

# The COVID-19 Cytokine Storm is Brewing, and Here's How Terpenes Can Help

By Susan Trapp, Ph.D., Terpedia

While terpenes are known for flavor, scents, and aromas in cannabis and other plants, their therapeutic benefits are less well-defined. Terpenes in the form of herbal remedies and essential oils have been utilized for centuries in traditional medicine practices, and yet there are still so many questions left unresolved within the scientific community. However, due to the increased interest in cannabinoids and terpenes, more research is being investigated, such as the way in which cannabis and all of the plant's phytochemicals interact with our immune system. This is laying the groundwork allowing us to understand the mechanisms of action (MOA) at biochemical levels. [1,2]

A recent study showing promise in the lab is the potential for cannabinoids and terpenes to act as an adjunctive treatment for COVID-19 patients. [3] Preliminary results from an ongoing collaborative study by the Israeli companies Eybna and CannaSoul Analytics, specializing in terpene and cannabis R&D, suggest that terpenes are almost twice as effective than a conventional corticosteroid (dexamethasone) for reducing the "cytokine storm", a necessary step for treating infectious diseases like COVID-19. [3] More research is needed and this study still requires peer-review; however, the findings demonstrate an intriguing role that cannabis phytochemicals — terpenes and cannabidiol (CBD) — may play in quelling the deadly "cytokine storm."

## What is a Cytokine?

Cytokines are a functionally diverse network of small proteins that are secreted by specific cells of the immune system for the purpose of cell communication. Inflammatory cytokines, notably interleukins (IL) IL-1, IL-6, IL-8, and TNF- $\alpha$  (tumor necrosis factor), are increased during an immune response to an antigen, or an invading foreign substance or pathogen that is not recognized by the body. Typically,

this is a microorganism such as a virus, bacteria, fungi, or parasite. In a healthy immune system, cytokines signal to other immune cells to respond appropriately. Generally, this involves ingesting invaders, killing them, repairing the damage, and finally bringing the system back to internal balance (homeostasis). [4-6]

## What is the Cytokine Storm?

The term "cytokine storm" refers to an immune system that has gone haywire in which the normal inflammatory response is flaring out of control and essentially harming instead of helping your system return to homeostasis. The cytokine storm has been associated with a wide variety of infectious diseases and noninfectious diseases such as multiple sclerosis, pancreatitis, and graft-versus-host disease. [4,7] Symptoms typically include a fever or reactions from the nervous system that could lead to headaches, seizures, or coma. [4,6-8]

The "cytokine storm" occurs when there is a severe immune reaction where the body releases too many cytokines into the blood too quickly during an immune response to an antigen. The immune cells move beyond the infected body tissues and commence attacking healthy tissue, devouring red and white blood cells, and damaging the liver. [4,6,7] The pathology may include swelling of blood vessels to let in immune cells from surrounding tissues; however, these vessels become so leaky that the lungs may fill up with fluid, blood pressure drops, and blood clots occur throughout the body inhibiting further blood flow. Finally, organs begin shutting down due to limited blood supply, shock can occur, and ultimately death or permanent organ damage. [4,6-8]

## The COVID-19 Cytokine Storm

Over the past ten months, it has become clear that COVID-19 infection causes inflammation and a "cytokine storm." This



results in a range of symptoms from none to mild, severe COVID-19-induced comorbidities, and mortality. [9] Symptoms in severe cases include excessive inflammation, swelling, blood clotting, respiratory distress, fatigue, pain, loss of organ function, and death. Current treatment and partial successes have included convalescent plasma, antiviral drugs such as remdesivir, and corticosteroids. [8-10] Even though the Moderna and Pfizer vaccine administrations have been initiated, there are many unknowns before herd immunity is achieved. In the meantime, adjunctive therapies and other lines of treatment are necessary for a successful global COVID-19 viral pandemic mitigation strategy.

