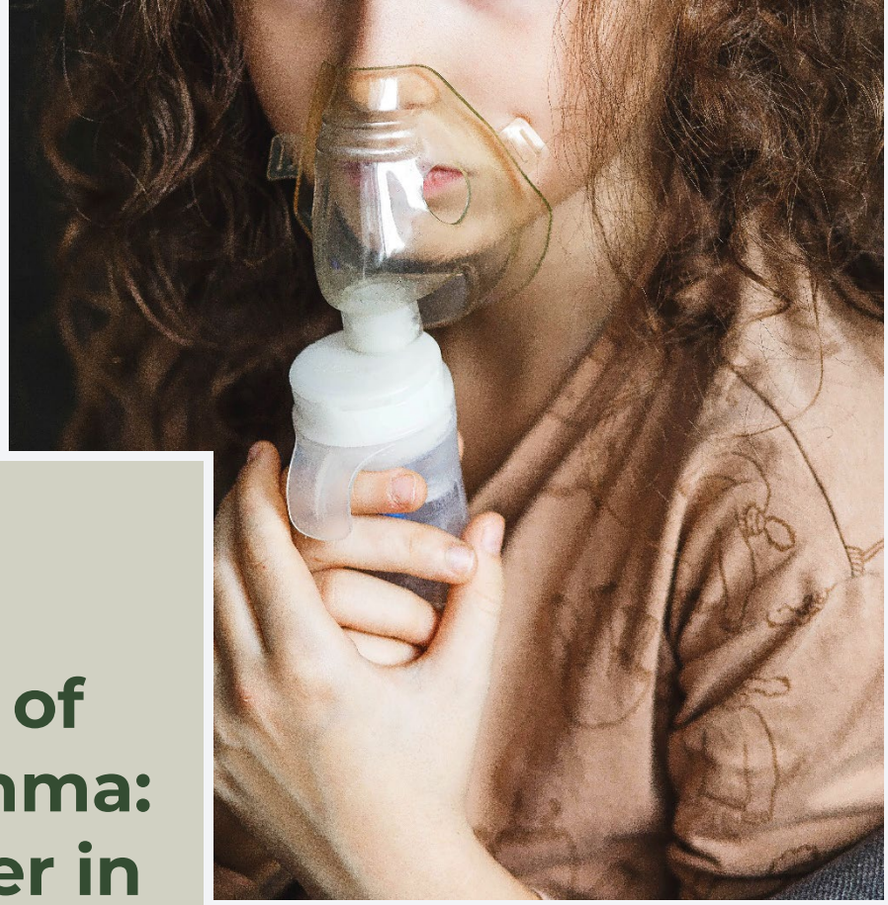

The Potential of CBDa for Asthma: A New Frontier in Respiratory Care

A Whitepaper on the Anti-Inflammatory and Bronchodilatory Potential of Cannabidiolic Acid

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Executive Summary

Affecting over 260 million people, asthma remains a major health issue despite the availability of standard medications and treatments.[1] In 2013, it was estimated that in the United States alone, about $80 billion annually is spent or lost due to asthma-related medical bills, missed work and school days, and early deaths.[2] Although patients are burdened with high medical costs, they continue to experience uncontrolled symptoms, medication side effects, or diminishing efficacy, necessitating the need for alternative treatment regimens. One such potential remedy may be cannabinoids like CBDa.

CBDa (cannabidiolic acid) is the raw, unheated form of cannabidiol (CBD) that is found in the hemp variety of the cannabis species. It is emerging as a powerful natural compound with promising therapeutic potential, which is more potent than CBD. Unlike its decarboxylated counterpart, CBDa has been shown to exhibit strong anti-inflammatory, immunomodulatory, and antioxidant properties, which may be directly relevant to asthma pathophysiology.[3]

This white paper reviews the emerging scientific literature on CBDa, focusing on mechanisms that may intersect with inflammatory pathways relevant to respiratory disease. While current evidence remains limited and largely preclinical, these findings highlight areas where further investigation may be warranted.

