A NOVEL TOPICAL ANALGESIC CREAM

SIGNIFICANTLY REDUCES CHRONIC LOW BACK PAIN

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INTRODUCTION:

Chronic musculoskeletal pain is a frequent outcome of injury, pathophysiological degenerative processes, and post-surgical complications. Musculoskeletal pain is experienced by approximately 80% of Americans at least once in their lifetime. As recognized by the Institute of Medicine at the National Academy of Science, musculoskeletal pain is the most common type of chronic pain; with low back pain (LBP) being the most prevalent. LBP is generally considered chronic if symptoms persist for greater than 3 months. Nearly a third of people seeking treatment for low back pain will have persistent moderate pain for one year following an acute episode. In addition, it is estimated that seven million adults within the United States have activity limitations as a result of their chronic LBP (1, 2, 3). LBP is the fifth most common reason for physician visits, resulting in healthcare costs estimated at $100 billion annually (4, 5). The current socioeconomic burden of LBP within the United States is quite extensive, and it is anticipated to further increase.

There are many factors that can contribute to pain conditions, including tissue injury, inflammatory responses, and nerve irritation. To address the need for more effective treatment modalities, Philia Group LLC has developed a topical analgesic cream that can readily be applied to a local region of pain, resulting in significant relief. Focusing on pain mitigation for generalized chronic low back pain (6, 7, 8), our research and development team strategically formulated a multimodal topical medication, capable of treating various underlying factors that contribute to pain. This novel analgesic cream (TruU Balance™) incorporates a transcutaneous small molecule delivery system which helps to efficiently deliver two active therapeutic agents, lidocaine 4% and menthol 1%, as well as full spectrum cannabidiol (CBD) 0.44% (4.4 mg per gram).

Lidocaine is a well-known topical anesthetic that is often used in the treatment of postherpetic neuralgia. A study by Argoff and co-workers on postherpetic neuralgia demonstrated that a lidocaine 5% patch provided significant improvement against the control (13). The anesthetic ability of lidocaine was shown to be capable of reducing pain at the site of application.

Menthol is a well-known natural crystalline substance often used topically for its cooling effect, as well as its ability to act as a “counter irritant”, imparting an analgesic and anti-inflammatory response with subsequent desensitization of the targeted receptor (9, 10).

Cannabidiol (CBD) is a “major” non-psychoactive cannabinoid produced by the *Cannabis sativa* plant, commonly known as hemp. Among other clinical applications, cannabidiol has been used for its analgesic and anti-inflammatory properties. A number of studies have characterized the

potential activity of cannabinoids, both endogenous and exogenous, on humans and other animals, as it relates to pain and other correlates of injury. A review by Burstein (12) described the effects of cannabidiol and related substances on inflammation. The therapeutic actions provided by cannabidiol in Burstein's review strongly support the use of cannabidiol in this novel topical analgesic cream. Further support for the use of cannabidiol is found in recent studies using mice (4). The study reported that CB2 receptor agonists have analgesic activity, without psychotropic effects. The experimental mouse study found that operant self-administration of the CB2 agonist JWH133 occurred in both wild-type and knockout mice lacking CB2. As noted in the study (4), this "reflected drug-taking behavior to alleviate spontaneous pain, nociceptive and affective manifestations", that is, the mice chose to consume the proffered drug, because it reduced their pain and its associated effects. This study (4) also reported that CB2-positive lymphocytes have the capacity to infiltrate an injured nerve and appeared to transfer CB2 to neurons within the injured nerve. This observation further supports the idea that CB2 protects against neuropathic pain. A review by Guindon (5) identifies the molecular targets – again it is the CB2 receptors that are involved in persistent pain. This allows us to exploit CB2 receptors in order to effectively suppress acute, inflammatory, and neuropathic pain states.

