A PATIENT GUIDE FROM BELLYMD

Beta-Caryophyllene: What the evidence shows.

A plain-language look at a plant compound found in black pepper and cloves, why it activates one half of your body's cannabinoid system without producing a high, and what the published research does and does not support.

About this guide. Beta-caryophyllene appears in *MGB+ Calm* at 100 mg per daily serving, as part of a six-ingredient formula built to support people with brain-gut hyperreactivity patterns, morning queasiness, and cyclical stomach upset. This handout covers the published evidence behind beta-caryophyllene so you can read it yourself and decide what makes sense for you.

CHAPTER ONE

What is beta-caryophyllene?

> *A short answer first. Beta-caryophyllene is a plant compound, not a cannabinoid in the way most people use that word. You have already eaten it, probably today. It is one of the molecules that gives black pepper its bite, cloves their warmth, and oregano its sharpness.*[1]

The technical name is a sesquiterpene, which means a class of plant compounds with fifteen carbon atoms. Sesquiterpenes are the building blocks of many plant aromas and flavors. They are part of how plants signal to insects, fight off microbes, and respond to stress. When you smell fresh-cracked pepper or a clove pomander, the warm woody note is mostly beta-caryophyllene drifting off the surface.[1,2]

You will sometimes see it written as BCP for short, or as (E)-beta-caryophyllene with that E in italics. The E refers to the geometry of one of its chemical bonds, which is a detail that matters to chemists but not to consumers. For the rest of this brief we will call it beta-caryophyllene.

Where it occurs

Beta-caryophyllene is one of the most widely distributed plant compounds in the food supply. It shows up in much higher concentrations in common kitchen spices than it does in cannabis. Black pepper is roughly fifteen to thirty percent beta-caryophyllene by essential-oil weight. Cloves are similar. Hops, used in beer, contain it. So do cinnamon, oregano, rosemary, basil, and copaiba balsam.[1,2] It is also present in cannabis essential oils, which is where most of the recent attention came from, but the cannabis content is not what makes the plant intoxicating.

The U.S. Food and Drug Administration lists beta-caryophyllene as a flavoring substance generally recognized as safe, the regulatory shorthand for which is GRAS. It has been used as a food and beverage flavor agent for decades.[3]

The 2008 discovery that changed how people thought about it

For most of its history beta-caryophyllene was treated as a flavor molecule. That changed in 2008, when a research group led by Jurg Gertsch at the University of Bern in Switzerland published a paper in the *Proceedings of the National Academy of Sciences* showing that beta-caryophyllene binds tightly and selectively to one of the two main receptors in the body's endocannabinoid system, called the CB2 receptor.[1] The endocannabinoid system is the signaling system your body has for managing pain, inflammation, mood, and gut function. The Gertsch paper was titled "Beta-caryophyllene is a dietary cannabinoid."

The headline was that a compound people had been eating in pepper and oregano for thousands of years turned out to act on the same receptor family that scientists had been studying in cannabis. Importantly, it acts on only one half of that family, which is the part of the next chapter.[1,4]

> **THE SHORT VERSION**
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> Beta-caryophyllene is a plant terpene found in much higher amounts in black pepper, cloves, and hops than in cannabis. In 2008 researchers discovered that it binds one of the body's two cannabinoid receptors, the CB2 receptor, which sits mainly on immune cells and in the gut and does not produce a high.