Introduction

Asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness, episodic airflow obstruction, and mucus production. Despite advances in pharmacological treatments such as inhaled corticosteroids and beta-agonists, many patients continue to struggle with persistent symptoms, adverse drug effects, or a decline in therapeutic response over time.

Increasing attention has been directed toward biological pathways that regulate inflammation and immune signaling. Among these, the endocannabinoid system (ECS) has emerged as a regulatory network involved in immune modulation and inflammatory signaling.

Cannabinoids derived from the *Cannabis sativa* plant, including cannabidiol (CBD) and its acidic precursor cannabidiolic acid (CBDa), have been investigated for their biological effects on these pathways. Although research on CBDa remains limited, early studies suggest it may interact with several molecular targets involved in inflammatory responses.

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[1] World. Asthma. *Who.int.* Published May 6, 2024. Accessed March 10, 2026. https://www.who.int/news-room/fact-sheets/detail/asthma

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Asthma Pathophysiology

Modern immunological research has revealed that, rather than being a single disease, chronic airway obstruction is a highly heterogeneous condition driven by distinct inflammatory pathways, or "endotypes." The most common of these is the 'type 2-high' endotype, which is orchestrated by T helper 2 (Th2) cells and innate lymphoid cells [4].[4]

This inflammatory cascade often begins at the airway epithelium, and rather than acting as a physical barrier, it acts as a first responder. When these cells are exposed to various environmental triggers, they release signaling proteins known as alarmins. This in turn initiates a complex immune response that prompts the release of type 2 cytokines, namely IL-4, IL-5, and IL-13. Together, these cytokines are the primary drivers of respiratory distress: IL-5 promotes the recruitment and activation of eosinophils, while IL-4 and IL-13 contribute to mucus hypersecretion and bronchial hyperresponsiveness [4].[4] Over time, this persistent cycle of immune activation and cellular damage can lead to airway remodeling, including smooth muscle thickening and subepithelial fibrosis, which permanently reduces lung elasticity.

Because this inflammatory cascade is driven by a complex web of immune signaling and cellular communication, single-target therapies often yield only partial relief for patients. This has directed scientific attention toward the body's endocannabinoid system (ECS). By naturally modulating immune cell activity and regulating inflammatory cytokine production, the ECS offers a promising, multi-targeted pathway to support balanced respiratory function.

The Role of the Endocannabinoid System in Respiratory Homeostasis

The endocannabinoid system (ECS) has been studied for its role in immune regulation and inflammatory signaling across many tissues, including the respiratory tract. Components of the ECS have been identified in several airway and immune cell types, including airway epithelial cells, pulmonary macrophages, dendritic cells, mast cells, and eosinophils, all of which express cannabinoid (CB) receptors.[5] These findings suggest that cannabinoid signaling may influence immune activity within the lungs.

Cannabinoid receptors are also present in airway tissue. CB1 receptors have been detected in airway smooth muscle and neural pathways involved in bronchial regulation, whereas CB2 receptors are primarily expressed on immune cells. Experimental studies suggest CB1 signaling may influence airway smooth muscle activity through neural mechanisms, whereas CB2 receptors appear to suppress the overproduction of pro-inflammatory cytokines and mitigate tissue damage.[6]

Because inflammation is a key factor in asthma development, these findings have led researchers to examine whether cannabinoid-related signaling pathways interact with the mechanisms behind airway inflammation and immune regulation. However, the role of the ECS in respiratory disease remains a topic of ongoing research.

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Pharmacological Profile of Cannabidiolic Acid (CBDa)

Cannabidiolic acid (CBDa) is a naturally occurring cannabinoid found in raw hemp and cannabis plants. It is the precursor to cannabidiol (CBD) and converts to CBD through decarboxylation when exposed to heat, light, or extended storage. In its natural form, CBDa retains its original carboxylic acid group.

This structural difference contributes to a pharmacological profile that differs from that of decarboxylated cannabinoids. Laboratory studies have shown that CBDa can interact with several molecular targets involved in inflammatory and sensory signaling, including serotonin receptors and certain transient receptor potential (TRP) channels. These interactions have led researchers to explore whether CBDa may influence biological pathways involved in inflammation and cellular signaling.[3]

Although research on CBDa remains limited compared to that on CBD, early mechanistic studies indicate that the compound may have biological activity different from that of other cannabinoids. More research is needed to understand how these molecular interactions affect physiological effects in humans.

