



Preventing and Treating Long-Haul COVID-19 and Other Types of Inflammation

All active ingredients being included are considered GRAS in the US. **Generally recognized as safe (GRAS)** is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.

β-caryophyllene (BCP)

β-Caryophyllene, A Natural Dietary CB2 Receptor Selective Cannabinoid can be a Candidate to Target the Trinity of Infection, Immunity, and Inflammation in COVID-19:

Based on its pharmacological properties, molecular mechanisms, and the therapeutic potential of BCP as an immunomodulator, anti-inflammatory, organ-protective, and antiviral, we hypothesize that BCP could be a promising therapeutic and/or preventive candidate to target the triad of infection, immunity, and inflammation in COVID-19.

Further, BCP exerted a potent immunomodulatory effect by simultaneously inhibiting both Th1 cytokines, including IL-2 and IFN-γ, and Th2 cytokines, including IL-4, IL-5, and IL-10, in primary splenocytes ([Ku and Lin, 2013](#)). Also, BCP is present in many plants, such as *Chrysanthemum indicum* L. ([Hwang and Kim, 2013](#)), *Pterodonem arginatus* Vogel ([Alberti et al., 2014](#)), *Myracrodruon urundeuva* Allemão ([Carvalho et al., 2017](#)), *Schizonepeta tenuifolia* (Benth.) Briq. ([Ng et al., 2018](#)), and copaiba oil ([Urasaki et al., 2020](#)), in which it exerts immunomodulatory activity. Taken together, the studies demonstrate that CB2R play a key role in balancing the immune response and BCP by activating CB2R, holding promise in the therapeutic modulation of immune-inflammatory changes in patients with SARS-CoV-2 infection.

In COVID-19, the use of immunomodulators is receiving attention and being regarded as a “sub etiological treatment” in the absence of an effective antiviral drug. Additionally, BCP was shown to reduce ACE activity, which may be useful as ACE2 receptors, as the gateways of the virus entry, play a role from the entry of the virus to viremia and from respiratory distress to sepsis ([Adefegha et al., 2017](#); [Ajiboye et al., 2019](#)). The immunomodulatory role of BCP is represented in [Figure 3](#). Given the role of immunomodulators on the modulation of the hyperimmune-inflammatory response in COVID-19 patients, BCP may be a potential candidate for modulating immunity in patients at risk of infection and chronic metabolic and/or degenerative diseases, as well as in preventing the development and reducing the severity of COVID-19.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8163236/>

A focused review on CB2 receptor-selective pharmacological properties and therapeutic potential of β -caryophyllene, a dietary cannabinoid:

The focus of the present manuscript is to represent the CB2R selective agonist mediated pharmacological mechanisms and therapeutic potential of BCP. The present narrative review summarizes insights into the CB2R-selective pharmacological properties and therapeutic potential of BCP such as cardioprotective, hepatoprotective, neuroprotective, nephroprotective, gastroprotective, chemopreventive, antioxidant, anti-inflammatory, and immunomodulator. The available evidences suggest that BCP, can be an important candidate of plant origin endowed with CB2R selective properties that may provide a pharmacological rationale for its pharmacotherapeutic application and pharmaceutical development like a drug. Additionally, given the wide availability in edible plants and dietary use, with safety, and no toxicity, BCP can be promoted as a nutraceutical and functional food for general health and well-being.

<https://www.sciencedirect.com/science/article/pii/S0753332221004248>

β -Caryophyllene: A Sesquiterpene with Countless Biological Properties:

β -Caryophyllene (BCP), a natural bicyclic sesquiterpene, is a selective phytocannabinoid agonist of type 2 receptors (CB2-R). It isn't psychogenic due to the absence of an affinity to cannabinoid receptor type 1 (CB1). Among the various biological activities, BCP exerts anti-inflammatory action via inhibiting the main inflammatory mediators, such as inducible nitric oxide synthase (iNOS), Interleukin 1 beta (IL-1 β), Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), nuclear factor kappa B (NF- κ B), cyclooxygenase 1 (COX-1), cyclooxygenase 2 (COX-2). Peroxisome proliferator activated receptors alpha (PPAR- α) effects are also mediated by the activation of PPAR- α and PPAR- γ receptors. In detail, many studies, in vitro and in vivo, suggest that the treatment with β -caryophyllene improves the phenotype of animals used to model various inflammatory pathologies, such as nervous system diseases (Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, stroke), atherosclerosis, and tumours (colon, breast, pancreas, lymphoma, melanoma and glioma cancer). Furthermore, pre-clinical data have highlighted that BCP is potentially useful in *Streptococcus* infections, osteoporosis, steatohepatitis, and exerts anticonvulsant, analgesic, myorelaxing, sedative, and antidepressive effects. BCP is non-toxic in rodents, with a Lethal dose, 50% (LD50) greater than 5000 mg/kg. Nevertheless, it inhibits various cytochrome P450 isoforms (above all, CYP3A4), which metabolise xenobiotics, leading to adverse effects, due to drug levels over therapeutic window. All the reported data have highlighted that both pharmacological and toxicological aspects need to be further investigated with clinical trials.



<https://www.mdpi.com/2076-3417/9/24/5420/htm>

Protective Effects of (E)- β -Caryophyllene (BCP) in Chronic Inflammation:

(E)- β -caryophyllene (BCP) is a bicyclic sesquiterpene widely distributed in the plant kingdom, where it contributes a unique aroma to essential oils and has a pivotal role in the survival and evolution of higher plants. Recent studies provided evidence for protective roles of BCP in animal cells, highlighting its possible use as a novel therapeutic tool. Experimental results show the ability of BCP to reduce pro-inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), thus ameliorating chronic pathologies characterized by inflammation and oxidative stress, in particular metabolic and neurological diseases. Through the binding to CB2 cannabinoid receptors and the interaction with members of the family of peroxisome proliferator-activated receptors (PPARs), BCP shows beneficial effects on obesity, non-alcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) liver diseases, diabetes, cardiovascular diseases, pain and other nervous system disorders. This review describes the current knowledge on the biosynthesis and natural sources of BCP, and reviews its role and mechanisms of action in different inflammation-related metabolic and neurologic disorders.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7692661/>

For further details and the list of all ingredients please click on the link or visit our website www.rheumcare.com/research-ingredient-nutraceutical

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