CHAPTER TWO

The key distinction: CB2, not CB1

> *This is the most important page in the brief. It is the question almost everyone asks first and it deserves a clean answer.*

Your body has two main cannabinoid receptors, called CB1 and CB2. They were discovered in the late 1980s and early 1990s. They sit in very different parts of the body and they do very different jobs.[5]

What CB1 does

CB1 is the cannabinoid receptor in your brain. It is most concentrated in regions that handle mood, memory, appetite, and the way you perceive time and sensation. When THC, the main psychoactive compound in cannabis, reaches your brain and activates CB1, the result is the high. The same activation, repeated daily for months or years, is the pattern behind cannabis dependence and behind cannabinoid hyperemesis syndrome, which is a cyclical vomiting pattern that develops in some long-term cannabis users.[5,6]

What CB2 does

CB2 sits almost entirely outside the brain. It is on immune cells, on the cells that line the gut, on mast cells, which are immune cells that release inflammatory signals when triggered, and on certain cells in the bone and skin. Its main role is to tune down inflammation and to keep immune signaling proportionate to the actual problem. Activating CB2 does not produce a high. CB2 is not part of the brain's reward circuitry. It is part of the body's quiet background work.[5,7]

What beta-caryophyllene actually binds

Beta-caryophyllene binds CB2. It does this with high affinity, meaning it sticks well, and it is a full agonist, meaning it fully activates the receptor when it binds. In the 2008 binding experiments, beta-caryophyllene showed essentially no measurable activity at the CB1 receptor at the concentrations that activated CB2. The selectivity is not a small preference. It is the basic shape of the molecule's interaction with the system.[1,4,7]

THE PLAIN ANSWER

Beta-caryophyllene does not bind CB1. It binds CB2. CB1 is the receptor responsible for the high of cannabis use and for the cycle of dependence. CB2 is the immune and gut receptor that does not produce a high when activated. This is why beta-caryophyllene is not psychoactive even though it acts on a cannabinoid receptor.[1,4,7]

And it does not cross efficiently into the brain

A second reason beta-caryophyllene does not produce psychoactive effects at standard oral doses is that it does not pass easily through the blood-brain barrier, the protective layer around your brain that keeps most things out. Beta-caryophyllene is fat-soluble, also called lipophilic, but its specific chemistry limits how much of an oral dose reaches the brain. The amount that does reach the brain still acts on CB2 receptors in microglia, which are the immune cells of the brain, not on CB1 receptors in mood and reward centers.[4,8]

What this means in practice

You can take beta-caryophyllene with breakfast and drive a car. You can take it before bed and not have your sleep architecture rearranged. You can take it every day without entering a tolerance and dependence cycle of the kind that happens with regular cannabinoid use. None of this is a claim about benefit. It is a claim about safety mechanism: the molecule simply does not act in the parts of the brain where the high and the dependence cycle live.[1,4,7]

For anyone who has lived with the brain-gut hyperreactivity pattern that follows long-term cannabis use, this distinction is not academic. It is the difference between a daily-support molecule and a molecule that would compound the underlying problem. Beta-caryophyllene is in the first category.

CHAPTER THREE

How it works in your body

> *Activating CB2 is the headline mechanism. The picture is broader than that. Beta-caryophyllene also touches several other parts of the body's inflammation and signaling network, and most of those touches happen in the gut wall and in the immune cells that live there.*

It calms immune cells in the gut wall

Most of the body's CB2 receptors live on immune cells. When immune cells in the gut wall encounter something they read as a threat, they release inflammatory signals such as cytokines, prostaglandins, and histamine. In acute infections this is appropriate and protective. In chronic low-grade inflammation, the same signaling becomes background noise that the gut wall and the brain both have to keep responding to. Activating CB2 dampens that signaling without shutting it off.[7,9,10]

In experimental models of inflammatory bowel disease, beta-caryophyllene reduced the inflammatory markers that drive tissue damage and improved markers of intestinal barrier health.[9,10] The effect was reversed when researchers blocked CB2 with an experimental compound, which is the standard way of showing that CB2 is the relevant pathway and not some unrelated activity.[9]

It quiets mast cells

Mast cells are a particular kind of immune cell concentrated in the lining of the gut, the airways, and the skin. They release histamine and other inflammatory signals when triggered. People with brain-gut hyperreactivity patterns often have mast-cell systems that are too easy to set off, sometimes from foods, sometimes from stress, sometimes from no obvious trigger at all. In experimental work, beta-caryophyllene reduced mast-cell activation through a CB2-linked pathway, with downstream effects on the antioxidant defenses inside those cells.[11]

