Terpenes in Cannabis: Review of therapeutic benefits and application to Distillate and Decarboxylated Rosin products.

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1 Introduction

Terpenes are a class of volatile organic compounds found in *Cannabis sativa*, and have drawn growing interest for their potential therapeutic properties and supposed role in enhancing the effects of cannabinoids [1], [2], [3]. Our previous report provided an overview of their chemical and biological significance and reviewed the pharmacological relevance of key terpenes found in *Cannabis*. Building on that foundation, this report continues the assessment of terpene profiles of additional in-house product cultivars from GES Labs and evaluation of their therapeutic potential for targeted medical applications.

1.1 Overview of terpene benefits

The pharmacological benefits of the common terpenes found in *C. sativa* have been summarised and broadly discussed in our previous publication. These benefits primarily included anti-inflammatory, analgesic and anti-anxiety effects. An extension to this table includes the effects of alpha-bisabolol and cis-nerolidol, which have shown promising results in preclinical studies for their potential roles in managing various health conditions.

Like several other terpenes and terpenoids listed in Table 1, alpha-bisabolol has been studied for its anti-inflammatory, analgesic and antinociceptive effects. Analgesic compounds reduce the conscious perception of pain, while antinociceptive agents act earlier in the pain pathway by inhibiting the transmission of pain signals before they reach conscious awareness. In mouse and cell culture models of osteoarthritis, doses between 1 - 30 mg/kg significantly reduced inflammation and the secretion of proinflammatory cytokines (small group of proteins important in cell signalling) [4]. In another model of chronic inflammatory pain, 50 mg/kg of alpha-bisabolol reduced inflammation in the spinal cord and alleviated pain in mice [5]. At higher doses of 50 - 200 mg/kg, it was effective in reducing visceral nociception in mice [6], [7]. This points to potential application for the easing of inflammatory or neuropathic conditions where pain results from malfunctioning nociceptive pathways. Based on the literature reviewed, α-bisabolol consistently demonstrated potent effects across both inflammatory and pain-related pathways, highlighting its potential as a therapeutic compound in inflammation and pain management.

Table 1: Common terpenes/terpenoids found in C. sativa and their proven pharmacological effects.

Compound	Class	Effects	References
Alpha-Bisabolol	**Sesquiterpenoid**	**Anti-inflammatory, analgesic, antinociception**	[4], [5], [6], [7]
Alpha-Humulene	Sesquiterpene	Anti-inflammatory, anti-allergy	[8], [9], [10]
Beta-Caryophyllene	Sesquiterpene	Anti-inflammatory, anti-anxiety, analgesic	[11], [12], [13], [14], [15], [16]
Beta-Myrcene	Monoterpene	Anti-inflammatory, analgesic, sedative	[17], [18], [19], [20]
cis-Nerolidol	**Sesquiterpenoid**	**Anti-inflammatory, anti-anxiety, antinociception**	[21], [22], [23], [24]
Limonene	Monoterpene	Anti-inflammatory, anti-anxiety, anticonvulsant	[25], [26], [27], [28], [29]
Linalool	Monoterpenoid	Anti-inflammatory, anti-anxiety, analgesic	[30], [31], [32], [33]

Several studies have explored the anti-inflammatory, antinociceptive and anxiolytic properties of cis-nerolidol. Recent reports showed it can significantly suppress inflammation at doses of 4 - 10 mg/kg in vitro and 100 - 150 mg/kg in vivo, particularly in models of colon inflammation [23], [24]. In pain models, cis-nerolidol at slightly higher doses of 200 - 400 mg/kg significantly reduced nociceptive behaviour in mice which suggested modulation of cytokine activity in mice [22]. In anxiety-related models, doses of 5 - 2.5 mg/kg produced anxiolytic effects in mice, as evidenced by improved performance in behavioural tests and pain relief without impairing movement [21]. These studies suggest that cis-nerolidol could be effective in managing physiological or psychological symptoms due to its broad pharmacological activity.

1.2 In-house produced cultivars

GES Labs uses two active pharmaceutical ingredient (API) sources to produce inhalation cartridges. The first source is a distillate that is formulated by adding back volatile compounds after distillation, and the second is a solventless extract known as rosin, which naturally retains its terpene content. The terpene profiles for ten distillate cultivars and two rosin cultivars were analysed and the most abundant terpenes were determined as a mass percentage of the quantified terpene profile, as determined by GC-FID by an external validated testing laboratory. The distillate cultivars analysed were Creamy Kees, Karel's Haze, Lemon Fire Haze, Royal Gorilla, Critical Kush, White Lemon, Slurricane, Original Blitz, UK Cheese and

Orange Kush Cake (OKC), and the rosin cultivars were Platinum and Cookie Pie. The results of the terpene analysis are given in **Error! Reference source not found.**, where each terpene is reported as its relative percentage of the quantified terpene fraction.