Cannabis sativa (hemp) full spectrum cannabinoid isolation through extraction and short path distillation (5) results in a high concentration of cannabidiol (CBD), as well as low concentrations of other naturally occurring "minor" cannabinoids, such as cannabigerol (CBG), cannnabichromene (CBC), and tetrahydrocannabinol (THC). The topical analgesic cream used in the study contains tetrahydrocannabinol concentrations that are less than 0.3% on a dry weight basis. Cannabidiol in conjunction with other "minor" cannabinoids appear capable of providing a synergistic response, commonly known as the "entourage effect" (17, 18). A fairly large number of studies have supported the presence of the entourage effect, although, there are opposing views on its existence and function(s), as well as its involvement with multiple identifiable binding sites on individual cells. A study by Finlay et al (20) studied cannabis terpenoids for evidence of receptor-mediated activity, using receptor-based radioimmunoassays, for binding to the major cannabinoid receptors, CB1 and CB2. This study showed no measurable binding to those receptors; additionally, terpene functional effects were not detected, either alone or in combination with THC, CBD or 2-arachidonoyoglycerol (20). Given the observed cellular responses at the organism level, it seems likely that a synergistic action does exist, yet allows for variation based on the function or source of substances under study. With many different cell types and conditions, more research is needed to learn about their role, and their potential pathology, within the range of conditions that elicit pain.

SAFETY TESTING:

An IRB approved randomized three-arm phase I safety study was completed in 2013 at the Insight Institute of Neurosurgery & Neuroscience (Flint, MI). This safety study measured the uptake kinetics with transcutaneous delivery of lidocaine using our patented small molecule delivery system.

We consented 34 subjects (20 females and 14 males), treating each subject twice (0 and 4 h) with 1mL of topical anesthetic cream containing our small molecule delivery system along with lidocaine as its active therapeutic agent. Venous blood samples were taken at 0, 1, 3, 5, 7, 9 and 11 hours after application of the cream. Blood samples were analyzed by gas chromatography at

NMS Labs (Willow Grove, PA), using a method that measures 15 to 20-fold below the therapeutic reference range. This method was selected to allow quantitation of sub-clinical levels of lidocaine and its primary metabolite, monoethylglycinexylidide (MEGX). Lidocaine toxicity typically occurs at levels greater than 6.0 mcg/mL, with symptoms including central nervous excitation, lightheadedness, dizziness, tinnitus, confusion, and blurred or double vision.

Among the 239 serum samples that were analyzed, there was no detectible level of lidocaine, and only 1 sample gave a measurable result of MEGX, which was only slightly greater than the detection level of the analytical method. There were no reports of adverse effects related to drug activity. A few subjects experienced slight lightheadedness that appeared to result from venipuncture, as the onset of symptoms was after each blood draw.

We conclude from toxicology studies and the absence of adverse effects, that the doses of lidocaine in our topical analgesic cream, consisting of our advanced small molecule delivery system, are well below the levels of concern for lidocaine toxicity.

MATERIALS & METHODS:

The topical analgesic cream (TruU Balance™) used in this open label phase I efficacy study was developed by Philia Group LLC. Study subjects were solicited through Musculoskeletal Medicine & Pain Management Associates, P.C., which is owned and operated by Dr. Christopher Norval, a principal of the study, who also holds a position at Philia Group LLC. Each subject was selected based on their presentation of chronic low back pain, while in the course of their routine medical care. Subjects were selected to interview based on their general health, chronic pain diagnosis, and prior response to treatment. Subjects were verbally interviewed regarding the goals of the study and its protocol.

SUBJECT SELECTION:

All of the 25 subjects we consented were suffering from debilitating chronic low back pain, lasting greater than 6 months. Most of them had been receiving standard medical care for their low back condition for several years. All subjects were under the care of a chronic pain specialist and had previously failed conservative management for their low back condition. Additionally, all subjects were currently receiving opioid analgesic therapy as their primary mode of treatment. Despite requiring high levels of opioid analgesic medication (averaging a mean Morphine Milligram Equivalent (MME) of 322mg per day), all study participants continued to experience significant breakthrough pain.

The majority of subjects had previously undergone extensive interventional procedures, including lumbar epidural steroid injections, as well as one or more major surgical intervention, such as lumbar spine decompressions, multi-level lumbar spine fusions, and Harrington rod placement.

Of the 25 subjects, 23 completed the study and provided their recorded data to the principal investigator. Of the 23 subjects who completed the study, 8 participants were female, and 15 participants were male, with an age range of 36 to 64 years-old, and a mean age of 52.