### **Cannabis and Its Terpenes**

A recent editorial review in *Future Science* reported on the potential for cannabis and cannabinoid adjunctive treatment for COVID-19 patients by quelling the “cytokine storm,” which has been previously demonstrated for HIV, and further suggests that cannabinoid receptors could be a therapeutic target. [5,9] The endocannabinoid system (ECS) is a key regulator of the immune system and plant-derived cannabinoid activity is mediated by the ECS. Cannabinoids play significant roles in regulating the immune system. As part of a therapeutic regime, activation by cannabinoids and cannabis as part of the immune response includes the suppression of the cytokines, inhibiting immune cell growth, migration, and antibody production, and ideally allowing the ECS to exercise command over viral spread. But more studies and trials are required for further understanding. [6,9]

As previously mentioned, preliminary results of an ongoing Israeli study suggest that terpenes *alone* intriguingly may be more effective than CBD alone, or the current conventional method, which utilizes a corticosteroid (dexamethasone) to inhibit the cytokine activity. [3,11] The study was initiated to investigate if Eybna’s proprietary blend of 30 anti-inflammatory terpenes (called NT-VRL) would decrease the cytokine storm and how they compare to other available treatments.

The investigation was done *in vitro*, which in this particular case means they used human blood cells containing four cytokines (IL-1, IL-6, IL-8, and TNF-alpha) and tested various treatments of NT-VRL, CBD, or both in tandem, for their ability to inhibit cytokine activity. [3,5] Dexamethasone was used as a control to compare experimental treatments to the standard steroid treatment due to its ability to reduce allergic-type reactions, redness, and swelling. According to the researchers, the results were striking and a bit unexpected.

The NT-VRL terpene formulation performed better than CBD or the steroid. On average, CBD alone inhibited approximately



75% of the cytokines, while terpenes alone inhibited approximately 80%. Better yet, the formulation combining terpenes and CBD inhibited approximately 90% of the cytokines on average, compared to dexamethasone which inhibited nearly 30%. [3]

These findings suggest that CBD and NT-VRL may be twice as effective as dexamethasone. In a recent study within the UK, mortality was reduced by one-third utilizing this corticosteroid to reduce inflammation with COVID-19 patients on ventilators. [3,8,10,11] The preliminary results still require peer-review evaluation and extensive validation by the scientific community. However, should the results prove accurate and repeatable, they could lead to clinical human trials to study as treatment for COVID-19 cytokine storm syndrome.

A recent review evaluated anti-viral activity of essential oils and their terpenes against coronaviruses. [2] The article discussed the conceivability that some essential oils would demonstrate defense against COVID-19 given previous studies that showed their efficacy against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and avian Infectious Bronchitis Virus (*Avian coronavirus*).

Another Israeli study reported on specific anti-inflammatory properties of distinct terpene compositions, addressing a more in-depth look of what terpenes are doing in the cytokine storm. [1] Gallily's group teased out the effects of terpenes versus the cannabinoids, suggesting that CBD exerts a prolonged immunosuppression and might be used in chronic inflammation, whereas the terpenoids showed only a transient immunosuppression and might be useful for relieving acute inflammation. [1] This study also reported on specific terpene candidates within three cultivars that are beneficial for inflammation. The relative top terpenes were myrcene, trans-caryophyllene, trans-B-ocimene, terpinolene, alpha-humulene, and alpha- and beta-pinene. Based upon this study and various reviews [1,2,12], one can surmise that these are highly desirable for anti-inflammation formulations. Network pharmacology and further investigation is required before we fully understand the proper dosing, terpene chemoprofiles, ratios, and minor terpenes that are found within a winning formulation.

### Conclusion

This is not the first study to investigate the role that terpenes play in our immune system and it certainly won't be the last. These small molecules pack a punch, with or without cannabinoids, and remain effective for various human medical indications. However, lack of public acceptance in concert with the flood of misinformation is one battle we will continue to fight until federal legalization and perhaps beyond. There are still so many unanswered questions, but if alternative treatments utilizing cannabis and terpenes are indeed the answer to maintaining control over a global health crisis, one can only hope that they are welcomed with open arms.

### About the Author

*Susan Trapp, Ph.D., is a 20-year biotechnology expert with a vision to accelerate patient-centric cannabis and endocannabinoid discoveries and solutions through education and research. Dr. Trapp's scientific career took off after working alongside Craig Venter, Ph.D., on the Human Genome Project. Dr. Trapp's doctoral and postdoctoral training focused on the molecular evolution of plant and fungal terpenoids (terpenes), and as a sought-after terpene subject expert, she has shifted focus to botanicals including the cannabis and hemp industries. Dr. Trapp earned her crown as the 'Queen of Terpenes' by serving as a scientific advisor and valued consultant for cannabis and hemp companies as they navigate the function of terpenes in products. Trapp also serves as an instructor for the Cannabinoid Industry Association's accredited courses. Her current projects include launching two terpene and cannabinoid-focused startups: Terpedia and EndoSyn.*

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