



BOTANICAL SOLUTIONS

Cannabichromene

A Cannabinoid that Packs a Punch

Background

Cannabichromene (CBC) is one of the estimated 100+ cannabinoids found in *C. sativa* and was simultaneously discovered in 1966 by two independent groups [1, 2, 32]. Although CBC is normally found in relatively small amounts in modern cannabis plants, it was originally classified as a major cannabinoid along with cannabidiol (CBD) and tetrahydrocannabinol (Δ 9-THC). While they vary in structure, CBC, CBD and Δ 9-THC share similar biosynthetic pathways and have identical chemical composition (Figure 1).

Like CBD, CBC is a non-intoxicating, non-psychoactive compound. However, unlike CBD and Δ 9-THC, CBC is not a DEA scheduled compound [3] and can therefore be used in foods, beverages, dietary supplements and cosmetics as long as the appropriate regulatory requirements are met. CBC has been reported to have broad, health-promoting effects, discussed in detail below, throughout the body (Figure 2).

Our CBC is produced to greater than 95% purity via a proprietary synthetic process that is nearly identical to the natural biosynthetic process as shown in Figure 1.

CBC Function

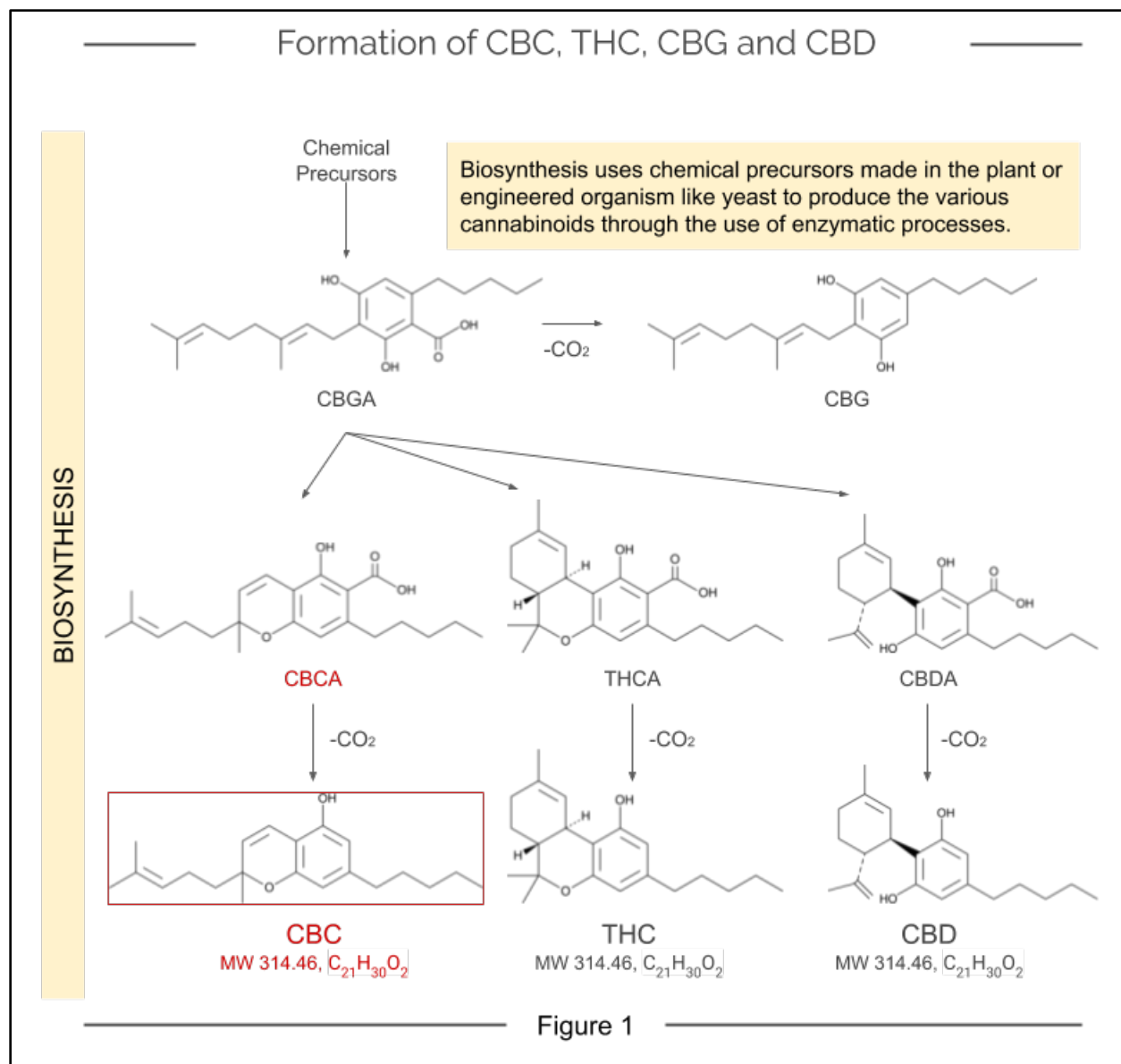
CBC modulates physiological responses by engaging with a variety of cell surface receptors. Cannabinoid receptors 1 and 2 (CB1 and CB2, respectively) are the canonical cannabinoid