12 subjects were permanently disabled and receiving social security disability benefits due to their chronic pain condition, 3 subjects were currently not working due to their chronic pain condition, and 8 subjects were employed on either a part-time or full-time basis.

Subjects were excluded from the study if they had a known allergy to any of the active or inactive agents, or if the skin was broken or irritated in the intended region where TruU Balance™ (TB cream) was to be applied.

STUDY DESIGN:

The principal investigator provided each subject with a unique identification number, reviewed the study consent form, answered any questions, and obtained signatures from both the subject and a witness. All subjects were provided written instructions, pain score sheets, study questionnaire, targeted surface diagram (300cm2 to 400cm2), and a pre-loaded calibrated syringe containing 32 grams of TB cream. One gram (g) of TB cream by weight is equal to one cubic centimeter (cc) of TB cream by volume.

Subjects were provided verbal instructions for pre-application visual skin screening, along with recording their baseline pain scores (time = 0 minutes) on the provided visual analog scale (100mm) prior to each application. Subjects recorded their pain scores throughout the study, using the provided visual analog scale at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, and 6 hours following each application of TB cream.

Subjects were provided verbal instruction along with demonstration on how to accurately dispense each dose of TB cream from the calibrated syringe, and then gently massage the cream for approximately 60 seconds, until the cream is evenly distributed over the region of the low back.

Subjects were asked to complete the provided study questionnaire following the last application of TB cream, as well as complete a verbal exit interview with the principle investigator.

PRODUCT DOSE & ROUTE OF ADMINISTRATION:

Subjects were instructed to apply 4 grams of TB cream over the cutaneous region of their low back, every 6 hours, for a total of 8 applications, over 48 to 72 hours. A fixed 4-gram dose of TB cream was dispensed and then applied to the painful region of the low back every 6 hours for a total of 8 applications. Subjects applied TB cream on a minimum surface area of approximately 300cm^2 and a maximum surface area of approximately 400cm^2. Following visual inspection, each subject, or a designated family member, was asked to record skin assessment findings, along with the subject's baseline pain score.

DISCUSSION & RESULTS:

Recent research has provided evidence for a multiplicity of possible functions of cannabinoids along with their receptors and the enzymes responsible for their synthesis and degradation (14). These may be referred to as component parts of an endocannabinoid system that consists of endogenous ligands, cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors, and the enzymes responsible for their synthesis and degradation. General functions likely include cannabinoid activation or modulation of the descending pain modulatory pathway (15). Evidence

is mounting that indicates cannabinoid involvement in modulating incoming sensory inputs, including cognitive and emotional processing. There is mounting preclinical evidence that modulation of the endocannabinoid system may be a promising therapeutic approach; the last decade has seen experimental evidence suggesting the endocannabinoid system may be interrogated to modify many physiological/pathological functions. This may include neurodegenerative disorders, tissue injury and pain, and a host of others. Examples include multiple targets within the endocannabinoid system where, in preclinical studies, derivatives of endogenous cannabinoid ligands have been shown to have moderate to high affinity for cannabinoid receptors and can inhibit interactions with physiological outcomes (16). While there is a multitude of details, targeting of cannabinoid receptors continues to show the promise of improving outcomes, particularly as relates to pain.

The pain scores presented in both Figure 1 and Figure 2 summarize the pain value provided by each subject, at each recorded time interval. Figure 1 shows the average reduction in pain over the 6-hour treatment intervals: On average, their sustained pain levels dropped approximately 20% or more, between 30 minutes and 2 hours after application of TB cream. This data provides an opportunity to estimate, within certain limits, the extent of moderate to severe chronic pain relief that can be experienced when applying TB cream. Notably, the reduction in pain between 15 minutes and 4 hours after administration averaged 20 – 25% for the group, which was considered a significant reduction in pain for each of the chronic pain subjects. Understandably, each subject had been living with moderate to severe pain on a daily basis and many were extremely pleased to have such a high level of pain reduction achieved with TB cream. We cannot guarantee this level of pain relief, particularly due to the multitude of insults pertaining to the biopsychosocial complexities of how each individual experiences pain. These results indicate that TB cream can become an extremely important tool in the armamentarium for the treatment of moderate to severe pain. In furthering our research, Philia Group LLC, makers of TruU Balance™, will continue to develop additional phase I and phase II safety and efficacy studies.

