**Terpene Recommendations for Pain:**

**An Addition to Current CBD Crème Product**

**on the Market**

**(Briefing)**

**\*\*\*DRAFT v2\*\*\***

**Prepared by Dr. Susan Trapp**

BioBiz Consulting, LLC

**For Client**

Good**FOR**

Jeff Ullman

6/10/2020

**PROJECT SUMMARY**

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| --- | --- |
| Project ID: | 150 |
| Project Name: | Terpene Recommendations for Pain – use in addition to CBD pain crème Formulation |
| Written by: | Dr. Susan Trapp |
| Draft Date: | 06/16/2020 |

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| --- | --- |
| Cost estimate\* | $ 1000 – flat fee *(agreed upon 6/11/2020)* |
| Start date: | 06/11/2020 |
| Draft 1 due date: | 06/16/2020 |
| Revision week: | 06/16/2020– 06/18/2020 *(this is only an estimate)* |
| Final deliverables: | 06/18/2020 *(this is only an estimate)* |
| Total Working hours: |  |
| Hourly rate: |  |
| Estimated hours |  |

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| --- | --- | --- |
| TEAM MEMBERS | Role |  |
| Susan Trapp, PhD | Principal Investigator | Consultant  Biobíz Consulting, LLC |
| Paul Bregman, MD | Chief Medical Advisor & Project Manager | Good**FOR** |
| Dan McShan, PhD | Chief Technical Officer & Manufacturing Project manager | Good**FOR** |
| Consultant #1 - practicianer | Veterinarian with clinical cannabinoid & terpene product practice | Consultant to Dr. Trapp |
| Consultant 5 |  |  |

# INTRODUCTION

The purpose of this proposal was to develop recommendations for the goal of adding additional terpenes specific for pain (analgesic and anti-inflammation) to the current Good**FOR** product **Relief Level 10**. The specific aim of the proposal was to 1a) perform decision validation on the current 3 terpenes chosen internally by Good**FOR** (-carophyllene, -humulene, and d-limonene) and 1b) confirm, validate or recommend other terpenes (or terpenoids) that may be more beneficial and 2) identify dosing (as defined by 1 dose per application) of specific terpenes chosen for new product formulation of current **GoodFOR Relief Level 10.**

The primary question being addressed (1) by Good**FOR** is “what are the most effective(Singal et al, 2014) terpenes to add to Good**FOR Relief Level 10** for general pain caused by inflammation, either from general injury, arthritis, or other general pain occurrences (e.g. post surgery). Second question being addressed (2) is what are the specific proportions of each terpene to add for a 2.5 oz container of Good**FOR Relief Level 10.** A subset of questions, here, revolve around understanding constituents of Good**FOR** Relief Level 10 and potential compound interactions with other constituents specifically CBD, CBG, 19 essential oils, and menthol and camphor (more details will be provided by Good**FOR** if necessary). The third question being addressed (3) is to identify a terpene vendor for purchasing terpenes. The fourth question being addressed (4) is what is the dosing of the terpenes for an effective pain relief. Other questions that require examination will be addressed (5) as Part II of this recommendation/research proposal and negotiation for compensation can be discussed and determined at a later date. Per information by CEO, Jeff Ullman, this project has a deadline of June 20th, 2020 of which Good**FOR** goes to manufacturing for improved Good**FOR Relief Level 10** *with terpene* **formulation.**

# BRIEFING

**Recommendation** of terpenes (addition):

* -myrcene (anti-inflammatory, analgesic, muscle relaxant)
* Linalool (local anesthetic, sedative, antianxiety)
* -terpineol (enhance skin penetration, anti-nociceptive, antioxidant, anticancer, anticonvulsant, antiulcer, antihypertensive,)

**Reasoning:** The three terpenes -carophyllene, -humulene, and d-limonene were briefly reviewed in the scientific literature (Russo 2011, Fidyl et al 2018, Cho et al, 2017, Small 2017, Rufino 2015, Rehman 2014) and indeed these have all been scientifically identified for their anti-inflammation properties. The terpene profile for the current Good**FOR** Relief level 10 formulations reveals that D-limonene and -carophyllene are in the top 3 (.054% and .032%, respectively) out of the 20 terpenes in regards to total percentage analyzed by Botanacor (total terpenes are 0.298%). Eucalyptol is the top terpene at 0.096% making up ~33% of total terpenes in the formulation currently. Alpha-humulene (.01%) #8 out 20 terpenes in percentage.