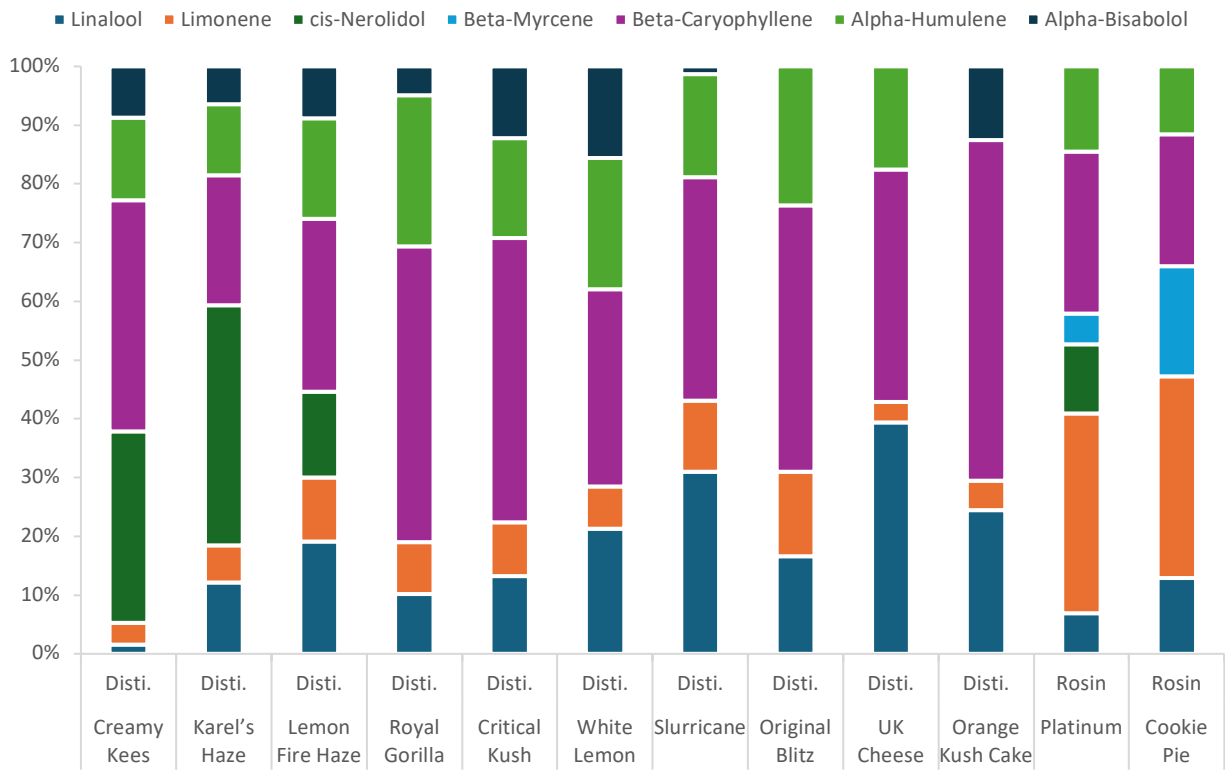

Figure 1: Relative terpene composition of our in-house produced inhalation products.

The average total terpene content for the inhalation products was approximately 16 mg/$g_{product}$ for the distillate cultivars and 65 mg/$g_{product}$ for the rosin cultivars. This difference was expected as distillation typically results in greater terpene loss compared to solventless extraction methods. Beta-caryophyllene was the most abundant terpene in the distillate products and was also present in the rosin products, but in smaller amounts. Although present in the distillate products, limonene was the most abundant terpene in the rosin cultivars. Substantial amounts of beta-myrcene were unique to the rosin cultivars, whereas alpha-bisabolol was detected in 80% of the distillate cultivars. Additionally, cis-nerolidol was found in three distillate cultivars (Creamy Kees, Karel's Haze, Lemon Fire Haze) as well as in relatively smaller amounts in one rosin cultivar (Platinum). All cultivars, except for OKC, contained significant amounts of alpha-humulene and linalool, with the distillate cultivars showing more than 10% relative abundance of linalool compared to the rosin cultivars. Table 2 provides a summarised overview of the terpene content for each cultivar, along with the potential benefits and applications of the inhalation products based on their terpene profiles.

Table 2: Top 3 terpenes available in our in-house inhalation products and possible benefits.