Figure 1 - Mean Pain Response to TruU Balance™

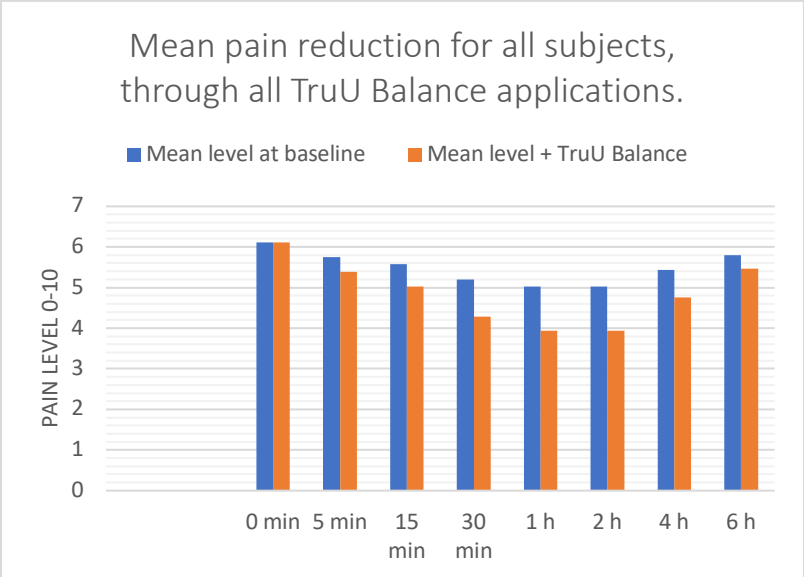

Figure 2 - Mean Pain Response to TruU Balance™

				Analysis				
	0 min	5 min	15 min	30 min	1 h	2 h	4 h	6 h
Grand mean per cycle	6.12	5.75	5.57	5.20	5.03	5.03	5.44	5.79
	var from 0	0.37	0.55	0.92	1.09	1.09	0.68	0.33
% reduction from	mean	6.5	9.8	17.7	21.7	21.7	12.6	5.8

Questionnaire Reporting – Product Satisfaction & Usage:

74% of study subjects (17) reported that they would use TB cream for the treatment of their chronic low back pain. 23 subjects responded to the question, 11 subjects reported that they would use TB cream on a daily basis, 6 subjects reported that they would use TB cream on an as-needed basis, and 6 subjects reported that they would not use TB cream.

Questionnaire Reporting – Functional Metric Analysis:

In addition to the recorded pain scores, all 23 subjects completed a self-reported study questionnaire after the last TB cream application was completed. The questionnaire addressed metrics beyond numerical pain scores, which are often affected by moderate to severe chronic pain, such as decreased range of motion, daily function, quality of sleep, general work activity, return to work, and opioid reduction. The results:

Range of Motion

54% of study subjects (12) who responded to the question reported improved low back range of motion when TB cream was applied. 23 subjects responded to the question, 1 subject was unsure if TB cream helped improve their low back range of motion, and 10 subjects reported no improvement in low back range of motion.

Daily Function

54% of study subjects (12) who responded to the question reported that TB cream would help improve their overall daily function. 22 subjects responded to the question, 3 subjects were unsure if TB cream would help improve their daily function, and 7 subjects reported that TB cream would not help improve their daily function.

Sleep Quality

54% of study subjects (12) who responded to the question reported improved quality of sleep due to the effect that TB cream had on their low back pain. 22 subjects responded, 2 subjects were unsure if TB cream would help improve their quality of sleep, and 8 subjects reported that TB cream would not help to improve their quality of sleep.

95% of study subjects (22) who responded to the question rated their quality of sleep using a 0 to 10 scale, both without, and then with TB cream applied to their low back. These 22 subjects reported a mean sleep quality score of 4.0, ranging from 0 to 7 without TB cream applied to their low back. The same 22 subjects reported a mean sleep quality score of 5.5, ranging from 2 to 10 with TB cream applied to their low back, indicating a 37% improvement in sleep quality with TB cream.