**-terpineol, B-myrcene, Linalool - recommendation**

As oppose to adding more of the top terpenes found in relatively high amounts already, I recommended adding additional terpenes found in less high amounts which also have interesting pain treatment properties and/or additional terpenes not currently in the formulation that also address pain treatment. Furthermore, -humulene does not smell good and may result in a poorly smelling formulation (*communication with Extract Consultant Vendor representative*). **-terpineol** not only has anti-nociceptive properties it apparently enhances skin penetration that may result in enhancing bioavailability of other terpenes and their biological activity (Kahleel et al., 2018). Furthermore -terpineol has a floral fragrance. It has lilac odor and sweet smell similar to peach (Dionisio, 2012**). B-myrcene** has substantial amount of scientific literature on its anti-inflammatory properties and is a known trvp1 activator (Ruffino et al. 2015, Cho et al. 2017, Russo 2011). **Linalool,** although relatively regarded as the anti-anxiety terpene, there is scientific evidence that it has anesthetic properties and anti-inflammatory activity (RE et al 2000, Peana et al 2000).

**Terpene Vendor Recommendation**: Extract Consultants, *103-year old terpene Co.*

A brief cost comparison was performed between Extract Consultants, Denver Terpenes and Floraplex. Floraplex and Extract Consultants based upon 1 oz. terpenes were considered fairly similar. Denver Terpenes on average seemed to be about a third more in cost than Extract Consultants for the basic terpenes and only has 7 terpenes isolates in their online catalog. Extract Consultants (EC) vendor was contacted to make sure that timing for ordering and shipping was a viable option. EC has the capability of 24-hour delivery. Duly noted their warehouse is in Seattle and will be shipped from there. (Local Contact in Littleton, Colorado: John Roald 1-888-541-9089; <https://extractconsultants.com/>).

**Regulatory Documentation:** The documents typically associated with each product include SDS, COA, Food Grade Certificate, Solvent Free Statement, Pesticide Statement and Technical Data Sheets. In addition to these documents EC is also capable of producing, where available, on request: Food Allergen, Gluten GMO, GRAS, Halal Heavy Metals, Natural, Origin, Pesticide, Prop 65, Technical Data Sheet, and Vegan Statements.

**Support & Domain Knowledge:** EC in Colorado and support team are actively involved in NCIA and Terpene and Testing. John Roald participates on the board of both and gives talks regularly in the cannabis space.

**Third Party Vetting:** This has not been done at this time, however it has been suggested as part of product formulation to perform third party testing on terpene products regardless of company (*personal communication with Milestone Extraction Company*).

**EC Pricing - Estimation:**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **16 oz.** | **2 units (32 oz.)** |  |
| -terpineol (99%) | $140 | $280 |  |
| B-myrcene (80%) | $130 | $260 |  |
| Linalool )99%) | $125 | $250 |  |

**Total $395 $790**

**Terpene Addition Calculations**

Additional **0.5% terpenes** in total will be added to the Good**FOR** Relief level 10. This will include approximately equal proportions of (-terpineol, B-myrcene, and Linalool) for initial testing of formulation (*personal communication Dan McShan*). Calculations were based upon 60 gallons of Good**FOR** Relief level 10 (7,680 oz. or ~215,040 mLs). If 1% Terpenes total added to mix that would be approximately 76.8 oz. If 0.05% terpenes total added to the mix that would be approximately 38.5 oz. (*estimation*) and a cost of ~$395 in terpenes for a 60 gallon batch.

**Dosing and Pharmacological Activity Literature Review**

The actual pharmacological activity of these compounds requires a more detailed literature review and will vary depending on model studied. Thus scientifically one has to start with estimation and test from there.

However Dr. Paul Bregman has provided credible estimations from Dr. Kevin Spelman, PhD who is a credible scientific leader in this space. He has stated to Dr. Bergman’s’ colleagues in an email that “the pharmacological activity probably starts somewhere in the range of 150 ppb - 1 ppm.”

He further states the pharmacological activities of two terpenes based upon his research – “linalool - 4.22 mg/mL, a-terpineol - 4.7 ng/mL, pinene - trace amounts, and limonene - non-detectable concentrations have all shown pharmacological activity at the previously mentioned serum concentrations (yes, even the non-detectable serum concentrations of limonene).” With this in mind and the development of a product with multiple potential active ingredients, the best way to examine effectiveness is to add a substantial amount and test within this range or perhaps 10X above or below.

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# APPENDIX

Definition

**Efficacy** can be defined as the performance of an intervention under ideal and controlled circumstances, whereas **effectiveness** refers to its performance under 'real-world' conditions

Reference1 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3912314/>)

**anti-nociceptive** - the action or process of blocking the detection of a painful or injurious stimulus by sensory neurons, (e.g. lidocaine).

