

White Paper on Maximizing Therapeutic Outcomes: Synergistic Effects of Terpenes and THC in Medical Cannabis

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Summary

Bazelet is optimizing the effect of its medical cannabis products via selecting terpene components that synergize with THC. Selections are based on Bazelet's scientific knowledge, advanced trials and mechanism models.

- To date, there are only two single-API (active pharmaceutical ingredients), cannabinoid-based drugs, approved by the FDA for a limited scope of indications. There is a general agreement that multiple-API medical cannabis compositions have the potential of being more efficient and with less adverse effects.
- On the other hand, many assume wrongly that efficacy of medical cannabis increases with the number of the APIs, or that 'whole-plant' compositions are always beneficial.
- For best effects, the composition of medical cannabis should be tailored to the specific indication and, in many cases, also to personal parameters. This is done at Bazelet by selecting the most appropriate components out of hundreds present in the cannabis plant, and at suitable ratios.
- Selection is complex, since the cannabis components affect multiple physiological functions in the body, such as pain sensation, inflammation, gastroenteric, sleep and mood. These effects are gained via interaction with various receptors of the endocannabinoids system (ECS), such as CB1, CB2, PPRA, TRPV, etc.
- Most past scientific work has focused on the two major cannabinoids, THC and CBD. Yet, cannabis also contains minor cannabinoids and terpenes, which are aromatic components responsible for the distinct scent of the various strains.
- Out of hundreds of known terpenes, many are known to have a therapeutic role of their own, but their dose in medical cannabis formulations is relatively small. That is why the main interest is in their potential for synergizing cannabinoids.
- Of particular interest is synergy with THC, which, if found, may reduce the required dose of THC and its adverse effect. There is no simple way to conclude from the molecular structure of a terpene, if it would contribute to such synergistic effect.
- A research conducted by Bazelet and published in *Biochemical Pharmacology*⁸, suggests that specific terpenes can modulate THC's effects on CB1 receptor activation, potentially augmenting its therapeutic activity. A similar research is being completed on CB2. Another Bazelet study has used molecular modelling and molecular dynamics to identify terpenes that synergize with THC.

These studies provide Bazelet with tools to optimize its products.

Introduction

Cannabis has a long history of medicinal use, and contemporary research is experiencing a surge as clinicians and patients alike explore its diverse therapeutic potential^{1,2}. This growing interest is reflected in the expanding use of medical cannabis programs. In the United States alone, over 39 states currently have such programs, highlighting a growing patient demand and accessibility.³

The plant's complex chemical composition includes a variety of cannabinoids, terpenes, and other compounds, each contributing to its wide-ranging effects. While tetrahydrocannabinol (THC) and cannabidiol (CBD) have been extensively studied, terpenes are gaining increasing attention for their potential therapeutic roles.^{1,2}

Terpenes, the aromatic compounds responsible for the distinct scent of each cannabis strain, are believed to interact synergistically with cannabinoids, a phenomenon known as the "entourage effect," where the combined impact of various phytochemicals is greater than the sum of their individual effects.^{1,4}

Recent studies have highlighted the potential therapeutic benefits of specific terpenes, such as myrcene, limonene, and beta-caryophyllene, demonstrating various pharmacological properties, including anti-inflammatory, analgesic, and anxiolytic effects^{5,6,7}. However, the complex interactions between terpenes and cannabinoids, particularly THC, are not fully understood, and further research is needed to elucidate their mechanisms of action.⁷

This White Paper delves into the current understanding of terpene-THC interactions and their implications for optimizing medical cannabis treatment. By evaluating recent research, including a notable study by the Bazelet Medical Cannabis Group, we explore how specific terpenes can synergize with THC to enhance CB1 receptor activity, potentially augmenting the therapeutic efficacy of cannabis-based treatments⁸. We will further explore the potential for terpene-THC combinations to reduce the required THC dosage, thereby minimizing adverse effects and improving patient outcomes.

Through this detailed examination, we aim to provide valuable insights for clinicians, researchers, and policymakers seeking to advance the field of medical cannabis and maximize the therapeutic potential of this complex plant.