It modulates neuroinflammation in the brain's immune cells

The brain has its own immune cells, called microglia. When microglia stay activated too long, they contribute to the kind of slow-burning brain inflammation that researchers now associate with mood disorders, persistent pain, and parts of the brain-gut axis. Microglia carry CB2 receptors. In animal studies, beta-caryophyllene reduced microglial activation and the inflammatory signaling that goes with it.[12,13] This is one of the mechanisms researchers have proposed for the molecule's effects on anxiety-like and depression-like behavior in animal models.[12,13,14]

WHY THIS MATTERS FOR GUT SYMPTOMS

Morning queasiness, cyclical stomach upset, and a sensitive-stomach pattern are rarely a single problem. They are usually a combination of an overresponsive immune system in the gut wall, a more reactive mast-cell population, and a brain that has learned to interpret normal gut signals as alarming. A molecule that touches all three layers, immune cells in the gut, mast cells, and the brain's own immune cells, is acting on the system rather than just one symptom.

It influences the endocannabinoid system more broadly

Beyond directly binding CB2, beta-caryophyllene appears to indirectly influence the broader endocannabinoid system. It has been shown in laboratory studies to interact with PPAR-gamma, a separate receptor family involved in inflammation and metabolism. Several of its effects in animal models, especially on inflammation and on neurobehavior, can be partially blocked by interfering with PPAR-gamma as well as by blocking CB2.[10,14] The practical interpretation is that beta-caryophyllene engages more than one inflammation-regulating system, which is part of why preclinical studies find effects across so many tissue types.

What it is not

Beta-caryophyllene is not a sedative. It does not work the way benzodiazepines work. It is not an antihistamine of the diphenhydramine type. It is not a painkiller of the opioid type, and it does not act on opioid receptors. It is not an antiemetic of the ondansetron type, which acts on serotonin receptors. Beta-caryophyllene works on its own pathway, which is why it is studied alongside those other medications rather than as a replacement for them.[7]

CHAPTER FOUR

What the studies show

Here is the published evidence by area. Most of the research on beta-caryophyllene is preclinical, meaning it was done in animals or in cells rather than in people. Human trials exist but are smaller and fewer. We will flag what is what.

Gut inflammation

ANIMAL MODELS · 2011 TO 2022

In a 2011 study by Bento and colleagues published in the *American Journal of Pathology*, mice with chemically induced colitis received beta-caryophyllene by mouth. The treated animals had less weight loss, less colon damage, lower levels of inflammatory cytokines, and better recovery of intestinal barrier markers than untreated animals. Blocking the CB2 receptor with an experimental compound abolished the effect, which is what investigators look for to confirm that CB2 is the relevant pathway.[9]

A 2022 study by Yeom and colleagues, also in mice with chemically induced colitis, reported similar findings using beta-caryophyllene extracted from cloves. The treated animals had less colon shortening, lower inflammatory cytokines, and changes in gut microbiota composition that favored less inflammation.[10]

What this means: there is consistent preclinical evidence that beta-caryophyllene reduces inflammation in the gut wall through CB2 activation. There is no large human trial yet for inflammatory bowel disease or for general gut hyperreactivity, and beta-caryophyllene is not a treatment for either condition.