Chemical Structure and Origin

In the living plant, CBDa biosynthesis is an enzyme-driven process. Beginning with the formation of olivetolic acid, which is then prenylated to create cannabigerolic acid (CBGa), the foundational precursor for multiple cannabinoids. From there, the enzyme cannabindiolic acid synthase (CBDAS) catalyzes the stereoselective oxyidocyclization of CBGA directly into CBDa.[3]

(insert a structure of CBDa and CBD here)

Mechanisms of Action

CBDa interacts with the body in ways that overlap and differ from those of CBD. Its known mechanisms include:

COX-2 Inhibition

Cyclooxygenase-2 (COX-2) is an enzyme that plays a key role in the body's inflammatory response by catalyzing the conversion of arachidonic acid into pro-inflammatory prostaglandins. COX-1 is typically expressed under normal physiological conditions and is involved in regular cellular functions. In contrast, COX-2 expression tends to increase during inflammatory signaling, cellular stress, or immune activation. Experimental research on animals suggests that CBDa acts as a selective inhibitor of COX-2.[7] Because this depends selectively on the carboxylic acid moiety present in CBDa, a structural feature lost when it converts to CBD, CBDa has a unique pharmacological profile. By selectively modulating this pathway, CBDa may offer a targeted, plant-based approach to support a balanced immune response without compromising the protective functions of COX-1.

5-HT1A Receptor Modulation

The 5-HT1A receptor is a subtype of serotonin receptors found in both the central and peripheral nervous systems. This receptor plays a role in regulating mood, stress responses, and specific inflammatory signaling pathways. In asthma, psychological stress and anxiety are known to worsen

[7] Takeda S, Misawa K, Yamamoto I, Watanabe K. Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metabolism and Disposition: The Biological Fate of Chemicals.* 2008;36(9):1917-1921. doi:https://doi.org/10.1124/dmd.108.020909

airway constriction and immune responses activation.[8] CBDa has demonstrated activity at the 5-HT1A receptor, showing significantly greater potency at this receptor than CBD, indicating a potentially superior role in stress-related inflammation conditions.[9]

PPAR Activation

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that regulate the expression of genes involved in immune responses and cellular metabolism. Recent immunological research has shown that the PPAR-γ isoform has a highly complex role in respiratory health. Specifically, PPAR-γ is essential in promoting the pathogenic activity of Th2 cells by upregulating IL-33 receptor expression, leading to the overproduction of type 2 cytokines. Additionally, innate lymphoid cells (ILC2s), which are heavily involved in airway inflammation, also depend on PPAR-γ regulation to function.[4] Because cannabinoids like CBDa interact with and modulate PPAR pathways, they present an interesting area of research.

TRP Channels

Transient receptor potential (TRP) channels act as polymodal environmental sensors within the respiratory tract. Recent studies suggest that specific isoforms, in particular TRPV1 and TRPA1, play critical roles in airway sensitivity and defense. These channels are expressed across airway sensory nerves, epithelial cells, and smooth muscle. When activated by environmental irritants or allergens, TRPV1 is notably involved in the epithelial secretion of the alarmin IL-33, while TRPA1 activation contributes to neurogenic inflammation and airway smooth muscle contraction.[10] CBDa may interact with these sensory signaling pathways, although the physiological significance of this interaction in respiratory disease remains unclear.[11]

While CBDa does not directly bind to CB1 or CB2 receptors, by interacting with these non-cannabinoid sensory pathways, CBDa may offer a complementary, multi-targeted mechanism to help the body manage environmental stressors, support healthy airway tone, and maintain balanced respiratory function.

Bioavailability and Stability

Preclinical pharmacokinetic studies suggest that CBDa may exhibit greater oral absorption than CBD under certain conditions. In a veterinary study, CBDa was reported to be absorbed at least twice as efficiently as CBD in dogs.[12]

Like many acid cannabinoids, however, CBDa is unstable and can convert to CBD through decarboxylation when exposed to heat, light, or prolonged storage. For this reason, maintaining CBDa in its native form requires processing and storage conditions that minimize environmental exposure.

