demand," and include N-arachidonoylethanolamine (anandamide, or AEA), a primary mediator of endocannabinoid signaling, and 2-arachidonoylglycerol (2-AG).[36,44–46] The endocannabinoids, as well as the phytocannabinoids found in cannabis, bind to and activate the CB1 and CB2 receptors with variable affinities.[47–49] AEA and 2-AG are released from the postsynaptic neuron terminals and travel retrograde across the synaptic cleft to presynaptic neuron terminals, where they bind the CB receptors.

The CB1 receptor is the most abundant G protein-coupled receptor in the brain and one of the most abundant in both the peripheral and central nervous system.[47] CB1 receptors are expressed primarily on presynaptic peripheral and central nerve terminals, and to a lesser degree on peripheral organs. They are found extensively in the anatomical pain pathways including the periaqueductal gray (PAG) matter, rostral ventrolateral medulla, dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons, peripheral nerves/nociceptors, as well as other brain regions such as the amygdala, cerebral cortex, hippocampus, substantia nigra pars reticulata, basal ganglia, globus pallidus (internal and external segments), and molecular layer of the cerebellum.[35,50–53] CB1 receptors mediate the behavioral and psychotropic effects of cannabinoids, including the "high" felt with some cannabis strains, activated by THC. Retrograde signaling receptor activation of the CB1 receptors leads to opening of potassium channels, hyperpolarization of the presynaptic terminal, closing of calcium channels, and inhibition of the release of stored inhibitory and excitatory neurotransmitters, including glutamate, 5-hydroxytryptamine (5-HT) (serotonin), acetylcholine, gamma-aminobutyric acid (GABA), noradrenaline, dopamine, D-aspartate, and cholecystokinin at both inhibitory and excitatory synapses.[35,36,38,46,52,54–56] Exogenous and endogenous cannabinoids are also known to modulate pain pathways involving opioid, serotonin, and N-methyl-d-aspartate (NMDA) receptors through other indirect mechanisms.[57]

The CB2 receptors are concentrated primarily in the peripheral tissues and immune cells where they influence the release of cytokines, chemokines, and cell migration including neutrophils and macrophages, and to a lesser degree in the nervous system.[52,58,59] The CB2 receptors are primarily concentrated in the peripheral tissues, especially cells of the immune system, but can be found in lower concentrations in some brain regions including the PAG and some neuronal subpopulations of astrocytes, microglia, and oligodendrocytes.[60–62] CB2 receptors may also contribute to pain relief by dopamine release modulation.[63,64]

CANNABIS AND CANNABINOIDS IN MIGRAINE, HEADACHE, AND FACIAL PAIN

The medical literature regarding treatment of headache, migraine, and facial pain disorders shows supporting evidence for cannabis/cannabinoids in the treatment of chronic headaches,[65–68] migraine including chronic migraine,[13,14,39,66,69–82] medication overuse headache,[83] cluster headache,[82,84–86] idiopathic intracranial hypertension,[87] and multiple sclerosis (MS) associated trigeminal neuralgia.[88] At the time of this writing, this majority of supporting literature consists primarily of case series, case studies, case reports, surveys, clinical/anecdotal reports, and one retrospective analysis. To date, there are no placebo-controlled studies of cannabis for headache disorders, although there is a multicenter (29 sites), double-blind, placebo-controlled study evaluating efficacy and safety of a synthetic THC, dronabinol, in a metered dose inhaler for the treatment of migraine with and without aura that has been completed, but results not published at the time of this writing (May 2018).[89] There are only two prospective trials containing a control group evaluating the use of cannabinoids in the treatment of headache disorders.[82,83]

The first of these two prospective trials was a randomized, double-blind, active-controlled crossover trial in two separate 8 week intervals involving 30 patients (26 completed) with treatment refractory medication overuse headache (MOH) with daily analgesic intake for at least 5 years who had failed at least 3 detoxification attempts. Patients completed a course of either ibuprofen 400 mg or nabilone 0.5 mg daily for 8 weeks, followed by a 1-week washout, and then a second 8 weeks of the other medication. Results showed that nabilone 0.5 mg daily, a synthetic cannabinoid, was superior in reducing daily analgesic intake, pain intensity, level of medication dependence, and improved quality of life in these patients.[83] There was no differentiation of the underlying type of daily headache that led to the medication overuse headache; chronic migraine versus chronic tension-type headache versus other forms of chronic daily headache. In addition, MOH has been attributed to overuse of NSAIDs, including ibuprofen, at more than 10 days per month.[90] Therefore, the significance of these results is uncertain, because taking daily ibuprofen may sustain MOH, rather than help it. Furthermore, there is a possibility that the improvement seen in the control daily ibuprofen group crossing over to nabilone could be due to cessation of the ibuprofen.

The second prospective trial was an abstract presented at the 3rd Congress of the European Academy of Neurology (EAN) in Amsterdam in June 2017.[82] The authors evaluated the use of cannabinoids as both a prophylaxis and acute treatment for both chronic migraine and chronic cluster headache. Patients were given a combination of 2 compounds; one contained 19% THC and the other contained a combination of 0.4% THC + 9% CBD. In phase 1, determination of the effective dose was performed with a group of 48 chronic migraine volunteers starting with an oral dose of 10 mg of the combination and titrated up. Doses less than 100 mg produced no benefit. Oral doses of 200 mg administered during a migraine attack decreased acute pain intensity by 55%. This dose was used in phase 2.

In phase 2, chronic migraine patients (n = 79) were randomly assigned to 3 months prophylaxis treatment with either amitriptyline 25 mg per day or THC + CBD 200 mg per day in a 200 mL 50% fat emulsion. Chronic cluster headache patients (n = 48) were randomly assigned to 1 month of prophylaxis treatment with either verapamil 480 mg per day or THC + CBD 200 mg per day in a 200 mL 50% fat emulsion. For acute pain attacks, additional dosing of THC + CBD 200 mg was allowed in both groups. In the migraine patients, the THC + CBD 200 mg prophylaxis led to a 40.4% improvement versus 40.1% with amitriptyline. In the cluster headache patients, the THC + CBD 200 mg prophylaxis provided minimal to no benefit. Additional acute THC + CBD 200 mg dosing decreased pain intensity in migraine patients by 43.5%. This same result was seen in cluster headache patients, but only if they had a history of migraine in childhood. In cluster headache patients without a previous history of childhood migraine, the additional THC-CBD 200 mg abortive treatment provided no benefit as an acute treatment.

There has been one retrospective study of cannabis use in the treatment of migraine, and it was strongly positive, although limitations exist.[74] In this study, the investigators reviewed charts of 121 adults from 2 medical marijuana specialty clinics in Colorado. These patients had the primary diagnosis of migraine and had been recommended by a physician for acute and/or preventive treatment with medicinal cannabis. There were 7 patients using only for daily prophylaxis, 4 patients using only for acute treatment, and 110 patients using for both acute and preventive management. The primary outcome was the mean number of migraines per month at initial vs follow-up visits. The mean number of migraines per month dropped from 10.4 to 4.6 ($P < .0001$). Overall, 103 (85.1%) patients reported a decrease in frequency of migraines per month, 15 (12.4%) reported the same number of migraines per month, and 3 (2.5%) had an increase in the number of migraines per month.

CANNABIS AND CANNABINOIDS IN CHRONIC PAIN

Despite the lack of prospective studies in migraine and headache, there are many well-designed prospective placebo and active controlled trials conferring benefit of cannabis/cannabinoids in the treatment of various chronic pain disorders, as summarized in Table 1. Although not all-inclusive, Table 1 includes most of these pertinent studies, in addition to the limited migraine studies. These studies were comprised of cannabis that was smoked, oromucosal cannabis extracts, or synthetic cannabinoids. Most studies involve varying amounts of THC, some with THC + CBD, but there are no trials of CBD alone.

In 2009, a systematic review and meta-analysis of 18 double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain determined that cannabis treatment is moderately efficacious for treatment of chronic pain.[134]

In 2011, a systematic review of 18 well designed randomized controlled trials evaluating cannabis/cannabinoids for treatment of chronic noncancer pain in 925 enrolled patients showed that 83% (15/18) of the trials confirmed cannabis/cannabinoids had statistically significant positive analgesic effects.[135] There were a total of 615 enrolled patients in these trials with statistically significant positive outcomes. Initially, there were 22 studies identified, but 4 of them were excluded because pain outcomes were not specifically examined, the number of participants was low, or there was a duplicated study group. The 15 studies that showed positive outcomes included neuropathic pain,[91–94,103,136] fibromyalgia,[122] rheumatoid arthritis,[105] and mixed chronic pain.[104,110,111,118,119,123,124] There was an additional study included in this review that evaluated oromucosal cannabis extracts in central neuropathic pain from brachial plexus root avulsion.[112] The cannabis preparations provided statistically significant reductions in pain and sleep disturbance, but fell short of the target hypothesis goal, so that study was not included as a positive study in this systematic review.

In 2013, a systematic review of 38 well designed randomized controlled trials evaluating cannabis/cannabinoids in the treatment of pain in 2,423 enrolled patients showed that 71% (27/38) of the trials confirmed cannabis/cannabinoids had statistically significant positive analgesic effects.[35] On further analysis of the 27 positive studies, 2 of them were not comparison studies, but rather open label extension studies[107,108] that followed their correlating initial randomized studies that were published separately.[104,137] Another study showed that dihydrocodeine was a better analgesic than nabilone and thus, a negative study, although a small number of patients did respond well to nabilone.[138] Two of the studies were separate publications of the same study sample and data, with additional

Table 1.—Studies Demonstrating Positive Analgesic Effects of Cannabis/Cannabinoids in Chronic Pain Syndromes

Agent	Control	Population	Enrolled / completed	Trial design	Results
Smoked cannabis (2.5%, 6%, 9.4% THC in 25 mg single inhalations/doses) tid × 5 days of each cycle, followed by 9 day washout[91]	Placebo	Chronic post-traumatic or postsurgical neuropathic pain with allodynia or hyperalgesia	23/21	Randomized, double-blind, placebo controlled, crossover trial for 8 weeks (4 treatment periods, each lasting 2 weeks)	25 mg inhalation of 9.4% THC tid × 5 days significantly reduced pain intensity + improved sleep. Mean daily pain intensity was lower among cannabis groups
Smoked cannabis (1-8% THC) titrated to tolerance day 1 followed by 4 days at tolerated dose, with 4 treatments per day separated by 90-120 minutes[92]	Placebo	HIV-associated distal sensory predominant polyneuropathy (DSPN)	34/28	Randomized, double-blind, placebo-controlled, crossover trial for 7 weeks	Significant pain reduction in all completers. NNT 3.5 for at least 30% pain reduction
Smoked cannabis (3.5%, 7% THC), 9 puffs per session[93]	Placebo	Chronic central and peripheral neuropathic pain (CRPS type I, spinal cord injury or MS, diabetic neuropathy, focal nerve injury)	38/32	Randomized, double-blind, placebo-controlled, crossover trial in three 6-hour sessions with 3-21 day intervals between sessions	Significant decrease in pain with both doses. 3.5% and 7% THC produced equal anti-nociception. Secondary outcomes of pain unpleasantness and global impression of change also improved with cannabis
Smoked cannabis (3.56% THC weighing average 0.9g/cigarette), 1 cigarette tid x 5 days[94]	Placebo	HIV sensory neuropathy	55/50	Randomized, double-blind, placebo-controlled trial	Smoking 1st cannabis cigarette reduced chronic pain ratings (AUC) 72% vs 15% placebo, compared with the last cannabis cigarette at 51% vs 5% placebo. Significant reduction in pain with median reduction of 34% (placebo 17%). 52% in cannabis group had ≥ 30% pain reduction (24% placebo). NNT for > 30% pain reduction 3.6
Smoked cannabis (4% THC weighing average 0.8g/cigarette), 1 cigarette/d × 3 days[95]	Placebo	Spasticity pain in MS	37/30	Randomized, double-blind, placebo-controlled, crossover trial for 17 days	Statistically significant reduction of both spasticity and pain. Cannabis reduced pain scores on the VAS by 5.28 points more than placebo
Smoked cannabis (low dose 2%, medium dose 4%, high dose 8% THC)[96]	Placebo	Healthy volunteers evaluated for pain and cutaneous hyperalgesia induced by intradermal capsaicin	19/15	Randomized, double-blind, placebo-controlled, crossover trial	Significant decrease in capsaicin induced pain with 4% (medium dose) and significant increase in pain with 8% (high dose) THC by 45 minutes after cannabis exposure. No effect seen with 2% (low dose). Authors suggested lower doses may decrease pain, while higher doses may increase pain
Smoked cannabis (3.55% THC)[97]	Placebo	Healthy volunteers who were regular marijuana users evaluated for dose dependent anti-nociception of marijuana, and whether pretreatment with naltrexone modulated this effect	13/5	Randomized, double-blind, placebo-controlled trial. Users participated in 3 sessions at least 3 days apart, each of which had 4 controlled smoking bouts per session, spaced at 40 minute intervals	Marijuana produced significant dose-dependent anti-nociception. Addition of naltrexone did not significantly influence marijuana dose-effect curves
Vaporized cannabis (low dose 1.29% THC, medium dose 3.53% THC), 8-12 puffs per session[98]	Placebo	Neuropathic pain (peripheral neuropathy, nerve injury, CRPS 1, spinal cord injury)	39/39	Randomized, double-blind, placebo-controlled, crossover trial consisting of three 6-hour treatment sessions. 3-14 day intervals between sessions	Significant improvement in pain and patient-rated global impression of change. 30% pain reduction in: 57% low dose 1.29% THC, 61% medium dose 3.53% THC, 26% placebo. NNT for 30% pain reduction: 3.2 for 1.29% THC vs. placebo, 2.9 for 3.53% THC vs placebo, 25 for 3.53% THC vs 1.29% THC. (Comparable anti-nociception between low and medium doses)
Vaporized cannabis (low (1% THC), medium (4% THC), high (7% THC)) dose by weight; cannabidiol <1%. At a weight of 400 mg of cannabis per administration, dosing therefore was controlled at 0, 4, 16 or 28 mg THC per dosing session[220]	Placebo	Short-term efficacy and tolerability of inhaled cannabis for treatment-refractory painful diabetic neuropathy	16/16	Randomized, short-term, placebo-controlled, four-period, cross-over study. Four-hour sessions separated by 2 weeks	Significant pain improvement with cannabis in placebo vs low ($P = .031$), medium ($P = .04$), high doses ($P < .001$). Also, significant improvement in high vs low and medium doses (both $P < .001$), but significant negative effect (impaired neuropsychological test performance) of the high dose
Vaporized cannabis[99]	N/A	Patients with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone	21/21	Participants admitted for 5-day inpatient stay. Inhaled vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5	Pain significantly decreased (average 27%) after addition of vaporized cannabis. Concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects
Novel portable thermal-metered-dose inhaler (tMDI) for cannabis: single 15.1 ± 0.1 mg dose of cannabis[100]	N/A	Chronic neuropathic pain	8/8	Single-dose, open-label study	Significant 45% reduction in pain intensity 20 minutes post inhalation ($P = .001$), turning back to baseline within 90 minutes

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Smoked, vaporized, edible, topical cannabis formulations.Mean monthly doses: smoked 1.59 oz, vaporized 2.64 oz, edible 2.59 oz, topical 2.73 oz (Specific strains and/or amounts/ratios of cannabinoids within products not consistently documented.)[74]	N/A	Adults with primary diagnosis of migraine, recommended medical cannabis for migraine treatment or prophylaxis by a physician	121/121	Retrospective observational chart review of 2 medical marijuana specialty clinics in Colorado	Migraine frequency decreased from 10.4 to 4.6 per month ($P<.0001$) with medical cannabis. Reasons for use: Migraine daily prophylaxis only (7 patients), acute treatment only (4 patients), both acute and preventive (110 patients) 103 (85.1%) reported a decrease in frequency of migraines/month, 15 (12.4%) had same number of migraines/month, 3 (2.5%) had increase in number of migraines/month
Standardized herbal cannabis (12.5% ± 1.5% THC). Median daily dosage 2.5g/d (range = .1-13.4; interquartile range = 1.5-3.0). 58 (27%) used smoking as only route of administration, 130 (61%) used a combination of smoking, oral, and vaporization, and 17 (8%) consumed cannabis orally only[101]	Chronic pain patients who were not cannabis users	Chronic non-cancer pain. Primary outcome: serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Secondary efficacy parameters included pain and other symptoms, mood, and quality of life	431/330	Prospective cohort study with a 1-year follow-up conducted in 7 clinical centers. Six clinical visits (1, 2, 3, 6, 9, and 12 months after baseline) and 3 telephone interviews (1, 2, and 3 weeks after the baseline visit) were scheduled for patients in the cannabis group; 2 clinical visits (6 and 12 months after baseline) and 5 telephone interviews (1, 2, and 3 weeks, 3 and 9 months after baseline) were scheduled for control patients	Concluded that cannabis at average doses of 2.5g/d may be safe as part of a carefully monitored pain management program when conventional treatments have failed. Significant reduction in average pain intensity over 1 year in cannabis group (change = .92) but not in control group (change = .18). After adjusting for confounders, greater reduction in pain observed among cannabis users than controls (difference = 1.10). No difference in risk of serious adverse events between groups. Medical cannabis users were at increased risk of non-serious adverse events which were mild to moderate. No differences in secondary safety assessments. Neurocognitive function improved in both groups. After adjusting for tobacco smoking and other covariates, no significant change in slow vital capacity, functional residual capacity, and total lung capacity over 1 year among cannabis users. Cannabis users had a mean 50-mL decrease in FEV1 and a mean 1% decrease in the FEV1/FVC ratio, and increase in non-serious respiratory adverse events such as bronchitis
Cannabis: smoking (11%), oral (46%) and combined (43%)[102]	Fibromyalgia patients who were not cannabis users	Fibromyalgia patients who were cannabis users	56/56	Observational study comparing 100-mm VAS scales (VAS) before and at 2 hours of cannabis consumptions, 36-item Short Form Health Survey (SF-36), Fibromyalgia Impact Questionnaire (FIQ), Pittsburg Sleep Quality Index (PSQI)	After 2 hours of cannabis use, VAS scores showed statistically significant ($P<.001$) reduction of pain and stiffness, enhancement of relaxation, and increase in somnolence and feeling of well being. The mental health component summary score of the SF-36 was significantly higher ($P<.05$) in cannabis users than in non-users
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[103]	Placebo	Peripheral neuropathic pain with allodynia	125/105	Randomized double-blind, placebo-controlled, parallel design trial. 5 weeks plus open label extension option	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Mean daily sprays 10.9 (THC 29.4 mg:CBD 27.3 mg). Significantly less pain with Sativex® with mean pain decrease 22% (placebo 8%); 26% had 30% reduction (NNT 8.6) (placebo 15%); 20% had 50% reduction (NNT 8.5) (placebo 8%). Sativex® group also had significant benefit in sleep, allodynia, pain disability index. Open label extension showed initial pain relief was maintained without dose escalation for 52 weeks
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[104]	Placebo	Central neuropathic pain in MS	66/64	Randomized double-blind, placebo-controlled, parallel design trial. Treatment phase over 4 weeks	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Mean daily sprays 9.6 (THC 25.9 mg:CBD 24 mg). Significant reductions in pain and sleep disturbance with Sativex®. NNT 3.7
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[105]	Placebo	Rheumatoid arthritis	58/54	Randomized double-blind, placebo-controlled, parallel design trial. Treatment phase over 5 weeks	Mean daily sprays 5.4 (THC 14.6 mg:CBD 13.5 mg). Significant improvements in pain on movement, pain at rest, quality of sleep
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[106]	Placebo	Peripheral neuropathic pain with allodynia	246/173	Randomized, double-blind, placebo-controlled, parallel design trial. Treatment phase over 14 weeks	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 24 sprays/24 hours (THC 64.8 mg:CBD 60 mg). Mean daily sprays 8.9 (THC 24 mg:CBD 22.3 mg). 34 patients in active treatment group had 30% or greater reduction in pain vs 19 in placebo (statistically significant). Also, statistically significant improvement in sleep

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) [107]	N/A	Central neuropathic pain in MS	63/34 completed >1 year; 28 completed full 2 year extension	Uncontrolled open label, 2-year extension trial for long term efficacy and tolerability. This followed a prior randomized double-blind, placebo-controlled, parallel design trial'[4] which lasted 5 weeks (4 weeks treatment)	Mean NRS-11 pain scores in final week of initial randomized trial: 3.8 (5.0 placebo). In 28 subjects completing full 2-year open label extension, mean NRS-11 in final week: 2.9. Mean sprays per day by all patients after 1 year: 6.1 (THC 16.5 mg:CBD 15.3 mg), and 6.5 (THC 17.6 mg:CBD 16.3 mg) at 2 years. No evidence of tolerance
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids)[108]	N/A	MS associated pain, spasms	137/79 (92 followed for at least 1 year). These 137 patients (out of 160) were those whom felt benefit from Sativex in the initial randomized trial	Open label extension study assessing long-term efficacy. This followed a prior 6 week randomized double-blind, placebo-controlled, parallel design trial'[5] which ended with a 4 week open label trial. (10 weeks total for initial study)	Sativex appeared to provide maintenance of symptom relief over the long term. Results showed that MS patients receiving symptom relief in the 1st 10 weeks maintain that relief over an extended time without needing an increased dose. Also, suddenly stopping Sativex did not cause any withdrawal syndrome, but MS symptoms did return over 5-10 days. Mean duration of study participation 434 days for patients remaining on treatment (79), and 225 days for patients who stopped (58). Mean sprays per day: 11 (THC 30 mg:CBD 28 mg). No evidence of tolerance
Standardized oromucosal tincture spray (Sativex®; 0.1 mL sublingual spray = THC 2.7 mg:CBD 2.5 mg) with additional cannabis-based compounds (minor cannabinoids, terpenes, flavonoids). Evaluated low dose (1-4 sprays/day), medium dose (6-10 sprays/day), high dose (11-16 sprays/day)[109]	Placebo	Adjunct to opioid-refractory cancer pain	360/263	Multicenter, randomized, double-blind, placebo-controlled, parallel group, graded-dose study for 5 week treatment periods	Secondary responder analysis of average daily pain was statistically significant for Sativex vs placebo overall, and specifically in the low and medium dose groups. Low dose group achieved 26% improvement in pain compared with baseline. However, primary endpoint of 30% pain reduction was not significant for Sativex. Significant sleep improvement with low dose, and non-significant sleep benefit with medium dose
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and:a) THC 2.5 mg + CBD 2.5 mgb) 2.5 mg THC alonec) 2.5 mg CBD alone[110]	Placebo	Chronic pain	34/24	Initial 2-week open label period followed by 8-week randomized, double-blind, placebo-controlled, single-patient crossover trial. Subjects randomly received each of the 3 medications and placebo for two separate 1-week periods	Significant reduction in pain. and quality of sleep. Extracts that contained THC showed most benefit. Dose ranges varied between 1 and 8 sprays for a single dose
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and: a) THC 2.5 mg + CBD 2.5 mg; b) 2.5 mg THC alone; c) 2.5 mg CBD alone[111]	Placebo	Neurogenic symptoms in spinal cord injury (4), MS (18), brachial plexus injury (1), limb amputation (1)	24/20	Randomized, double-blind, placebo-controlled, single-patient crossover trial in 2 week study periods	CBD significantly improved pain. THC significantly improved pain, muscle spasm, spasticity, and appetite. THC:CBD combination significantly improved muscle spasm and sleep. Max permitted dose 120 mg/24 hours
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®) vs THC 2.7 mg[112]	Placebo	Neuropathic pain from brachial plexus avulsion	48/45	Randomized, double-blind, placebo-controlled, 3 period crossover trial in 2 week treatment periods. Followed by open label extension study of Sativex® (36/45; 83% entered)	Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Statistically significant reductions in pain and sleep disturbance, but not to full 2 point reduction defined in study hypothesis. NNT for Sativex® 9, NNT for THC only 7.7
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®) vs THC 2.7 mg only[113]	Placebo	Adjunct to opioid-refractory cancer pain	177/144	Multicenter, randomized double-blind, placebo-controlled, parallel design trial over 2 weeks	Primary endpoint of change from baseline mean pain numerical rating score statistically significant in favor of Sativex. 43% (greater than half) of Sativex group had >30% pain reduction compared to placebo (21%). Associated odds ratio statistically significant. The THC only group showed a non-significant improvement in pain. Sativex group had reduced breakthrough opioid dosing. Max dose 8 sprays/3 hours (THC 21.6 mg:CBD 20 mg), or 48 sprays/24 hours (THC 129.6 mg:CBD 120 mg). Average 8-12 sprays/d (22-32 mg THC, 20-30 mg/d CBD)

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Standardized oromucosal 0.1 mL sublingual tincture spray of cannabis-based compounds (minor cannabinoids, terpenes, flavonoids) and THC 2.7 mg:CBD 2.5 mg (Sativex®).[114] Max dose 12 sprays/24 hours	Placebo	Central neuropathic pain in MS	339/297	Multicenter (33 sites) phase III, 14 weeks parallel group randomized controlled double-blind trial, followed by 14 week open label extension	Statistically significant decrease in pain (>30% improvement from baseline) vs placebo at 10 weeks (P=.046), while at 14 weeks lower pain scores persisted for treatment group but not statistically significant. Secondary endpoints of mean change from baseline in Pain Numerical Rating Scale (NRS) (P=.028) and sleep quality NRS (0.015) both statistically significant in favor of treatment group
Oral cannabis extract (THC 2.5 mg bid titrated to effect/tolerability to a max 25 mg daily + CBD 0.8-1.8 mg)[115]	Placebo	Muscle stiffness and pain in MS	279/224	Randomized, double-blind, placebo-controlled, phase III trial over 12 weeks	Cannabis extract gave significant improvement in muscle stiffness (almost twice compared to placebo), pain, sleep, and spasms. Only 47% titrated up to THC 25 mg daily dose, most averaged 10 mg or 15 mg daily
Oral cannabis extract (Cannador) 5, 10, or 15 mg THC + variable CBD. THC:CBD ratios were 1:0.3 for the 5-mg dose (THC 5 mg:CBD 1.5 mg) and 1:0.5 for the 10 mg (THC 10 mg:CBD 5 mg) and 15 mg (THC 15 mg:CBD 7.5 mg) doses[116]	N/A	Postoperative patients requiring overnight patient-controlled analgesia with morphine	20/20	Multicenter randomized controlled dose-escalation trial. Pain relief, pain intensity, and side effects recorded over 6 hours	Rescue analgesia requested by 100% of patients receiving 5 mg, 50% of patients receiving 10 mg, and 25% of patients receiving 15 mg Cannador. NNT to prevent 1 rescue analgesia request for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 and 1.3, respectively. Overall, 10 mg was optimal dose in providing pain relief without serious side effects
Dronabinol 2.5 mg bid vs oral cannabis extract (THC 2.5 mg:CBD 1.25 mg and <5% other cannabinoids) bid. Dosing weight based; 30-49kg: 4 capsules daily, 50-69kg: 6 capsules daily, 70-89kg: 8 capsules daily, >89kg: 10 capsules daily[117]	Placebo	MS associated spasticity and pain	630/611	Multicenter, randomized, double-blind, placebo-controlled, parallel design trial for 15 weeks	Significant improvements in pain (Dronabinol: 50%, Cannabis extract: 57%, placebo: 37%) and spasticity (Dronabinol: 60%, Cannabis extract: 61%, placebo: 46%) reported by patients subjectively, although no improvement on spasticity by objective Ashworth scale
Dronabinol 10 mg vs 20 mg daily[118]	Placebo	Chronic non-cancer pain on opioids	30/29	Phase I: Randomized, single-dose, double-blinded, placebo-controlled, crossover trial, over three 8 hour visits. Phase II: Extended 4 week open-label multi-dose titrated trial as add-on to baseline opioid use	Phase I: Significant decrease in pain intensity with both 10 mg and 20 mg once daily doses.Phase II: Significant decrease from baseline pain scores
Dronabinol 5 mg bid[119,120]	Placebo	Central pain in MS	24/24	Randomized, double-blind, placebo-controlled, crossover trial in 3 week treatment periods	Significant reduction in pain. NNT for 50% relief 3.5. On quality of life scale, bodily pain and mental health indicated benefit
Dronabinol 20 mg vs morphine 30 mg vs Dronabinol-morphine 20 mg-30 mg[121]	Placebo	Healthy volunteers undergoing experimental pain tests (heat, cold, pressure, single and repeated transcutaneous electrical stimulation)	12/12	Randomized, double-blind, placebo-controlled, crossover trial in 8-hour study periods	Dronabinol-morphine statistically significant pain improvement compared to placebo and additively effective compared to morphine alone in repeated mode electrical stimulation. A slight additive analgesic effect was seen with Dronabinol-morphine in the single mode electrical stimulation compared to morphine alone. Dronabinol alone did not significantly reduce pain, and caused hyperalgesia in cold and heat tests, which was completely neutralized by Dronabinol-morphine. No analgesic effect in the pressure and heat test with Dronabinol or Dronabinol-morphine
Nabilone 0.5-1 mg. Titration from 0.5 mg qhs to 1 mg bid over 4 weeks[122]	Placebo	Fibromyalgia	40/33	Randomized, double-blind, placebo-controlled, parallel design trial	Significant decrease in both anxiety and pain at 4 weeks on 1 mg bid
Nabilone 1 mg[123]	Placebo	Spasticity related pain in upper motor neuron syndrome	13/11	Randomized, double-blind, placebo-controlled, crossover trial in 4 week treatment periods	Significant decrease in spasticity related pain with Nabilone 1 mg/day, but no significant decrease in spasticity itself
Nabilone 0.25-1 mg[124]	Placebo	Chronic musculoskeletal spinal pain (although "headache" was also monitored)	30/21	Randomized, double-blind, placebo-controlled, crossover trial in 4 week treatment periods followed by 16 week medication switch with free choice of study drugs	Significant decrease in spinal pain with Nabilone. Also noted significant decrease in headache intensity, increase in headache-free days, and increase in quality of life. In medication switch period, number of subjects favoring Nabilone was > 4x higher than those favoring placebo
Nabilone 0.5 m g daily[83]	Ibuprofen 400 mg daily	Medication overuse headache (MOH)	30/26	Randomized, double-blind, active-controlled, crossover trial in 8 week treatment periods	Nabilone superior in reducing daily analgesic intake, pain intensity, level of medication dependence, and improve quality of life