The Role of Terpenes in Cannabis

Cannabis plants produce a diverse array of terpenes, which are responsible for the plant's aromatic qualities and significantly contribute to its therapeutic properties. Over 200 different terpenes have been identified in cannabis, each varying in concentration.^{1,9} The therapeutic potential of these terpenes is primarily determined by their concentration rather than the specific strain or growing conditions.^{1,9}

The most notable terpenes include:

- * **Myrcene:** Known for its musky, earthy aroma, myrcene is abundant in many cannabis strains and is believed to have sedative and muscle relaxant effects.¹⁰
- * **Limonene:** Characterized by its citrus scent, limonene is associated with mood enhancement and stress relief. It may have anti-anxiety and antidepressant effects¹¹.
- * **Beta-Caryophyllene:** This spicy and woody-scented terpene can act as a cannabinoid by binding to CB2 receptors and is known for its anti-inflammatory and analgesic properties¹².
- * **Linalool:** With a floral scent, linalool is also found in lavender and is known for its calming and anxiolytic effects, as well as its analgesic and anti-inflammatory properties¹³.
- * **Pinene:** This pine-scented terpene may have anti-inflammatory, bronchodilator, and memory-enhancing effects, beneficial for respiratory conditions and cognitive function⁸.

The Potential Therapeutic Benefits of Terpenes

Terpenes are gaining recognition for their potential therapeutic effects, particularly in managing pain, anxiety, and inflammation:

- * **Pain Management:** Terpenes like myrcene and beta-caryophyllene have significant analgesic properties^{14,15}.
- * **Anxiety Relief:** Limonene and linalool are well-studied for their anxiolytic and mood-enhancing effects^{11,16}.
- * **Anti-Inflammatory Effects:** Beta-caryophyllene and pinene exhibit strong anti-inflammatory properties, potentially useful for conditions like arthritis and multiple sclerosis^{17,18}.

Examination of the Current Understanding of How Terpenes Interact with THC and Other Cannabinoids

The "entourage effect" describes the proposed synergistic interaction between terpenes and cannabinoids, suggesting their combined effects may enhance cannabis's therapeutic potential.¹

- * **Potential Synergistic Effects with THC:** Some studies have suggested that terpenes might modulate the effects of THC. For example, β -caryophyllene has been shown to interact with CB2 receptors, potentially complementing THC's effects.¹²

- * **Modulation of Effects:** Certain terpenes have been hypothesized to mitigate some of THC's adverse effects. For instance, linalool has demonstrated anxiolytic properties in animal models, which could be relevant in the context of THC use.¹⁶
- * **Interactions with CBD:** In vitro studies have indicated that some terpenes, when combined with CBD, might have enhanced anti-inflammatory effects, though more research is needed to confirm these interactions.

It's important to note that while these potential interactions have been proposed, much of the evidence has been based on in vitro studies or observational data. The specific mechanisms and clinical relevance of these interactions in humans were not fully understood prior to more recent research.

Synergistic Effects of Terpenes with THC; New study findings from Bazelet Medical Cannabis Group

The study conducted by the Bazelet Medical Cannabis Group, detailed in the paper "*Selected cannabis terpenes synergize with THC to produce increased CB1 receptor activation*," aimed to understand how specific terpenes interact with THC to influence CB1 receptor activity. They utilized a controlled in-vitro system to quantify this activation (Raz et al., 2023).

Methods:

- * The study utilized *Xenopus* oocytes (unfertilized frog egg cells) as the expression system for human CB1 receptors.
- * Individual terpenes were tested for their ability to activate CB1 receptors.
- * THC was tested alone and in combination with each of the sixteen terpenes.
- * The CB1 receptor activity was measured using a cAMP assay, which captures changes in intracellular cAMP levels as an indicator of receptor activation.

Results:

- * **Individual Terpene Activity:**
 - All tested terpenes activated CB1 receptors to some extent, achieving 10-50% of the activation observed with similar THC concentrations.
- * **Synergistic Effects with THC:**
 - Certain terpenes, when combined with THC, significantly increased CB1 receptor activity compared to THC alone.
 - These synergies were observed at terpene-to-THC ratios similar to those found in the natural cannabis plant.
- * **The magnitude of Enhancement:**
 - The enhancement in CB1 receptor activity ranged from modest increases to several folds higher than the activity observed with THC alone.
 - For example, the inclusion of limonene increases CB1 activity by more than 3-fold compared to THC alone.

Discussion of the Findings

The study's primary findings indicate a notable synergistic effect between certain terpenes and THC, leading to increased CB1 receptor activation. Specifically:

- **Beta-Caryophyllene:** While known primarily as a CB2 receptor agonist, this study found that it also synergized with THC to enhance CB1 receptor activation.
- **Limonene:** Demonstrated enhanced anxiolytic effects when combined with THC, contributing to greater CB1 receptor activation and potential mood-stabilizing benefits.
- **Other terpenes:** The study identified several other terpenes, including β -pinene and linalool, that showed synergistic effects with THC in activating CB1 receptors.