receptors in the body. CB1 functions primarily in the central and peripheral nervous systems, and its engagement via Δ^9 -THC results in psychoactive effects. CB2 is primarily found in the peripheral nervous system and in immune system tissues [4]. Signaling through CB2 modulates inflammation and other aspects of immune system function. CBC was recently found to bind CB2 rather than CB1 [5], suggesting a role in pain reduction and modulation of the immune system response.

Supporting CBC's role in pain modulation, CBC along with CBD and a number of naturally occurring endocannabinoids – endogenous compounds produced by the body that interact with CB1 and CB2 – have also been shown to antagonize the TRPV1 receptor. Activation of TRPV1 has been correlated with a reduction in pain [6, 7]. Taken together the effects of CBC and related compounds on TRPV1 receptors provides valuable insight into a possible mechanism for pain reduction and support the concept of the “entourage effect” where multiple compounds are

believed to act in concert to produce effects that are greater than when a single compound is administered individually [8].

CBC also interacts with another vanilloid receptor, TRPV4, but acts to downregulate its expression

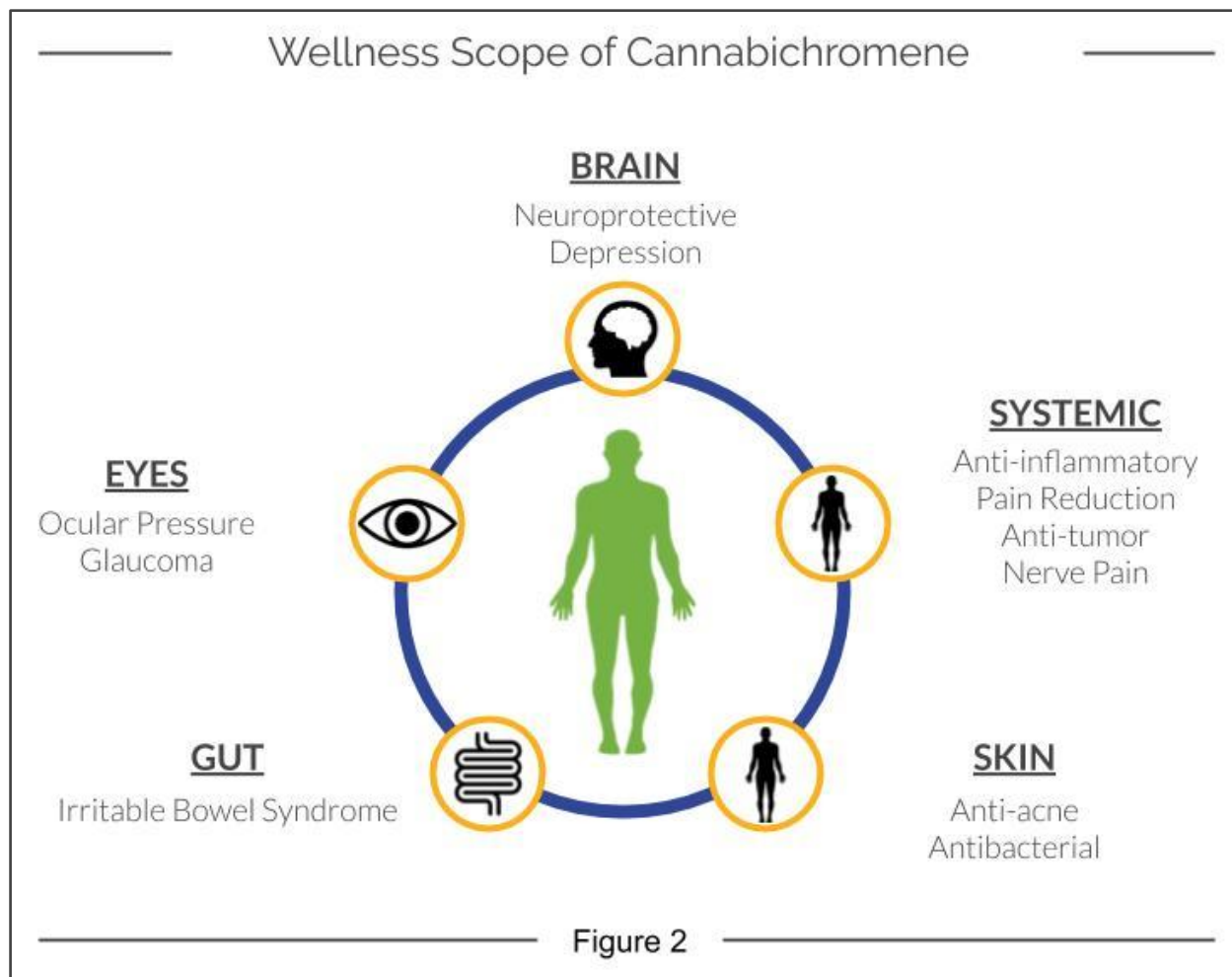


[6]. Through its role in sensation and regulation of osmotic pressure, TRPV4 is believed to impact the physiology not just of pain, but also of skin, vascular, intestinal and musculoskeletal function [6]. As CBC is known to modulate a number of these systems, the ability of CBC to downregulate TRPV4 expression provides insight into a possible mechanism of action.

Another receptor class that is an attractive target for the modulation of pain perception is the TRP ankyrin-type, in particular TRPA1. CBC is a potent agonist of TRPA1 and has been shown to

act synergistically with partial TRPA1 agonists CBG and Δ^9 -THC [9], furthering the idea that administration of multiple cannabinoids simultaneously may have increased effectiveness compared to treatment with individual cannabinoids alone.