Table 1.—*(Continued)*

Agent	Control	Population	Enrolled / completed	Trial design	Results
Nabilone 0.5 mg bid titrated to 1-2 mg bid over initial 4 week phase. Dose achieved continued for next 5 week phase.[125]	Placebo	Diabetic neuropathy	Phase 1: 34/37Phase 2:25/26 (1 placebo dropped out due to lack of efficacy)	Randomized, double-blind, placebo-controlled, parallel design trial with 4 week single blind flexible dose phase, followed by 5 week double blind maintenance phase for subjects receiving >30% pain improvement in initial single blind phase (26/37)	Nabilone significantly more effective at improving pain, sleep, and anxiety. 11/13 (Nabilone) vs 5/13 (placebo) had 30% or greater reduction in pain in second double blind phase; 26/37 received >30% pain improvement in initial single blind phase
Nabilone 1 mg bid adjunct to Gabapentin[126]	Placebo	MS neuropathic pain	15/14	Randomized, double-blind, placebo-controlled, parallel design trial for 9 weeks (4 week titration, 5 week maintenance)	Significant improvement in pain and patient-rated global impression of change with addition of Nabilone
Oral THC 10 mg, 20 mg vs codeine 60 mg, 120 mg[127]	Placebo	Cancer pain	36/34	Randomized, double-blind, placebo-controlled trial	Analgesia of THC 10 mg comparable to codeine 60 mg, and THC 20 mg comparable to codeine 120 mg. Analgesic effect of THC 20 mg was statistically significant compared to placebo, but this was outweighed by sedation
Oral THC 5 mg, 10 mg, 15 mg, 20 mg[128]	Placebo	Cancer pain	10/10	Randomized, double-blind, placebo-controlled trial	Significant trend toward progressive relief of pain with increasing THC doses. Pain relief with THC was significantly higher than placebo at high dose levels of 15 mg and 20 mg. Low doses of 5 mg and 10 mg showed a trend toward greater pain relief than placebo. Analgesic effect of THC developed gradually and was prolonged. Sedation outweighed benefit at 20 mg
Oral THC daily dose of 2.5-15 mg, with a weekly increase of 2.5 mg if tolerating[129]	N/A	Fibromyalgia	9/4	Treatment over 3 month period	Electrically induced pain was significantly attenuated after doses of 10-15 mg THC ($P<.05$). Daily recorded pain levels were significantly reduced ($P<.01$)
Oral THC 5 mg vs codeine 50 mg[130]	Placebo	Spasticity and pain due to spinal cord injury	1/1	Single case, randomized double-blind, placebo-controlled trial. The 3 options were applied in a randomized pattern 18 times in a single patient and compared	THC and codeine both had an analgesic effect compared to placebo, but only THC showed a significant benefit on spasticity
Combination of 2 compounds; one 19% THC and the other 0.4% THC + 9% CBD 200 mg doses of this compound combination in a 200 mL 50% fat emulsion was studied as prophylaxis, as well as additional acute dosing[82]	Amitriptyline 25 mg daily in chronic migraine prophylaxis group Verapamil 480 mg daily in chronic cluster prophylaxis group	Prophylaxis and acute treatment in both chronic migraine and chronic cluster headache	Phase 1: 48/48 chronic migrainePhase 2:79/79 chronic migraine48/48 chronic cluster	Phase 1: dose finding to determine effective acute dosing in 48 chronic migraine volunteers starting with an oral dose of 10 mg of cannabinoid combination and titrated up Phase 2: Chronic migraine randomly assigned to 3 months prophylaxis treatment with 25 mg/day Amitriptyline or THC+CBD 200 mg/day. Chronic cluster randomly assigned to 1 month prophylaxis with Verapamil 480 mg/day or THC+CBD 200 mg/day. For acute pain attacks, additional dosing of THC+CBD 200 mg was allowed in both groups	Phase 1: Doses < 100 mg THC-CBD produced no benefit. With 200 mg THC-CBD, acute migraine pain intensity decreased by 55% Phase 2: THC+CBD 200 mg prophylaxis led to a 40.4% improvement vs 40.1% with Amitriptyline in migraine group, but no benefit in cluster group. Additional acute THC+CBD 200 mg dosing decreased pain intensity in migraine patients by 43.5%. This same result was seen in cluster headache patients, but only if they had a history of migraine in childhood. In cluster headache patients without a previous history of childhood migraine, the additional THC-CBD 200 mg treatment provided no benefit as an acute treatment
Synthetic nitrogen analog of tetrahydrocannabinol (NIB). 1st trial compared NIB 4 mg with codeine 50 mg. The 2nd trial compared NIB 4 mg with secobarbital 50 mg[131]	Placebo	Advanced cancer pain	1st trial: 30/26 2nd trial: 15/15	2 consecutive randomized, double-blind, placebo-controlled, crossover trials. 3 successive days on each treatment in each trial	1st trial: NIB superior to placebo and equivalent to codeine 50 mg 2nd trial: NIB superior to both placebo and secobarbital 50 mg
Ajulemic acid (AJA), or CT3: synthetic analog of the THC metabolite THC-11-oic acid. 20 mg bid x 4 days, then 40 mg bid x 3 days[132,136]	Placebo	Chronic neuropathic pain with hyperalgesia and allodynia	21/19	Randomized, double-blind, placebo-controlled, crossover 5-week trial in two 7-day treatment periods	Significant improvement in pain intensity 3 hours after AJA. Mechanical hypersensitivity also showed a strong tendency toward decreasing sensitivity in the AJA group, but not statistically significant. NNT for 30% pain relief were 2.14 for 1st treatment group and 5.29 for 2nd treatment group

outcomes data reported in the second study.[132,136] There was a total of 1889 enrolled patients in the trials with statistically significant positive outcomes in 56 studies identified initially, but 18 of them were excluded because they did not specifically examine pain outcomes, instead examining spasticity, cramps, or other global measure of benefit. The 27 studies showing positive outcomes included experimentally induced pain in healthy volunteers,[96,97,121] cancer-related pain,[113,131] chronic neuropathic pain with hyperalgesia and allodynia,[93,103,132,136,138] chronic pain in fibromyalgia,[122] chronic pain in rheumatoid arthritis,[105] chronic pain in MS,[104,107,108,117,119,120] chronic pain from chronic upper motor neuron syndrome/spasticity,[111,123,130] unspecified chronic noncancer pain,[110,118,124] and chronic neuropathic pain from HIV, complex regional pain syndrome (CRPS), trauma, or surgery.[91,92,94]

In 2015, the same authors of the 2011 systematic review[135] published an updated systematic review of additional randomized controlled trials evaluating cannabis/cannabinoids in the treatment of chronic noncancer pain.[139] They found 11 additional well designed randomized controlled trials evaluating 1135 enrolled patients, of which 64% (7/11) of the trials demonstrated statistically significant analgesic effects of cannabis/cannabinoids compared to controls. There was a total of 672 enrolled patients in these trials with statistically significant positive outcomes. The 7 studies showing positive outcomes included reduction in daily analgesic intake, pain intensity, and level of dependence in medication overuse headache,[83] diabetic neuropathy,[125] MS pain, muscle stiffness and spasticity pain,[95,115,126] neuropathic pain associated with allodynia,[106] and neuropathic pain.[98] There was an additional study included in this review that evaluated a THC/CBD oromucosal cannabis spray in central neuropathic pain in MS.[114] It showed a statistically significant reduction in pain compared to placebo at 10 weeks, but not at 14 weeks, so it was not included as a positive study in this systematic review.

A systematic review and meta-analysis published in *JAMA* in 2015 evaluated 79 trials involving cannabis/cannabinoids for medicinal use (28 in chronic pain) and concluded that there was moderate-quality evidence to support their use for the treatment of chronic pain and spasticity. Compared with placebo, cannabis/cannabinoids were associated with reduction in pain, greater average reduction in numerical scale pain assessment, and average reduction in the Ashworth spasticity scale.[140] A second 2015 *JAMA* medical literature review included 6 trials involving 325 patients examining chronic pain, 6 trials involving 396 patients investigating neuropathic pain, and 12 trials involving 1600 patients focusing on MS.[141] They conclude that the use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. A third systematic review in 2015 assessing the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain in 13 trials also suggested that these therapies may provide effective analgesia in conditions that are refractory to other treatments.[142]

The FDA approved 188 novel drugs for 206 indications based on 448 pivotal efficacy trials between 2005 and 2012.[143] The median number of pivotal trials per approved indication was only 2, although 74 indications (36.8%) were approved on the basis of only one pivotal trial. There were 4 drugs approved without any pivotal efficacy trial. Nearly all trials were randomized, double-blinded, and used either a placebo or an active comparator. The median number of patients enrolled per indication among all pivotal trials was 760. Another review of the new drugs available in the last 30 years showed that more than 35% of them had a direct natural origin, and that number rose to over 60% when taking into account all drugs whose structure was based from a natural pharmacophore.[144,145] Taking this into account, the number of studies and amount of evidence for the use of cannabis/cannabinoids in the treatment of pain continues to grow, and thus it is now considered a plausible option. The Canadian Pain Society now recommends cannabinoids as a third-level therapy for chronic neuropathic pain.[22] The US National Academies of Sciences, Engineering, and Medicine now states that cannabis use for the treatment of pain is supported by well-controlled clinical trials with substantial evidence that it is an effective treatment for chronic pain in adults.[23]

CANNABIS AND CANNABINOIDS IN THE OPIOID EPIDEMIC

Given the supporting evidence of cannabis/cannabinoids in pain management, some advocate for using them as a replacement for opioids. Substituting cannabis for alcohol, illicit drugs, and/or prescription medication has been observed in cross sectional surveys that suggested a harm reduction role in their use, along with implications for abstinence-based substance use treatment strategies.[146–148] The "opioid-sparing effect" of cannabinoids has been well described with extensive supporting evidence showing synergy between cannabis and opioids that results in decreased opioid dose requirements.[99,149] CB1 receptors are 10 times more concentrated then mu-opioid receptors in the brain, and cannabinoid receptors co-localize with opioid receptors in many regions involved in pain circuitry including the dorsal horn of the spinal cord. This results in synergistic augmentation of the analgesic opioid effects and decreased opioid dose requirements.[99,150–160] The interaction is suspected to be from pharmacodynamic mechanisms, since studies have

shown cannabis use did not affect blood levels of oxycodone or morphine.[99,151] Cannabinoid receptor agonists raise endogenous opioid peptide release, and chronic THC use increases endogenous opioid precursor gene expression in supraspinal and spinal structures involved in pain perception.[99,151,161,162]

In a study of chronic pain patients on a daily regimen of morphine or oxycodone, the addition of vaporized cannabis augmented the analgesic effect of opioids.[99] Pain significantly decreased (average 27%) after the addition of vaporized cannabis, and there was no effect on plasma opioid levels. Another large meta-analysis showed that 17 of 19 preclinical studies provided good evidence of synergistic effects from opioid and cannabinoid co-administration, and that the median effective dose (ED50) of morphine administered with THC is 3.6 times lower than the ED50 of morphine alone.[149] The ED50 for codeine administered with THC was 9.5 times lower than the ED50 of codeine alone. In summary, the authors stated that preclinical studies provide robust evidence of the opioid-sparing effect of cannabinoids.[149]

States with medicinal cannabis laws have a 24.8% lower mean annual opioid overdose mortality rate compared with states without medicinal cannabis laws.[163] There is an association between the implementation of medicinal cannabis laws and opioid mortality. In each year following the implementation of the law, the rates of overdose mortality declined, a trend that continued over time: year 1 (–19.9%; $P = .002$), year 2 (–25.2%; $P = .01$), year 3 (–23.6%; $P = .04$), year 4 (–20.2%; $P = .02$), year 5 (–33.7%; $P = .008$), and year 6 (–33.3%; $P < .001$).

The reduction of opioid dosing when used in combination with cannabis/cannabinoids reduces side effects and allows for easier detoxification and weaning due to less of a tolerance and withdrawal from opiates, and rekindling of opiate analgesia after prior dosages have worn off.[159] Because of the cannabis-opioid synergistic interactions as suggested by available data, cannabis has been suggested as a tool in the opioid detoxification and weaning process.[148,164–166] Some pain specialists have suggested the use of medicinal cannabis in addition to or as a replacement for opiates to help reduce overdose mortality and morbidity associated with opiate use.[167]

In a prospective study, chronic pain patients who used cannabis had improved pain and functional outcomes as well as a significant reduction in opioid use.[168] Medical cannabis use was associated with decreased opiate use, improvement in quality of life, and better side effect profile in a retrospective cross-sectional survey of chronic pain patients.[169]

Unfortunately, most chronic pain management programs have rules and "opioid contracts" mandating patients to be free of cannabis/cannabinoid use for enrollment and ongoing treatment. Given the abundance of evidence-based medicine and research on cannabinoid-opioid synergy, these policies seem quite outdated and should be re-evaluated. Patients using cannabis/cannabinoids may inadvertently be assisting their own detox and weaning from opiates. Chronic pain management programs should harness this potential benefit within their treatment program and use it to their patients' advantage.

THE CANNABINOIDS

Over 540 phytochemicals, 18 different chemical classes, and more than 100 different phytocannabinoids have been described in cannabis.[21,145] Phytocannabinoids accumulate and are concentrated in the secretory cavity of the glandular trichomes, primarily in female flowers and aerial parts of the plant.[145] Phytocannabinoid levels in hempseeds and hempseed oil are very low, as the seed and the stem contain only trace amounts of THC or CBD.[170,171] This point is important to those purchasing "CBD oil" and "hemp oil" seed-based products because the phytocannabinoid levels are subtherapeutic. Cannabinoid acids are found as the primary metabolite precursors to the cannabinoids in raw and live cannabis and have no psychotropic qualities. These acidic phytocannabinoids are decarboxylated by heat (such as from smoking or vaporizing), UV exposure, and prolonged storage to form the active cannabinoids. The predominant cannabinoid acids are tetrahydrocannabinolic acid (THCA) that is converted to Δ^9-tetrahydrocannabinol (THC), cannabidiolic acid (CBDA) that is converted to cannabidiol (CBD), cannabinolic acid (CBNA) that is converted to cannabinol (CBN), cannabigerolic acid (CBGA) that is converted to cannabigerol (CBG), cannabichromenic acid (CBCA) that is converted to cannabichromene (CBC), tetrahydrocannabivarin acid (THCVA) that is converted to tetrahydrocannabivarin (THCV), and cannabidivarinic acid (CBDVA) that is converted to cannabidivarin (CBDV).[145,172,173]

THC is a major cannabinoid and the most researched in cannabis. It is the primary source of the psychoactive side effects of cannabis. THC is a partial agonist at CB1 and CB2 receptors with preferential binding to CB1, and is also an agonist at the PPAR-γ and TRPA1 receptors.[49] Other reported mechanisms include 5HT3A antagonism, glycine receptor activation enhancement by allosteric modification, reducing elevated intracellular calcium levels from TRPM8 activity (cold and menthol receptor 1 [CMR1]), elevating calcium levels by TRPA1 or TRPV2, and stimulating G protein receptor 18 and other nuclear receptors.[173–182] Its actions at the CB1 receptor account for its psychoactive effects, thought to be mediated to some extent by modulation of both glutamate and GABA systems.[49,62,183–185]

NMDA mechanisms play a significant role in secondary and tertiary hyperalgesia in chronic pain syndromes such as fibromyalgia and chronic migraine.[186] THC reduces NMDA responses by 30-40% with associated antioxidant neuroprotective effects,[187–189] inhibits CGRP activity,[190] blocks capsaicin-induced hyperalgesia,[191] decreases 5HT reuptake, increases cerebral 5HT production, and inhibits 5HT release from platelets. All of these mechanisms could certainly influence trigeminovascular migraine circuitry.[14–16,161]

THC has well documented analgesic and anti-inflammatory benefits including arthritic and inflammatory conditions,[49,127–130,187,192–216] is 20 times more anti-inflammatory than aspirin, and twice as anti-inflammatory as hydrocortisone. [217] THC enhances analgesia from kappa opioid receptor agonist medications.[155,160,218,219] Intrathecal and intraventricular administration of THC produces analgesia similar to opioids.[204] THC also stimulates production of beta-endorphin and increases proenkephalin mRNA levels in brainstem regions involved in pain processing.[158,159,162]

There are numerous positive studies in various chronic pain syndromes showing a benefit of THC with smoked or vaporized cannabis and comparing different percentages of THC.[220,91–102] Unfortunately, percentages of other cannabinoids including CBD and other important compounds such as terpenes were not assessed in most of these trials. Because of the known entourage effects of cannabis[20,21] and the influence of the activity of cannabinoids and terpenes on one another, it is unclear if these study results are due to THC alone or due to the contribution of other undefined cannabinoids and terpenes.

There have been multiple studies confirming benefit in various chronic pain syndromes with an oral-mucosal spray called nabiximols (Sativex),[103–115,117,137,221–231] which has been approved in 30 countries. This is a tincture of cannabis made from cannabis plants rather than a synthetic form.[232] Each spray delivers a standardized dose of 2.7 mg THC and 2.5 mg CBD, along with additional cannabinoids, flavonoids, and terpenes in unmeasured small amounts. Despite the standardized THC:CBD ratio, the company doesn't mention what the actual concentrations of terpenes and other compounds are or how much variability exists. Similar to the smoked and vaporized studies, this missing information adds a layer of uncertainty as to what components are providing most of the benefit. Of note, one of these studies compared 3 varieties of this spray; 1:1 THC:CBD vs THC alone vs CBD alone. The spray that contained THC showed the most pain benefit.[110] Other cannabis extract studies of varying amounts of THC and CBD have also shown pain benefit.[115,116]

THC has potent anti-emetic benefits in adults[49,192,193,233–273] and children.[270,274–276] Migraine-associated nausea and vomiting would certainly be another therapeutic benefit. The antiemetic effects led to FDA approval for 2 synthetic forms of THC in the treatment of chemotherapy related nausea and vomiting, dronabinol,[277] and nabilone.[278] These 2 synthetic forms of THC have also been shown to have analgesic benefit.[81,83,84,117-126,279–282] There have been other benefits of THC reported also, including antioxidant and neuroprotective,[187,189,283–286] Alzheimer's disease,[287–291] amyotrophic lateral sclerosis (ALS),[292–296] MS,[104,106-108,114,115,117,137,197,221,224–231,297–299] autism,[300–304] Parkinson's,[305–312] Tourette's syndrome,[312–318] Huntington's disease/chorea,[319–321] depression,[322–324] posttraumatic stress disorder (PTSD),[325–329] sickle cell disease pain,[330,331] traumatic brain injury (TBI),[285,332–334] hypothermia,[335–339] duodenal ulcers,[340] anorexia and cachexia,[341–354] inflammatory bowel disease,[355–358] spinal cord injury,[359–361] antispasmodic, muscle relaxation, and spasticity,[130,229,298,299,362–366] antibacterial effects against methicillin-resistant *Staphylococcus aureus* (MRSA) strains,[367] anti-proliferative/pro-apoptotic against tumor cell lines of multiple organ systems including brain, breast, colon, and blood,[368–379] psoriasis,[380,381] bronchodilatation and asthma,[382–384] diabetes,[385] obesity,[386] glaucoma,[387–399] and as an antipruritic in cholestatic jaundice.[400]

CBD is the second major cannabinoid and has gained attention as a therapeutic agent over the past several years due to its lack of psychoactivity. In November 2017, The World Health Organization (WHO) announced that CBD in humans exhibits no evidence for abuse or dependence potential, and that there is no evidence of public health related problems associated with the use of pure CBD.[401] In January 2018, the World Anti-Doping Agency (WADA) removed CBD from their prohibited list, no longer banning use by athletes.[402]

CBD has much lower affinity for CB1 and CB2 receptors as compared to THC, and it acts as a noncompetitive CB1 and CB2 receptor antagonist.[403] This activity underlies its neutralizing actions on THC side effects such as anxiety, tachycardia, and sedation.[404–409] CBD seems to attenuate some of the negative side effects of THC when the CBD:THC ratio is at least 8:1 (± 11.1), but CBD may potentiate some of the THC side effects when the CBD:THC ratio is around 2:1 (± 1.4).[407,409] CBD was also shown to reduce cognitive and memory impairments that have been attributed to THC.[410] It is an inverse agonist at the CB2 receptor, which may contribute to its anti-inflammatory effects.[403]

CBD also interacts with a variety of ion channels, enzymes, and other receptors.[49,62,192,193,259,411] It inhibits AEA uptake and metabolism and acts as a TRPV1 agonist, similar to capsaicin, although without the noxious sides effects.[177–179,368,412] It acts as a positive allosteric modulator at α1 and α1β glycine receptors.[413] This has been suggested to play a role in chronic pain after inflammation or nerve injury, because glycine acts as an inhibitory postsynaptic neurotransmitter in the dorsal

horn of the spinal cord. CBD acts as a μ opioid receptor ligand and a positive allosteric modulator at μ and δ opioid receptors suggesting that it may enhance opiate effects.[49] CBD has additional actions that may account for its anti-inflammatory and analgesic effects including TRPA1 agonist, TRPV1 agonist, TRPM8 antagonist,[177–179] TRPV2 agonist by mediating CGRP release from dorsal root ganglion neurons,[414] T-type calcium^{2+} channel inhibitor,[415] suppresses tryptophan degradation (precursor to 5HT),[416] and phospholipase A2 modulator.[417] CBD has powerful analgesic and anti-inflammatory effects[49,142,187,192–194,196–199,209,330,403,411,418–437] mediated by both cyclooxygenase and lipoxygenase inhibition. In animal studies, its anti-inflammatory effect proved to be several hundred times more potent than aspirin.[217,438] There are other mechanisms by which CBD works in different pathways including 5-HT1A agonist,[49,439] regulator of intracellular calcium^{2+},[440,441] fatty acid amide hydrolase (FAAH; breaks down AEA) inhibition,[368] GPR55 antagonist,[43] adenosine uptake competitive inhibitor,[442] PPARγ agonist,[443] 5-lipoxygenase and 15-lipoxygenase inhibitors,[444] and antagonism of the abnormal-CBD receptor.[49,445]

There is medical evidence showing that CBD may be effective in treatment of a wide range of disorders[446] including epilepsy (particularly medically-refractory pediatric epilepsy syndromes),[49,447–472] Alzheimer's disease,[473–488] Parkinson'sdisease,[305,310–312,411,487–497] MS,[104,106–108,111,114,115,117,137,197,221,224–231,297,431–433,498–502] Huntington's disease,[321,485,503–505] ALS,[292,293,506] anxiety disorders including PTSD,[325,327,334,494,507–527] depression,[322,509,510,528–530] dystonia,[531,532] Meige's syndrome,[533] schizophrenia and psychosis,[493,509,534–545] stroke and hypoxic-ischemic injury,[478,546–554] antioxidant,[187,189,283] TBI,[552,553,555–558] spinal cord injury,[360,361] inflammatory disorders,[197,429–433,500] psoriasis,[380,381] rheumatoid arthritis,[421] a wide range of cancers across multiple organ systems including brain, blood, breast, lung, prostate, and colon,[262,368,369,379,446,559–582] graft vs host disease,[583] prion disease,[584] infection against MRSA,[367] inflammatory bowel diseases,[357,358,585–588] nausea,[259,589–591] appetite suppressant and weight loss,[592–594] bone formation, osteoporosis and fracture healing,[595–598] hepatic encephalopathy and cirrhosis,[599–603] cardiovascular diseases including hypertension, cardiomyopathy and myocardial ischemia,[426,604–609] and diabetic complications,[609–613] including diabetes-induced peripheral neuropathy.[434] There have been no studies evaluating pure CBD in the treatment of chronic pain or headache disorders to date.

The 2 main cannabinoid acids that have shown medicinal benefit are CBDA and THCA. CBDA is often obtained through consumption of raw cannabis juice and is a TRPA1 agonist,[177] TRPV1 agonist,[368] and TRPM8 antagonist.[177] This may reflect a potential role as an analgesic and anti-inflammatory[193,199,614] via selective COX2 inhibition. Other benefits include anti-proliferative/pro-apoptotic effects against breast, thyroid, glioma cancer cells,[368,561,615,616] and anti-nausea effects.[272,617]

THCA has anti-inflammatory[199] and anti-nausea effects.[618] It is a TRPA1 partial agonist,[177] and TRPM8 antagonist[177] which may reflect a potential role in analgesia. It has insecticidal effects,[619] potential anti-Parkinson's benefits,[305] and benefit in prostate cancer.[620] CBGA also has insecticidal effects.[619]

The most common minor cannabinoids include CBN, CBG, CBC, THCV, and CBDV. CBN is a product of THCA oxidation. As dried cannabis ages, THCA converts to CBNA, which then converts to CBN. Therefore, the older that dried cannabis is, the more CBN it contains. It has approximately 10% of the activity of THC and is a weak CB1 and CB2 partial agonist that binds stronger to CB2 than CB1.[49,173] It is the most sedative[621–625] of the cannabinoids, suggesting a potential role in insomnia and sleep disorders. Other benefits include anti-inflammatory,[105,217,417,626] analgesic,[203] anticonvulsant,[363,463,623,624] burn relief by TRPV2 agonism and mediation of CGRP release,[203,414] ALS,[506] antibacterial effects against MRSA strains,[367] promotion of bone formation,[595,627–629] appetite stimulant,[592] glaucoma,[388,630] and psoriasis.[380,381]

CBG is found in larger quantities in low THC cannabis strains, and especially in hemp strains. It is a CB1 and CB2 partial agonist,[49] CB1 antagonist,[631] TRPA1 agonist, TRPV1 agonist,[368] TRPV2 agonist, TRPV3 agonist, TRPV4 agonist and TRPM8 antagonist,[44,176–179,368] which may reflect a potential role in analgesia that has been described.[422] CBG is anti-inflammatory by phospholipase A2 modulation and reduction of PGE2,[105,417] and an inhibitor of AEA reuptake.[368] CBG has GABA uptake inhibitor effects,[632] and is a potent α2-adrenoreceptor agonist suggesting a potential role in α2-adrenoceptor-mediated analgesia.[631] CBG has antidepressant effects,[633] and a potent 5HT1A receptor antagonist that has been a proposed mechanism for potential antidepressant activity.[631] Benefits have been described for several issues including Huntington's disease,[634] as an appetite stimulant,[635] antibacterial effects against MRSA strains,[367] antifungal effects,[636] psoriasis,[381] inflammatory bowel disease,[637] anti-proliferative/pro-apoptotic against tumor cell lines of multiple organ systems,[178,179,368,638,639] glaucoma,[630,640] and potential benefit for detrusor overactivity and bladder pain.[641,642]

CBC is a potent TRPA1 agonist[177] that may reflect a potential role in analgesia, and a weak AEA reuptake inhibitor.[368] It interacts at TRPV1-4, and TRPV8 receptors.[643] Sedation, analgesic, and strong anti-inflammatory effects including superiority to phenylbutazone have been shown.[105,202,363,437,644–646] It may have antimicrobial effects against fungi and bacteria

including MRSA,[367,636,645] cytotoxicity in cancer cell lines,[368] antianxiety/antidepressant effects, promotion of neurogenesis,[322,647,648] potential use in inflammatory bowel disease,[649] and the ability to reduce THC intoxication symptoms.[650]

THCV is a propyl analog of THC. THCV antagonizes THC at the CB1 receptor at doses less than 3 mg/kg, is a CB1 agonist at doses greater than 10 mg/kg, and is also a CB2 partial agonist.[49,651,652] It increases GABA release, central nervous system inhibitory neurotransmission,[653] and has shown efficacy in experimental epilepsy models.[49,654] It has anti-nociception and anti-inflammatory effects.[49,655,656] Similar to synthetic CB1 antagonists, it causes decreased food intake, anorexia, and thus a potential weight loss treatment for obesity,[657–659] was effective in obesity-associated glucose intolerance,[660] and had beneficial effects on bone formation and fracture healing.[595,596]

Cannabidivarin (CBDV) is the propyl analog of CBD, but has an unknown mechanism of action. It has anticonvulsant activity in the hippocampus, comparable to felbamate and phenobarbitone,[456,654] and has bone formation and fracture healing benefits.[595,596]

TERPENES (TERPENOIDS)

The terpenes and terpenoids are major constituents of plant resins and essential oils, and are attributed to the pharmacological properties of many medicinal herbs, including cannabis. Terpenes are basic hydrocarbons as opposed to terpenoids that contain extra functional groups of a wide range of chemical elements. However, these terms are often used interchangeably in the literature. Terpenes form the largest group of phytochemicals.[145] Cannabis contains up to 200 different terpenes,[21] although this publication will focus on the primary and secondary terpenes which are generally present in the greatest concentrations. Terpenes are fragrant essential oils secreted by many different types of plants and herbs, including cannabis. They are the source of variable aromas, flavors, and other characteristics that help differentiate between cannabis strains.