Formulation and Delivery Methods

Standard commercial cannabinoid extraction depends on heat and chemical solvents, which quickly

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degrade acidic cannabinoids. To preserve CBDa in its active form, Nesa's Hemp uses a proprietary low-temperature extraction process. This approach prevents degradation, maintaining the plant's natural chemistry and original profile of cannabinoids, terpenes, and flavonoids. For those seeking daily respiratory and immune support, the delivery method matters just as much.

While inhalation offers rapid absorption, it can irritate sensitive airways. Sublingual oils and tinctures provide a better alternative, allowing highly absorbable CBDa to swiftly enter the bloodstream and reach systemic targets efficiently and consistently, without causing pulmonary irritation.[13]

Safety Profile and Regulatory Considerations

Unlike THC, CBDa is a non-intoxicating compound. It does not bind directly to CB1 or CB2 receptors. Because of this mechanism, it avoids the intoxicating or cardiovascular effects associated with THC and other intoxicating cannabinoids.[14]

Pharmacological data reveal two distinct potential safety advantages of CBDa. First, it has shown a strong affinity for the 5-HT1A serotonin receptor, which has been linked to gastric comfort and stress resilience. Second, and maybe the most important, CBDa selectively inhibits the COX-2 enzyme. With some traditional treatments, the COX-1 enzyme is suppressed, which has been associated with severe gastrointestinal bleeding and irritation.[15] Because CBDa does not inhibit the COX-1 enzyme, it may have potential to manage inflammation while protecting gut health.

From a regulatory standpoint, CBDa is recognized as the primary phytocannabinoid naturally present in the hemp variety of the cannabis plant. Nesa's Hemp operates in strict accordance with U.S. federal law, using CBDa derived solely from certified hemp with less than 0.3% delta-9 THC, in full compliance with the 2018 Farm Bill. To guarantee consumer safety, dosage consistency, and product purity, each batch is manufactured under Good Manufacturing Practices (GMP) and undergoes rigorous third-party laboratory testing to ensure compliance with all federal standards.

Preclinical and Clinical Evidence on CBDa for Asthma

Clinical research on cannabinoid acids remains in its infancy. Yet the foundational research we already have demonstrates a sharp contrast between CBDa and its decarboxylated counterpart, CBD. Data published in *Drug Metabolism and Disposition* confirms this. The study found CBDa acts as a highly selective COX-2 inhibitor, having 9x the affinity over COX-1.[7] The specific molecular structure of CBDa allows it to target the body's inflammatory response without the potential gastrointestinal harm associated with typical anti-inflammatory treatments.

A study in the *British Journal of Pharmacology* looking at sensory pathways found that CBDa activates the TRPA1 channel. After activation, the receptor is rapidly desensitized, causing the channel to ignore subsequent environmental irritants. As a result of this mechanism, CBDa may blunt this sensory trigger, helping maintain normal airway tone.[11]

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Conclusion

Early preclinical research on CBDa highlights its potential as a natural compound to support respiratory health and immune balance. Due to its unique profile, CBDa interacts with key physiological pathways in ways that are distinct from those of other cannabinoids, such as CBD. CBDa has shown early promise in promoting healthy airways and a balanced inflammatory response.

Nesa's Hemp is committed to advancing the emerging field of medical cannabis science by providing full-spectrum, raw extracts that maintain the integrity of the plant's natural compounds. Looking ahead, rigorous clinical trials will be integral in confirming the safety, optimal dosing, and efficacy of CBDa in asthma care. There is also a clear opportunity to explore personalized delivery systems, regulatory pathways, and combination therapies that integrate CBDa into comprehensive respiratory care models.

We invite research institutions, clinicians, and scientific collaborators to partner with us in conducting clinical trials and exploratory studies using our full-spectrum CBDa extract. Together, we can advance the science, validate the outcomes, and bring a natural, effective option to the forefront of asthma management.

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