The complex interactions between cannabinoids of *C. sativa* and endogenous cannabinoids with a milieu of targets, are still to be mapped. The emerging evidence is that these interactions have the ability to modulate a wide variety of medical conditions.



The Role of CBC in Wellness

Inflammation & Pain

Pain and inflammation are the most well described conditions for which the effects of CBC have been studied. As early as 1981 CBC was shown to be a potent anti-inflammatory compound in two different in vivo scenarios [10, 11]. These results have been recently corroborated and expanded upon in a 2010 study [12]. This report confirmed the potent anti-inflammatory effects of CBC and also demonstrated that there was an additive, “entourage” effect when combined with $\Delta 9$ -THC. Interestingly, the effects of $\Delta 9$ -THC were CB1-dependent, while the effects of CBC did not involve either CB1 or CB2, indicating another route of action, perhaps via TRP receptors. The same study also demonstrated that CBC reduced the response to pain and that, similar to

inflammation, a synergistic effect resulted from co-administration with $\Delta 9$ -THC. Additional studies have also demonstrated a similar pain-modulating effect of CBC [5, 13, 14, 15].

Digestive System & IBS

Irritable Bowel Syndrome (IBS) is a condition characterized by chronic abdominal discomfort and irregular bowel movements. An estimated 25 to 45 million people in the United States, two-thirds of whom are female, experience IBS. Although the precise cause of IBS is unknown, it is considered an inflammatory condition that may be regulated by the TRPA1 and TRPV1 receptors located in the nervous tissue of the colon [16]. As CBC is a potent agonist of TRPA1 and an agonist of TRPV1 its use in modulating IBS has been recently studied [17, 18]. The reports found that CBC normalized intestinal function in a well-established model of intestinal inflammation and when bowel inflammation was not present, no unwanted effects were observed.