They are lipophilic and have widely variable sites of action including neurotransmitter receptors, muscle and neuronal ion channels, G-protein receptors, enzymes, cell membranes, and second messenger systems.[21,661,662] Terpenes work both individually and synergistically with the cannabinoids for a variety of therapeutic effects. Terpenes may also increase the blood-brain barrier permeability, which led to a patent for a transdermal cannabinoid patch using a terpene as the permeation agent.[145,663] Terpenes may also influence the binding of THC to CB1 receptors, and interact with other neurotransmitter receptors that contribute to cannabinoid-mediated analgesia effects.[21,664] They have medicinal benefits including anti-inflammatory, analgesia, anxiolytic, antidepressant, anti-insomnia, skin penetration enhancement, cancer chemoprevention, antiviral, antibacterial, antifungal, anti-parasitic, and anti-hyperglycemic effects,[665] although it is important to note that the vast majority of these data come from preclinical studies involving animal models or in vitro studies. Some of the reported benefits attributed to individual terpenes come from studies evaluating whole essential oils or plants in which the specified terpene may be a predominant constituent. It is important to note that the therapeutic contribution from some of the other minor terpenes in some of these studies cannot be excluded. The most common primary terpenes found in cannabis are β-caryophyllene, myrcene, α-pinene, humulene, linalool, limonene, terpinolene, terpineol, ocimene, valencene, and geraniol. Some of the more common secondary terpenes in cannabis are α-bisabolol, nerolidol, caryophyllene oxide, phytol, borneol, δ-3-carene, terpinene, camphene, sabinene, cineole (eucalyptol), phellandrene, guaiol, isoborneol, cedrene, geranyl acetate, fenchol, camphor, menthol, isopulegol, cymene, citral, and citronellol.

Beta-caryophyllene (β-caryophyllene) is the more common of two forms of caryophyllene. It is found in cinnamon, cloves, black pepper, oregano, basil, rosemary, and hops. It has analgesic effects in inflammatory and neuropathic pain,[666] and has potent anti-inflammatory,[667–670] local anesthetic,[671] antioxidant,[672–674] anti-cancer,[672,675–678] and gastric cytoprotector effects.[679,680] Its anti-inflammatory effects occur via PGE-1,[681] with similar efficacy to indomethacin and etodolac,[682,683] and comparable to phenylbutazone.[681] β-caryophyllene is anti-fungal, anti-bacterial against *Staphylococcus aureus*,[684] anti-malarial,[685] beneficial in inflammatory bowel disease,[686] and anti-pruritic in contact dermatitis.[687] It is a selective CB2 agonist.[672,688,689] CB2 receptors have been implicated in anxiety and depression disorders, and caryophyllene has shown anxiolytic and antidepressant-like effects.[690] Research has also suggested that CB2 receptors play a major role in alcohol reward and the CB2 receptor system appears to be involved in alcohol[688] and cocaine[691] dependence and sensitivity via modulation of dopamine reward pathways. β-caryophyllene has been shown to reduce voluntary alcohol intake and attenuate ethanol-induced place preference and sensitivity in mice,[688] as well as decrease cocaine self-administration.[691] It may therefore represent a potential pharmacological target for the treatment of alcohol and cocaine abuse, and perhaps other abused substances in which the dopamine reward pathways are central to the pathophysiology. Trans-caryophyllene was shown to suppress hypoxia-induced neuroinflammatory responses,[692] and help regulate lipids.[693]

Myrcene is common in highly aromatic plants such as sweet basil, bay leaves, lemongrass, wild thyme, parsley, tropical fruits such as mango, and hops. It has potent anti-inflammatory, analgesic, and anxiolytic properties[694,695] and is used extensively in the cosmetics industry. The analgesic effects of myrcene were antagonized by naloxone suggesting an opioid-mediated mechanism.[695,696] It also has effects as a muscle relaxant, hypnotic, prominent sedation,[697] sleep aid,[698] and antioxidant.[699] It has significant anti-inflammatory effects[700] via prostaglandin E2[695] and anti-catabolic effects in human chondrocytes suggesting potential anti-osteoarthritic activity and the ability to halt, or at least slow down cartilage destruction and osteoarthritis progression.[701] It has also been shown to block hepatic carcinogenesis by aflatoxin in rats,[699] although there was concern of potential carcinogenesis in a separate rodent study.[702]

Alpha-pinene (α-pinene) accounts for the aroma of fresh pine needles, conifers, and sage, and is produced by many herbs such as parsley, rosemary, basil, and dill. It is the most commonly occurring terpene in nature.[703] It has shown antioxidant activity[704,705] and anti-inflammatory effects[706,707] in human chondrocytes suggesting potential anti-osteoarthritic activity,[708,709] as well as anti-inflammatory effects by PGE-1.[710] Anti-inflammatory effects in acute pancreatitis[711] and anti-nociception effects[712] have been demonstrated. It is an acetylcholinesterase inhibitor that may aid in memory and help to counter short-term memory loss associated with THC.[713–715] It has anti-fungal and broad-spectrum anti-bacterial effects[716–721] including against gram negative and positive bacteria such as *Staphylococcus aureus*, including MRSA.[684,722–724] Alpha-pinene has bronchodilator effects,[21,725] antiviral action[726] against anti-infectious bronchitis virus (IBV),[727] activity against herpes simplex virus-1 (HSV1) and severe acute respiratory syndrome (SARS),[728] and is an insect repellent.[703,729] It showed antiproliferative effects[678] and reduced melanoma tumor growth,[730] and has anti-cancer effects[717] against neuroblastoma cells[705] and in hepatic carcinoma cell lines.[731]

Humulene (α-caryophyllene) is an isomer of β-caryophyllene and plays a strong role in many of the distinguishing characteristics between different cannabis strains. It is found in herbs and spices such as hops, clove, basil, sage, ginger, spearmint, and ginseng as well as some fruits and vegetables. It has strong anti-inflammatory properties comparable to dexamethasone systemically, topically, and in allergic airway inflammation,[667–669,732,733] as well as anti-nociceptive and analgesic properties.[733] It has anti-cancer activity,[675,676,734] is anti-bacterial including activity against *Staphylococcus aureus*,[684] and insecticidal/larvicidal effects[735] have been documented. There are anecdotal reports that it causes weight loss and appetite suppression. Humulene was shown to increase the rate of Interleukin-8 (IL-8) secretion in human intestinal epithelial cells, but the significance is unclear.[736]

Linalool is found in many spices and flowers including lavender, citrus, coriander, rosewood, and laurels, birch trees, and is widely used in the cosmetics industry. It exhibits properties including anti-inflammatory and analgesic,[737–739] anti-nociception via activation of opioidergic and cholinergic systems,[737] anti-anxiety/stress,[740–743] sedation,[742,744–746] anti-depressant, modulation of motor movements and locomotion,[742] anti-bacterial, potent anti-leishmanial,[747] antimalarial,[748] anticonvulsant via anti-glutamatergic and GABA neurotransmitter systems,[749–753] anti-insomnia,[21] and antioxidant properties.[754] Its local anesthetic effects[755] were equal to procaine and menthol.[756] Analgesic effects have also been attributed to adenosine A_{2A} activity[757] and by ionotropic glutamate receptors including AMPA, NMDA, and kainate.[758] Linalool significantly decreased morphine opioid usage in gastric banding surgical patients following lavender inhalation vs placebo.[759]

Limonene is found in the rinds of all citrus fruits. It is the second most commonly occurring terpenoid in nature.[703] It is used in many household cleaners, perfumes, and foods. Studies have shown characteristics including anti-inflammatory,[701,706,760–762] analgesic,[763] antioxidant,[754,764,765] antidepressant and immunostimulating benefit,[763,766] anti-cancer against skin cancer, breast cancer, prostate cancer, other advanced solid tumors such as recurrent glioblastoma,[760,761,766–770] anti-bacterial, anti-fungal, and antimalarial,[748,764] and acts as insect repellent.[729] Limonene is active against acne,[771] dermatophytes,[764,772] and GERD.[773] It has been associated with bronchodilator effects in asthma.[760] It has also been shown to cause muscle relaxation and sleep in mice,[697] to be a powerful anxiolytic,[774–777] and reduced anxiety in patients with chronic myeloid leukemia.[778] Limonene has been shown to increase the metabolic turnover of dopamine in the hippocampus and serotonin in the prefrontal cortex and striatum, suggesting anxiolytic and antidepressant-like effects may occur by the suppression of dopamine activity related to enhanced serotonergic neurons, especially via 5-HT1A.[779]

Terpinolene is found in lilac, apples, nutmeg, cumin, conifers, tea tree, and sometimes used in perfumes, lotions, and soaps. It has shown anti-oxidant,[765,780,781] anti-bacterial and anti-fungal,[782,783] anti-cancer,[781,784] sedative,[785] and insecticidal[786] properties. It has also been suggested a potential treatment for heart disease by preventing low-density lipoprotein oxidation.[787]

Terpineol is found in pine trees, lilacs, eucalyptus, and lime blossoms, and used commonly in soap, perfume, and lotion. It reduced hyperalgesia in a chronic muscle pain fibromyalgia model presumably by affecting the opioid and

serotonergic receptors.[788] It has anti-inflammatory and analgesic actions,[788–790] antioxidant properties,[791]anti-proliferative and anti-cancer effects especially in small cell lung carcinoma,[678,792] antibacterial,[793,794] antifungal,[795] and antiviral[726] effects. It also has skin penetration enhancing effects,[796] airway smooth muscle relaxation in asthma,[797] vasorelaxation and blood pressure reduction effects,[798] and anxiolytic and sedative effects.[744,746]

Ocimene is found in many fruits and plants such as mango, mint, pepper, oregano, basil, parsley, orchids, hops, kumquat, pepper, and lavender. It has a sweet, fragrant, aroma that is used in perfumes. It has anti-inflammatory,[706] antifungal,[799] antiviral,[728] and antibacterial[800] benefits.

Valencene is found in Valencia oranges, grapefruit, tangerines, and other citrus fruits. It has anti-inflammatory effects,[801] insecticidal benefits,[802] and is a tick repellent.[803]

Geraniol is found in geraniums, rose, citronella, lemongrass, and is commonly added to perfumes. Its properties are anti-nociceptive,[804] anti-inflammatory,[805] antioxidant in inflammatory lung disease,[806] skin penetration enhancing effects,[807] antibacterial,[808–810] antifungal,[811,812] and antiparasitic.[813]

Alpha-bisabolol (α-bisabolol; levomenol) is produced by some plants such as the chamomile flower. It is used in making tea and in the cosmetics industry. It has anti-inflammatory effects in the skin,[814] as well as anti-nociceptive and neuroprotective benefit.[815] It was a pro-apoptotic agent for primary human acute leukemia cells[816] and glioma cells in both humans and rats,[817] breast cancer,[818] highly malignant human pancreatic carcinoma cell lines,[819] and anti-mutagenic/antioxidant.[820] Bisabolol has also shown protection against cisplatin-induced nephrotoxicity,[821] and successful treatment of visceral leishmaniasis.[822] It has also been shown be antibacterial,[823] and enhanced sensitization of *Staphylococcus aureus* to multiple antibiotic therapies.[824]

Nerolidol (trans-nerolidol) is found in many herbs and spices including ginger, jasmine, lavender, lemon grass, tea tree, oranges, and present in low levels in orange and other citrus peels. It has many applications in cooking and is approved by the US FDA as a food-flavoring agent. It has anti-insomnia and sedative properties,[825] anti-leishmanial activity,[826] anti-parasitic effects against *Babesia* parasites,[827] antifungal effects[828] against Microsporum gypseum,[829] anti-malarial effects,[748,830] and enhanced sensitization of *Staphylococcus aureus* and *Escherichia coli* to multiple antibiotic therapies.[824] It diminished large bowel adenomas[831] and enhanced skin penetration of 5-fluorouracil.[832]

Caryophyllene oxide is found in lemon balm, rosemary, lavender, cloves, hops, basil, oregano, black pepper, and eucalyptus, and often a metabolic byproduct of caryophyllene. It is used as a preservative in drugs, food, and cosmetics. It has analgesic and anti-inflammatory activity comparable to aspirin.[833] Carophyllene has anti-fungal[828] properties including onychomycosis comparable to sulconazole and ciclopiroxolamine,[834] insecticidal,[835] and anti-ischemic and anti-platelet aggregation properties.[836]

Phytol is a breakdown product of chlorophyl and tocopherol. It is found in green tea and wild lettuce. It has anti-insomnia and relaxing effects and has been postulated to increase levels of GABA through its inhibitory action on one of the GABA degradative enzymes, succinic semialdehyde dehydrogenase (SSADH).[837] It also prevented vitamin-A induced teratogenesis by converting retinol to a harmful metabolite.[838]

Borneol is found in camphor, rosemary, and mint. It has analgesic and anti-insomnia properties as well as bronchodilator and anti-septic effects.[839] It has a greater inhibitory potential on the nicotinic acetylcholine receptor than lidocaine, suggesting it could be an even more potent anesthetic.[840] Borneol has anti-inflammatory and analgesic effects,[841–845] insecticidal benefits,[846] anti-fibrosis properties,[847] wound-healing properties,[848] anti-cancer in a molecular relative (bornyl),[849] potentiator of cancer treatments,[850,851] enhancer for brain-targeting delivery systems,[852] and anticoagulant benefits[853] that were strong enough to prevent ischemic stroke in an animal model.[854]

Delta-3-carene (δ-3-carene) can be found in cedar, basil, pine, rosemary, and bell pepper, has shown anti-inflammatory effects,[710] and is known to dry out excess body fluids such as tears and mucus (well-known cannabis side effects of dry mouth and red eyes). It promotes bone growth and repair,[855] and has insecticidal and repellent qualities.[856–858]

Terpinene can be found in tea tree oil and some other plants. It is often used in the cosmetic and food industries. It is anti-inflammatory,[706,859] and has strong antioxidant properties.[860]

Camphene can be found in turpentine, camphor oil, citronella oil, ginger oil, cypress oil, and valerian. It is used as a food additive for flavoring and infused into topical creams and perfumes for fragrance. Camphene has antioxidant and analgesic effects[861] even when used topically,[843] antifungal action,[862] lowers cholesterol and triglycerides,[863] and acts as an antioxidant in inflammatory lung disease.[806] In traditional medicine it is often used as a topical treatment of bacterial and fungal infections, eczema, psoriasis, and athlete's foot.

Sabinene is found in various plants including marjoram, holm oak, juniper, Norway spruce, black pepper, nutmeg, and is a major component of carrot seed oil. It has benefits in digestion, antioxidant, inflammation, arthritis, soothing skin conditions,[707,864,865] and is anti-bacterial and anti-fungal.[721]

Cineole (Eucalyptol) is found in tea tree, rosemary, sweet basil, wormwood, tea trees, mugwort, bay leaves, common sage, and eucalyptus, and has historically been used as a topical to the gums and skin. It is one of the terpenes that is also

supported by several randomized placebo-controlled trials. According to the Natural Health Research Institute, it has been proven to improve memory and cognitive learning. Because of its cholinesterase inhibitory activity, it has potential for use in Alzheimer's disease,[715,866] and protection against amyloid beta-induced inflammation.[867] Cineole has anti-oxidative,[868] anti-inflammatory and analgesic properties,[869] and has been suggested as a potential long-term therapy in the prevention of COPD exacerbations and asthma control,[870–874] inflammatory bowel disease,[875] and acute pancreatitis.[876] It helps treat nasal and sinus inflammation and secretions in acute nonpurulent rhinosinusitis[877] and is used as a nasal decongestant and cough suppressant.[878] It is anti-fungal[879] including activity against onychomycosis,[880] anti-cancer,[881,882] antibacterial,[883] anti-tuberculosis,[884] insecticidal,[885,886] and inhibits cholesterol synthesis.[887]

Phellandrene is found in eucalyptus, water fennel, lavender, grand fir, and found in several herbs and spices including cinnamon, dill garlic, ginger and parsley. It has analgesic and anti-depressive effects.[763]

Guaiol is found in guaiacum and cypress pine. It has anti-inflammatory[683] and antimicrobial,[888] and insecticidal[889] benefits.

Isoborneol is found in mugwort and other plants. It has antioxidant effects that may be helpful in neurodegenerative diseases such Parkinson's disease that is associated oxidative stress.[890] It has anti-inflammatory,[845,891] antimicrobial,[892] and antiviral properties including a potent inhibitor of HSV1.[726,893]

Cedrene is found in cedar and has anti-cancer[894,895] antiparasitic,[896] and antifungal[897] properties.

Geranyl acetate is found in citronella, sassafras, roses, lemongrass, geranium, coriander, and carrot. It has antimicrobial,[898,899] antifungal, and anti-inflammatory properties.[900]

Fenchol is found in basil and is used in perfumes. It has antioxidant and antibacterial properties.[901]

Camphor comes primarily from the camphor tree, is easily absorbed through the skin, and produces a cooling sensation like menthol. It is used in inflammation-related disorders including sprains, rheumatism, muscle pains, and is antipruritic because of its local anti-inflammatory, anesthetic and analgesic properties.[902–904] Camphor desensitizes TRPV1 receptors more rapidly and completely than capsaicin, activates TRPV3, and inhibits TRPA1, correlating to its analgesic properties.[905] Camphor is used as a nasal decongestant and cough suppressant,[878] is an antioxidant,[902] has antibiotic properties,[906] and is antifungal against onychomycosis.[880] It has cholinesterase inhibitory activity, suggesting benefit in dementia and cognitive disorders.[715]

Menthol comes from corn mint, peppermint, or other mint oils. It is an analgesic used topically for inflammatory pain such as sprains, joint and muscle pains, and is antipruritic.[903] Central and peripheral analgesic mechanisms include activation of sensory neurons at the TRPM8 receptor,[907] selective activation of kappa-opioid receptors, inhibition of voltage gated sodium and calcium channels, and activation of GABA A receptors.[907–909] It is used as a nasal decongestant and cough suppressant,[878] is antifungal including activity against onychomycosis,[880] antibacterial, anti-cancer, and enhances the dermal penetration of pharmaceuticals.[910]

Isopulegol is a precursor to menthol. Its properties include anti-inflammatory and gastroprotective,[911] antidepressant and antianxiety,[912] and antioxidant and anticonvulsant properties.[913]

Cymene is found in cumin, thyme, coriander, and oregano. It has analgesic and anti-inflammatory properties including opioid system involvement, [914,915] antibacterial,[916] antifungal,[917] and is protective against acute lung injury.[918]

Citral is found in lemon balm, lemongrass, and citrus fruits. It has antioxidant,[754,919] antibacterial and antifungal,[920] muscle relaxation including gastrointestinal,[921] and sleep benefits.[697]

Citronellol is found in roses, geranium, sandalwood, lemongrass, chamomile, basil and lavender. It has shown promotion of wound healing, anti-cancer, anti-inflammatory, analgesic, and antioxidant benefits.[922,923] Citronellol has anti-hypertensive,[924] antifungal, and antibacterial effects.[925,926] It also acts as an insect repellent.

FLAVONOIDS

Cannabis also contains phenolic compounds (phenylpropanoids), one of which is called the flavonoids. These compounds normally act as antioxidants in plants and protect against oxidative stress.[145] They also contribute to the vibrant color in many fruits and vegetables. There have been about 20 different flavonoids identified in cannabis.[927] These include apigenin, luteolin, quercetin, kaempferol, cannflavin A, cannflavin B (unique to cannabis), β-sitosterol, vitexin, isovitexin, kaempferol, and orientin.[145] There have been correlations between dietary phenolic compound intake and reduced incidence of chronic diseases such as neurodegenerative diseases, cancers, and cardiovascular disorders.[928] Similar to terpenes, many of these compounds have also been shown to have anti-inflammatory, neuroprotective, and anti-cancer effects.[929] Apigenin has anxiolytic effects,[930] and inhibits TNF-α[931] which is involved in many inflammatory conditions. Cannflavin A and B have potent anti-inflammatory effects,[932] with Cannflavin A shown to inhibit PGE-2 30 times more potently than aspirin.[933]

β-sitosterol was shown to reduce topical inflammation by 65% and chronic edema by 41% in skin models.[934] Other phenolic compounds found in cannabis include the stilbenes, phenolic amides, and lignans.[145] There is much less research available on these various compounds at this time, and medicinal characteristics have yet to be differentiated.

CANNABIS STRAINS

Cannabis sativa strains are commonly described as energetic, uplifting, creative, euphoric, spacey, cerebrally focused effects, and better for day use. Cannabis indica strains are described as relaxing, calming, sedative, having full body effects such as "body buzz," and better for night use. These effects are not purely due to CBD:THC ratios according to research, as there are no significant differences in CBD:THC ratios between sativa and indica strains. These different subjective effects are most likely due to varying ratios of major cannabinoids, minor cannabinoids, terpenes and probably additional phytochemicals.[21,935–939] High CBD strains are sativa or indica strains that have been crossed with high CBD hemp strains (1:1 CBD:THC up to approximately 5:1 CBD:THC), while pure CBD strains (ratios of >10:1 CBD:THC up to approximately 50:1 CBD:THC) are considered hemp strains.[939]

Terpene concentration studies[940] show that "mostly indica" strains are often dominant in β-myrcene with limonene or α-pinene as the second most commonly present terpenes. "Mostly sativa" strains were more complex. Some strains were more dominant in terpinolene or α-pinene, while others were dominant in β-myrcene. Terpinolene or ocimene are the second most abundant terpenoids. Regardless, most strains used today are hybrids bred with specific and standardized ratios of THC, CBD, minor cannabinoids, and terpenes with a goal of targeting specific symptoms and predictable user effects. Cannabis science has evolved to classify strains not only based on THC and CBD compositions, but also based on minor cannabinoids, terpenes, and ultimately classified according to end-user effects and responses. In a recent study evaluating cannabis use patterns among medicinal cannabis patients who were treating for migraine and headache, hybrid strains were the most preferred. More specifically, "OG Shark," a high THC/THCA, low CBDA/CBD strain with β-caryophyllene followed by β-myrcene as the predominant terpenes, was the most preferred strain in these groups.[939] This could reflect the potent analgesic, anti-inflammatory, and anti-emetic properties of THC, along with documented anti-inflammatory and analgesic properties of β-caryophyllene and β-myrcene. Vaporizing and joint use were the most common primary methods of use, likely reflecting the need for a quick acting inhaled or nonorally ingested therapy in migraine attacks before severe pain and nausea and vomiting become prominent.

The health and medicinal benefits of many fruits, vegetables, whole grains, and other plant foods are the result of synergy between the various nutrients and bioactive compounds within the food rather than a single compound.[941] Similarly, cannabis exerts its medicinal effects via synergistic interactions between its cannabinoids, terpenes, flavonoids, and other compounds. To illustrate, in a rat model of neuropathic pain (thermal hyperalgesia), a controlled cannabis sativa extract containing multiple cannabinoids in a defined ratio along with other noncannabinoid compounds such as terpenes and flavonoids provided better and total relief of neuropathic pain compared to pure cannabinoids alone.[435]

CONCLUSIONS

The synergistic interactions between the many cannabis compounds are termed the "entourage effects." A variety of therapeutic benefits and effects reflect the cannabis entourage effects. Cannabis should be thought of as a broad category of medicines comprised of many different strains varying in their targets, responses, and side effects. This is synonymous to the broad category of antidepressants, comprised of many different medication classes varying in their neurotransmitter targets, responses and side effects.

There is growing evidence for therapeutic benefits of cannabis/cannabinoids in many diseases and symptoms, especially in the treatment of chronic pain with extension to migraine and headache, as well as a potential weapon in battling the opioid epidemic. More data are needed to determine what the most effective therapeutic ratios of cannabinoids, terpenes, flavonoids, and other compounds may be for these pain syndromes, as well as for other diseases and symptoms. These data will ultimately unveil optimal reproducible strain combinations to be bred for maximum predictable therapeutic efficacies.

CLINICAL HIGHLIGHTS

- There are numerous cannabis strains with variably unique and predictable characteristics, benefits, and side effects, depending on the ratios of cannabinoids, terpenes, flavonoids, and other phytochemicals working together synergistically.
- Many of the individual cannabinoids, terpenes, and flavonoids, have strong anti-inflammatory and analgesic properties that work individually and synergistically to provide the well-described analgesic benefits of cannabis/cannabinoids.
- The National Academies of Sciences, Engineering, and Medicine now state that the use of cannabis for the treatment

of pain is supported by well-controlled clinical trials with substantial evidence that cannabis is an effective treatment for chronic pain in adults. This benefit may extend to migraine and headache based on overlapping neurobiological mechanisms of pain and early research, although prospective studies are necessary.

- The well-documented opioid-sparing effect of cannabis/cannabinoids in conjunction with opioid use leads to lower opioid dose requirements, allowing for easier detoxification and weaning, and a potential tool against the opioid epidemic.
- Cannabis science is a rapidly growing new medical sector and industry involving sophisticated crossbreeding of specific strains for standardized compositions of cannabinoids, terpenes, and other phytochemicals, to target individualized diseases and/or symptoms including migraine and headache.

References

1. Robbins MS, Lipton RB. The epidemiology of primary headache disorders. *Semin Neurol.* 2010;30:107-119.
2. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 2017;16:877-897.
3. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P. Headache disorders are third cause of disability worldwide. *J Headache Pain.* 2015;16:58.
4. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA.* 2003;290:2443-2454.
5. Rice AS, Smith BH, Blyth FM. Pain and the global burden of disease. *Pain.* 2016;157:791-796.
6. Evers S, Afra J, Frese A, European Federation of Neurological Societies, et al. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. *Eur J Neurol.* 2009;16:968-981.
7. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78:1346-1353.
8. Diener HC, Limmroth V. Advances in pharmacological treatment of migraine. *Expert Opin Investig Drugs.* 2001;10:1831-1845.
9. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia.* 2002;22:633-658.
10. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet.* 2001;358:1668-1675.
11. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: What a long strange trip it's been …. *Headache.* 2015;55:885-916.
12. Lochte BC, Beletsky A, Samuel NK, Grant I. The use of cannabis for headache disorders. *Cannabis Cannabinoid Res.* 2017;2:61-71.
13. Russo E. Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. *J Cannabis Ther.* 2001;1:21-92.
14. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain.* 1998;76:3-8.
15. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and "triptan" receptors: implications in migraine. *J Neurosci.* 2013;33:14869-14877.
16. Akerman S, Holland PR, Goadsby PJ. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. *J Pharmacol Exp Ther.* 2007;320:64-71.
17. Akerman S, Kaube H, Goadsby PJ. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. *J Pharmacol Exp Ther.* 2004;309:56-63.
18. Woodhams SG, Chapman V, Finn DP, Hohmann AG, Neugebauer V. The cannabinoid system and pain. *Neuropharmacology.* 2017;124:105-120.
19. Woodhams SG, Sagar DR, Burston JJ, Chapman V. The role of the endocannabinoid system in pain. *Handb Exp Pharmacol.* 2015;227:119-143.
20. Ben-Shabat S, Fride E, Sheskin T, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *Eur J Pharmacol.* 1998;353:23-31.
21. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol.* 2011;163:1344-1364.
22. Moulin D, Boulanger A, Clark AJ, Canadian Pain Society, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag.* 2014;19:328-335.
23. Committee of the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids. *The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press; 2017.
24. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. *Eur J Clin Pharmacol.* 2013;69:1575-1580.
25. Ilgen MA, Bohnert K, Kleinberg F, et al. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend.* 2013;132:654-659.
26. Medical Marijuana Registry Statistics. Colorado Department of Health and Environment. (Accessed December 1, 2017, at https://www.colorado.gov/pacific/cdphe/medicalmarijuana).