Anxiety-like and depression-like behavior

ANIMAL MODELS · 2012 TO 2024

In a 2012 study by Galdino and colleagues, beta-caryophyllene reduced anxiety-like behavior in mice in the elevated plus maze, a standard rodent test of anxiety.[15] A larger 2014 study by Bahi and colleagues using a wider range of behavioral tests, including the forced swim test commonly used to model depression-like behavior, replicated those findings and showed that blocking CB2 reversed the effect, again pointing to CB2 as the relevant pathway.[14] Subsequent work by Youssef and colleagues in 2019 extended these findings to a diet-stress model in rats, with similar reductions in anxiety-like and depression-like behavior.[16]

A 2024 review by Ricardi and colleagues in the *International Journal of Molecular Sciences* pooled the preclinical literature on beta-caryophyllene in emotional and cognitive disorders and concluded that the molecule shows consistent effects across multiple rodent models, with neuroinflammation reduction as the proposed mechanism.[13]

What this means: the preclinical signal is consistent. Properly designed human trials in clinical anxiety or depression have not yet been published, and beta-caryophyllene is not a treatment for either condition.

Pain, especially neuropathic and inflammatory

ANIMAL MODELS · 2014 TO 2019

Neuropathic pain is pain that comes from injured or dysfunctional nerves rather than from injured tissue, the kind of pain people describe as burning or shooting. It is notoriously hard to treat. In a 2014 study by Klauke and colleagues in *European Neuropsychopharmacology*, beta-caryophyllene given by mouth reduced pain behavior in two different mouse models, one of inflammatory pain and one of neuropathic pain. The effect did not lose strength with repeated dosing, which is unusual and clinically interesting, and it was abolished in mice genetically lacking the CB2 receptor.[17]

A 2019 study by Aly and colleagues in *Molecules* showed that beta-caryophyllene reduced mechanical sensitivity in mice with antiretroviral-drug-induced neuropathy, a model of the kind of nerve pain that some HIV medications cause.[18]

What this means: the preclinical evidence for pain modulation, especially CB2-driven neuropathic pain, is some of the strongest in the beta-caryophyllene literature. Human trials in chronic pain are limited and beta-caryophyllene is not a treatment for any pain condition.

Nausea and the broader gut-brain axis

PRECLINICAL · MECHANISM LEVEL

Direct beta-caryophyllene human trials specifically for nausea or vomiting have not been published. The mechanism evidence is indirect. CB2 receptors are present in parts of the brainstem and gut that participate in nausea signaling, and broader endocannabinoid system activity is known to modulate nausea, which is part of why cannabis has a long history of antiemetic use at low doses.[5,19] Beta-caryophyllene's effect on gut wall inflammation and on mast-cell signaling is a plausible reason it might modulate the brain-gut hyperreactivity pattern that produces morning queasiness and cyclical stomach upset, but this is mechanism reasoning, not a proven clinical effect.[7,9,10]

What this means: beta-caryophyllene is included in MGB+ Calm for its broader gut-brain mechanism profile, not because a randomized trial has shown it stops vomiting. Anyone telling you the molecule has been proven to treat nausea is overstating the data.

Neuroprotection

ANIMAL MODELS · 2016 ONWARD

In a 2016 study by Ojha and colleagues, beta-caryophyllene reduced oxidative stress, neuroinflammation, and dopaminergic neuron loss in a rat model of Parkinson's disease.[12] Related work has shown effects in models of stroke, Alzheimer's-type changes, and other neurodegenerative pathways, again driven by CB2 activation and reduced microglial activation.[7,13]

What this means: the neuroprotection literature is mechanistically interesting but entirely preclinical. It is one of several reasons researchers are pursuing CB2 as a therapeutic target. It is not a basis for marketing beta-caryophyllene as a treatment for any neurological disease, and this brief does not do that.

Diabetes and metabolic inflammation

ANIMAL MODELS · REVIEWS 2020 TO 2021

A 2020 review by Hashiesh and colleagues in *Nutrients* pulled together the preclinical literature on beta-caryophyllene in diabetes and its complications. The data, almost all from rodent studies, point to improvements in inflammatory markers, glucose handling, and kidney and liver markers in diabetic animals.[20]

What this means: the diabetes evidence is preclinical and beta-caryophyllene is not a treatment for diabetes. The same anti-inflammatory mechanism that produces these effects in animal models is part of the broader case for the molecule's role in inflammation-driven conditions.