These findings suggest that specific terpenes can modulate THC's effects on CB1 receptor activation, potentially influencing the overall effects of cannabis. However, it's important to note that this study focused on CB1 receptor activation in vitro, and further

research is needed to understand how these interactions translate to physiological effects in humans.

Potential Implications for Medical Cannabis

The Bazelet study's findings on terpene interactions with THC and CB1 receptor activation have several potential implications for medical cannabis:

- * **Synergistic Effects:** The observed synergy between certain terpenes and THC in activating CB1 receptors suggests that carefully selected combinations of cannabinoids and terpenes may offer enhanced effects compared to isolated THC.
- * **Terpene Selection:** The study highlights the importance of specific terpenes in modulating THC's effects. Careful selection of terpene profiles in medical cannabis products could be more beneficial than simply using "full spectrum" extracts.
- * **Dosage Considerations:** The increased potency observed with certain terpene-THC combinations may allow for lower THC dosages to achieve therapeutic effects. This could potentially reduce THC-related side effects while maintaining efficacy. **Personalized Medicine Approach:** Different terpene-cannabinoid combinations could be developed to target specific symptoms or conditions more effectively, opening up possibilities for more tailored treatments.
- * **Need for Further Research:** While promising, these in vitro findings require further investigation through clinical trials to confirm their relevance in human patients. Bazelet Group is actively conducting clinical trials in various fields, including acute pain management, ADHD, and ASD. Some of these studies are ongoing, while others are set to begin soon.
- * **Product Development:** Cannabis companies may use this information to develop more targeted products, leveraging data about how different combinations of cannabinoids and terpenes produce various effects.
- * **Standardization Considerations:** The study underscores the importance of considering the full chemical profile of cannabis products, not just THC or CBD content. This highlights the need for comprehensive testing and labelling practices in the medical cannabis industry.

Conclusions and Future Directions

The exploration of terpene-THC synergy in medical cannabis, as evidenced by the significant findings of the Bazelet Medical Cannabis Group study, underscores a promising frontier in cannabinoid therapeutics. The study highlights the enhanced activation of CB1 receptors by specific terpenes, such as myrcene, beta-caryophyllene, and limonene, combined with THC. This synergy not only amplifies therapeutic effects like analgesia, anti-inflammation, and anxiolysis but also demonstrates potential in reducing the required dosage of THC, thereby minimizing adverse effects.

Key takeaways from this White Paper include:

- * **Synergistic Interactions:** The study supports the concept of specific terpenes synergistically interacting with THC, enhancing CB1 receptor activation and potentially improving therapeutic efficacy
- * **Specific Terpenes:** Limonene, linalool, and terpineol significantly enhance CB1 receptor activity when combined with THC. Beta-caryophyllene shows potential for CB2 receptor activation in unpublished findings.
- * **Clinical Integration:** The integration of terpene-THC combinations in clinical practice could revolutionize medical cannabis use by enabling lower THC doses while maintaining or enhancing therapeutic outcomes.

Future Directions

The findings from the Bazelet Medical Cannabis Group highlight several promising avenues for future research and development:

1. **Clinical Trials:** Bazelet Group conducts rigorous clinical trials in selected fields to validate the in vitro findings and determine the efficacy and safety of specific terpene-THC and terpene-CBD combinations in human patients. These ongoing studies will provide crucial insights into the therapeutic potential of these combinations.

2. **Mechanistic Studies:** Additional research is required to elucidate the mechanisms by which terpenes enhance CB1 receptor activation and modulate THC's effects. Bazelet Group has conducted computational modelling studies and continues to perform advanced in-vitro studies to explore the mechanisms by which terpenes enhance CB1 receptor activation and modulate THC's effects. This ongoing research will deepen our understanding of the complex interactions between terpenes and cannabinoids.
3. **Product Development:** Bazelet Group is leveraging these findings to develop innovative products that capitalize on the synergistic effects of specific terpene-cannabinoid combinations. This approach aims to create more targeted and effective cannabis-based medicines tailored to specific therapeutic needs.
4. **Continued Research:** As the field of medical cannabis evolves, ongoing research will be crucial to refine further our understanding of terpene-cannabinoid interactions and their therapeutic applications. Bazelet remains committed to advancing this research to improve patient outcomes and expand the potential of cannabis-based medicines

By focusing on these key areas, Bazelet Group aims to translate its ground breaking research into practical, effective solutions for patients, potentially revolutionizing the field of medical cannabis. The company's integrated approach, combining basic research, clinical trials, and product development, positions it at the forefront of innovation in cannabis-based therapeutics.

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