27. Medical Cannabis Registry. Minnesota Department of Health. (Accessed December 1, 2017, at http://www.health.state.mn.us/topics/cannabis/registry.html).
28. Medical cannabis patient registry program. Illinois Department of Public Health. (Accessed December 1, 2017, at http://www.dph.illinois.gov/topics-services/prevention-wellness/medical-cannabis).
29. Medical cannabis program. Hawaii Department of Health. (Accessed December 1, 2017, at http://health.hawaii.gov/medicalcannabis/).
30. Oregon Medical Marijuana Program Statistics. Oregon Health Authority. (Accessed December 1, 2017, at http://www.oregon.gov/oha/PH/DISEASESCONDITIONS/CHRONICDISEASE/MEDICALMARIJUANAPROGRAM/Pages/data.aspx).
31. Medicinal Marijuana Program. State of New Jersey Department of Health. (Accessed December 1, 2017, at http://www.nj.gov/health/medicalmarijuana/).
32. Medical Marijuana - Reports. Arizona Department of Health Services. (Accessed December 1, 2017, at http://www.azdhs.gov/licensing/medical-marijuana/index.php#reports).
33. Medical Marijuana Patient Cardholder Registry Monthly Reports. Nevada Division of Public and Behavioral Health (DPBH). (Accessed December 1, 2017, at http://dpbh.nv.gov/Reg/MM-Patient-Cardholder-Registry/dta/Monthly_Reports/Medical_Marijuana_Cardholder_Registry_-_Monthly_Reports/).
34. Michigan Medical Marihuana Act Statistical Reports. The Michigan Department of Licensing and Regulatory Affairs, Bureau of Medical Marihuana Regulation. (Accessed December 1, 2017; at http://www.michigan.gov/lara/0,4601,7-154-79571_82631-448788-,00.html).
35. Aggarwal SK. Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain.* 2013;29:162-171.
36. Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. *Pharmacol Ther.* 2011;132:215-241.
37. Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. *Alcohol Alcohol.* 2005;40:2-14.
38. Maccarrone M, Gasperi V, Catani MV, et al. The endocannabinoid system and its relevance for nutrition. *Annu Rev Nutr.* 2010;30:423-440.
39. Greco R, Gasperi V, Maccarrone M, Tassorelli C. The endocannabinoid system and migraine. *Exp Neurol.* 2010;224:85-91.
40. Howlett AC. Efficacy in CB1 receptor-mediated signal transduction. *Br J Pharmacol.* 2004;142:1209-1218.
41. Mallat A, Teixeira-Clerc F, Deveaux V, Manin S, Lotersztajn S. The endocannabinoid system as a key mediator during liver diseases: new insights and therapeutic openings. *Br J Pharmacol.* 2011;163:1432-1440.
42. Galve-Roperh I, Rueda D, Gomez del Pulgar T, Velasco G, Guzman M. Mechanism of extracellular signal-regulated kinase activation by the CB(1) cannabinoid receptor. *Mol Pharmacol.* 2002;62:1385-1392.
43. Ryberg E, Larsson N, Sjogren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol.* 2007;152:1092-1101.
44. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab.* 2009;23:1-15.
45. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science.* 1992;258:1946-1949.
46. Battista N, Di Tommaso M, Bari M, Maccarrone M. The endocannabinoid system: an overview. *Front Behav Neurosci.* 2012;6:9.
47. Di Marzo V, Piscitelli F, Mechoulam R. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. *Handb Exp Pharmacol.* 2011;(203):75-104.
48. Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. *Annu Rev Med.* 2006;57:553-574.
49. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol.* 2008;153:199-215.
50. Guindon J, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets.* 2009;8:403-421.
51. Guindon J, Beaulieu P. The role of the endogenous cannabinoid system in peripheral analgesia. *Curr Mol Pharmacol.* 2009;2:134-139.
52. Kraft B. Is there any clinically relevant cannabinoid-induced analgesia?. *Pharmacology.* 2012;89:237-246.
53. Ramikie TS, Nyilas R, Bluett RJ, et al. Multiple mechanistically distinct modes of endocannabinoid mobilization at central amygdala glutamatergic synapses. *Neuron.* 2014;81:1111-1125.
54. Grant I, Atkinson JH, Gouaux B, Wilsey B. Medical marijuana: clearing away the smoke. *Open Neurol J.* 2012;6:18-25.
55. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev.* 2010;62:588-631.
56. Katona I, Freund TF. Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. *Nat Med.* 2008;14:923-930.
57. Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A. Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high'. *J Exp Biol.* 2012;215:1331-1336.
58. Iversen L. Cannabis and the brain. *Brain.* 2003;126:1252-1270.
59. Napchan U, Buse DC, Loder EW. The use of marijuana or synthetic cannabinoids for the treatment of headache. *Headache.* 2011;51:502-505.
60. Mackie K. Signaling via CNS cannabinoid receptors. *Mol Cell Endocrinol.* 2008;286:S60-S65.
61. Klein TW, Cabral GA. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. *J Neuroimmune Pharmacol.* 2006;1:50-64.

62. Koppel BS, Brust JC, Fife T, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2014;82:1556-1563.
63. Zhang HY, Gao M, Liu QR, et al. Cannabinoid CB2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. *Proc Natl Acad Sci U S A.* 2014;111:E5007-E5015.
64. Zhang HY, Gao M, Shen H, et al. Expression of functional cannabinoid CB2 receptor in VTA dopamine neurons in rats. *Addict Biol.* 2017;22:752-765.
65. Noyes R, Jr, Baram DA. Cannabis analgesia. *Compr Psychiatry.* 1974;15:531-535.
66. Schnelle M, Grotenhermen F, Reif M, Gorter RW. Results of a standardized survey on the medical use of cannabis products in the German-speaking area. *Forsch Komplementarmed.* 1999;6:28-36.
67. Mackenzie S. Remarks on the value of Indian hemp in the treatment of a certain type of headache. *Br Med J.* 1887;1:97-98.
68. Nunberg H, Kilmer B, Pacula RL, Burgdorf J. An analysis of applicants presenting to a medical marijuana specialty practice in California. *J Drug Policy Anal.* 2011;4. www.ncbi.nlm.nih.
69. el-Mallakh RS. Marijuana and migraine. *Headache.* 1987;27:442-443.
70. Grinspoon L, Bakalar JB. *Marihuana: The Forbidden Medicine*. New Haven, CT: Yale University; 1993.
71. Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *Int J Clin Pharmacol Res.* 1985;5:243-246.
72. el-Mallakh RS. Migraine headaches and drug abuse. *South Med J.* 1989;82:805.
73. Gorji A. Pharmacological treatment of headache using traditional Persian medicine. *Trends Pharmacol Sci.* 2003;24:331-334.
74. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of medical marijuana on migraine headache frequency in an adult population. *Pharmacotherapy.* 2016;36:505-510.
75. Donovan M. On the physical and medicinal qualities of Indian hemp (Cannabis indica); with observations on the best mode of administration, and cases illustrative of its powers. *Dublin J Med Sci.* 1845;26:368-461.
76. Reynolds JR. On some of the therapeutical uses of Indian hemp. *Arch Med.* 1868;2:154-160.
77. Waring EJ. *Practical Therapeutics*. Philadelphia: Lindsay & Blakiston; 1874.
78. Ringer S. *A Handbook of Therapeutics*. London: H.K. Lewis; 1886.
79. Hare HA. Clinical and physiological notes on the action of Cannabis indica. *There Gaz.* 1887;11:225-228.
80. Suckling C. On the therapeutic value of Indian hemp. *Br Med J.* 1891;2:11-12.
81. Mikuriya TH, *Chronic Migraine Headache: five Cases Successfully Treated with Marinol and/or Illicit Cannabis*. Berkeley, CA: Schaffer Library of Drug Policy; 1991.
82. Nicolodi M, Sandoval V, Terrine A, Therapeutic use of cannabinoids - Dose Finding, Effects, and Pilot Data of Effects in Chronic Migraine and Cluster Headache. Abstract presentation at 3rd Congress of the European Academy of Neurology (EAN), Amsterdam, 6/24/17.
83. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain.* 2012;13:677-684.
84. Robbins MS, Tarshish S, Solomon S, Grosberg BM. Cluster attacks responsive to recreational cannabis and dronabinol. *Headache.* 2009;49:914-916.
85. Leroux E, Taifas I, Valade D, Donnet A, Chagnon M, Ducros A. Use of cannabis among 139 cluster headache sufferers. *Cephalalgia.* 2013;33:208-213.
86. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Société Française d'Etude des Migraines et Céphalées (SFEMC), et al. Chronic cluster headache: a French clinical descriptive study. *J Neurol Neurosurg Psychiatry.* 2007;78:1354-1358.
87. Evans RW, Ramadan NM. Are cannabis-based chemicals helpful in headache?. *Headache.* 2004;44:726-727.
88. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol.* 1997;38:44-48.
89. A, Multicenter Randomized, Double-blind, Parallel-group, Placebo-controlled, Efficacy, Safety and Tolerability Study of Dronabinol MDI in the Acute Treatment of Migraine Headache. ClinicalTrials.gov Identifier: NCT00123201. Global Clinical Director Solvay Pharmaceuticals. (Accessed December 15, 2017, at https://clinicaltrials.gov/ct2/show/study/NCT00123201).
90. Bigal ME, Lipton RB. Overuse of acute migraine medications and migraine chronification. *Curr Pain Headache Rep.* 2009;13:301-307.
91. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMA J.* 2010;182:E694-E701.
92. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology.* 2009;34:672-680.
93. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008;9:506-521.
94. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68:515-521.
95. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMA J.* 2012;184:1143-1150.
96. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology.* 2007;107:785-796.
97. Greenwald MK, Stitzer ML. Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug Alcohol Depend.* 2000;59:261-275.

98. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain.* 2013;14:136-148.
99. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther.* 2011;90:844-851.
100. Eisenberg E, Ogintz M, Almog S. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. *J Pain Palliat Care Pharmacother.* 2014;28:216-225.
101. Ware MA, Wang T, Shapiro S, Collet JP. COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J Pain.* 2015;16:1233-1242.
102. Fiz J, Duran M, Capella D, Carbonell J, Farre M. Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. *PLoS One.* 2011;6:e18440.
103. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain.* 2007;133:210-220.
104. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology.* 2005;65:812-819.
105. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford).* 2006;45:50-52.
106. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain.* 2014;18:999-1012.
107. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin Ther.* 2007;29:2068-2079.
108. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler.* 2006;12:639-645.
109. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain.* 2012;13:438-449.
110. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia.* 2004;59:440-452.
111. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil.* 2003;17:21-29.
112. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain.* 2004;112:299-306.
113. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage.* 2010;39:167-179.
114. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol.* 2013;260:984-997.
115. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry.* 2012;83:1125-1132.
116. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology.* 2006;104:1040-1046.
117. Zajicek J, Fox P, Sanders H, UK MS Research Group, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet.* 2003;362:1517-1526.
118. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain.* 2008;9:254-264.
119. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ.* 2004;329:253.
120. Svendsen KB, Jensen TS, Bach FW. Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis–secondary publication. *Ugeskr Laeger.* 2005;167:2772-2774.
121. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain.* 2003;105:79-88.
122. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9:164-173.
123. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol.* 2006;253:1337-1341.
124. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Polz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain–a randomized controlled trial. *Wien Klin Wochenschr.* 2006;118:327-335.
125. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain.* 2012;153:2073-2082.

126. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. *Pain Med.* 2015;16:149-159.
127. Noyes R, Jr, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther.* 1975;18:84-89.
128. Noyes R, Jr, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol.* 1975;15:139-143.
129. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin.* 2006;22:1269-1276.
130. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Clin Neurosci.* 1990;240:1-4.
131. Staquet M, Gantt C, Machin D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther.* 1978;23:397-401.
132. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. *Neuropharmacology.* 2005;48:1164-1171.
133. Karst M, Wippermann S, Ahrens J. Role of cannabinoids in the treatment of pain and (painful) spasticity. *Drugs.* 2010;70:2409-2438.
134. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med.* 2009;10:1353-1368.
135. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol.* 2011;72:735-744.
136. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA.* 2003;290:1757-1762.
137. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler.* 2004;10:434-441.
138. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ.* 2008;336:199-201.
139. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol.* 2015;10:293-301.
140. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA.* 2015;313:2456-2473.
141. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA.* 2015;313:2474-2483.
142. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *J Oral Facial Pain Headache.* 2015;29:7-14.
143. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA.* 2014;311:368-377.
144. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod.* 2012;75:311-335.
145. Andre CM, Hausman JF, Guerriero G. Cannabis sativa: The plant of the thousand and one molecules. *Front Plant Sci.* 2016;7:19.
146. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy.* 2017;42:30-35.
147. Lucas P, Walsh Z, Crosby K, et al. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. *Drug Alcohol Rev.* 2016;35:326-333.
148. Lucas P. Rationale for cannabis-based interventions in the opioid overdose crisis. *Harm Reduct J.* 2017;14:58-017-0183-9.
149. Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: A systematic review and meta-analysis. *Neuropsychopharmacology.* 2017;42:1752-1765.
150. McGeeney BE. Cannabinoids and hallucinogens for headache. *Headache.* 2013;53:447-458.
151. Bushlin I, Rozenfeld R, Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Curr Opin Pharmacol.* 2010;10:80-86.
152. Parolaro D, Rubino T, Vigano D, Massi P, Guidali C, Realini N. Cellular mechanisms underlying the interaction between cannabinoid and opioid system. *Curr Drug Targets.* 2010;11:393-405.
153. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. *J Pharmacol Exp Ther.* 1992;262:10-18.
154. Pugh G, Jr, Smith PB, Dombrowski DS, Welch SP. The role of endogenous opioids in enhancing the antinociception produced by the combination of delta 9-tetrahydrocannabinol and morphine in the spinal cord. *J Pharmacol Exp Ther.* 1996;279:608-616.
155. Smith FL, Cichewicz D, Martin ZL, Welch SP. The enhancement of morphine antinociception in mice by delta9-tetrahydrocannabinol. *Pharmacol Biochem Behav.* 1998;60:559-566.
156. Cichewicz DL, Welch SP, Smith FL. Enhancement of transdermal fentanyl and buprenorphine antinociception by transdermal delta9-tetrahydrocannabinol. *Eur J Pharmacol.* 2005;525:74-82.
157. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement mu opioid antinociception by oral delta9-tetrahydrocannabinol: dose-response analysis and receptor identification. *J Pharmacol Exp Ther.* 1999;289:859-867.
158. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci.* 2004;74:1317-1324.
159. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther.* 2003;304:1010-1015.

160. Smith PA, Selley DE, Sim-Selley LJ, Welch SP. Low dose combination of morphine and delta9-tetrahydrocannabinol circumvents antinociceptive tolerance and apparent desensitization of receptors. *Eur J Pharmacol.* 2007;571:129-137.
161. Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag.* 2008;4: 245-259.
162. Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. *Brain Res Mol Brain Res.* 1998;55:126-132.
163. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174:1668-1673.
164. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. Recreational cannabis legalization and opioid-related deaths in Colorado, 2000-2015. *Am J Public Health.* 2017;107:1827-1829.
165. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. *Am J Addict.* 2013;22:344-351.
166. Raby WN, Carpenter KM, Rothenberg J, et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *Am J Addict.* 2009;18:301-308.
167. Collen M. Prescribing cannabis for harm reduction. *Harm Reduct J.* 2012;9:1.
168. Haroutounian S, Ratz Y, Ginosar Y, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: A prospective open-label study. *Clin J Pain.* 2016;32:1036-1043.
169. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *J Pain.* 2016;17:739-744.
170. Leizer C, Ribnicky D, Poulev A, Dushenkov S, Raskin I. The composition of hemp seed oil and its potential as an important source of nutrition. *J Nutraceutical Funct Med Food.* 2000;2:35-54.
171. Ross SA, Mehmedic Z, Murphy TP, Elsohly MA. GC-MS analysis of the total delta9-THC content of both drug- and fiber-type cannabis seeds. *J Anal Toxicol.* 2000;24:715-717.
172. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci.* 2005;78:539-548.
173. 174. Marcu JP. An overview of major and minor phytocannabinoids. In: Preedy V, ed. *Neuropathology of Drug Addictions and Substance Misuse, Volume* 1*: Foundations of Understanding, Tobacco, Alcohol, Cannabinoids and Opioids*. London: Academic Press; 2016:672-678.
174. O'Sullivan SE, Kendall DA, Randall MD. Time-dependent vascular effects of Endocannabinoids mediated by peroxisome proliferator-activated receptor gamma (PPARgamma). *PPAR Res.* 2009;2009:1.
175. O'Sullivan SE, Kendall DA. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. *Immunobiology.* 2010;215:611-616.
176. De Petrocellis L, Orlando P, Moriello AS, et al. Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiol (Oxf).* 2012;204:255-266.
177. De Petrocellis L, Vellani V, Schiano-Moriello A, et al. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *J Pharmacol Exp Ther.* 2008;325:1007-1015.
178. De Petrocellis L, Di Marzo V. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol.* 2010;5:103-121.
179. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol.* 2011;163:1479-1494.
180. Barann M, Molderings G, Brüss M, Bönisch H, Urban BW, Göthert M. Direct inhibition by cannabinoids of human 5-HT3A receptors: probable involvement of an allosteric modulatory site. *Br J Pharmacol.* 2002;137:589-596.
181. Hejazi N, Zhou C, Oz M, Sun H, Ye JH, Zhang L. Delta9-tetrahydrocannabinol and endogenous cannabinoid anandamide directly potentiate the function of glycine receptors. *Mol Pharmacol.* 2006;69:991-997.
182. McHugh D, Page J, Dunn E, Bradshaw HB. Delta(9) -Tetrahydrocannabinol and N-arachidonyl glycine are full agonists at GPR18 receptors and induce migration in human endometrial HEC-1B cells. *Br J Pharmacol.* 2012;165:2414-2424.
183. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. *Curr Med Chem.* 2010;17:1360-1381.
184. Hajos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. *Neuroscience.* 2001;106:1-4.
185. Govaerts SJ, Hermans E, Lambert DM. Comparison of cannabinoid ligands affinities and efficacies in murine tissues and in transfected cells expressing human recombinant cannabinoid receptors. *Eur J Pharm Sci.* 2004;23:233-243.
186. Nicolodi M, Volpe AR, Sicuteri F. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: their common clues. *Cephalalgia.* 1998;18: 41-44.
187. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A.* 1998;95:8268-8273.
188. Hampson AJ, Bornheim LM, Scanziani M, et al. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. *J Neurochem.* 1998;70:671-676.

189. Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Ann N Y Acad Sci.* 2000;899:274-282.
190. Wilkinson JD, Kendall DA, Ralevic V, Delta 9-tetrahydrocannabinol inhibits electrically-evoked CGRP release and capsaicin-sensitive sensory neurogenic vasodilatation in the rat mesenteric arterial bed. *Br J Pharmacol* 2007;152(5):709-716.
191. Li J, Daughters RS, Bullis C, et al. The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. *Pain.* 1999;81:25-33.
192. Brown AJ. Novel cannabinoid receptors. *Br J Pharmacol.* 2007;152:567-575.
193. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci.* 2009;30:515-527.
194. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics.* 2009;6:713-737.
195. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.* 2006;58:389-462.
196. Srivastava MD, Srivastava BI, Brouhard B. Delta9 tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmacology.* 1998;40:179-185.
197. Kozela E, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z. Cannabinoids Delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells. *J Biol Chem.* 2010;285:1616-1626.
198. Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease. *Eur J Rheumatol.* 2017;4:210-218.
199. Ruhaak LR, Felth J, Karlsson PC, Rafter JJ, Verpoorte R, Bohlin L. Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from Cannabis sativa. *Biol Pharm Bull.* 2011;34:774-778.
200. Martin BR, Compton DR, Thomas BF, et al. Behavioral, biochemical, and molecular modeling evaluations of cannabinoid analogs. *Pharmacol Biochem Behav.* 1991;40:471-478.
201. Martin BR, Lichtman AH. Cannabinoid transmission and pain perception. *Neurobiol Dis.* 1998;5:447-461.
202. DeLong GT, Wolf CE, Poklis A, Lichtman AH. Pharmacological evaluation of the natural constituent of Cannabis sativa, cannabichromene and its modulation by Delta(9)-tetrahydrocannabinol. *Drug Alcohol Depend.* 2010;112:126-133.
203. Zygmunt PM, Andersson DA, Hogestatt ED. Delta 9-tetrahydrocannabinol and cannabinol activate capsaicin-sensitive sensory nerves via a CB1 and CB2 cannabinoid receptor-independent mechanism. *J Neurosci.* 2002;22:4720-4727.
204. Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. *Curr Neuropharmacol.* 2006;4:239-257.
205. Burston JJ, Sagar DR, Shao P, et al. Cannabinoid CB2 receptors regulate central sensitization and pain responses associated with osteoarthritis of the knee joint. *PLoS One.* 2013;8:e80440.
206. Gui H, Liu X, Wang ZW, He DY, Su DF, Dai SM. Expression of cannabinoid receptor 2 and its inhibitory effects on synovial fibroblasts in rheumatoid arthritis. *Rheumatology (Oxford).* 2014;53:802-809.
207. Clayton N, Marshall FH, Bountra C, O'Shaughnessy CT. CB1 and CB2 cannabinoid receptors are implicated in inflammatory pain. *Pain.* 2002;96:253-260.
208. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. *Future Med Chem.* 2009;1:1333-1349.
209. Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: A review of basic science and clinical evidence. *Curr Pain Headache Rep.* 2015;19:50.
210. Weber J, Schley M, Casutt M, et al. Tetrahydrocannabinol (Delta 9-THC) treatment in chronic central neuropathic pain and fibromyalgia patients: Results of a Multicenter Survey. *Anesthesiol Res Pract.* 2009;2009:1.
211. Weber M, Goldman B, Truniger S. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: A randomised, double-blind crossover trial. *J Neurol Neurosurg Psychiatry.* 2010;81:1135-1140.
212. Smith PB, Martin BR. Spinal mechanisms of delta 9-tetrahydrocannabinol-induced analgesia. *Brain Res.* 1992;578:8-12.
213. Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of delta9-tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav.* 1998;60:183-191.
214. Walker JM, Huang SM. Cannabinoid analgesia. *Pharmacol Ther.* 2002;95:127-135.
215. Walker JM, Strangman NM, Huang SM. Cannabinoids and pain. *Pain Res Manag.* 2001;6:74-79.
216. Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. *Life Sci.* 1999;65:665-673.
217. Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. *Planta Med.* 1991;57:S60-S67.
218. Fine PG, Rosenfeld MJ. The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Med J.* 2013;4:e0022.
219. Welch SP. Blockade of cannabinoid-induced antinociception by norbinaltorphimine, but not N,N-diallyl-tyrosine-Aib-phenylalanine-leucine, ICI 174,864 or naloxone in mice. *J Pharmacol Exp Ther.* 1993;265:633-640.
220. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain.* 2015;16:616-627.
221. Serpell MG, Notcutt W, Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *J Neurol.* 2013;260:285-295.
222. Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study

of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex(R) (nabiximols). *Mult Scler.* 2012;18:219-228.

223. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage.* 2013;46:207-218.
224. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry.* 2005;76:1664-1669.
225. Zajicek JP, Apostu VI. Role of cannabinoids in multiple sclerosis. *CNS Drugs.* 2011;25:187-201.
226. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler.* 2004;10:417-424.
227. Collin C, Davies P, Mutiboko IK, Ratcliffe S. Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol.* 2007;14:290-296.
228. Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res.* 2010;32:451-459.
229. Syed YY, McKeage K, Scott LJ. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex(R)): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis. *Drugs.* 2014;74:563-578.
230. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC Neurol.* 2009;9:59.
231. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin Pharmacother.* 2006;7:607-615.
232. GW Pharmaceuticals. Sativex Product Monograph; 2010.
233. Sallan SE, Zinberg NE, Frei E. 3rd., Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med.* 1975;293:795-797.
234. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med.* 1980;302:135-138.
235. Vinciguerra V, Moore T, Brennan E. Inhalation marijuana as an antiemetic for cancer chemotherapy. *N Y State J Med.* 1988;88:525-527.
236. Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: research problems and issues. *Ann Intern Med.* 1983;99:106-114.
237. Lucas VS, Jr, Laszlo J. delta 9-Tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. *JAMA.* 1980;243:1241-1243.
238. Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. *A comparison with prochlorperazine and a placebo. Ann Intern Med.* 1979;91:825-830.
239. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. *Cancer.* 1982;50:636-645.
240. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch Intern Med.* 1980;140:1431-1433.
241. Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *J Clin Pharmacol.* 1981;21:76S-80S.
242. Levitt M, Wilson A, Bowman D, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. *J Clin Pharmacol.* 1981;21:103S-109S.
243. McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. *Invest New Drugs.* 1988;6:243-246.
244. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol.* 1985;8:336-340.
245. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med.* 1979;300:1295-1297.
246. Vincent BJ, McQuiston DJ, Einhorn LH, Nagy CM, Brames MJ. Review of cannabinoids and their antiemetic effectiveness. *Drugs.* 1983;25(Suppl 1): 52-62.
247. Einhorn L. Nabilone: an effective antiemetic agent in patients receiving cancer chemotherapy. *Cancer Treat Rev.* 1982;9: 55-61.
248. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol.* 1981;21:64S-69S.
249. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer.* 1983;48:657-663.
250. Garb S, Beers AL, Bograd M. Two-pronged study of tetrahydrocannabinol (THC) prevention of vomiting for cancer chemotherapy. *IRCS Med. Sci.* 1980;8:203-204.
251. Lane M, Smith FE, Sullivan RA, Plasse TF. Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. *Am J Clin Oncol.* 1990;13:480-484.
252. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage.* 1991;6:352-359.
253. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav.* 1991;40:695-700.

254. Cunningham D, Forrest GJ, Soukop M, Gilchrist NL, Calder IT, McArdle CS. Nabilone and prochlorperazine: a useful combination for emesis induced by cytotoxic drugs. *Br Med J (Clin Res Ed).* 1985;291:864-865.
255. Gonzalez-Rosales F, Walsh D. Intractable nausea and vomiting due to gastrointestinal mucosal metastases relieved by tetrahydrocannabinol (dronabinol). *J Pain Symptom Manage.* 1997;14:311-314.
256. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med.* 1979;91:819-824.
257. Staquet M, Bron D, Rozencweig M, Kenis Y. Clinical studies with a THC analog (BRL-4664) in the prevention of cisplatin-induced vomiting. *J Clin Pharmacol.* 1981;21:60S-63S.
258. Sharkey KA, Darmani NA, Parker LA. Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. *Eur J Pharmacol.* 2014;722:134-146.
259. Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. *Br J Pharmacol.* 2011;163:1411-1422.
260. Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ.* 2001;323:16-21.
261. Sutton IR, Daeninck P. Cannabinoids in the management of intractable chemotherapy-induced nausea and vomiting and cancer-related pain. *J Support Oncol.* 2006;4:531-535.
262. Pisanti S, Malfitano AM, Grimaldi C, et al. Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. *Best Pract Res Clin Endocrinol Metab.* 2009;23:117-131.
263. Gurley RJ, Aranow R, Katz M. Medicinal marijuana: a comprehensive review. *J Psychoactive Drugs.* 1998;30:137-147.
264. Tortorice PV, O'Connell MB. Management of chemotherapy-induced nausea and vomiting. *Pharmacotherapy.* 1990;10:129-145.
265. Cunningham D, Bradley CJ, Forrest GJ, et al. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. *Eur J Cancer Clin Oncol.* 1988;24:685-689.
266. Soderpalm AH, Schuster A, de Wit H. Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacol Biochem Behav.* 2001;69:343-350.
267. Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl).* 2008;17:431-443.
268. Musty R, Rossi R. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. *J Cannabis Therapeutics.* 2001;1:29-42.
269. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin.* 2007;23:533-543.
270. Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Med J Aust.* 1979;2:657-659.
271. Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci.* 2012;367:3353-3363.
272. Rock EM, Connolly C, Limebeer CL, Parker LA. Effect of combined oral doses of Delta(9)-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models. *Psychopharmacology (Berl).* 2016;233:3353-3360.
273. Green ST, Nathwani D, Goldberg DJ, Kennedy DH. Nabilone as effective therapy for intractable nausea and vomiting in AIDS. *Br J Clin Pharmacol.* 1989;28:494-495.
274. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics.* 1987;79:946-952.
275. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. *Arch Dis Child.* 1986;61:502-505.
276. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci.* 1995;56:2097-2102.
277. Abbott Products Inc. Marinol Product Monograph; 2010.
278. Valeant Canada. Cesamet Product Monograph; 2009.
279. Notcutt WG, Price M, Chapman G. Clinical experience with nabilone for chronic pain. *Pharm Sci.* 1997;3:551-555.
280. Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. *Lancet.* 1999;353:560.
281. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med.* 2006;7:25-29.
282. Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet.* 1995;345:579.
283. Hampson AJ, Axelrod J, Grimaldi M, Cannabinoids as antioxidants and neuroprotectants. U.S. Patent #6,630,507. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6630507.PN.&OS=PN/6630507&RS=PN/6630507. 2003.
284. Sanchez AJ, Garcia-Merino A. Neuroprotective agents: cannabinoids. *Clin Immunol.* 2012;142:57-67.
285. van der Stelt M, Veldhuis WB, Bär PR, Veldink GA, Vliegenthart JF, Nicolay K. Neuroprotection by Delta9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *J Neurosci.* 2001;21:6475-6479.