Anticancer activity

CELL CULTURE · REVIEW 2016

A 2016 review by Fidyt and colleagues in *Cancer Medicine* summarized the cell-culture work showing that beta-caryophyllene and its oxidized form affect growth and survival of several cancer cell lines.[21]

What this means: cell-culture findings are an early hypothesis-generating step, not a clinical claim. Beta-caryophyllene is not a cancer treatment.

The clinical evidence gap

HONEST SUMMARY

For all of the mechanism strength, the published randomized human trial evidence on beta-caryophyllene specifically is small. A 2016 comprehensive review by Sharma and colleagues in *Current Pharmaceutical Design* made the same observation and called for more clinical work.[22] A 2021 review by Hashiesh and colleagues reached the same conclusion. The preclinical case is strong, consistent, and mechanistically coherent. The clinical case is emerging.[7] Anyone reading this brief deserves to know the difference.

CHAPTER FIVE

About dose and timing

> *There is no formally approved human dose for beta-caryophyllene because it is sold as a food ingredient and a dietary supplement, not as a prescription drug. The published research has used a wide range of doses, and MGB+ Calm sits well inside that range.*

What the literature has used

DAILY DOSE	TYPICAL USE IN PUBLISHED RESEARCH	FORM
Animal models converted to typical human-equivalent: roughly 30 to 250 mg daily	Anti-inflammatory, anxiety-like, pain, and gut studies in rodents.[9,10,14,17]	Pure beta-caryophyllene

DAILY DOSE	TYPICAL USE IN PUBLISHED RESEARCH	FORM
50 to 300 mg daily	Most published human dietary supplement use and emerging clinical work.[7,22]	Pure beta-caryophyllene
100 mg per daily dose	The dose used in MGB+ Calm, sitting in the middle of the published human range.	Pure beta-caryophyllene
Tens of milligrams from food	Typical dietary intake from black pepper, oregano, cloves, and other culinary spices in a regular diet.[1,3]	Beta-caryophyllene as part of essential oils in food

How to read that table

The 100 mg daily dose in MGB+ Calm is in the middle of the range used in human supplement studies and toward the lower end of the animal-converted dose range. It is well above ordinary dietary intake from spices alone. The intent is steady daily exposure consistent with what the published research has tested, not a pharmacologic loading dose.

Time to effect

The animal studies that measure behavior, such as the anxiety-like and pain models, show effects within hours of a single dose. In daily-dosing studies, effects tend to be more pronounced after one to four weeks of consistent intake.[14,17] A reasonable expectation for daily support is at least four weeks of consistent daily use before judging effect on background symptoms.

With or without food

Beta-caryophyllene is fat-soluble, which is the technical way of saying it mixes with fats and oils rather than with water. Taking it with a meal that contains some fat, even a small amount, generally improves absorption of fat-soluble compounds. This is why most supplement studies have dosed beta-caryophyllene with food.[2,7]

CHAPTER SIX

Safety and what to know

> *Beta-caryophyllene has one of the cleaner safety records of any compound discussed in the cannabinoid space, in part because humans have been eating it in food for centuries and in part because, as the previous chapter explains, it does not act on the brain receptor responsible for cannabinoid dependence.*

FDA flavoring status

Beta-caryophyllene is listed by the U.S. Food and Drug Administration as a flavoring substance generally recognized as safe, abbreviated GRAS. This is the regulatory category that covers most spice-derived food and

beverage ingredients.[3] In 2022, the Research Institute for Fragrance Materials published a comprehensive safety assessment of beta-caryophyllene covering toxicity, genotoxicity, reproductive effects, and other endpoints, and concluded that current use as a fragrance and food ingredient is supported by the available data.[3]

Track record in trials and reviews

Across the preclinical and emerging clinical literature, beta-caryophyllene has been associated with few and mild adverse events at the doses studied. The 2021 Hashiesh review and the 2016 Sharma review both characterized the safety profile as favorable.[7,22] This is consistent with the long human dietary history.