Work Activity

45% of study subjects (10) who responded to the question reported that TB cream would help improve their typical work activities. 22 subjects responded, 2 subjects were unsure if TB cream would help improve their typical work activities, and 10 subjects reported that TB cream would not help improve their typical work activities.

Return To Work

52% of study subjects (12) reported being permanently disabled and receiving social security disability benefits. 23 subjects responded to the question, 3 subjects were not working due to their chronic pain condition, and 8 subjects were currently working on either a part-time or full-time basis.

13% of the study subjects (2) who reported being disabled and receiving social security disability benefits (12), also reported that they feel the effect of TB cream on their low back pain could potentially improve their ability to return to work, even on a limited basis.

Opioid Analgesic Therapy

35% of study subjects (8) reported that they could expect to reduce opioid medication long-term if TB cream was available to them on a regular basis. 23 subjects responded, 2 subjects were unsure if they could reduce opioid medication long-term, and 13 subjects reported that they would not be able to reduce opioid medication long-term.

Questionnaire Reporting – Topical Analgesic Comparisons:

The study questionnaire also provided a self-reported comparison between the effect of TB cream with other commercially available over-the-counter analgesic agents. Each subject rated the effect of TB cream on their low back pain using a 0 to 10 scale and then provided a direct comparison to the commercially available topical analgesic agent they used, with the same 0 to 10 scale.

TruU Balance™ (Lidocaine 4%) Vs. Prescription Lidocaine 5% Patches

52% of study subjects (12) reported having used prescription strength lidocaine patches for low back pain. The mean effectiveness score of prescription lidocaine patches among the subjects who responded was 4.4, ranging from 0 to 8. The mean effectiveness score of TruU Balance™ in comparison to prescription lidocaine patches was 6.8, ranging from 2 to 10, indicating that TruU Balance™ was 55% more effective than prescription lidocaine patches.

TruU Balance™ Vs. IcyHot®

8 study subjects reported using IcyHot® for low back pain. Subjects reported a mean effectiveness score of 2.7 for IcyHot®, ranging from 1 to 8. The same 8 subjects provided a mean effectiveness score of 5.8 for TruU Balance™ ranging from 0 to 10 in comparison to IcyHot®, indicating that TruU Balance™ was 115% more effective than IcyHot®.

TruU Balance™ Vs. IcyHot® with Lidocaine

5 study subjects reported using IcyHot® with Lidocaine for low back pain. Subjects reported a mean effectiveness score of 1.6 for IcyHot® with Lidocaine, ranging from 0 to 3. The same 5 subjects provided a mean effectiveness score of 7.4 for TruU Balance™, ranging from 2 to 10 in comparison to IcyHot® with Lidocaine, indicating that TruU Balance™ was 362% more effective than IcyHot® with Lidocaine.

TruU Balance™ Vs. Biofreeze®

4 study subjects reported using Biofreeze® for low back pain. Subjects reported a mean effectiveness score of 4.3 for Biofreeze® ranging from 2 to 10. The same 4 subjects provided a mean effectiveness score of 7.5 for TruU Balance™, ranging from 4 to 10 in comparison to Biofreeze®, indicating that TruU Balance™ was 74% more effective than Biofreeze®.

TruU Balance™ Vs. Aspercreme®

4 study subjects reported using Aspercreme® for low back pain. Subjects reported a mean effectiveness score of 2.0 for Aspercreme®, ranging from 0 to 6. The same 4 subjects provided a mean effectiveness score of 5.5 for TruU Balance™, ranging from 2 to 8 in comparison to Aspercreme®, indicating that TruU Balance™, was 175% more effective than Aspercreme®.

TruU Balance™ Vs. Aspercreme® with Lidocaine

2 subjects reported using Aspercreme® with Lidocaine for low back pain. Those 2 subjects reported a mean effectiveness score of 3.0 for Aspercreme® with Lidocaine, ranging from 2 to 4. The same 2 subjects provided a mean effectiveness score of 6.5 for TruU Balance™, ranging from 4 to 9 in comparison to Aspercreme® with Lidocaine, indicating that TruU Balance™, was 117% more effective than Aspercreme® with Lidocaine.