286. van der Stelt M, Di Marzo V. Cannabinoid receptors and their role in neuroprotection. *Neuromolecular Med.* 2005;7:37-50.
287. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry.* 1997;12:913-919.
288. Eubanks LM, Rogers CJ, Beuscher AE, 4th, et al. A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Mol Pharm.* 2006;3:773-777.
289. Cao C, Li Y, Liu H, et al. The potential therapeutic effects of THC on Alzheimer's disease. *J Alzheimers Dis.* 2014;42:973-984.
290. Passmore MJ. The cannabinoid receptor agonist nabilone for the treatment of dementia-related agitation. *Int J Geriatr Psychiatry.* 2008;23:116-117.
291. Walther S, Mahlberg R, Eichmann U, Kunz D. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl).* 2006;185:524-528.
292. Carter GT, Abood ME, Aggarwal SK, Weiss MD. Cannabis and amyotrophic lateral sclerosis: hypothetical and practical applications, and a call for clinical trials. *Am J Hosp Palliat Care.* 2010;27:347-356.
293. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care.* 2004;21:95-104.
294. Bilsland LG, Dick JR, Pryce G, et al. Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice. *FASEB J.* 2006;20:1003-1005.
295. Raman C, McAllister SD, Rizvi G, Patel SG, Moore DH, Abood ME. Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2004;5:33-39.
296. Gelinas DF, Miller RG, Abood M. Pilot Study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2002;3:23-24.
297. Buccellato E, Carretta D, Utan A, et al. Acute and chronic cannabinoid extracts administration affects motor function in a CREAE model of multiple sclerosis. *J Ethnopharmacol.* 2011;133:1033-1038.
298. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse.* 1987;7:39-50.
299. Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther.* 1996;34:446-452.
300. Kurz R, Blass K. Use of dronabinol (delta-9-THC) in autism: A prospective single-case-study with an early infantile autistic child. *Cannabinoids.* 2010;5:4-6.
301. Foldy C, Malenka RC, Sudhof TC. Autism-associated neuroligin-3 mutations commonly disrupt tonic endocannabinoid signaling. *Neuron.* 2013;78:498-509.
302. Hadland SE, Knight JR, Harris SK. Medical marijuana: review of the science and implications for developmental-behavioral pediatric practice. *J Dev Behav Pediatr.* 2015;36:115-123.
303. Siniscalco D, Sapone A, Giordano C, et al. Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders. *J Autism Dev Disord.* 2013;43:2686-2695.
304. Bou Khalil R. Would some cannabinoids ameliorate symptoms of autism?. *Eur Child Adolesc Psychiatry.* 2012;21:237-238.
305. Moldzio R, Pacher T, Krewenka C, et al. Effects of cannabinoids Delta(9)-tetrahydrocannabinol, Delta(9)-tetrahydrocannabinolic acid and cannabidiol in MPP+ affected murine mesencephalic cultures. *Phytomedicine.* 2012;19:819-824.
306. Zeissler ML, Eastwood J, McCorry K, Hanemann CO, Zajicek JP, Carroll CB. Delta-9-tetrahydrocannabinol protects against MPP+ toxicity in SH-SY5Y cells by restoring proteins involved in mitochondrial biogenesis. *Oncotarget.* 2016;7:46603-46614.
307. Zeissler ML, Eastwood J, Hanemann CO, Zajicek J, Carroll C. Δ9–Tetrahydrocannabinol is protective through PPARTγ dependent mitochondrial biogenesis in a cell culture model of Parkinson's Disease. *J Neurol Neurosurg Psychiatry.* 2013;84:e2.58.
308. Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. *Clin Neuropharmacol.* 2014;37:41-44.
309. Carroll CB, Zeissler ML, Hanemann CO, Zajicek JP. Delta(9)-tetrahydrocannabinol (Delta(9)-THC) exerts a direct neuroprotective effect in a human cell culture model of Parkinson's disease. *Neuropathol Appl Neurobiol.* 2012;38:535-547.
310. Stampanoni Bassi M, Sancesario A, Morace R, Centonze D, Iezzi E. Cannabinoids in Parkinson's Disease. *Cannabis Cannabinoid Res.* 2017;2:21-29.
311. Sieradzan KA, Fox SH, Hill M, Dick JP, Crossman AR, Brotchie JM. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. *Neurology.* 2001;57:2108-2111.
312. Muller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Cannabis in movement disorders. *Forsch Komplementarmed.* 1999;6(Suppl 3): 23-27.
313. Muller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *Am J Psychiatry.* 1999;156:495.
314. Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry.* 2001;34:19-24.
315. Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry.* 2002;35:57-61.
316. Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. *Expert Opin Pharmacother.* 2003;4:1717-1725.
317. Muller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry.* 2003;64:459-465.
318. Muller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with

delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. *Neuropsychopharmacology.* 2003;28:384-388.
319. Curtis A, Rickards H. Nabilone could treat chorea and irritability in Huntington's disease. *J Neuropsychiatry Clin Neurosci.* 2006;18:553-554.
320. Curtis A, Mitchell I, Patel S, Ives N, Rickards H. A pilot study using nabilone for symptomatic treatment in Huntington's disease. *Mov Disord.* 2009;24:2254-2259.
321. Blazquez C, Chiarlone A, Sagredo O, et al. Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease. *Brain.* 2011;134:119-136.
322. El-Alfy AT, Ivey K, Robinson K, et al. Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L. *Pharmacol Biochem Behav.* 2010;95:434-442.
323. Denson TF, Earleywine M. Decreased depression in marijuana users. *Addict Behav.* 2006;31:738-742.
324. Bossong MG, van Hell HH, Jager G, Kahn RS, Ramsey NF, Jansma JM. The endocannabinoid system and emotional processing: a pharmacological fMRI study with 9-tetrahydrocannabinol. *Eur Neuropsychopharmacol.* 2013;23:1687-1697.
325. Betthauser K, Pilz J, Vollmer LE. Use and effects of cannabinoids in military veterans with posttraumatic stress disorder. *Am J Health Syst Pharm.* 2015;72:1279-1284.
326. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs.* 2014;46:73-77.
327. Passie T, Emrich HM, Karst M, Brandt SD, Halpern JH. Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence. *Drug Test Anal.* 2012;4:649-659.
328. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neurosci Ther.* 2009;15:84-88.
329. Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral delta(9)-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig.* 2014;34:587-591.
330. Kohli DR, Li Y, Khasabov SG, et al. Pain-related behaviors and neurochemical alterations in mice expressing sickle hemoglobin: modulation by cannabinoids. *Blood.* 2010;116:456-465.
331. Signorelli AA, Ribeiro SB, Moraes-Souza H, et al. Pain measurement as part of primary healthcare of adult patients with sickle cell disease. *Rev Bras Hematol Hemoter.* 2013;35:272-277.
332. Lopez-Rodriguez AB, Siopi E, Finn DP, et al. CB1 and CB2 cannabinoid receptor antagonists prevent minocycline-induced neuroprotection following traumatic brain injury in mice. *Cereb Cortex.* 2015;25:35-45.
333. Nguyen BM, Kim D, Bricker S, et al. Effect of marijuana use on outcomes in traumatic brain injury. *Am Surg.* 2014;80:979-983.
334. Akirav I. Targeting the endocannabinoid system to treat haunting traumatic memories. *Front Behav Neurosci.* 2013;7:124.
335. Fitton AG, Pertwee RG. Changes in body temperature and oxygen consumption rate of conscious mice produced by intrahypothalamic and intracerebroventricular injections of delta 9-tetrahydrocannabinol. *Br J Pharmacol.* 1982;75:409-414.
336. Malone DT, Taylor DA. Modulation of delta9-tetrahydrocannabinol-induced hypothermia by fluoxetine in the rat. *Br J Pharmacol.* 1998;124:1419-1424.
337. Compton DR, Aceto MD, Lowe J, Martin BR. In vivo characterization of a specific cannabinoid receptor antagonist (SR141716A): inhibition of delta 9-tetrahydrocannabinol-induced responses and apparent agonist activity. *JPharmacol Exp Ther.* 1996;277:586-594.
338. Compton DR, Johnson MR, Melvin LS, Martin BR. Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents. *J Pharmacol Exp Ther.* 1992;260:201-209.
339. Fennessy MR, Taylor DA. The effect of delta9-tetrahydrocannabinol on body temperature and brain amine concentrations in the rat at differnt ambient temperatures. *Br J Pharmacol.* 1977;60:65-71.
340. Douthwaite AH. Choice of drugs in the treatment of duodenal ulcer. *Br Med J.* 1947;2:43-47.
341. Andries A, Frystyk J, Flyvbjerg A, Stoving RK. Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. *Int J Eat Disord.* 2014;47:18-23.
342. Cota D, Marsicano G, Lutz B, et al. Endogenous cannabinoid system as a modulator of food intake. *Int J Obes Relat Metab Disord.* 2003;27:289-301.
343. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage.* 1995;10:89-97.
344. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *JPain Symptom Manage.* 1997;14:7-14.
345. Nauck F, Klaschik E. Cannabinoids in the treatment of the cachexia-anorexia syndrome in palliative care patients. *Schmerz.* 2004;18:197-202.
346. Nelson K, Walsh D, Deeter P, Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *JPalliat Care.* 1994;10:14-18.
347. Mattes RD, Engelman K, Shaw LM, Elsohly MA. Cannabinoids and appetite stimulation. *Pharmacol Biochem Behav.* 1994;49:187-195.
348. Regelson W, Butler JR, Schultz J, Delta-9-THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients. In: *Int Conf Pharmacol Cannabis*. Savannah: Raven; 1974.
349. Regelson W, Butler JR, Schulz J, Delta-9-tetracannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara S, eds. *The Pharmacology of Marijuana*. New York: Raven Press; 1976:763-775.
350. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Ann Intern Med.* 1997;126:791-798.

351. Gorter R, Seefried M, Volberding P. Dronabinol effects on weight in patients with HIV infection. *Aids.* 1992;6:127.
352. Gorter RW. Cancer cachexia and cannabinoids. *Forsch Komplementarmed.* 1999;6(Suppl 3): 21-22.
353. Gorter RW. Experiences with dronabinol (delta-tetrahydrocannabinol) in oncological patients with anorexia-cachexia syndrome. Illustration of clinical problems and therapy based on 2 case reports. *Schmerz.* 2004;18: S31-S33.
354. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol.* 2011;22:2086-2093.
355. Ravikoff Allegretti J, Courtwright A, Lucci M, Korzenik JR, Levine J. Marijuana use patterns among patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2013;19:2809-2814.
356. Weiss A, Friedenberg F. Patterns of cannabis use in patients with Inflammatory Bowel Disease: A population based analysis. *Drug Alcohol Depend.* 2015;156:84-89.
357. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol.* 2013;11:1276-1280.e1.
358. Naftali T, Lev LB, Yablecovitch D, Yablekovitz D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J.* 2011;13:455-458.
359. Hong J, Nandiwada V, Jones V, et al. CB1 cannabinoid receptor agonist inhibits matrix metalloproteinase activity in spinal cord injury: A possible mechanism of improved recovery. *Neurosci Lett.* 2015;597:19-24.
360. Kwiatkoski M, Guimaraes FS, Del-Bel E. Cannabidiol-treated rats exhibited higher motor score after cryogenic spinal cord injury. *Neurotox Res.* 2012;21:271-280.
361. Arevalo-Martin A, Garcia-Ovejero D, Sierra-Palomares Y, et al. Early endogenous activation of CB1 and CB2 receptors after spinal cord injury is a protective response involved in spontaneous recovery. *PLoS One.* 2012;7:e49057.
362. Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler.* 2010;16:1349-1359.
363. Turner CE, Elsohly MA, Boeren EG. Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *J Nat Prod.* 1980;43:169-234.
364. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy.* 2013;33:195-209.
365. Petro DJ, Ellenberger C Jr. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *J Clin Pharmacol.* 1981;21:413S-416S.
366. Hagenbach U, Luz S, Ghafoor N, et al. The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord.* 2007;45:551-562.
367. Appendino G, Gibbons S, Giana A, et al. Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J Nat Prod.* 2008;71:1427-1430.
368. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther.* 2006;318:1375-1387.
369. Scott KA, Dalgleish AG, Liu WM. Anticancer effects of phytocannabinoids used with chemotherapy in leukaemia cells can be improved by altering the sequence of their administration. *Int J Oncol.* 2017;51:369-377.
370. Salazar M, Carracedo A, Salanueva IJ, et al. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. *J Clin Invest.* 2009;119:1359-1372.
371. Liu WM, Scott KA, Shamash J, Joel S, Powles TB. Enhancing the in vitro cytotoxic activity of Delta9-tetrahydrocannabinol in leukemic cells through a combinatorial approach. *Leuk Lymphoma.* 2008;49:1800.
372. Powles T, te Poele R, Shamash J, et al. Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway. *Blood.* 2005;105:1214-1221.
373. Caffarel MM, Sarrio D, Palacios J, Guzman M, Sanchez C. Delta9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. *Cancer Res.* 2006;66:6615-6621.
374. Caffarel MM, Moreno-Bueno G, Cerutti C, et al. JunD is involved in the antiproliferative effect of Delta9-tetrahydrocannabinol on human breast cancer cells. *Oncogene.* 2008;27:5033-5044.
375. Caffarel MM, Andradas C, Mira E, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Mol Cancer.* 2010;9:196.
376. Greenhough A, Patsos HA, Williams AC, Paraskeva C. The cannabinoid delta(9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. *Int J Cancer.* 2007;121:2172-2180.
377. Preet A, Ganju RK, Groopman JE. Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. *Oncogene.* 2008;27:339-346.
378. Guzman M, Duarte MJ, Blazquez C, et al. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer.* 2006;95:197-203.
379. Marcu JP, Christian RT, Lau D, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Mol Cancer Ther.* 2010;9:180-189.
380. Norooznezhad AH, Norooznezhad F. Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation. *Med Hypotheses.* 2017;99:15-18.
381. Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *J Dermatol Sci.* 2007;45:87-92.
382. Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax.* 1976;31:720-723.

383. Abboud RT, Sanders HD. Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. *Chest.* 1976;70:480-485.
384. Hartley JP, Nogrady SG, Seaton A. Bronchodilator effect of delta1-tetrahydrocannabinol. *Br J Clin Pharmacol.* 1978;5:523-525.
385. Rajavashisth TB, Shaheen M, Norris KC, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open.* 2012;2:e000494.
386. Le Foll B, Trigo JM, Sharkey KA, Le Strat Y. Cannabis and Delta9-tetrahydrocannabinol (THC) for weight loss?. *Med Hypotheses.* 2013;80:564-567.
387. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. *Jama.* 1971;217:1392.
388. Colasanti BK. Ocular hypotensive effect of marihuana cannabinoids: correlate of central action or separate phenomenon?. *J Ocul Pharmacol.* 1986;2:295-304.
389. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J Glaucoma.* 2006;15:349-353.
390. Tomida I, Pertwee RG, Azuara-Blanco A. Cannabinoids and glaucoma. *Br J Ophthalmol.* 2004;88:708-713.
391. Green K. Marijuana smoking vs cannabinoids for glaucoma therapy. *Arch Ophthalmol.* 1998;116:1433-1437.
392. Green K, Wynn H, Bowman KA. A comparison of topical cannabinoids on intraocular pressure. *Exp Eye Res.* 1978;27:239-246.
393. Merritt JC, Perry DD, Russell DN, Jones BF. Topical delta 9-tetrahydrocannabinol and aqueous dynamics in glaucoma. *J Clin Pharmacol.* 1981;21:467S-71S.
394. Maor D, Treves T, Korczyn AD. Lack of effect of cannabinoids on carbonic anhydrase. *J Neural Transm.* 1980;49:205-206.
395. Merritt JC, Olsen JL, Armstrong JR, McKinnon SM. Topical delta 9-tetrahydrocannabinol in hypertensive glaucomas. *J Pharm Pharmacol.* 1981;33:40-41.
396. Flach AJ. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. *Trans Am Ophthalmol Soc.* 2002;100:215-222. discussion 222-4.
397. Wan MJ, Daniel S, Kassam F, et al. Survey of complementary and alternative medicine use in glaucoma patients. *J Glaucoma.* 2012;21:79-82.
398. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology.* 1980;87:222-228.
399. Zhan GL, Camras CB, Palmberg PF, Toris CB. Effects of marijuana on aqueous humor dynamics in a glaucoma patient. *J Glaucoma.* 2005;14:175-177.
400. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol.* 2002;97:2117-2119.
401. Cannabidiol (CBD) Pre-Review Report. World Health Organization: Expert Committee on Drug Dependence. (Accessed December 20, 2017, at http://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf).
402. "Prohibited List: January 2018". The World Anti-Doping Code International Standard. World Anti-Doping Agency (WADA). (Accessed 4/23, 2018, at https://www.wada-ama.org/sites/default/files/prohibited_list_2018_en.pdf).
403. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol.* 2007;150:613-623.
404. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses.* 2006;66:234-246.
405. Murillo-Rodriguez E, Millan-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker CR. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. *FEBS Lett.* 2006;580:4337-4345.
406. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol.* 2004;24:305-313.
407. Zuardi AW, Hallak JE, Crippa JA. Interaction between cannabidiol (CBD) and (9)-tetrahydrocannabinol (THC): influence of administration interval and dose ratio between the cannabinoids. *Psychopharmacology (Berl).* 2012;219:247-249.
408. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl).* 1982;76:245-250.
409. Zuardi AW, Finkelfarb E, Bueno OF, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol. *Arch Int Pharmacodyn Ther.* 1981;249:137-146.
410. Wright MJ, Jr, Vandewater SA, Taffe MA. Cannabidiol attenuates deficits of visuospatial associative memory induced by Delta(9) tetrahydrocannabinol. *Br J Pharmacol.* 2013;170:1365-1373.
411. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr.* 2008;30:271-280.
412. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol.* 2001;134:845-852.
413. Ahrens J, Demir R, Leuwer M, et al. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology.* 2009;83:217-222.
414. Qin N, Neeper MP, Liu Y, Hutchinson TL, Lubin ML, Flores CM. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *J Neurosci.* 2008;28:6231-6238.
415. Ross HR, Napier I, Connor M. Inhibition of recombinant human T-type calcium channels by Delta9-tetrahydrocannabinol and cannabidiol. *J Biol Chem.* 2008;283:16124-16134.
416. Jenny M, Santer E, Pirich E, Schennach H, Fuchs D. Delta9-tetrahydrocannabinol and cannabidiol

modulate mitogen-induced tryptophan degradation and neopterin formation in peripheral blood mononuclear cells in vitro. *J Neuroimmunol.* 2009;207:75-82.
417. Evans AT, Formukong E, Evans FJ. Activation of phospholipase A2 by cannabinoids. Lack of correlation with CNS effects. *FEBS Lett.* 1987;211:119-122.
418. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol.* 2002;42:11S-19S.
419. Pagano E, Capasso R, Piscitelli F, et al. An orally active cannabis extract with high content in cannabidiol attenuates chemically-induced intestinal inflammation and hypermotility in the mouse. *Front Pharmacol.* 2016;7:341.
420. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol–recent advances. *Chem Biodivers.* 2007;4:1678-1692.
421. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci U S A.* 2000;97:9561-9566.
422. Formukong EA, Evans AT, Evans FJ. Analgesic and anti-inflammatory activity of constituents of Cannabis sativa L. *Inflammation.* 1988;12:361-371.
423. Formukong EA, Evans AT, Evans FJ. The medicinal uses of cannabis and its constituents. *Phytother Res.* 1989;3:219-231.
424. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol.* 2007;556:75-83.
425. Costa B, Colleoni M, Conti S, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedebergs Arch Pharmacol.* 2004;369:294-299.
426. Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radic Biol Med.* 2011;51:1054-1061.
427. McHugh D, Tanner C, Mechoulam R, Pertwee RG, Ross RA. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: evidence for a site distinct from CB1 and CB2. *Mol Pharmacol.* 2007;73:441-450.
428. Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. *Pharmaceuticals (Basel).* 2012;5:529-552.
429. Ribeiro A, Almeida VI, Costola-de-Souza C, et al. Cannabidiol improves lung function and inflammation in mice submitted to LPS-induced acute lung injury. *Immunopharmacol Immunotoxicol.* 2015;37:35-41.
430. Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, et al. Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. *Eur J Pharmacol.* 2012;678:78-85.
431. Kozela E, Lev N, Kaushansky N, et al. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *Br J Pharmacol.* 2011;163:1507-1519.
432. Mecha M, Feliu A, Inigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. *Neurobiol Dis.* 2013;59:141-150.
433. Mecha M, Torrao AS, Mestre L, Carrillo-Salinas FJ, Mechoulam R, Guaza C. Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress. *Cell Death Dis.* 2012;3:e331.
434. Comelli F, Bettoni I, Colleoni M, Giagnoni G, Costa B. Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress. *Phytother Res.* 2009;23:1678-1684.
435. Comelli F, Giagnoni G, Bettoni I, Colleoni M, Costa B. Antihyperalgesic effect of a Cannabis sativa extract in a rat model of neuropathic pain: mechanisms involved. *Phytother Res.* 2008;22:1017-1024.
436. Howard J, Anie KA, Holdcroft A, Korn S, Davies SC. Cannabis use in sickle cell disease: a questionnaire study. *Br J Haematol.* 2005;131:123-128.
437. Maione S, Piscitelli F, Gatta L, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *Br J Pharmacol.* 2011;162:584-596.
438. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs.* 2000;60:1303-1314.
439. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res.* 2005;30:1037-1043.
440. Drysdale AJ, Ryan D, Pertwee RG, Platt B. Cannabidiol-induced intracellular Ca2+ elevations in hippocampal cells. *Neuropharmacology.* 2006;50:621-631.
441. Ryan D, Drysdale AJ, Lafourcade C, Pertwee RG, Platt B. Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels. *J Neurosci.* 2009;29:2053-2063.
442. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A.* 2006;103:7895-7900.
443. O'Sullivan SE, Sun Y, Bennett AJ, Randall MD, Kendall DA. Time-dependent vascular actions of cannabidiol in the rat aorta. *Eur J Pharmacol.* 2009;612:61-68.
444. Takeda S, Usami N, Yamamoto I, Watanabe K. Cannabidiol-2',6'-dimethyl ether, a cannabidiol derivative, is a highly potent and selective 15-lipoxygenase inhibitor. *Drug Metab Dispos.* 2009;37:1733-1737.
445. Walter L, Franklin A, Witting A, et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. *J Neurosci.* 2003;23:1398-1405.
446. Pisanti S, Malfitano AM, Ciaglia E, et al. Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacol Ther.* 2017;175:133-150.
447. Devinsky O, Cross JH, Laux L, Cannabidiol in Dravet Syndrome Study Group, et al. Trial of Cannabidiol for

Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med.* 2017;376:2011-2020.
448. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol.* 2016;15:270-278.
449. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia.* 2014;55:791-802.
450. De Caro C, Leo A, Citraro R, et al. The potential role of cannabinoids in epilepsy treatment. *Expert Rev Neurother.* 2017;17:1069-1079.
451. O'Connell BK, Gloss D, Devinsky O. Cannabinoids in treatment-resistant epilepsy: A review. *Epilepsy Behav.* 2017;70:341-348.
452. Crippa JA, Crippa AC, Hallak JE, Martin-Santos R, Zuardi AW. Delta9-THC intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy: Full remission after switching to purified cannabidiol. *Front Pharmacol.* 2016;7:359.
453. Hess EJ, Moody KA, Geffrey AL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. *Epilepsia.* 2016;57:1617-1624.
454. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia.* 2015;56:1246-1251.
455. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol.* 1981;21:417S-427S.
456. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther.* 2010;332:569-577.
457. Friedman D, Sirven JI. Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s. *Epilepsy Behav.* 2017;70:298-301.
458. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. *N Engl J Med.* 2015;373:1048-1058.
459. Katona I. Cannabis and endocannabinoid signaling in epilepsy. *Handb Exp Pharmacol.* 2015;231:285-316.
460. Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and epilepsy. *Neurotherapeutics.* 2015;12:747-768.
461. Rosenberg EC, Patra PH, Whalley BJ. Therapeutic effects of cannabinoids in animal models of seizures, epilepsy, epileptogenesis, and epilepsy-related neuroprotection. *Epilepsy Behav.* 2017;70:319-327.
462. Hofmann ME, Frazier CJ. Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention. *Exp Neurol.* 2013;244:43-50.
463. Karler R, Cely W, Turkanis SA. The anticonvulsant activity of cannabidiol and cannabinol. *Life Sci.* 1973;13:1527-1531.
464. Blair RE, Deshpande LS, DeLorenzo RJ. Cannabinoids: is there a potential treatment role in epilepsy?. *Expert Opin Pharmacother.* 2015;16:1911-1914.
465. Szaflarski JP, Bebin EM. Cannabis, cannabidiol, and epilepsy–from receptors to clinical response. *Epilepsy Behav.* 2014;41:277-282.
466. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav.* 2013;29:574-577.
467. Hussain SA, Zhou R, Jacobson C, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav.* 2015;47:138-141.
468. Cunha JM, Carlini EA, Pereira AE, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology.* 1980;21:175-185.
469. Karler R, Turkanis SA. Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. *Br J Pharmacol.* 1980;68:479-484.
470. Karler R, Turkanis SA. The cannabinoids as potential antiepileptics. *J Clin Pharmacol.* 1981;21:437S-48S.
471. Consroe P, Martin A, Singh V. Antiepileptic potential of cannabidiol analogs. *J Clin Pharmacol.* 1981;21:428S-436S.
472. Chiu P, Olsen DM, Borys HK, Karler R, Turkanis SA. The influence of cannabidiol and delta 9-tetrahydrocannabinol on cobalt epilepsy in rats. *Epilepsia.* 1979;20:365-375.
473. Esposito G, Scuderi C, Valenza M, et al. Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. *PLoS One.* 2011;6:e28668-8.
474. Esposito G, Scuderi C, Savani C, et al. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. *Br J Pharmacol.* 2007;151:1272-1279.
475. Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *J Mol Med (Berl).* 2006;84:253-258.
476. Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. *Neurosci Lett.* 2006;399:91-95.
477. Watt G, Karl T. In vivo evidence for therapeutic properties of cannabidiol (CBD) for Alzheimer's disease. *Front Pharmacol.* 2017;8:20.
478. Hayakawa K, Mishima K, Nozako M, et al. Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism. *J Neurochem.* 2007;102:1488-1496.
479. Martin-Moreno AM, Reigada D, Ramirez BG, et al. Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease. *Mol Pharmacol.* 2011;79:964-973.
480. Scuderi C, Steardo L, Esposito G. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARgamma involvement. *Phytother Res.* 2014;28:1007-1013.
481. Cheng D, Spiro AS, Jenner AM, Garner B, Karl T. Long-term cannabidiol treatment prevents the development of social

recognition memory deficits in Alzheimer's disease transgenic mice. *J Alzheimers Dis.* 2014;42:1383-1396.
482. Cheng D, Low JK, Logge W, Garner B, Karl T. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1E9 mice. *Psychopharmacology (Berl).* 2014;231:3009-3017.
483. Ramirez BG, Blazquez C, Gomez del Pulgar T, Guzman M, de Ceballos ML. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *J Neurosci.* 2005;25:1904-1913.
484. Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem.* 2004;89:134-141.
485. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders?. *CNS Neurosci Ther.* 2009;15:65-75.
486. Campbell VA, Gowran A. Alzheimer's disease; taking the edge off with cannabinoids?. *Br J Pharmacol.* 2007;152:655-662.
487. da Silva VK, de Freitas BS, da Silva Dornelles A, et al. Cannabidiol normalizes caspase 3, synaptophysin, and mitochondrial fission protein DNM1L expression levels in rats with brain iron overload: implications for neuroprotection. *Mol Neurobiol.* 2014;49:222-233.
488. Fernandez-Ruiz J, Sagredo O, Pazos MR, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?. *Br J Clin Pharmacol.* 2013;75:323-333.
489. Santos NA, Martins NM, Sisti FM, et al. The neuroprotection of cannabidiol against MPP(+)-induced toxicity in PC12 cells involves trkA receptors, upregulation of axonal and synaptic proteins, neuritogenesis, and might be relevant to Parkinson's disease. *Toxicol in Vitro.* 2015;30:231-240.
490. Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiol Dis.* 2005;19:96-107.
491. Chagas MH, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. *J Psychopharmacol.* 2014;28:1088-1098.
492. Chagas MH, Eckeli AL, Zuardi AW, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther.* 2014;39:564-566.
493. Zuardi AW, Crippa JA, Hallak JE, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. *J Psychopharmacol.* 2009;23:979-983.
494. Campos AC, Fogaca MV, Sonego AB, Guimaraes FS. Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacol Res.* 2016;112:119-127.
495. Garcia-Arencibia M, Garcia C, Fernandez-Ruiz J. Cannabinoids and Parkinson's disease. *CNS Neurol Disord Drug Targets.* 2009;8:432-439.
496. García-Arencibia M, González S, de Lago E, Ramos JA, Mechoulam R, Fernández-Ruiz J. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res.* 2007;1134:162-170.
497. Fernandez-Ruiz J, Moreno-Martet M, Rodriguez-Cueto C, et al. Prospects for cannabinoid therapies in basal ganglia disorders. *Br J Pharmacol.* 2011;163:1365-1378.
498. Kozela E, Juknat A, Gao F, Kaushansky N, Coppola G, Vogel Z. Pathways and gene networks mediating the regulatory effects of cannabidiol, a nonpsychoactive cannabinoid, in autoimmune T cells. *J Neuroinflammation.* 2016;13:136.
499. Kozela E, Juknat A, Kaushansky N, Ben-Nun A, Coppola G, Vogel Z. Cannabidiol, a non-psychoactive cannabinoid, leads to EGR2-dependent anergy in activated encephalitogenic T cells. *J Neuroinflammation.* 2015;12:52.
500. Kozela E, Juknat A, Kaushansky N, Rimmerman N, Ben-Nun A, Vogel Z. Cannabinoids decrease the Th17 inflammatory autoimmune phenotype. *J Neuroimmune Pharmacol.* 2013;8:1265-1276.
501. Giacoppo S, Pollastro F, Grassi G, Bramanti P, Mazzon E. Target regulation of PI3K/Akt/mTOR pathway by cannabidiol in treatment of experimental multiple sclerosis. *Fitoterapia.* 2017;116:77-84.
502. Giacoppo S, Soundara Rajan T, Galuppo M, et al. Purified Cannabidiol, the main non-psychotropic component of Cannabis sativa, alone, counteracts neuronal apoptosis in experimental multiple sclerosis. *Eur Rev Med Pharmacol Sci.* 2015;19:4906-4919.
503. Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernández-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. *J Neurosci Res.* 2011;89:1509-1518.
504. Sagredo O, Ramos JA, Decio A, Mechoulam R, Fernandez-Ruiz J. Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. *Eur J Neurosci.* 2007;26:843-851.
505. Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav.* 1991;40:701-708.
506. Weydt P, Hong S, Witting A, Möller T, Stella N, Kliot M. Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2005;6:182-184.
507. Resstel LBM, Tavares RF, Lisboa SFS, Joca SRL, Corrêa FMA, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol.* 2009;156:181-188.
508. Soares V. d P, Campos AC, Bortoli V. C d, Zangrossi H, Guimarães FS, Zuardi AW. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. *Behav Brain Res.* 2010;213:225-229.