Cultivar	Terpene	Relative Abundance (%)	Potential Treatments
Creamy Kees	Beta-Caryophyllene cis-Nerolidol Alpha-Humulene	39 33 14	Inflammation, general and nociceptive pain, allergies, anxiety
Karel's Haze	cis-Nerolidol Beta-Caryophyllene Alpha-Humulene	41 22 14	Inflammation, general and nociceptive pain, allergies, anxiety
Lemon Fire Haze	Beta-Caryophyllene Linalool Alpha-Humulene	29 19 17	Inflammation, general pain, anxiety, allergies
Royal Gorilla	Beta-Caryophyllene Alpha-Humulene Linalool	50 26 10	Inflammation, general (and nociceptive) pain, allergies, anxiety
Critical Kush	Beta-Caryophyllene Alpha-Humulene Linalool	48 17 13	Inflammation, general (and nociceptive) pain, allergies, anxiety
White Lemon	Beta-Caryophyllene Alpha-Humulene Linalool	34 22 21	Inflammation, general (and nociceptive) pain, allergies, anxiety
Slurricane	Beta-Caryophyllene Linalool Alpha-Humulene	38 31 17	Inflammation, general (and nociceptive) pain, allergies, anxiety
Original Blitz	Beta-Caryophyllene Alpha-Humulene Linalool	45 24 17	Inflammation, general pain, anxiety, allergies
UK Cheese	Beta-Caryophyllene Linalool Alpha-Humulene	40 39 18	Inflammation, general pain, anxiety, allergies
Orange Kush Cake	Beta-Caryophyllene Linalool Alpha-Bisabolol	58 24 13	Inflammation, general and nociceptive pain, anxiety, allergies
Platinum	Limonene Beta-Caryophyllene Alpha-Humulene	34 28 14	Inflammation, general pain, anxiety, seizures, allergies
Cookie Pie	Limonene Beta-Caryophyllene Beta-Myrcene	34 22 19	Inflammation, general pain, anxiety, seizures

Within the distillate products, the cultivars could be grouped into three distinct groups based on their three most abundant terpenes. For Creamy Kees and Karel's Haze, the most abundant terpenes were beta-caryophyllene, cis-nerolidol and alpha-humulene. From the literature, beta-caryophyllene has potential benefits for anti-inflammatory, analgesic, and anti-anxiety application. The significant abundance of cis-nerolidol extends the analgesic benefits to include antinociceptive properties, therefore inhibiting the transmission of pain signals and supporting its potential use in pain management. Alpha-humulene has potential in combatting the symptoms of allergies, which is included in these cultivars' therapeutic potential.

The second group of distillate products reported beta-caryophyllene, linalool, and alpa-humulene as the three most abundant terpenes, with beta-caryophyllene being the most abundant in all cultivars within this group. These cultivars included: Limon Fire Haze, Slurricane, Royal Gorilla, Critical Kush, White Lemon, Original Blitz, and UK Cheese. Both beta-caryophyllene and linalool have proven use for anti-anxiety, where linalool is more effective for treating other symptoms of stress such as immune responses from sustained anxiety. It has also been reported that linalool has potential in the use of rapid stress relief, and can therefore potentially be more effective in high-stress environment, or situations where immediate or rapid stress-relief is required. As with the previous group, the significant presence of alpha-humulene shows potential application in combatting the symptoms of allergies. Other potential benefits of this terpene profile include analgesic and anti-inflammatory properties.

The last distillate group contains a single cultivar, OKC, with the three most abundant terpenes being beta-caryophyllene, linalool, and alpha-bisabolol (in order of descending abundance). As with the previous group, this profile has potential use as anti-inflammatory, analgesic, and anti-anxiety agents. The presence with alpha-bisabolol also extends the analgesic benefits to include antinociceptive properties. Overall, all distillate cultivars contain high amounts of terpenes with therapeutic properties targeted to the treatment of anxiety, pain, and inflammation.

Regarding the rosin cultivars, both Platinum and Cookie Pie contained limonene and beta-caryophyllene as the dominant terpenes. Both these terpenes have proven results for reducing stress and anxiety in literature, however these reactions were slower when compared to linalool. Limonene also has the additional benefit of having potential use as an anticonvulsant, and could therefore be useful in the easing of symptoms in seizure patients. The discrepancies were that the third most abundant terpene for Platinum was alpha-humulene as well as a significant amount of cis nerolidol (~12% relative abundance), while Cookie Pie contained beta-myrcene. Alpha-humulene has the benefit of combatting allergy symptoms, whereas cis-

nerolidol shows potential analgesic and antinociceptive benefits. Beta-Myrcene is known for its sedative properties in higher concentrations (>5 mg/g).

Overall, these findings provide valuable insight into the terpene diversity of in-house cultivars and highlight opportunities to formulate targeted inhalation products by blending strains with complementary terpene profiles to achieve desired therapeutic effects.

1.3 Conclusions

The therapeutic properties of various terpenes are well-established in literature, with many demonstrating anti-inflammatory, analgesic, and anxiolytic effects. Building on this foundation, GES Labs has developed terpene profiling into the evaluation of different cannabis production methods and cultivars to explore their potential treatment applications. Cultivars processed through rosin pressing were found to have higher amounts of limonene, a terpene associated not only with anti-inflammatory and analgesic benefits but also with the potential to relieve seizure symptoms. On the other hand, the most abundant terpene in the distillate cultivars was beta-caryophyllene which could be used for stress relief in addition to anti-inflammatory and analgesic effects.

Understanding these mechanisms could inform the design of clinical trials by identifying specific scents and metabolic by-products to monitor. Blends of products will be proposed to target either sensory or therapeutic goals. This will allow for more specificity in production and will further aid in the standardising of *Cannabis* as medicine for targeting specific patient symptoms. Additionally, the energising or sedative effects of various terpenes is set to be investigated with the goal of standardising the classification of “Day” or “Night” cultivars based on their terpene profiles.

1.4 References

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