TruU Balance™ Vs. CBDol®

4 subjects reported using CBDol® salve for low back pain. Subjects reported a mean effectiveness score of 4.8 for CBDol®, ranging from 1 to 9. The same 4 subjects provided a mean effectiveness score of 5.5 for TruU Balance™, ranging from 1 to 9 in comparison to CBDol®, indicating that TruU Balance™ was 15% more effective than CBDol®.

It should be noted that during the exit interviews, two of the study participants mentioned that they had inadvertently applied approximately 50% less TruU Balance™ cream (2 grams) than what was instructed in the study protocol for each application (4 grams). Despite a reduction in protocol dosing their recorded pain scores are reflected in the presented data. These two participants also provided a direct comparison between TruU Balance™ cream and CBDol® salve. Despite a reduction in protocol dosing, their recorded comparison ratings are also reflected in the presented data.

REFERENCES:

1. Institute of Medicine of the National Academy of Science. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research; Institute of Medicine: Washington, DC, USA, 2011; p. 5.
2. Gatchel 2015. The continuing and growing epidemic of chronic low back pain. Healthcare 3(3):838-45; doi:10.3390/Healthcare3030838.
3. Katz, J.N. Lumbar disc disorders and low-back pain: Socioeconomic factors and consequences. JBJS 2006, 88, 21–24.
4. Physiopedia (https://www.physio-pedia.com/Chronic_Low_Back_Pain).
5. Guindon J, Hohmann AG. 2007. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Brit J Pharmacol 153,319-34.
6. Luo, X.; Pietrobon, R.; Sun, S.X.; Liu, G.G.; Hey, L. Estimates and patterns of direct health care expenditures among individuals with back pain in the United States.
7. Castillo ER, Lieberman, DE. Lower back pain. Spine 2003, 29, 79–86.
8. Davies et al, 2004;64(9):937-47. doi: 10.2165/00003495-200464090-00002. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia.
9. Smoker J, Cohen A, Rasouli MR, Schwenk ES. Transdermal lidocaine for perioperative pain: a systematic review of the literature. Curr Pain Headache Rep. 2019 Nov 14;23(12):89. doi: 10.1007/s11916-019-0830-9.PMID: 31728770
10. Yousefshahi F, Predescu O, Francisco Asenjo. The efficacy of systemic lidocaine in the management of chronic pain: A Literature Review. J. Anesth Pain Med. 2017 Apr 22;7(3):e44732. doi: 10.5812/aapm.44732. eCollection 2017 Jun.
11. Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 1996 Apr;65(1):39-44. doi: 10.1016/0304-3959(95)00146-8.
12. Burstein, S. (2015). Cannabidiol (CBD) and its analogs: A review of their effects on inflammation. Bioorganic & Medicinal Chemistry. 23. 10.1016/j.bmc.2015.01.059.
13. Argoff CE, Galer BS, Jensen MP, Oleka N, Gammaitoni AR. (2004). Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. Curr Med Res Opin; 20 Suppl 2:S21-S28. doi:10.1185/030079904X12960
14. Bouchet, CA and Ingram, SL. 2020, Cannabinoids in the descending pain modulatory circuit: Role in inflammation. J Pharmacher 2020,107495.
15. Pacher, P and G Kunos. 2013. Modulating the endocannabinoid system in human health and disease – successes and failures. FEBS J.280:1918-1943.
16. Gado, F, et al. 2020. Modification on the 1,2-dihydro-2-oxo-pyridine-3-carboxamide core to obtain multi-target modulators of endocannabinoid system. Bioorg Chem 94:103353.

17. Russo, EB. 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 163(7):1344-64.
18. Russo, EB. 2019. The case for the entourage effect and conventional breeding of clinical cannabis: no "strain," no gain. Front Plant Sci. Jan 9;9:1969.
19. Tomko AM, Whynot EG, Ellis LD and Dupre DJ. 2020. Cancers (Basel) 12(7):1985.
20. Finlay DB, Sircombe KJ, Nimick M, Jones C, Glass M. 2020. Terpenoids from cannabis do not mediate an entourage effect by acting at cannabinoid receptors. Front Pharmacol 11:359.