509. Campos AC, Fogaca MV, Scarante FF, et al. Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabidiol in psychiatric disorders. *Front Pharmacol.* 2017;8:269.
510. Schier A, Ribeiro N, Coutinho D, et al. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa. *CNS Neurol Disord Drug Targets.* 2014;13:953-960.
511. Lemos JI, Resstel LB, Guimaraes FS. Involvement of the prelimbic prefrontal cortex on cannabidiol-induced attenuation of contextual conditioned fear in rats. *Behav Brain Res.* 2010;207:105-111.
512. Almeida V, Levin R, Peres FF, et al. Cannabidiol exhibits anxiolytic but not antipsychotic property evaluated in the social interaction test. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;41:30-35.
513. Moreira FA, Wotjak CT. Cannabinoids and anxiety. *Curr Top Behav Neurosci.* 2010;2:429-450.
514. Moreira FA, Aguiar DC, Guimaraes FS. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:1466-1471.
515. Moreira FA, Grieb M, Lutz B. Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. *Best Pract Res Clin Endocrinol Metab.* 2009;23:133-144.
516. Schier AR, Ribeiro NP, Silva AC, et al. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. *Rev Bras Psiquiatr.* 2012;34(Suppl 1): S104-S110.
517. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology.* 2011;36:1219-1226.
518. Marinho AL, Vila-Verde C, Fogaca MV, Guimaraes FS. Effects of intra-infralimbic prefrontal cortex injections of cannabidiol in the modulation of emotional behaviors in rats: contribution of 5HT(1)A receptors and stressful experiences. *Behav Brain Res.* 2015;286:49-56.
519. Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology.* 2012;62:373-384.
520. Patel S, Hill MN, Cheer JF, Wotjak CT, Holmes A. The endocannabinoid system as a target for novel anxiolytic drugs. *Neurosci Biobehav Rev.* 2017;76:56-66.
521. Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics.* 2015;12:825-836.
522. Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol.* 2011;25:121-130.
523. Crippa JA, Zuardi AW, Hallak JE. Therapeutical use of the cannabinoids in psychiatry. *Rev Bras Psiquiatr.* 2010;32: S56-S66.
524. Campos AC, Ferreira FR, Guimaraes FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. *J Psychiatr Res.* 2012;46:1501-1510.
525. Crippa JA, Zuardi AW, Martin-Santos R, et al. Cannabis and anxiety: a critical review of the evidence. *Hum Psychopharmacol.* 2009;24:515-523.
526. Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Front Behav Neurosci.* 2013;7:100.
527. Campos AC, Ortega Z, Palazuelos J, et al. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. *Int J Neuropsychopharmacol.* 2013;16:1407-1419.
528. Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol.* 2010;159:122-128.
529. Linge R, Jimenez-Sanchez L, Campa L, et al. Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. *Neuropharmacology.* 2016;103:16-26.
530. Shoval G, Shbiro L, Hershkovitz L, et al. Prohedonic effect of cannabidiol in a rat model of depression. *Neuropsychobiology.* 2016;73:123-129.
531. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci.* 1986;30:277-282.
532. Sandyk R, Snider SR, Consroe P, Elias SM. Cannabidiol in dystonic movement disorders. *Psychiatry Res.* 1986;18:291.
533. Snider SR, Consroe P. Treatment of Meige's syndrome with cannabidiol. *Neurology.* 1984;34:147.
534. Crippa JA, Hallak JE, Abilio VC, de Lacerda AL, Zuardi AW. Cannabidiol and sodium nitroprusside: two novel neuromodulatory pharmacological interventions to treat and prevent psychosis. *CNS Neurol Disord Drug Targets.* 2015;14:970-978.
535. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *Am J Psychiatry.* 2018;175:225-231.
536. Hahn B. The potential of cannabidiol treatment for cannabis users with recent-onset psychosis. *Schizophr Bull.* 2018;44:46-53.
537. Renard J, Norris C, Rushlow W, Laviolette SR. Neuronal and molecular effects of cannabidiol on the mesolimbic dopamine system: Implications for novel schizophrenia treatments. *Neurosci Biobehav Rev.* 2017;75:157-165.
538. Rohleder C, Muller JK, Lange B, Leweke FM. Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. *Front Pharmacol.* 2016;7:422.
539. Fakhoury M. Could cannabidiol be used as an alternative to antipsychotics? *J Psychiatr Res.* 2016;80:14-21.
540. Gomes FV, Llorente R, Del Bel EA, Viveros M-P, López-Gallardo M, Guimarães FS. Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol. *Schizophr Res.* 2015;164:155-163.

541. Zuardi AW, Crippa JA, Hallak JE, et al. A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. *Curr Pharm Des.* 2012;18:5131-5140.
542. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimaraes FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res.* 2006;39:421-429.
543. Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R. Antipsychotic effect of cannabidiol. *J Clin Psychiatry.* 1995;56:485-486.
544. Schubart CD, Sommer IE, Fusar-Poli P, de Witte L, Kahn RS, Boks MP. Cannabidiol as a potential treatment for psychosis. *Eur Neuropsychopharmacol.* 2014;24:51-64.
545. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry.* 2012;2:e94.
546. Mohammed N, Ceprian M, Jimenez L, Pazos MR, Martinez-Orgado J. Neuroprotective effects of cannabidiol in hypoxic ischemic insult. The therapeutic window in newborn mice. *CNS Neurol Disord Drug Targets.* 2017;16:102-108.
547. Mishima K, Hayakawa K, Abe K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke.* 2005;36:1071-1082.
548. Lafuente H, Pazos MR, Alvarez A, et al. Effects of cannabidiol and hypothermia on short-term brain damage in newborn piglets after acute hypoxia-ischemia. *Front Neurosci.* 2016;10:323.
549. Lafuente H, Alvarez FJ, Pazos MR, et al. Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. *Pediatr Res.* 2011;70:272-277.
550. Hayakawa K, Mishima K, Fujiwara M. Therapeutic potential of non-psychotropic cannabidiol in ischemic stroke. *Pharmaceuticals (Basel).* 2010;3:2197-2212.
551. Hayakawa K, Irie K, Sano K, et al. Therapeutic time window of cannabidiol treatment on delayed ischemic damage via high-mobility group box1-inhibiting mechanism. *Biol Pharm Bull.* 2009;32:1538-1544.
552. Pazos MR, Mohammed N, Lafuente H, et al. Mechanisms of cannabidiol neuroprotection in hypoxic-ischemic newborn pigs: role of 5HT(1A) and CB2 receptors. *Neuropharmacology.* 2013;71:282-291.
553. Pazos MR, Cinquina V, Gomez A, et al. Cannabidiol administration after hypoxia-ischemia to newborn rats reduces long-term brain injury and restores neurobehavioral function. *Neuropharmacology.* 2012;63:776-783.
554. Ruiz-Valdepeñas L, Martínez-Orgado JA, Benito C, Millán Á, Tolón RM, Romero J. Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study. *J Neuroinflammation.* 2011;8:5.
555. Castillo A, Tolon MR, Fernandez-Ruiz J, Romero J, Martinez-Orgado J. The neuroprotective effect of cannabidiol in an in vitro model of newborn hypoxic-ischemic brain damage in mice is mediated by CB(2) and adenosine receptors. *Neurobiol Dis.* 2010;37:434-440.
556. Mechoulam R, Shohami E. Endocannabinoids and traumatic brain injury. *Mol Neurobiol.* 2007;36:68-74.
557. Mechoulam R, Spatz M, Shohami E. Endocannabinoids and neuroprotection. *Sci STKE.* 2002;2002:re5.
558. Shohami E, Cohen-Yeshurun A, Magid L, Algali M, Mechoulam R. Endocannabinoids and traumatic brain injury. *Br J Pharmacol.* 2011;163:1402-1410.
559. Parolaro D, Massi P. Cannabinoids as potential new therapy for the treatment of gliomas. *Expert Rev Neurother.* 2008;8:37-49.
560. Allister SDM, Chan C, Taft RJ, et al. Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells. *J Neurooncol.* 2005;74:31-40.
561. McAllister SD, Murase R, Christian RT, et al. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Res Treat.* 2011;129:37-47.
562. Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther.* 2011;10:1161-1172.
563. Pisanti S, Bifulco M. Endocannabinoid system modulation in cancer biology and therapy. *Pharmacol Res.* 2009;60:107-116.
564. Pisanti S, Picardi P, D'Alessandro A, Laezza C, Bifulco M. The endocannabinoid signaling system in cancer. *Trends Pharmacol Sci.* 2013;34:273-282.
565. Scott KA, Dennis JL, Dalgleish AG, Liu WM. Inhibiting heat shock proteins can potentiate the cytotoxic effect of cannabidiol in human glioma cells. *Anticancer Res.* 2015;35:5827-5837.
566. Scott KA, Shah S, Dalgleish AG, Liu WM. Enhancing the activity of cannabidiol and other cannabinoids in vitro through modifications to drug combinations and treatment schedules. *Anticancer Res.* 2013;33:4373-4380.
567. Ramer R, Merkord J, Rohde H, Hinz B. Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1. *Biochem Pharmacol.* 2010;79:955-966.
568. Ramer R, Rohde A, Merkord J, Rohde H, Hinz B. Decrease of plasminogen activator inhibitor-1 may contribute to the anti-invasive action of cannabidiol on human lung cancer cells. *Pharm Res.* 2010;27:2162-2174.
569. Ramer R, Bublitz K, Freimuth N, et al. Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. *FASEB J.* 2012;26:1535-1548.
570. Ramer R, Heinemann K, Merkord J, et al. COX-2 and PPAR-γ confer cannabidiol-induced apoptosis of human lung cancer cells. *Mol Cancer Ther.* 2013;12:69-82.
571. Ramer R, Fischer S, Haustein M, Manda K, Hinz B. Cannabinoids inhibit angiogenic capacities of endothelial cells via release of tissue inhibitor of matrix metalloproteinases-1 from lung cancer cells. *Biochem Pharmacol.* 2014;91:202-216.
572. Ramer R, Hinz B. New insights into antimetastatic and antiangiogenic effects of cannabinoids. *Int Rev Cell Mol Biol.* 2015;314:43-116.
573. Ramer R, Hinz B. Cannabinoids as anticancer drugs. *Adv Pharmacol.* 2017;80:397-436.

574. Rocha FC, Dos Santos Junior JG, Stefano SC, da Silveira DX. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *J Neurooncol.* 2014;116:11-24.
575. McAllister SD, Christian RT, Horowitz MP, Garcia A, Desprez PY. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *Mol Cancer Ther.* 2007;6:2921-2927.
576. Orellana-Serradell O, Poblete CE, Sanchez C, et al. Proapoptotic effect of endocannabinoids in prostate cancer cells. *Oncol Rep.* 2015;33:1599-1608.
577. Nabissi M, Morelli MB, Santoni M, Santoni G. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis.* 2013;34:48-57.
578. McKallip RJ, Jia W, Schlomer J, Warren JW, Nagarkatti PS, Nagarkatti M. Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression. *Mol Pharmacol.* 2006;70:897-908.
579. Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther.* 2004;308:838-845.
580. Solinas M, Massi P, Cinquina V, et al. Cannabidiol, a non-psychoactive cannabinoid compound, inhibits proliferation and invasion in U87-MG and T98G glioma cells through a multitarget effect. *PLoS One.* 2013;8:e76918-e76919.
581. Massi P, Solinas M, Cinquina V, Parolaro D. Cannabidiol as potential anticancer drug. *Br J Clin Pharmacol.* 2013;75:303-312.
582. Romano B, Borrelli F, Pagano E, Cascio MG, Pertwee RG, Izzo AA. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. *Phytomedicine.* 2014;21:631-639.
583. Yeshurun M, Shpilberg O, Herscovici C, et al. Cannabidiol for the prevention of graft-versus-host-disease after allogeneic hematopoietic cell transplantation: Results of a phase II study. *Biol Blood Marrow Transplant.* 2015;21:1770-1775.
584. Dirikoc S, Priola SA, Marella M, Zsurger N, Chabry J. Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity. *J Neurosci.* 2007;27:9537-9544.
585. De Filippis D, Esposito G, Cirillo C, et al. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. *PLoS One.* 2011;6:e28159.
586. Sacerdote P, Martucci C, Vaccani A, et al. The nonpsychoactive component of marijuana cannabidiol modulates chemotaxis and IL-10 and IL-12 production of murine macrophages both in vivo and in vitro. *J Neuroimmunol.* 2005;159:97-105.
587. Couch DG, Tasker C, Theophilidou E, Lund JN, O'Sullivan SE. Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. *Clin Sci (Lond).* 2017;131:2611-2626.
588. Esposito G, Filippis DD, Cirillo C, et al. Cannabidiol in inflammatory bowel diseases: a brief overview. *Phytother Res.* 2013;27:633-636.
589. Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport.* 2002;13:567-570.
590. Rock EM, Limebeer CL, Mechoulam R, Parker LA, Cannabidiol (the non-psychoactive component of cannabis) may act as a 5-HT1A auto-receptor agonist to reduce toxin-induced nausea and vomiting. Proceedings 19th Annual Symposium on the Cannabinoids. International Cannabinoid Research Society. 2009;29.
591. Rock EM, Limebeer CL, Mechoulam R, Piomelli D, Parker LA. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. *Psychopharmacology (Berl).* 2008;196:389-395.
592. Farrimond JA, Whalley BJ, Williams CM. Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. *Psychopharmacology (Berl).* 2012;223:117-129.
593. Ignatowska-Jankowska B, Jankowski MM, Swiergiel AH. Cannabidiol decreases body weight gain in rats: involvement of CB2 receptors. *Neurosci Lett.* 2011;490:82-84.
594. Silvestri C, Paris D, Martella A, et al. Two non-psychoactive cannabinoids reduce intracellular lipid levels and inhibit hepatosteatosis. *J Hepatol.* 2015;62:1382-1390.
595. Scutt A, Williamson EM. Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcif Tissue Int.* 2007;80:50-59.
596. Napimoga MH, Benatti BB, Lima FO, et al. Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. *Int Immunopharmacol.* 2009;9:216-222.
597. Bab I, Zimmer A, Melamed E. Cannabinoids and the skeleton: from marijuana to reversal of bone loss. *Ann Med.* 2009;41:560-567.
598. Kogan NM, Melamed E, Wasserman E, et al. Cannabidiol, a major non-psychotropic cannabis constituent enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts. *J Bone Miner Res.* 2015;30:1905-1913.
599. Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM. Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation. *Br J Pharmacol.* 2010;159:950-957.
600. Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM. Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation. *J Hepatol.* 2009;51:528-534.
601. Avraham Y, Grigoriadis N, Poutahidis T, et al. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. *Br J Pharmacol.* 2011;162:1650-1658.
602. Lim MP, Devi LA, Rozenfeld R. Cannabidiol causes activated hepatic stellate cell death through a mechanism of endoplasmic reticulum stress-induced apoptosis. *Cell Death Dis.* 2011;2:e170.
603. Mukhopadhyay P, Rajesh M, Horvath B, et al. Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating inflammatory signaling and response, oxidative/nitrative stress, and cell death. *Free Radic Biol Med.* 2011;50:1368-1381.

604. Sultan SR, Millar SA, England TJ, O'Sullivan SE. A systematic review and meta-analysis of the haemodynamic effects of cannabidiol. *Front Pharmacol.* 2017;8:81.
605. Jadoon KA, Tan GD, O'Sullivan SE. A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study. *J CI Insight.* 2017;2.
606. Stanley CP, Hind WH, O'Sullivan SE. Is the cardiovascular system a therapeutic target for cannabidiol? *Br J Clin Pharmacol.* 2013;75:313-322.
607. Stanley CP, Hind WH, Tufarelli C, O'Sullivan SE. Cannabidiol causes endothelium-dependent vasorelaxation of human mesenteric arteries via CB1 activation. *Cardiovasc Res.* 2015;107:568-578.
608. Durst R, Danenberg H, Gallily R, et al. Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. *Am J Physiol Heart Circ Physiol.* 2007;293:H3602-H3607.
609. Rajesh M, Mukhopadhyay P, Batkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol.* 2010;56:2115-2125.
610. Weiss L, Zeira M, Reich S, et al. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. *Neuropharmacology.* 2008;54:244-249.
611. Weiss L, Zeira M, Reich S, et al. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. *Autoimmunity.* 2006;39:143-151.
612. Rajesh M, Mukhopadhyay P, Batkai S, et al. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. *Am J Physiol Heart Circ Physiol.* 2007;293:H610-H619.
613. El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai NT, Caldwell RB, Liou GI. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. *Am J Pathol.* 2006;168:235-244.
614. Takeda S, Misawa K, Yamamoto I, Watanabe K. Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metab Dispos.* 2008;36:1917-1921.
615. Takeda S, Okazaki H, Kohro-Ikeda E, et al. DNA microarray analysis of genes in highly metastatic 4T1E/M3 murine breast cancer cells following exposure to cannabidiolic acid. *Fundam Toxicol Sci.* 2015;2:89-94.
616. Takeda S, Okajima S, Miyoshi H, et al. Cannabidiolic acid, a major cannabinoid in fiber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration. *Toxicol Lett.* 2012;214:314-319.
617. Bolognini D, Rock EM, Cluny NL, et al. Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. *Br J Pharmacol.* 2013;168:1456-1470.
618. Rock EM, Kopstick RL, Limebeer CL, Parker LA. Tetrahydrocannabinolic acid reduces nausea-induced conditioned gaping in rats and vomiting in Suncus murinus. *Br J Pharmacol.* 2013;170:641-648.
619. Sirikantaramas S, Taura F, Tanaka Y, Ishikawa Y, Morimoto S, Shoyama Y. Tetrahydrocannabinolic acid synthase, the enzyme controlling marijuana psychoactivity, is secreted into the storage cavity of the glandular trichomes. *Plant Cell Physiol.* 2005;46:1578-1582.
620. De Petrocellis L, Ligresti A, Schiano Moriello A, et al. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *Br J Pharmacol.* 2013;168:79-102.
621. Musty RE, Karniol IG, Shirikawa I, Takahashi RN, Knobel E, Interactions of delta-9-tetrahydrocannabinol and cannabinol in man. In: Braude MC, Szara S, eds. *The Pharmacology of Marihuana*, Vol 2. New York: Raven Press; 1976:559-563.
622. Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE. Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology.* 1975;13:502-512.
623. Yoshida H, Usami N, Ohishi Y, Watanabe K, Yamamoto I, Yoshimura H. Synthesis and pharmacological effects in mice of halogenated cannabinol derivatives. *Chem Pharm Bull (Tokyo).* 1995;43:335-337.
624. Usami N, Kobana K, Yoshida H, et al. Synthesis and pharmacological activities in mice of halogenated delta 9-tetrahydrocannabinol derivatives. *Chem Pharm Bull (Tokyo).* 1998;46:1462-1467.
625. Takahashi RN, Karniol IG. Pharmacologic interaction between cannabinol and delta9-tetrahydrocannabinol. *Psychopharmacologia.* 1975;41:277-284.
626. Croxford JL, Yamamura T. Cannabinoids and the immune system: potential for the treatment of inflammatory diseases? *J Neuroimmunol.* 2005;166:3-18.
627. Idris AI, Sophocleous A, Landao-Bassonga E, van't Hof RJ, Ralston SH. Regulation of bone mass, osteoclast function, and ovariectomy-induced bone loss by the type 2 cannabinoid receptor. *Endocrinology.* 2008;149:5619-5626.
628. Idris AI, van 't Hof RJ, Greig IR, et al. Regulation of bone mass, bone loss and osteoclast activity by cannabinoid receptors. *Nat Med.* 2005;11:774-779.
629. Ofek O, Karsak M, Leclerc N, et al. Peripheral cannabinoid receptor, CB2, regulates bone mass. *Proc Natl Acad Sci U S A.* 2006;103:696-701.
630. Colasanti BK, Craig CR, Allara RD. Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. *Exp Eye Res.* 1984;39:251-259.
631. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *Br J Pharmacol.* 2010;159:129-141.
632. Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *J Pharmacol Exp Ther.* 1975;194:74-81.
633. Musty R, Deyo R. A cannabigerol extract alters behavioral despair in an animal model of depression. Proceedings June 26; Symposium on the Cannabinoids. *Int Cannabinoid Res Soc.* 2006;32.

634. Valdeolivas S, Navarrete C, Cantarero I, Bellido ML, Muñoz E, Sagredo O. Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice. *Neurotherapeutics.* 2015;12:185-199.
635. Brierley DI, Samuels J, Duncan M, Whalley BJ, Williams CM. Cannabigerol is a novel, well-tolerated appetite stimulant in pre-satiated rats. *Psychopharmacology (Berl).* 2016;233:3603-3613.
636. Eisohly HN, Turner CE, Clark AM, Eisohly MA. Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *J Pharm Sci.* 1982;71:1319-1323.
637. Borrelli F, Fasolino I, Romano B, et al. Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochem Pharmacol.* 2013;85:1306-1316.
638. Baek SH, Kim YO, Kwag JS, Choi KE, Jung WY, Han DS. Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Arch Pharm Res.* 1998;21:353-356.
639. Borrelli F, Pagano E, Romano B, et al. Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. *Carcinogenesis.* 2014;35:2787-2797.
640. Colasanti BK. A comparison of the ocular and central effects of delta 9-tetrahydrocannabinol and cannabigerol. *J Ocul Pharmacol.* 1990;6:259-269.
641. Mukerji G, Yiangou Y, Corcoran SL, et al. Cool and menthol receptor TRPM8 in human urinary bladder disorders and clinical correlations. *BMC Urol.* 2006;6.
642. Pagano E, Montanaro V, D, Girolamo A, Pistone A, et al. Effect of non-psychotropic plant-derived cannabinoids on bladder contractility: Focus on cannabigerol. *Nat Prod Commun.* 2015;10:1009-1012.
643. Pertwee RG. Elevating endocannabinoid levels: pharmacological strategies and potential therapeutic applications. *Proc Nutr Soc.* 2014;73:96-105.
644. Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. *Gen Pharmacol.* 1983;14:247-252.
645. Turner CE, Elsohly MA. Biological activity of cannabichromene, its homologs and isomers. *J Clin Pharmacol.* 1981;21:283S-291S.
646. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. Anti-inflammatory properties of cannabichromene. *Life Sci.* 1980;26:1991-1995.
647. Deyo R, Musty R, A cannabichromene (CBC) extract alters behavioral despair on the mouse tail suspension test of depression. Proceedings 2003 Symposium on the Cannabinoids. International Cannabinoid Research Society. 2003;146.
648. Shinjyo N, Di Marzo V. The effect of cannabichromene on adult neural stem/progenitor cells. *Neurochem Int.* 2013;63:432-437.
649. Izzo AA, Capasso R, Aviello G, et al. Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice. *Br J Pharmacol.* 2012;166:1444-1460.
650. Hatoum NS, Davis WM, Elsohly MA, Turner CE. Cannabichromene and delta 9-tetrahydrocannabinol: interactions relative to lethality, hypothermia and hexobarbital hypnosis. *Gen Pharmacol.* 1981;12:357-362.
651. Thomas A, Stevenson LA, Wease KN, et al. Evidence that the plant cannabinoid Delta9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist. *Br J Pharmacol.* 2005;146:917-926.
652. Dennis I, Whalley BJ, Stephens GJ. Effects of Delta9-tetrahydrocannabivarin on [35S]GTPgammaS binding in mouse brain cerebellum and piriform cortex membranes. *Br J Pharmacol.* 2008;154:1349-1358.
653. Ma YL, Weston SE, Whalley BJ, Stephens GJ. The phytocannabinoid Delta(9)-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum. *Br J Pharmacol.* 2008;154:204-215.
654. Hill AJ, Weston SE, Jones NA, et al. Δ^9Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia.* 2010;51:1522-1532.
655. Pertwee RG, Thomas A, Stevenson LA, et al. The psychoactive plant cannabinoid, Delta9-tetrahydrocannabinol, is antagonized by Delta8- and Delta9-tetrahydrocannabivarin in mice in vivo. *Br J Pharmacol.* 2007;150:586-594.
656. Bolognini D, Costa B, Maione S, et al. The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *Br J Pharmacol.* 2010;160:677-687.
657. Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. *Br J Pharmacol.* 2009;156:1154-1166.
658. Cawthorne MA, Wargent E, Zaibi M, Stott C, Wright S. The CB1 antagonist, delta-9-tetrahydrocannabivarin (THCV) has anti-oebesity activity in dietary-induced obese (DIO) mice. Proceedings 17th Annual Symposium on the Cannabinoids. *Int Cannabinoid Res Soc.* 2007;141.
659. Robinson L, Fadda P, McKillop-Smith S, Fratta W, Pertwee RG, Riedel G, Phytocannabinoid induced anorexic behavior in fasted and non-fasted mice. IACM Fourth Conference on Cannabinoids in Medicine; 2007.
660. Wargent ET, Zaibi MS, Silvestri C, et al. The cannabinoid Delta(9)-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity. *Nutr Diabetes.* 2013;3:e68.
661. Buchbauer G, Bohusch R, Biological activities of essential oils: An update. In: Husnu Can Baser K, Buchbauer G, eds. *Handbook of Essential Oils: Science, Technology, and Applications*. 2nd Edition. Boca Raton, FL: CRC Press; 2015:281-322.
662. Strano G. *The Chemistry of Aromatherapeutic Oils*. Crows Nest NSW, Australia: Allen & Unwin; 2005.
663. Smith N, Transdermal Cannabinoid Patch, U.S. Patent No. 20,150,297,556. 2015.
664. McPartland JM, Russo EB. Cannabis and Cannabis Extracts: greater than. *The sum of their parts? J Cannabis Therapeut.* 2001;1:103-132.