**TRPV1 receptors** = transient receptor potential vanilloid type 1. **TRPV1** is a non-selective cation channel; when it is **activated** by capsaicin, sodium and calcium ions flowing through **TRPV1** into the cell to depolarize nociceptive neurons, leading to action potential firing and finally the sensation of spiciness (Caterina et al., 1997).Jan 2, 2017 – Wikipedia

The **vanilloids** are compounds which possess a [vanillyl group](https://en.wikipedia.org/wiki/Vanillyl_group). They include [vanillyl alcohol](https://en.wikipedia.org/wiki/Vanillyl_alcohol), [vanillin](https://en.wikipedia.org/wiki/Vanillin), [vanillic acid](https://en.wikipedia.org/wiki/Vanillic_acid), [acetovanillon](https://en.wikipedia.org/wiki/Acetovanillon), [vanillylmandelic acid](https://en.wikipedia.org/wiki/Vanillylmandelic_acid), [homovanillic acid](https://en.wikipedia.org/wiki/Homovanillic_acid), [capsaicin](https://en.wikipedia.org/wiki/Capsaicin), etc. Isomers are the [isovanilloids](https://en.wikipedia.org/wiki/Isovanilloids). A number of vanilloids, most notably capsaicin, bind to the [transient receptor potential vanilloid type 1](https://en.wikipedia.org/wiki/TRPV1) (TRPV1) receptor, an [ion channel](https://en.wikipedia.org/wiki/Ion_channel) which naturally responds to noxious stimuli such as high temperatures and acidic [pH](https://en.wikipedia.org/wiki/PH).[[1]](https://en.wikipedia.org/wiki/Vanilloids" \l "cite_note-1) This action is responsible for the burning sensation experienced after eating [spicy peppers](https://en.wikipedia.org/wiki/Capsicum).

Outside the food industry vanilloids such as [nonivamide](https://en.wikipedia.org/wiki/Nonivamide) are used commercially in [pepper spray](https://en.wikipedia.org/wiki/Pepper_spray) formulations.

Other vanilloids which act at TRPV1 include [resiniferatoxin](https://en.wikipedia.org/wiki/Resiniferatoxin) and [olvanil](https://en.wikipedia.org/w/index.php?title=Olvanil&action=edit&redlink=1).

(<https://www.google.com/search?q=vanilloid+definition&oq=vannilloid&aqs=chrome.3.69i57j0l5j46j0.9981j0j8&sourceid=chrome&ie=UTF-8>)

**EMAIL FINAL RECOMMENDATION SUMMARY of 6/22/2020**

Greetings Jeff and Paul!

The Recommendation Summary for Good**FOR’**s “improved” **Relief Level 10** is the following:

**ADDITION 1**: alpha-terpineol; prepare a small batch to test the “effectiveness” prior to preparing a large 60 gallon batch.

1. add alpha-terpineol (cost is $140 per 16 oz).
2. To 60 gallons, you will be adding an additional 0.5% alpha-terpineol
3. To add 0.5% to 60 gallons.
   1. 128 oz = 1 gallon (*conversion to oz*)
   2. 60 gallons = 7,680 oz
   3. add 38.4 oz of alpha-terpineol
   4. TOTAL COST: $140 x **3 UNITS (16 oz)** = **$420** total plus tax & shipping
4. **Reasoning 1 to add alpha-terpineol; -terpineol** not only has **anti-nociceptive** (block pain)properties it apparently **enhances skin penetration** that may result in enhancing bioavailability of other terpenes and their biological activity (Kahleel et al., 2018). Furthermore -terpineol has a floral fragrance. It has lilac odor and sweet smell similar to peach (Dionisio, 2012**). (SEE p. 5 of BIoBiz Briefing).** Currently there is undetectable amounts of -terpineol.
5. **Reasoning 2:** when analyzing effectiveness or improvement the best way to test this is to change ONLY 1 variable at a time (this means one terpene at time). If you choose to add more than 1 terpene. I would recommend creating small batches and adding each one, additionally, at a time in which your maximum amount of terpenes added is0.05%. This means that you would then
6. **Reasoning 3:** The current **Relief Level 10** has a substantial amount of the top 5 terpenes already (Botanacor terpene COA). Given there is already ample amount of these terpenes added, it is unknown *without testing* if adding more will have an effect on enhancing pain relief. As oppose to adding more of these top 5, I would recommend the 3 terpenes recommended in the *BRIEFING* which includes linalool, myrcene and along with already discussed terpineol.

**Summary of the TOP 5 terpenes with anti-inflammatory indications evaluated in literature and clinician recommendation** (discussed on 6/17 with all and 6/22 with Paul B.):I researched what the top 5 topical terpenes that have anti-inflammatory/ analgesics both within the scientific literature AND conferred with colleague (veterinarian clinician) who utlilizes terpenes as part of her medicine practice. These are as follows in order of priority: Beta-caryophyllene, beta-myrcene, alpha-pinene, alpha-humulene, d-limonene. Beta-caryophyllene has the most evidence in the literature for pharmacological effects as it binds to eCB2, and inhibits other inflammatory markers PGE1, PGE2, TNF-alpha, PPAR gamma agonist.) All of these terpenes are in a reasonable amount within in the current

OTHER: Additions per request by Paul Bregman