What is not a side effect

Because beta-caryophyllene does not activate CB1, it does not produce the cognitive and motor effects associated with cannabis. It does not impair driving. It does not produce a high. It is not a controlled substance and is not handled by the Drug Enforcement Administration. It is not addictive in the way regular cannabinoid use can be.[1,4,7]

Drug interactions

Beta-caryophyllene is processed in the liver, partly through the same enzyme family, called cytochrome P450 enzymes, that handles many prescription drugs. In laboratory studies, beta-caryophyllene has modest interactions with several of these enzymes, which means that very high doses could in principle change the levels of certain prescription medications.[7] At the doses used in food and in standard supplements, including the 100 mg in MGB+ Calm, this is unlikely to be clinically meaningful for most people. If you take a prescription medication with a narrow therapeutic window, meaning a small difference between an effective dose and a toxic dose, your physician or pharmacist is the right person to consult before adding any new daily supplement.

Pregnancy and lactation

Beta-caryophyllene has not been formally studied in controlled pregnancy or breastfeeding trials at supplement-level doses. The dietary intake from food, which has occurred for centuries, is not the same as concentrated daily supplementation. The conservative recommendation is to avoid beta-caryophyllene supplementation during pregnancy and lactation unless your physician advises otherwise.

> **WHEN TO TALK TO YOUR PHYSICIAN FIRST**
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> - You are pregnant or nursing.
> - You take a prescription medication with a narrow therapeutic window, such as warfarin, certain seizure medications, or certain transplant medications.
> - You are managing a significant medical condition where any new supplement should be discussed with your care team.
> - You are considering giving beta-caryophyllene to a child.

CHAPTER SEVEN

The bigger picture

> *Why beta-caryophyllene sits inside a multi-ingredient formula rather than standing alone, and how to think about it if cannabinoid hyperemesis syndrome is part of your history.*

Brain-gut hyperreactivity is rarely a single problem. People who deal with morning queasiness, cyclical stomach upset, or a sensitive-stomach pattern usually have several layers contributing at once: an overresponsive immune system in the gut wall, a more reactive mast-cell population, a brain that has learned to read normal gut signals as alarming, and sometimes a history of repeated exposures that has trained the system to stay on alert. Different ingredients in MGB+ Calm act on different parts of that picture. Beta-caryophyllene contributes one mechanism, namely CB2-driven immune calming in the gut wall and lower-level dampening of the brain's own immune cells.

One careful paragraph on cannabinoid hyperemesis syndrome. CHS is a cyclical vomiting pattern that develops in some people after months or years of regular cannabis use. The biology involves changes in how CB1, the brain receptor responsible for the high, responds to repeated cannabinoid exposure, along with shifts in the stress response and the brain-gut axis.[6] Beta-caryophyllene's CB2-only profile is mechanistically distinct from those CB1 dynamics. It is not a treatment for CHS. The only proven curative step for CHS is stopping cannabis use, and that step is not optional for someone with the diagnosis. MGB+ Calm and beta-caryophyllene are positioned as daily support for the brain-gut hyperreactivity pattern, regardless of where someone is in that process, not as a substitute for the cessation work.

The same logic applies to people who have never used cannabis and have a brain-gut hyperreactivity pattern from other causes, which is most of the people this formula is built for. The mechanism does not require a cannabis history. CB2 receptors do their job in the gut wall whether or not someone has ever encountered THC.

> **HOW TO USE THIS BRIEF**
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> Bring it to your physician. Read the references. If you decide to add MGB+ Calm to your daily routine, give it at least four weeks at a consistent dose before judging effect, and track how you feel in whatever way works for you. Real data, your data, beats marketing claims from either side.

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CITATIONS

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All references are real, PubMed-indexed publications. PMID numbers are listed where assigned. DOIs are included where available for direct linking.

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