665. Paduch R, Kandefer-Szerszen M, Trytek M, Fiedurek J. Terpenes: substances useful in human healthcare. *Arch Immunol Ther Exp (Warsz).* 2007;55:315-327.
666. Klauke AL, Racz I, Pradier B, et al. The cannabinoid CB(2) receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain. *Eur Neuropsychopharmacol.* 2014;24:608-620.
667. Passos GF, Fernandes ES, da Cunha FM, et al. Anti-inflammatory and anti-allergic properties of the essential oil and active compounds from Cordia verbenacea. *J Ethnopharmacol.* 2007;110:323-333.
668. Rogerio AP, Andrade EL, Leite DF, Figueiredo CP, Calixto JB. Preventive and therapeutic anti-inflammatory properties of the sesquiterpene alpha-humulene in experimental airways allergic inflammation. *Br J Pharmacol.* 2009;158:1074-1087.
669. Medeiros R, Passos GF, Vitor CE, et al. Effect of two active compounds obtained from the essential oil of Cordia verbenacea on the acute inflammatory responses elicited by LPS in the rat paw. *Br J Pharmacol.* 2007;151:618-627.
670. Horvath B, Mukhopadhyay P, Kechrid M, et al. β-Caryophyllene ameliorates cisplatin-induced nephrotoxicity in a cannabinoid 2 receptor-dependent manner. *Free Radic Biol Med.* 2012;52:1325-1333.
671. Ghelardini C, Galeotti N, Di Cesare Mannelli L, Mazzanti G, Bartolini A. Local anaesthetic activity of beta-caryophyllene. *Farmaco.* 2001;56:387-389.
672. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. *Proc Natl Acad Sci USA.* 2008;105:9099-9104.
673. Calleja MA, Vieites JM, Montero-Meléndez T, et al. The antioxidant effect of beta-caryophyllene protects rat liver from carbon tetrachloride-induced fibrosis by inhibiting hepatic stellate cell activation. *Br J Nutr.* 2013;109:394-401.
674. Pant A, Mishra V, Saikia SK, et al. Beta-caryophyllene modulates expression of stress response genes and mediates longevity in Caenorhabditis elegans. *Exp Gerontol.* 2014;57:81-95.
675. Legault J, Pichette A. Potentiating effect of beta-caryophyllene on anticancer activity of alpha-humulene, isocaryophyllene and paclitaxel. *J Pharm Pharmacol.* 2007;59:1643-1647.
676. Legault J, Dahl W, Debiton E, Pichette A, Madelmont JC. Antitumor activity of balsam fir oil: production of reactive oxygen species induced by alpha-humulene as possible mechanism of action. *Planta Med.* 2003;69:402-407.
677. Kim C, Cho SK, Kim KD, et al. β-Caryophyllene oxide potentiates TNF-α-induced apoptosis and inhibits invasion through down-modulation of NF-κB-regulated gene products. *Apoptosis.* 2014;19:708-718.
678. Lampronti I, Saab AM, Gambari R. Antiproliferative activity of essential oils derived from plants belonging to the Magnoliophyta division. *Int J Oncol.* 2006;29:989-995.
679. Singh B, Sharma RA. Plant terpenes: defense responses, phylogenetic analysis, regulation and clinical applications. *3 Biotech.* 2015;5:129-151.
680. Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. *Planta Med.* 1996;62:469-470.
681. Basile AC, Sertie JA, Freitas PC, Zanini AC. Anti-inflammatory activity of oleoresin from Brazilian Copaifera. *J Ethnopharmacol.* 1988;22:101-109.
682. Ozturk A, Ozbek H. The anti-inflammatory activity of *Eugenia caryophyllata* essential oil: an animal model of anti-inflammatory activity. *Eur J Gen Med.* 2005;2:159-163.
683. Apel MA, Lima ME, Sobral M, et al. Anti-inflammatory activity of essential oil from leaves of Myrciaria tenella and Calycorectes sellowianus. *Pharm Biol.* 2010;48:433-438.
684. Pichette A, Larouche PL, Lebrun M, Legault J. Composition and antibacterial activity of Abies balsamea essential oil. *Phytother Res.* 2006;20:371-373.
685. Campbell WE, Gammon DW, Smith P, Abrahams M, Purves TD. Composition and antimalarial activity in vitro of the essential oil of Tetradenia riparia. *Planta Med.* 1997;63:270-272.
686. Bento AF, Marcon R, Dutra RC, et al. β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPAR-γ pathway. *Am J Pathol.* 2011;178:1153-1166.
687. Karsak M, Gaffal E, Date R, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. *Science.* 2007;316:1494-1497.
688. Al Mansouri S, Ojha S, Al Maamari E, Al Ameri M, Nurulain SM, Bahi A. The cannabinoid receptor 2 agonist, beta-caryophyllene, reduced voluntary alcohol intake and attenuated ethanol-induced place preference and sensitivity in mice. *Pharmacol Biochem Behav.* 2014;124:260-268.
689. Gertsch J. Anti-inflammatory cannabinoids in diet: Towards a better understanding of CB(2) receptor action?. *Commun Integr Biol.* 2008;1:26-28.
690. Bahi A, Al Mansouri S, Al Memari E, Al Ameri M, Nurulain SM, Ojha S. β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. *Physiol Behav.* 2014;135:119-124.
691. Xi ZX, Peng XQ, Li X, et al. Brain cannabinoid CB(2) receptors modulate cocaine's actions in mice. *Nat Neurosci.* 2011;14:1160-1166.
692. Guo K, Mou X, Huang J, Xiong N, Li H. Trans-caryophyllene suppresses hypoxia-induced neuroinflammatory responses by inhibiting NF-kappaB activation in microglia. *J Mol Neurosci.* 2014;54:41-48.
693. Zheng X, Sun T, Wang X. Activation of type 2 cannabinoid receptors (CB2R) promotes fatty acid oxidation through the SIRT1/PGC-1alpha pathway. *Biochem Biophys Res Commun.* 2013;436:377-381.
694. Van Cleemput M, Cattoor K, De Bosscher K, Haegeman G, De Keukeleire D, Heyerick A. Hop (Humulus lupulus)-derived bitter acids as multipotent bioactive compounds. *J Nat Prod.* 2009;72:1220-1230.

695. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. *J Ethnopharmacol.* 1991;34:43-48.
696. Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. *J Pharm Pharmacol.* 1990;42:877-878.
697. do Vale TG, Furtado EC, Santos JG, Jr, Viana GS. Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from Lippia alba (Mill.) n.e. Brown. *Phytomedicine.* 2002;9:709-714.
698. Bisset NG, Wichtl M. *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis*, 3rd edn. Boca Raton, FL: Medpharm Scientific Publishers: Stuttgart; CRC Press; 2004.
699. De-Oliveira AC, Ribeiro-Pinto LF, Paumgartten JR. In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. *Toxicol Lett.* 1997;92:39-46.
700. Souza MC, Siani AC, Ramos MF, Menezes-de-Lima OJ, Henriques MG. Evaluation of anti-inflammatory activity of essential oils from two Asteraceae species. *Pharmazie.* 2003;58:582-586.
701. Rufino AT, Ribeiro M, Sousa C, et al. Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. *Eur J Pharmacol.* 2015;750:141-150.
702. National Toxicology Program. NTP technical report on the toxicology and carcinogenesis studies of beta-myrcene (CAS No. 123-35-3) in F344/N rats and B6C3F1 mice (Gavage studies). *Natl Toxicol Program Tech Rep Ser.* 2010;(557):1-163.
703. Noma Y, Asakawa Y, Biotransformation of monoterpenoids by microorganisms, insects, and mammals. In: Baser KHC, Buchbauer G, eds. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010:585-736.
704. Wang W, Wu N, Zu YG, Fu YJ. Antioxidative activity of Rosmarinus officinalis L. essential oil compared to its main components. *Food Chem.* 2008;108:1019-1022.
705. Aydin E, Türkez H, Geyikoğlu F. Antioxidative, anticancer and genotoxic properties of α-pinene on N2a neuroblastoma cells. *Biologia.* 2013;68:1004-1009.
706. Kim MJ, Yang KW, Kim SS, et al. Chemical composition and anti-inflammation activity of essential oils from Citrus unshiu flower. *Nat Prod Commun.* 2014;9:727-730.
707. Bais S, Abrol N, Prashar Y, Kumari R. Modulatory effect of standardised amentoflavone isolated from Juniperus communis L. agianst Freund's adjuvant induced arthritis in rats (histopathological and X Ray anaysis). *Biomed Pharmacother.* 2017;86:381-392.
708. Rufino AT, Ribeiro M, Judas F, et al. Anti-inflammatory and chondroprotective activity of (+)-alpha-pinene: structural and enantiomeric selectivity. *J Nat Prod.* 2014;77:264-269.
709. Neves A, Rosa S, Goncalves J, et al. Screening of five essential oils for identification of potential inhibitors of IL-1-induced Nf-kappaB activation and NO production in human chondrocytes: characterization of the inhibitory activity of alpha-pinene. *Planta Med.* 2010;76:303-308.
710. Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. *Pharmazie.* 1989;44:284-287.
711. Bae GS, Park KC, Choi SB, et al. Protective effects of alpha-pinene in mice with cerulein-induced acute pancreatitis. *Life Sci.* 2012;91:866-871.
712. Him A, Ozbek H, Turel I, Oner AC. Antinociceptive activity of α-pinene and fenchone. *Pharmacol Online.* 2008;3:363-369.
713. Kennedy DO, Dodd FL, Robertson BC, et al. Monoterpenoid extract of sage (Salvia lavandulaefolia) with cholinesterase inhibiting properties improves cognitive performance and mood in healthy adults. *J Psychopharmacol.* 2011;25:1088-1100.
714. Miyazawa M, Yamafuji C. Inhibition of acetylcholinesterase activity by bicyclic monoterpenoids. *J Agric Food Chem.* 2005;53:1765-1768.
715. Perry NS, Houghton PJ, Theobald A, Jenner P, Perry EK. In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. *J Pharm Pharmacol.* 2000;52:895-902.
716. Damien Dorman HJ, Figueiredo AC, Barroso JG, Deans SG. In vitro evaluation of antioxidant activity of essential oils and their components. *Flavour and Fragrance Journal.* 2000;15:12-16.
717. Wang W, Li N, Luo M, Zu Y, Efferth T. Antibacterial activity and anticancer activity of Rosmarinus officinalis L. essential oil compared to that of its main components. *Molecules.* 2012;17:2704-2713.
718. Griffiths ET, Bociek SM, Harries PC, Jeffcoat R, Sissons DJ, Trudgill PW. Bacterial metabolism of alpha-pinene: pathway from alpha-pinene oxide to acyclic metabolites in Nocardia sp. strain P18.3. *J Bacteriol.* 1987;169:4972-4979.
719. Rivas da Silva AC, Lopes PM, Barros de Azevedo MM, Costa DC, Alviano CS, Alviano DS. Biological activities of alpha-pinene and beta-pinene enantiomers. *Molecules.* 2012;17:6305-6316.
720. Nissen L, Zatta A, Stefanini I, et al. Characterization and antimicrobial activity of essential oils of industrial hemp varieties (Cannabis sativa L.). *Fitoterapia.* 2010;81:413-419.
721. Glisic S, Milojevic S, Dimitrijevic S, Orlovic A, Skala D. Antimicrobial activity of the essential oil and different fractions of *Juniperus communis* L. and a comparison with some commercial antibiotics. *J Serb Chem Soc.* 2007;72:311-320.
722. Leite AM, Lima EO, Souza EL, Diniz MFFM, Trajano VN, Medeiros IA. Inhibitory effect of β-pinene, α-pinene and eugenol on the growth of potential infectious endocarditis causing Gram-positive bacteria. *Braz J Pharm Sci.* 2007;43:121-126.
723. Kose EO, Deniz IG, Sarikurkcu C, Aktas O, Yavuz M. Chemical composition, antimicrobial and antioxidant activities of the essential oils of Sideritis erythrantha Boiss. and Heldr. (var. erythrantha and var. cedretorum P.H. Davis) endemic in Turkey. *Food Chem Toxicol.* 2010;48:2960-2965.
724. Ozek G, Demirci F, Ozek T, et al. Gas chromatographic-mass spectrometric analysis of volatiles obtained by four different techniques from Salvia rosifolia Sm., and evaluation for biological activity. *J Chromatogr A.* 2010;1217:741-748.

725. Falk AA, Hagberg MT, Lof AE, Wigaeus-Hjelm EM, Wang ZP. Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scand J Work Environ Health.* 1990;16:372-378.
726. Astani A, Reichling J, Schnitzler P. Comparative study on the antiviral activity of selected monoterpenes derived from essential oils. *Phytother Res.* 2010;24:673-679.
727. Yang Z, Wu N, Zu Y, Fu Y. Comparative anti-infectious bronchitis virus (IBV) activity of (-)-pinene: effect on nucleocapsid (N) protein. *Molecules.* 2011;16: 1044-1054.
728. Loizzo MR, Saab AM, Tundis R, et al. Phytochemical analysis and in vitro antiviral activities of the essential oils of seven Lebanon species. *Chem Biodivers.* 2008;5:461-470.
729. Nerio LS, Olivero-Verbel J, Stashenko E. Repellent activity of essential oils: a review. *Bioresour Technol.* 2010;101:372-378.
730. Kusuhara M, Urakami K, Masuda Y, et al. Fragrant environment with alpha-pinene decreases tumor growth in mice. *Biomed Res.* 2012;33:57-61.
731. Chen WQ, Xu B, Mao JW, et al. Inhibitory effects of alpha-pinene on hepatoma carcinoma cell proliferation. *Asian Pac J Cancer Prev.* 2014;15:3293-3297.
732. Fernandes ES, Passos GF, Medeiros R, et al. Anti-inflammatory effects of compounds alpha-humulene and (-)-trans-caryophyllene isolated from the essential oil of Cordia verbenacea. *Eur J Pharmacol.* 2007;569:228-236.
733. Chaves JS, Leal PC, Pianowisky L, Calixto JB. Pharmacokinetics and tissue distribution of the sesquiterpene alpha-humulene in mice. *Planta Med.* 2008;74:1678-1683.
734. Tundis R, Loizzo MR, Bonesi M, et al. In vitro cytotoxic effects of Senecio stabianus Lacaita (Asteraceae) on human cancer cell lines. *Nat Prod Res.* 2009;23:1707-1718.
735. Govindarajan M, Rajeswary M, Arivoli S, Tennyson S, Benelli G. Larvicidal and repellent potential of Zingiber nimmonii (J. Graham) Dalzell (Zingiberaceae) essential oil: an eco-friendly tool against malaria, dengue, and lymphatic filariasis mosquito vectors?. *Parasitol Res.* 2016;115:1807-1816.
736. Satsu H, Matsuda T, Toshimitsu T, et al. Regulation of interleukin-8 secretion in human intestinal epithelial Caco-2 cells by alpha-humulene. *Biofactors.* 2004;21:137-139.
737. Peana AT, D'Aquila PS, Chessa ML, Moretti MD, Serra G, Pippia P. (-)-Linalool produces antinociception in two experimental models of pain. *Eur J Pharmacol.* 2003;460:37-41.
738. Peana AT, D'Aquila PS, Panin F, Serra G, Pippia P, Moretti MD. Anti-inflammatory activity of linalool and linalyl acetate constituents of essential oils. *Phytomedicine.* 2002;9:721-726.
739. Peana AT, Marzocco S, Popolo A, Pinto A. (-)-Linalool inhibits in vitro NO formation: Probable involvement in the antinociceptive activity of this monoterpene compound. *Life Sci.* 2006;78:719-723.
740. Nakamura A, Fujiwara S, Matsumoto I, Abe K. Stress repression in restrained rats by (R)-(-)-linalool inhalation and gene expression profiling of their whole blood cells. *J Agric Food Chem.* 2009;57:5480-5485.
741. Russo EB. *Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Remedies for Psychiatric Conditions*. Binghamton, NY: Haworth Press; 2001.
742. Cline M, Taylor JE, Flores J, Bracken S, McCall S, Ceremuga TE. Investigation of the anxiolytic effects of linalool, a lavender extract, in the male Sprague-Dawley rat. *AANA J.* 2008;76:47-52.
743. Cheng BH, Sheen LY, Chang ST. Evaluation of anxiolytic potency of essential oil and S-(+)-linalool from Cinnamomum osmophloeum ct. linalool leaves in mice. *J Tradit Complement Med 2014.* 2015;5:27-34.
744. Buchbauer G, Jirovetz L, Jager W, Dietrich H, Plank C. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. *Z Naturforsch C.* 1991;46:1067-1072.
745. Jirovetz L, Buchbauer G, Jager W, Woidich A, Nikiforov A. Analysis of fragrance compounds in blood samples of mice by gas chromatography, mass spectrometry, GC/FTIR and GC/AES after inhalation of sandalwood oil. *Biomed Chromatogr.* 1992;6:133-134.
746. Buchbauer G, Jirovetz L, Jager W, Plank C, Dietrich H. Fragrance compounds and essential oils with sedative effects upon inhalation. *J Pharm Sci.* 1993;82:660-664.
747. do Socorro S Rosa Mdo S, Mendonca-Filho RR, Bizzo HR, et al. Antileishmanial activity of a linalool-rich essential oil from Croton cajucara. *Antimicrob Agents Chemother.* 2003;47:1895-1901.
748. Rodrigues Goulart H, Kimura EA, Peres VJ, Couto AS, Aquino Duarte FA, Katzin AM. Terpenes arrest parasite development and inhibit biosynthesis of isoprenoids in Plasmodium falciparum. *Antimicrob Agents Chemother.* 2004;48:2502-2509.
749. de Sousa DP, Nobrega FF, Santos CC, de Almeida RN. Anticonvulsant activity of the linalool enantiomers and racemate: investigation of chiral influence. *Nat Prod Commun.* 2010;5:1847-1851.
750. Elisabetsky E, Marschner J, Souza DO. Effects of Linalool on glutamatergic system in the rat cerebral cortex. *Neurochem Res.* 1995;20:461-465.
751. Ismail M. Central properties and chemical composition of *Ocimum basilicum* essential oil. *Pharm Biol.* 2006;44:619-626.
752. Silva Brum LF, Emanuelli T, Souza DO, Elisabetsky E. Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. *Neurochem Res.* 2001;26:191-194.
753. Nunes DS, Linck VM, da Silva AL, Figueiro M, Elisabetsky E, Psychopharmacology of essential oils. In: Baser KHC, Buchbauer G, eds. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press, 2010:297-314.
754. Baschieri A, Ajvazi MD, Tonfack JLF, Valgimigli L, Amorati R. Explaining the antioxidant activity of some common non-phenolic components of essential oils. *Food Chem.* 2017;232:656-663.
755. Re L, Barocci S, Sonnino S, et al. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. *Pharmacol Res.* 2000;42:177-182.
756. Ghelardini C, Galeotti N, Salvatore G, Mazzanti G. Local anaesthetic activity of the essential oil

of Lavandula angustifolia. *Planta Med.* 1999;65: 700-703.
757. Peana AT, Rubattu P, Piga GG, et al. Involvement of adenosine A1 and A2A receptors in (-)-linalool-induced antinociception. *Life Sci.* 2006;78:2471-2474.
758. Batista PA, Werner MF, Oliveira EC, et al. Evidence for the involvement of ionotropic glutamatergic receptors on the antinociceptive effect of (-)-linalool in mice. *Neurosci Lett.* 2008;440:299-303.
759. Kim JT, Ren CJ, Fielding GA, et al. Treatment with lavender aromatherapy in the post-anesthesia care unit reduces opioid requirements of morbidly obese patients undergoing laparoscopic adjustable gastric banding. *Obes Surg.* 2007;17:920-925.
760. Hirota R, Roger NN, Nakamura H, Song HS, Sawamura M, Suganuma N. Anti-inflammatory effects of limonene from yuzu (Citrus junos Tanaka) essential oil on eosinophils. *J Food Sci.* 2010;75:H87-H92.
761. Chaudhary SC, Siddiqui MS, Athar M, Alam MS. D-Limonene modulates inflammation, oxidative stress and Ras-ERK pathway to inhibit murine skin tumorigenesis. *Hum Exp Toxicol.* 2012;31:798-811.
762. d'Alessio PA, Ostan R, Bisson J-F, Schulzke JD, Ursini MV, Béné MC. Oral administration of d-limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans. *Life Sci.* 2013;92:1151-1156.
763. Piccinelli AC, Santos JA, Konkiewitz EC, et al. Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, alpha-phellandrene, and essential oil from Schinus terebinthifolius fruits in a neuropathic pain model. *Nutr Neurosci.* 2015;18:217-224.
764. Singh P, Shukla R, Prakash B, et al. Chemical profile, antifungal, antiaflatoxigenic and antioxidant activity of Citrus maxima Burm. and Citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpene, DL-limonene. *Food Chem Toxicol.* 2010;48:1734-1740.
765. Choi HS, Song HS, Ukeda H, Sawamura M. Radical-scavenging activities of citrus essential oils and their components: detection using 1,1-diphenyl-2-picrylhydrazyl. *J Agric Food Chem.* 2000;48:4156-4161.
766. Komori T, Fujiwara R, Tanida M, Nomura J, Yokoyama MM. Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation.* 1995;2:174-180.
767. Crowell PL, Gould MN. Chemoprevention and therapy of cancer by d-limonene. *Crit Rev Oncog.* 1994;5:1-22.
768. Rabi T, Bishayee A. d -Limonene sensitizes docetaxel-induced cytotoxicity in human prostate cancer cells: Generation of reactive oxygen species and induction of apoptosis. *J Carcinog.* 2009;8:9.
769. Vigushin DM, Poon GK, Boddy A, et al. Phase I and pharmacokinetic study of D-limonene in patients with advanced cancer. Cancer Research Campaign Phase I/II Clinical Trials Committee. *Cancer Chemother Pharmacol.* 1998;42:111-117.
770. da Fonseca CO, Simao M, Lins IR, Caetano RO, Futuro D, Quirico-Santos T. Efficacy of monoterpene perillyl alcohol upon survival rate of patients with recurrent glioblastoma. *J Cancer Res Clin Oncol.* 2011;137:287-293.
771. Kim SS, Baik JS, Oh TH, Yoon WJ, Lee NH, Hyun CG. Biological activities of Korean Citrus obovoides and Citrus natsudaidai essential oils against acne-inducing bacteria. *Biosci Biotechnol Biochem.* 2008;72:2507-2513.
772. Sanguinetti M, Posteraro B, Romano L, et al. In vitro activity of Citrus bergamia (bergamot) oil against clinical isolates of dermatophytes. *J Antimicrob Chemother.* 2007;59:305-308.
773. Harris B. Phytotherapeutic uses of essential oils. In: Baser KHC, Buchbauer G, eds. *Handbook of Essential Oils: Science, Technology, and Applications*. Boca Raton, FL: CRC Press; 2010:315-352.
774. de Almeida AA, Costa JP, de Carvalho RB, de Sousa DP, de Freitas RM. Evaluation of acute toxicity of a natural compound (+)-limonene epoxide and its anxiolytic-like action. *Brain Res.* 2012;1448:56-62.
775. Carvalho-Freitas MI, Costa M. Anxiolytic and sedative effects of extracts and essential oil from Citrus aurantium L. *Biol Pharm Bull.* 2002;25:1629-1633.
776. Pultrini A. d M, Galindo LA, Costa M. Effects of the essential oil from Citrus aurantium L. in experimental anxiety models in mice. *Life Sci.* 2006;78:1720-1725.
777. Saiyudthong S, Marsden CA. Acute effects of bergamot oil on anxiety-related behaviour and corticosterone level in rats. *Phytother Res.* 2011;25:858-862.
778. Pimenta FC, Alves MF, Pimenta MB, et al. Anxiolytic effect of Citrus aurantium L. on patients with chronic myeloid leukemia. *Phytother Res.* 2016;30:613-617.
779. Komiya M, Takeuchi T, Harada E. Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. *Behav Brain Res.* 2006;172:240-249.
780. Turkez H, Aydin E, Geyikoglu F, Cetin D. Genotoxic and oxidative damage potentials in human lymphocytes after exposure to terpinolene in vitro. *Cytotechnology.* 2015;67:409-418.
781. Aydin E, Türkez H, Taşdemir S. Anticancer and antioxidant properties of terpinolene in rat brain cells. *Arh Hig Rada Toksikol.* 2013;64:415-424.
782. Eftekhar F, Yousefzadi M, Azizian D, Sonboli A, Salehi P. Essential oil composition and antimicrobial activity of Diplotaenia damavandica. *Z Naturforsch C.* 2005;60:821-825.
783. Shafagha A, Shafaghatlonbar M. Antimicrobial activity and chemical constituents of the essential oils from flower, leaf and stem of Gypsophila bicolor from Iran. *Nat Prod Commun.* 2011;6:275-276.
784. Okumura N, Yoshida H, Nishimura Y, Kitagishi Y, Matsuda S. Terpinolene, a component of herbal sage, downregulates AKT1 expression in K562 cells. *Oncol Lett.* 2012;3:321-324.
785. Ito K, Ito M. The sedative effect of inhaled terpinolene in mice and its structure-activity relationships. *J Nat Med.* 2013;67:833-837.
786. Chang KS, Shin EH, Park C, Ahn YJ. Contact and fumigant toxicity of Cyperus rotundus steam distillate constituents and related compounds to insecticide-susceptible and -resistant Blattella germanica. *J Med Entomol.* 2012;49:631-639.

787. Graßmann J, Hippeli S, Spitzenberger R, Elstner EF. The monoterpene terpinolene from the oil of Pinus mugo L. in concert with alpha-tocopherol and beta-carotene effectively prevents oxidation of LDL. *Phytomedicine.* 2005;12:416-423.
788. Oliveira MG, Brito RG, Santos PL, et al. α-Terpineol, a monoterpene alcohol, complexed with β-cyclodextrin exerts antihyperalgesic effect in animal model for fibromyalgia aided with docking study. *Chem Biol Interact.* 2016;254:54-62.
789. Held S, Schieberle P, Somoza V. Characterization of alpha-terpineol as an anti-inflammatory component of orange juice by in vitro studies using oral buccal cells. *J Agric Food Chem.* 2007;55:8040-8046.
790. Brand C, Ferrante A, Prager RH, et al. The water-soluble components of the essential oil of Melaleuca alternifolia (tea tree oil) suppress the production of superoxide by human monocytes, but not neutrophils, activated in vitro. *Inflamm Res.* 2001;50:213-219.
791. Burits M, Bucar F. Antioxidant activity of Nigella sativa essential oil. *Phytother Res.* 2000;14:323-328.
792. Hassan SB, Gali-Muhtasib H, Goransson H, Larsson R. Alpha terpineol: a potential anticancer agent which acts through suppressing NF-kappaB signalling. *Anticancer Res.* 2010;1911-1919.
793. Park SN, Lim YK, Freire MO, Cho E, Jin D, Kook JK. Antimicrobial effect of linalool and alpha-terpineol against periodontopathic and cariogenic bacteria. *Anaerobe.* 2012;18:369-372.
794. Zengin H, Baysal AH. Antibacterial and antioxidant activity of essential oil terpenes against pathogenic and spoilage-forming bacteria and cell structure-activity relationships evaluated by SEM microscopy. *Molecules.* 2014;19:17773-17798.
795. Hammer KA, Carson CF, Riley TV. Antifungal activity of the components of Melaleuca alternifolia (tea tree) oil. *J Appl Microbiol.* 2003;95:853-860.
796. Williams AC, Barry BW. Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. *Pharm Res.* 1991;08:17-24.
797. Zhu W, Liu X, Wang Y, Tong Y, Hu Y. Discovery of a novel series of alpha-terpineol derivatives as promising anti-asthmatic agents: Their design, synthesis, and biological evaluation. *Eur J Med Chem.* 2018;143:419-425.
798. Ribeiro TP, Porto DL, Menezes CP, et al. Unravelling the cardiovascular effects induced by alpha-terpineol: a role for the nitric oxide-cGMP pathway. *Clin Exp Pharmacol Physiol.* 2010;37:811-816.
799. Golfakhrabadi F, Khanavi M, Ostad SN, et al. Biological activities and composition of ferulago carduchorum essential oil. *J Arthropod Borne Dis.* 2014;9:104-115.
800. Shafaghat A. Antibacterial activity and composition of essential oils from flower, leaf and stem of Chaerophyllum macropodum Boiss from Iran. *Nat Prod Commun.* 2009;4:861-864.
801. Tsoyi K, Jang HJ, Lee YS, et al. (+)-Nootkatone and (+)-valencene from rhizomes of Cyperus rotundus increase survival rates in septic mice due to heme oxygenase-1 induction. *J Ethnopharmacol.* 2011;137:1311-1317.
802. Panella NA, Dolan MC, Karchesy JJ, et al. Use of novel compounds for pest control: insecticidal and acaricidal activity of essential oil components from heartwood of Alaska yellow cedar. *J Med Entomol.* 2005;42:352-358.
803. Dietrich G, Dolan MC, Peralta-Cruz J, et al. Repellent activity of fractioned compounds from Chamaecyparis nootkatensis essential oil against nymphal Ixodes scapularis (Acari: Ixodidae). *J Med Entomol.* 2006;43:957-961.
804. Santos PL, Araujo AA, Quintans JS, et al. Preparation, characterization, and pharmacological activity of Cymbopogon winterianus Jowitt ex Bor (Poaceae) leaf essential oil of beta-cyclodextrin inclusion complexes. *Evid Based Complement Alternat Med.* 2015;2015:502454.
805. Marcuzzi A, Pontillo A, De Leo L, et al. Natural isoprenoids are able to reduce inflammation in a mouse model of mevalonate kinase deficiency. *Pediatr Res.* 2008;64:177-182.
806. Tiwari M, Kakkar P. Plant derived antioxidants - Geraniol and camphene protect rat alveolar macrophages against t-BHP induced oxidative stress. *Toxicol in Vitro.* 2009;23:295-301.
807. Godwin DA, Michniak BB. Influence of drug lipophilicity on terpenes as transdermal penetration enhancers. *Drug Dev Ind Pharm.* 1999;25:905-915.
808. Thapa D, Losa R, Zweifel B, Wallace RJ. Sensitivity of pathogenic and commensal bacteria from the human colon to essential oils. *Microbiology.* 2012;158:2870-2877.
809. Miladinovic DL, Ilic BS, Kocic BD, Ciric VM, Nikolic DM. Antibacterial investigation of thyme essential oil and its main constituents in combination with tetracycline. *J Med Food.* 2015;18:935-937.
810. Solorzano-Santos F, Miranda-Novales MG. Essential oils from aromatic herbs as antimicrobial agents. *Curr Opin Biotechnol.* 2012;23:136-141.
811. Leite MC, de Brito Bezerra AP, de Sousa JP, de Oliveira Lima E. Investigating the antifungal activity and mechanism(s) of geraniol against Candida albicans strains. *Med Mycol.* 2015;53:275-284.
812. Juarez ZN, Bach H, Sanchez-Arreola E, Bach H, Hernandez LR. Protective antifungal activity of essential oils extracted from Buddleja perfoliata and Pelargonium graveolens against fungi isolated from stored grains. *J Appl Microbiol.* 2016;120:1264-1270.
813. Kpoviessi S, Bero J, Agbani P, et al. Chemical composition, cytotoxicity and in vitro antitrypanosomal and antiplasmodial activity of the essential oils of four Cymbopogon species from Benin. *J Ethnopharmacol.* 2014;151:652-659.
814. Maurya AK, Singh M, Dubey V, Srivastava S, Luqman S, Bawankule DU. Alpha-(-)-bisabolol reduces pro-inflammatory cytokine production and ameliorates skin inflammation. *Curr Pharm Biotechnol.* 2014;15:173-181.
815. Nurulain S, Prytkova T, Sultan AM, et al. Inhibitory actions of bisabolol on alpha7-nicotinic acetylcholine receptors. *Neuroscience.* 2015;306:91-99.
816. Cavalieri E, Rigo A, Bonifacio M, et al. Pro-apoptotic activity of alpha-bisabolol in preclinical models of primary human acute leukemia cells. *J Transl Med.* 2011;9:45.