Skin & Acne

Acne is a skin condition that affects up to 50 million people in the United States and can have lifelong negative implications. Recent preclinical studies have focused on the effects of various cannabinoids in an acne model. The authors determined that CBC suppressed oil production by sebaceous skin cells and reduced acne-like formation of fat and and suppressed pro-inflammatory responses by sebocytes [19, 20]. The study also showed that the minor cannabinoids cannabidivarin (CBDV) and tetrahydrocannabivarin (THCV) functioned in a similar manner. In addition to oil production, inflammation is also a key component of acne formation. As has been shown in numerous other studies, this report confirmed the strong anti-inflammatory actions of CBC, CBDV and THCV. Bacterial infection is a common co-factor in acne and CBC is known to be a potent antibacterial agent [10, 21]; and though not directly studied to date, the antibacterial effect of cannabinoids may be useful in reducing acne. Lastly, the possible synergistic, “entourage” effect of combining CBC with CBDV, and where legally permitted THCV, on skin conditions like dermatitis and acne remains an exciting field of study that has yet to be fully explored [18].

Glaucoma

Glaucoma is a condition where increased intraocular pressure in the eye leads to nerve damage that can have lifelong effects including blindness. One study showed that intravenous administration of CBC led to a significant reduction in ocular pressure [22]. The psychoactive cannabinoids, $\Delta 8$ -THC and $\Delta 9$ -THC also significantly reduced ocular pressure. As this study was

performed many years ago there is great interest to revisit the effects of cannabinoids on ocular pressure, particularly in light of recent advances in topical drug delivery techniques, such as nanoparticles.

Brain & Neurobehavioral

A number of studies have investigated the effects of cannabinoids, including CBC, on various aspects of neuronal cells. In a 2013 study it was shown that CBC, but not CBD or CBG, resulted in increased viability of adult neural stem progenitor cells (NSPC) and differentiation into neural cells – both essential for healthy brain function and plasticity [23]. Interestingly, inducing NSPC to regenerate lost neurons, a form of plasticity, could play an important role in mitigating the effects of Alzheimer’s disease [24].

CBC has also been studied in models of depression in vivo [25]. The results of this study revealed antidepressant-like activity of CBC and CBD, while CBG and CBN did not exhibit such activity. In this study CBC was shown to be 10X more effective than CBD. Like in other instances the combination of multiple cannabinoids may provide synergistic effects that exceed the impact of individual cannabinoids in mild depression.

Cancer

Once controversial, the etiological role of inflammation in cancer is now widely accepted in the scientific community after 2 decades of research. However, because of a decades long challenge of studying cannabinoids in the United States due to their controlled substance status, little research has been done exploring their potential role in chemoprevention. Despite this, the role cannabinoids, including CBC, may play in cancer could be profound and merits further study [26, 27, 28, 29, 30, 31].

Safety

CBC is a non-psychotropic cannabinoid that by virtue of its presence in *C. sativa* has been safely used by humans for thousands of years [8]. In addition, CBC has been the subject of numerous animal studies with no observable negative consequences at experimental usage levels. One older study attempted to determine the toxicity of CBC in mice, but few adverse effects were noted even at exposure at levels that far exceed any expected use in consumer or animal products[13]. CBC is currently undergoing rigorous safety and toxicology studies with the purpose

of achieving a Generally Recognized As Safe (GRAS) affirmation. Such designation is critical for the safe and legal inclusion of any ingredient into a food, beverage, or supplement.

Legality

CBC is not a controlled substance under the Controlled Substances Act [3] or the Synthetic Drug Abuse Prevention Act [33]. Furthermore, CBC, unlike cannabidiol (CBD), has not been the subject of an Investigational New Drug application and thus is not precluded from being used in a food, beverage, or dietary supplement, as the Food and Drug Administration (FDA) has alleged with respect to CBD.

Conclusions

With the recent, increased scrutiny of CBD by regulators in both the human and animal markets, we believe it is the optimal time to highlight the benefits of so-called *minor cannabinoids* like CBC. Upon completion of appropriate safety studies, CBC will be able to be used in many mainstream applications where the use of CBD may remain problematic. Research is ongoing to demonstrate that CBC is a Generally Recognized as Safe (GRAS) compound. Lastly, the research described above has shown that CBC shares a number of benefits similar to CBD and therefore that cannabinoids like CBC can readily be substituted for, or complement, CBD in many applications.

Disclaimer

The information provided herein may be subject to change and should be independently verified. These statements have not been evaluated by the Food and Drug Association and are not intended to diagnose, treat, cure, or prevent any disease.

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