817. Cavalieri E, Mariotto S, Fabrizi C, et al. alpha-Bisabolol, a nontoxic natural compound, strongly induces apoptosis in glioma cells. *Biochem Biophys Res Commun.* 2004;315:589-594.
818. Costarelli L, Malavolta M, Giacconi R, et al. In vivo effect of alpha-bisabolol, a nontoxic sesquiterpene alcohol, on the induction of spontaneous mammary tumors in HER-2/neu transgenic mice. *Oncol Res* 2010. 18:409-418.
819. Darra E, Abdel-Azeim S, Manara A, et al. Insight into the apoptosis-inducing action of alpha-bisabolol towards malignant tumor cells: involvement of lipid rafts and Bid. *Arch Biochem Biophys.* 2008;476:113-123.
820. Gomes-Carneiro MR, Dias DM, De-Oliveira AC, Paumgartten FJ. Evaluation of mutagenic and antimutagenic activities of alpha-bisabolol in the Salmonella/microsome assay. *Mutat Res.* 2005;585:105-112.
821. Al Mansoori M, Al Shamri N, Al Kendi N, Al Jaberi M, Sheikh A, Amir N, Nalin N, et al. Bisabolol ameliorates cisplatin-induced nephrotoxicity in rats. *Hamdan Med J.* 2015;8:77-78.
822. Corpas-López V, Morillas-Márquez F, Navarro-Moll MC, Merino-Espinosa G, Díaz-Sáez V, Martín-Sánchez J. Martin-Sanchez J. (-)-alpha-bisabolol, a promising oral compound for the treatment of visceral leishmaniasis. *J Nat Prod.* 2015;78:1202-1207.
823. Kurekci C, Padmanabha J, Bishop-Hurley SL, Hassan E, Al Jassim RA, McSweeney CS. Antimicrobial activity of essential oils and five terpenoid compounds against Campylobacter jejuni in pure and mixed culture experiments. *Int J Food Microbiol.* 2013;166:450-7.
824. Brehm-Stecher BF, Johnson EA. Sensitization of *Staphylococcus aureus* and *Escherichia coli* to antibiotics by the sesquiterpenoids nerolidol, farnesol, bisabolol, and apritone. *Antimicrob Agents Chemother.* 2003;47:3357-3360.
825. Binet L, Binet P, Miocque M, Roux M, Bernier A. Reserches sur les proprietes pharmcodynamiques (action sedative et action spasmolytique) de quelques alcools terpeniques aliphatiques. *Ann Pharm Fr.* 1972;30:611-616.
826. Arruda DC, D'Alexandri FL, Katzin AM, Uliana SR. Antileishmanial activity of the terpene nerolidol. *Antimicrob Agents Chemother.* 2005;49:1679-1687.
827. AbouLaila M, Sivakumar T, Yokoyama N, Igarashi I. Inhibitory effect of terpene nerolidol on the growth of Babesia parasites. *Parasitol Int.* 2010;59:278-282.
828. Langenheim JH. Higher plant terpenoids: A phytocentric overview of their ecological roles. *J Chem Ecol.* 1994;20:1223-1280.
829. Lee SJ, Han JI, Lee GS, et al. Antifungal effect of eugenol and nerolidol against Microsporum gypseum in a guinea pig model. *Biol Pharm Bull.* 2007;30:184-188.
830. Lopes NP, Kato MJ, Andrade EH, et al. Antimalarial use of volatile oil from leaves of Virola surinamensis (Rol.) Warb. by Waiapi Amazon Indians. *J Ethnopharmacol.* 1999;67:313-319.
831. Wattenberg LW. Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol). *Carcinogenesis.* 1991;12:151-152.
832. Cornwell PA, Barry BW. Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. *J Pharm Pharmacol.* 1994;46:261-269.
833. Chavan MJ, Wakte PS, Shinde DB. Analgesic and anti-inflammatory activity of Caryophyllene oxide from Annona squamosa L. bark. *Phytomedicine.* 2010;17:149-151.
834. Yang D, Michel L, Chaumont JP, Millet-Clerc J. Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis. *Mycopathologia.* 1999;148:79-82.
835. Bettarini F, Borgonovi GE, Fiorani T, et al. Antiparasitic compounds from East African plants: Isolation and biological activity of anonaine, matricarianol, canthin-6-one and caryophyllene oxide. *Insect Sci Appl.* 1993;14:93-99.
836. Lin WY, Kuo YH, Chang YL, et al. Anti-platelet aggregation and chemical constituents from the rhizome of Gynura japonica. *Planta Med.* 2003;69:757-764.
837. Bang MH, Choi SY, Jang TO, et al. Phytol, SSADH inhibitory diterpenoid of Lactuca sativa. *Arch Pharm Res.* 2002;25:643-646.
838. Arnhold T, Elmazar MM, Nau H. Prevention of vitamin A teratogenesis by phytol or phytanic acid results from reduced metabolism of retinol to the teratogenic metabolite, all-trans-retinoic acid. *Toxicol Sci.* 2002;66:274-282.
839. Stockman R. The physiological action of borneol. A contribution to the pharmacology of the camphor group. *J Physiol.* 1888;9:65-91.
840. Park TJ, Park YS, Lee TG, Ha H, Kim KT. Inhibition of acetylcholine-mediated effects by borneol. *Biochem Pharmacol.* 2003;65:83-90.
841. Ehrnhofer-Ressler MM, Fricke K, Pignitter M, et al. Identification of 1,8-cineole, borneol, camphor, and thujone as anti-inflammatory compounds in a Salvia officinalis L. infusion using human gingival fibroblasts. *J Agric Food Chem.* 2013;61:3451-3459.
842. Almeida JR, Souza GR, Silva JC, et al. Borneol, a bicyclic monoterpene alcohol, reduces nociceptive behavior and inflammatory response in mice. *ScientificWorldJournal.* 2013;2013:1.
843. Adams JD, Wang X. Control of pain with topical plant medicines. *Asian Pac J Trop Biomed.* 2015;5: 268-273.
844. Jiang J, Shen YY, Li J, Lin YH, Luo CX, Zhu DY. (+)-Borneol alleviates mechanical hyperalgesia in models of chronic inflammatory and neuropathic pain in mice. *Eur J Pharmacol.* 2015;757:53-58.
845. Guangchi J, Shenghua Y, Xujun F. School of Pharmacy, West China University of Medical Sciences Chdngdu 610041. Anti-inflammatory effect of borneol and isoborneol. *West China J Pharmaceutical Sci.* 1990;3.
846. Benelli G, Bedini S, Flamini G, et al. Mediterranean essential oils as effective weapons against the West Nile vector Culex pipiens and the Echinostoma intermediate host Physella acuta: what happens around? An acute toxicity survey on non-target mayflies. *Parasitol Res.* 2015;114:1011-1021.
847. Dai JP, Chen J, Bei YF, Han BX, Wang S. Influence of borneol on primary mice oral fibroblasts: a penetration enhancer

may be used in oral submucous fibrosis. *J Oral Pathol Med.* 2009;38:276-281.
848. Barreto RS, Quintans JS, Barreto AS, et al. Improvement of wound tissue repair by chitosan films containing (-)-borneol, a bicyclic monoterpene alcohol, in rats. *Int Wound J.* 2016;13:799-808.
849. Yang CB, Pei WJ, Zhao J, Cheng YY, Zheng XH, Rong JH. Bornyl caffeate induces apoptosis in human breast cancer MCF-7 cells via the ROS- and JNK-mediated pathways. *Acta Pharmacol Sin.* 2014;35:113-123.
850. Chen J, Li L, Su J, Chen T. Natural borneol enhances bisdemethoxycurcumin-induced cell cycle arrest in the G2/M phase through up-regulation of intracellular ROS in HepG2 cells. *Food Funct.* 2015;6:740-748.
851. Su J, Lai H, Chen J, et al. Natural borneol, a monoterpenoid compound, potentiates selenocystine-induced apoptosis in human hepatocellular carcinoma cells by enhancement of cellular uptake and activation of ROS-mediated DNA damage. *PLoS One.* 2013;8:e63502-11.
852. Zhang L, Han L, Qin J, Lu W, Wang J. The use of borneol as an enhancer for targeting aprotinin-conjugated PEG-PLGA nanoparticles to the brain. *Pharm Res.* 2013;30:2560-2572.
853. Li YH, Sun XP, Zhang YQ, Wang NS. The antithrombotic effect of borneol related to its anticoagulant property. *Am J Chin Med.* 2008;36:719-727.
854. Wu HY, Tang Y, Gao LY, et al. The synergetic effect of edaravone and borneol in the rat model of ischemic stroke. *Eur J Pharmacol.* 2014;740:522-531.
855. Jeong JG, Kim YS, Min YK, Kim SH. Low concentration of 3-carene stimulates the differentiation of mouse osteoblastic MC3T3-E1 subclone 4 cells. *Phytother Res.* 2008;22:18-22.
856. Kweka EJ, Nyindo M, Mosha F, Silva AG. Insecticidal activity of the essential oil from fruits and seeds of Schinus terebinthifolia Raddi against African malaria vectors. *Parasit Vectors.* 2011;4:129.
857. Silva AG, Almeida DL, Ronchi SN, et al. The essential oil of Brazilian pepper, Schinus terebinthifolia Raddi in larval control of Stegomyia aegypti (Linnaeus, 1762). *Parasit Vectors.* 2010;3:79.
858. Nzira L, Per M, Peter F, Claus B. Lippia javanica (Burm F) Spreng: its general constituents and bioactivity on mosquitoes. *Trop Biomed.* 2009;26:85-91.
859. Ramalho TR, Oliveira MT, Lima AL, Bezerra-Santos CR, Piuvezam MR. Gamma-terpinene modulates acute inflammatory response in mice. *Planta Med.* 2015;81:1248-1254.
860. Rudback J, Bergstrom MA, Borje A, Nilsson U, Karlberg AT. alpha-Terpinene, an antioxidant in tea tree oil, autoxidizes rapidly to skin allergens on air exposure. *Chem Res Toxicol.* 2012;25:713-721.
861. Quintans-Junior L, Moreira JC, Pasquali MA, et al. Antinociceptive activity and redox profile of the monoterpenes (+)-Camphene, p-Cymene, and geranyl acetate in experimental models. *ISRN Toxicol.* 2013;2013:1.
862. Marei GIK, Abdel Rasoul MA, Abdelgaleil SAM. Comparative antifungal activities and biochemical effects of monoterpenes on plant pathogenic fungi. *Pestic Biochem Physiol.* 2012;103:56-61.
863. Vallianou I, Peroulis N, Pantazis P, Hadzopoulou-Cladaras M. Camphene, a plant-derived monoterpene, reduces plasma cholesterol and triglycerides in hyperlipidemic rats independently of HMG-CoA reductase activity. *PLoS One.* 2011;6:e20516-11.
864. Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, Anwar F. Essential oils used in aromatherapy: A systemic review. *Asian Pac J Trop Biomed.* 2015;5:601-611.
865. Valente J, Zuzarte M, Goncalves MJ, et al. Antifungal, antioxidant and anti-inflammatory activities of Oenanthe crocata L. essential oil. *Food Chem Toxicol.* 2013;62:349-354.
866. Moss M, Oliver L. Plasma 1,8-cineole correlates with cognitive performance following exposure to rosemary essential oil aroma. *Ther Adv Psychopharmacol.* 2012;2:103-113.
867. Khan A, Vaibhav K, Javed H, et al. 1,8-cineole (eucalyptol) mitigates inflammation in amyloid Beta toxicated PC12 cells: relevance to Alzheimer's disease. *Neurochem Res.* 2014;39:344-352.
868. Cho KH. 1,8-Cineole protected human lipoproteins from modification by oxidation and glycation and exhibited serum lipid-lowering and anti-inflammatory activity in zebrafish. *BMB Rep.* 2012;45:565-570.
869. Santos FA, Rao VS. Antiinflammatory and antinociceptive effects of 1,8-cineole a terpenoid oxide present in many plant essential oils. *Phytother Res.* 2000;14:240-244.
870. Juergens UR. Anti-inflammatory properties of the monoterpene 1.8-cineole: current evidence for co-medication in inflammatory airway diseases. *Drug Res (Stuttg).* 2014;64:638-646.
871. Worth H, Schacher C, Dethlefsen U. Concomitant therapy with Cineole (Eucalyptole) reduces exacerbations in COPD: a placebo-controlled double-blind trial. *Respir Res.* 2009;10:69.
872. Worth H, Dethlefsen U. Patients with asthma benefit from concomitant therapy with cineole: a placebo-controlled, double-blind trial. *J Asthma.* 2012;49:849-853.
873. Juergens UR, Engelen T, Racké K, Stöber M, Gillissen A, Vetter H. Inhibitory activity of 1,8-cineol (eucalyptol) on cytokine production in cultured human lymphocytes and monocytes. *Pulm Pharmacol Ther.* 2004;17:281-287.
874. Juergens UR, Dethlefsen U, Steinkamp G, Gillissen A, Repges R, Vetter H. Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial. *Respir Med.* 2003;97:250-256.
875. Santos FA, Silva RM, Campos AR, De Araújo RP, Lima Júnior RCP, Rao VSN. 1,8-cineole (eucalyptol), a monoterpene oxide attenuates the colonic damage in rats on acute TNBS-colitis. *Food Chem Toxicol.* 2004;42:579-584.
876. Lima PR, de Melo TS, Carvalho KM, et al. 1,8-cineole (eucalyptol) ameliorates cerulein-induced acute pancreatitis via modulation of cytokines, oxidative stress and NF-kappaB activity in mice. *Life Sci.* 2013;92:1195-1201.

877. Kehrl W, Sonnemann U, Dethlefsen U. Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial. *Laryngoscope.* 2004;114:738-742.
878. Burrow A, Eccles R, Jones AS. The effects of camphor, eucalyptus and menthol vapour on nasal resistance to airflow and nasal sensation. *Acta Otolaryngol.* 1983;96:157-161.
879. Morcia C, Malnati M, Terzi V. In vitro antifungal activity of terpinen-4-ol, eugenol, carvone, 1,8-cineole (eucalyptol) and thymol against mycotoxigenic plant pathogens. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2011;29:1-22.
880. Ramsewak RS, Nair MG, Stommel M, Selanders L. In vitro antagonistic activity of monoterpenes and their mixtures against 'toe nail fungus' pathogens. *Phytother Res.* 2003;17:376-379.
881. Moteki H, Hibasami H, Yamada Y, Katsuzaki H, Imai K, Komiya T. Specific induction of apoptosis by 1,8-cineole in two human leukemia cell lines, but not a in human stomach cancer cell line. *Oncol Rep.* 2002;9:757-760.
882. Murata S, Shiragami R, Kosugi C, et al. Antitumor effect of 1, 8-cineole against colon cancer. *Oncol Rep.* 2013;30:2647-2652.
883. Chehregani A, Atri M, Yousefi S, Albooyeh Z, Mohsenzadeh F. Essential oil variation in the populations of Artemisia spicigera from northwest of Iran: chemical composition and antibacterial activity. *Pharm Biol.* 2013;51:246-252.
884. Ramos Alvarenga RF, Wan B, Inui T, Franzblau SG, Pauli GF, Jaki BU. Airborne antituberculosis activity of Eucalyptus citriodora essential oil. *J Nat Prod.* 2014;77:603-610.
885. Conti B, Flamini G, Cioni PL, Ceccarini L, Macchia M, Benelli G. Mosquitocidal essential oils: are they safe against non-target aquatic organisms? *Parasitol Res.* 2014;113:251-259.
886. Wang Y, You CX, Wang CF, et al. Chemical constituents and insecticidal activities of the essential oil from Amomum tsaoko against two stored-product insects. *J Oleo Sci.* 2014;63:1019-1026.
887. Rodenak Kladniew B, Polo M, Montero Villegas S, Galle M, Crespo R, García de Bravo M. Synergistic antiproliferative and anticholesterogenic effects of linalool, 1,8-cineole, and simvastatin on human cell lines. *Chem Biol Interact.* 2014;214:57-68.
888. Choudhary MI, Batool I, Atif M, Hussain S, Atta-Ur-Rahman. Microbial transformation of (-)-guaiol and antibacterial activity of its transformed products. *J Nat Prod.* 2007;70:849-852.
889. Liu T, Wang CJ, Xie HQ, Mu Q. Guaiol–a naturally occurring insecticidal sesquiterpene. *Nat Prod Commun.* 2013;8:1353-1354.
890. Tian LL, Zhou Z, Zhang Q, et al. Protective effect of (+/-) isoborneol against 6-OHDA-induced apoptosis in SH-SY5Y cells. *Cell Physiol Biochem.* 2007;20:1019-1032.
891. de Cassia da Silveira E, Sa R, Andrade LN, de Sousa DP. A review on anti-inflammatory activity of monoterpenes. *Molecules.* 2013;18:1227-1254.
892. Stojanović G, Palić I, Ursić-Janković J. Composition and antimicrobial activity of the essential oil of Micromeria cristata and Micromeria juliana. *Flavour Fragrance J.* 2006;21:77-79.
893. Armaka M, Papanikolaou E, Sivropoulou A, Arsenakis M. Antiviral properties of isoborneol, a potent inhibitor of herpes simplex virus type 1. *Antiviral Res.* 1999;43:79-92.
894. Alsemari A, Alkhodairy F, Aldakan A, et al. The selective cytotoxic anti-cancer properties and proteomic analysis of Trigonella Foenum-Graecum. *BMC Complement Altern Med.* 2014;14:114.
895. Al-Daghri NM, Alokail MS, Alkharfy KM, et al. Fenugreek extract as an inducer of cellular death via autophagy in human T lymphoma Jurkat cells. *BMC Complement Altern Med.* 2012;12:202.
896. Nibret E, Wink M. Trypanocidal and antileukaemic effects of the essential oils of Hagenia abyssinica, Leonotis ocymifolia, Moringa stenopetala, and their main individual constituents. *Phytomedicine.* 2010;17:911-920.
897. Al-Rahmah AN, Mostafa AA, Abdelb-Megeed A, Yakout SM, Hussein SA. Fungicidal activities of certain methanolic plant extracts against tomato phytopathogenic fungi. *Afr J Microbiol Res.* 2013;7:517-524.
898. Kakarla S, Ganjewala D. Antimicrobial activity of essential oils of four lemongrass (Cymbopogon flexuosus Steud) varieties. *Med Aromat Plant Sci Biotechnol.* 2009;3:107-109.
899. Asghari G, Jalali M, Sadoughi E. Antimicrobial activity and chemical composition of essential oil from the seeds of Artemisia aucheri Boiss. *Jundishapur J Nat Pharm Prod.* 2012;7:11-15.
900. Gonçalves MJ, Cruz MT, Tavares AC, et al. Composition and biological activity of the essential oil from Thapsia minor, a new source of geranyl acetate. *Ind Crops Prod.* 2012;35:166-171.
901. Guleria S, Tiku AK, Koul A, Gupta S, Singh G, Razdan VK. Antioxidant and antimicrobial properties of the essential oil and extracts of Zanthoxylum alatum grown in north-western Himalaya. *ScientificWorldJournal.* 2013;2013:1.
902. Lee HJ, Hyun EA, Yoon WJ, et al. In vitro anti-inflammatory and anti-oxidative effects of Cinnamomum camphora extracts. *J Ethnopharmacol.* 2006;103:208-216.
903. Burkhart CG, Burkhart HR. Contact irritant dermatitis and anti-pruritic agents: the need to address the itch. *J Drugs Dermatol.* 2003;2:143-146.
904. Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol.* 2003;30:523-528.
905. Xu H, Blair NT, Clapham DE. Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. *J Neurosci.* 2005;25:8924-8937.
906. Mahboubi M, Kazempour N. The antimicrobial activity of essential oil from Perovskia abrotanoides Karel and its main components. *Indian J Pharm Sci.* 2009;71:343-347.
907. Peier AM, Moqrich A, Hergarden AC, et al. A TRP channel that senses cold stimuli and menthol. *Cell.* 2002;108:705-715.
908. Galeotti N, Di Cesare Mannelli L, Mazzanti G, Bartolini A, Ghelardini C. Menthol: a natural analgesic compound. *Neurosci Lett.* 2002;322:145-148.
909. Pan R, Tian Y, Gao R, et al. Central mechanisms of menthol-induced analgesia. *J Pharmacol Exp Ther.* 2012;343:661-672.
910. Kamatou GP, Vermaak I, Viljoen AM, Lawrence BM. Menthol: a simple monoterpene with remarkable biological properties. *Phytochemistry.* 2013;96:15-25.

911. Silva MI, Moura BA, Neto MR, et al. Gastroprotective activity of isopulegol on experimentally induced gastric lesions in mice: investigation of possible mechanisms of action. *Naunyn Schmiedebergs Arch Pharmacol.* 2009;380:233-245.
912. Silva MI, de Aquino Neto MR, Teixeira Neto PF, et al. Central nervous system activity of acute administration of isopulegol in mice. *Pharmacol Biochem Behav.* 2007;88:141-147.
913. Silva MI, Silva MA, de Aquino Neto MR, et al. Effects of isopulegol on pentylenetetrazol-induced convulsions in mice: possible involvement of GABAergic system and antioxidant activity. *Fitoterapia.* 2009;80:506-513.
914. Bonjardim LR, Cunha ES, Guimaraes AG, et al. Evaluation of the anti-inflammatory and antinociceptive properties of p-cymene in mice. *Z Naturforsch C.* 2012;67:15-21.
915. de Santana MF, Guimaraes AG, Chaves DO, et al. The anti-hyperalgesic and anti-inflammatory profiles of p-cymene: Evidence for the involvement of opioid system and cytokines. *Pharm Biol.* 2015;53:1583-1590.
916. Kisko G, Roller S. Carvacrol and p-cymene inactivate *Escherichia coli* O157:H7 in apple juice. *BMC Microbiol.* 2005;5:36.
917. Segvic Klaric M, Kosalec I, Mastelic J, Pieckova E, Pepeljnak S. Antifungal activity of thyme (Thymus vulgaris L.) essential oil and thymol against moulds from damp dwellings. *Lett Appl Microbiol.* 2007;44:36-42.
918. Chen L, Zhao L, Zhang C, Lan Z. Protective effect of p-cymene on lipopolysaccharide-induced acute lung injury in mice. *Inflammation.* 2014;37:358-364.
919. Rabbani SI, Devi K, Khanam S, Zahra N. Citral, a component of lemongrass oil inhibits the clastogenic effect of nickel chloride in mouse micronucleus test system. *Pak J Pharm Sci.* 2006;19:108-113.
920. Onawunmi GO. Evaluation of the antimicrobial activity of citral. *Lett Appl Microbiol.* 1989;9:105-108.
921. Sadraei H, Ghannadi A, Malekshahi K. Relaxant effect of essential oil of Melissa officinalis and citral on rat ileum contractions. *Fitoterapia.* 2003;74:445-452.
922. Zhuang SR, Chen SL, Tsai JH, et al. Effect of citronellol and the Chinese medical herb complex on cellular immunity of cancer patients receiving chemotherapy/radiotherapy. *Phytother Res.* 2009;23:785-790.
923. Brito RG, Guimaraes AG, Quintans JS, et al. Citronellol, a monoterpene alcohol, reduces nociceptive and inflammatory activities in rodents. *J Nat Med.* 2012;66:637-644.
924. Bastos JF, Moreira IJ, Ribeiro TP, et al. Hypotensive and vasorelaxant effects of citronellol, a monoterpene alcohol, in rats. *Basic Clin Pharmacol Toxicol.* 2010;106:331-337.
925. Lopez-Romero JC, Gonzalez-Rios H, Borges A, Simoes M. Antibacterial effects and mode of action of selected essential oils components against *Escherichia coli* and *Staphylococcus aureus*. *Evid Based Complement Alternat Med.* 2015;2015:795435.
926. Pereira FdE O, Mendes JM, Lima IO, Mota KS, Oliveira WA, Lima Ede O. Antifungal activity of geraniol and citronellol, two monoterpenes alcohols, against Trichophyton rubrum involves inhibition of ergosterol biosynthesis. *Pharm Biol.* 2015;53:228-234.
927. Flores-Sanchez IJ, Verpoorte R. Secondary metabolism in *cannabis*. *Phytochem. Rev.* 2008;7:615-639.
928. Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. *Am J Clin Nutr.* 2005;81:317S-25S.
929. Andre CM, Larondelle Y, Evers D. Dietary antioxidants and oxidative stress from a human and plant perspective: A review. *Curr Nutr Food Sci.* 2010;6:2-12.
930. Murti K, Panchal MA, Gajera V, Solanki J. Pharmacological properties of *matricaria recutita*: a review. *Pharmcognosy.* 2012;3:348-351.
931. Gerritsen ME, Carley WW, Ranges GE, et al. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. *Am J Pathol.* 1995;147:278-292.
932. Werz O, Seegers J, Schaible AM, et al. Cannflavins from hemp sprouts, a novel cannabinoid-free hemp food product, target microsomal prostaglandin E2 synthase-1 and 5-lipoxygenase. *PharmaNutrition.* 2014;2:53-60.
933. Barrett ML, Scutt AM, Evans FJ. Cannflavin A and B, prenylated flavones from Cannabis sativa L. *Experientia.* 1986;42:452-453.
934. Gomez MA, Saenz MT, Garcia MD, Fernandez MA. Study of the topical anti-inflammatory activity of Achillea ageratum on chronic and acute inflammation models. *Z Naturforsch C.* 1999;54:937-941.
935. Fischedick JT, Hazekamp A, Erkelens T, Choi YH, Verpoorte R. Metabolic fingerprinting of Cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes. *Phytochemistry.* 2010;71:2058-2073.
936. Hillig KW. A chemotaxonomic analysis of terpenoid variation in Cannabis. *Biochem Syst Ecol.* 2004;32:875-891.
937. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *Am J Bot.* 2004;91:966-975.
938. Sawler J, Stout JM, Gardner KM, et al. The genetic structure of marijuana and hemp. *PLoS One.* 2015;10:e0133292.
939. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain.* 2018;19:1-28.
940. Casano S, Grassi G, Martini V, Michelozzi M. Variations in terpene profiles of different strains of Cannabis sativa L. *Acta Hortic.* 2011;925:115-121.
941. Liu RH. Health-promoting components of fruits and vegetables in the diet. *Adv Nutr.* 2013;4:384S-92S.