The Potential of Beta-Caryophyllene in the Prevention and Management of Metabolic Disorders

By Colonel Philip Blair, MD

Abstract

Metabolic disorders, including obesity, type 2 diabetes, and dyslipidemia, represent a significant health burden globally. Emerging research suggests that beta-caryophyllene (BCP), a natural bicyclic sesquiterpene found in various plants, exhibits promising therapeutic properties for these conditions. This paper reviews the molecular mechanisms and preclinical evidence supporting BCP's role in protecting against metabolic disorders. Key mechanisms include anti-inflammatory effects, modulation of the endocannabinoid system, and enhancement of insulin sensitivity.

Introduction

Metabolism is the process by which the body converts food into energy. Metabolic disorders or conditions result when this process is disrupted, such as having too many or too little hormones involved in metabolism, or when organs like the pancreas or liver do not work properly. Disruptions to this important process may trigger disease.

Metabolic disorders are complex and multifactorial, often involving dysregulated metabolism, chronic inflammation, and oxidative stress. They encompass a broad range of conditions characterized by abnormal processing of nutrients by the body. These disorders, including obesity, type 2 diabetes, and Metabolic-associated Fatty Liver Disease (MAFLD), formerly called non-alcoholic fatty liver disease (NAFLD), are on the rise globally and pose a significant health burden. Metabolic syndrome, also known as syndrome X or insulin resistance syndrome, is a group of conditions that often occur together, and can increase risk of serious health conditions such as diabetes, stroke, and heart disease.

Current treatment options often focus on managing symptoms rather than addressing underlying causes and pathophysiological mechanisms. Natural compounds like beta-caryophyllene offer potential alternative or complementary therapies due to their multifaceted biological activities.

Metabolic Disorders and Dysregulation

Metabolic disorders arise from disruptions in the body's ability to process carbohydrates, fats, and proteins. Common root causes include genetics, lifestyle factors (e.g., diet, physical inactivity), and chronic inflammation. These disruptions can lead to a cascade of events, including:

- **Insulin resistance:** Cells become less responsive to insulin; the hormone responsible for regulating blood sugar levels.
- **Chronic low-grade inflammation:** Inflammation contributes to insulin resistance and disrupts metabolic processes.
- **Oxidative stress:** An imbalance between free radicals and antioxidants damages cells and tissues.
- **Liver dysfunction:** Excess fat storage in the liver can impair its function.

These factors can interconnect, creating a vicious cycle that worsens metabolic health over time.

Common Types of Metabolic Disorders

Obesity

- **Definition:** Obesity is characterized by excessive fat accumulation that presents a risk to health. It is commonly assessed using the Body Mass Index (BMI), with a BMI of 30 or higher classified as obese.
- **Pathophysiology:** Obesity results from an imbalance between calorie intake and energy expenditure. It is influenced by genetic, environmental, and behavioral factors.
- **Complications:** It is a major risk factor for a variety of health issues, including cardiovascular diseases, type 2 diabetes, certain cancers, and musculoskeletal disorders.

Type 2 Diabetes Mellitus (T2DM)

- **Definition:** T2DM is a chronic condition characterized by insulin resistance and relative insulin deficiency, leading to high blood glucose levels.
- **Pathophysiology:** The interplay between genetic predisposition and lifestyle factors, such as poor diet and lack of physical activity, leads to insulin resistance. Pancreatic beta cells eventually fail to compensate with increased insulin production.
- **Complications:** Long-term complications include cardiovascular diseases, neuropathy, nephropathy, retinopathy, and increased susceptibility to infections.

Dyslipidemia

- **Definition:** Dyslipidemia involves abnormal levels of lipids in the blood, such as elevated LDL cholesterol, low HDL cholesterol, and high triglycerides.

- **Pathophysiology:** It can result from genetic factors, poor diet, obesity, and lack of exercise. It often accompanies other metabolic disorders like obesity and T2DM.
- **Complications:** Dyslipidemia significantly increases the risk of atherosclerosis, which can lead to coronary artery disease, stroke, and peripheral artery disease.

Metabolic Syndrome

- Definition: Metabolic syndrome is a cluster of conditions that occur together, increasing the risk of heart disease, stroke, and T2DM. "These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels.[1]" ("Metabolic syndrome - Symptoms and causes - Mayo Clinic")
- **Pathophysiology:** Central obesity and insulin resistance are key factors, with additional contributions from inflammation, genetic predisposition, and hormonal imbalances.
- **Complications:** The combined effect of these risk factors significantly elevates the likelihood of cardiovascular diseases and diabetes.

Understanding Metabolic Disorders and Their Impact on Health

Metabolic disorders encompass a spectrum of conditions that disrupt the body's normal metabolic processes, leading to complications such as obesity, insulin resistance, and dyslipidemia. These disorders not only impact an individual's physical health but also increase the risk of developing other chronic diseases like cardiovascular conditions and diabetes.

The rising prevalence of metabolic disorders, including obesity, type 2 diabetes, and dyslipidemia, poses a profound challenge to global health and economic systems. The prevalence of metabolic disorders is a growing concern globally, necessitating effective strategies for prevention and management. These conditions not only incur substantial direct healthcare costs but also generate significant indirect costs through loss of productivity and increased disability claims.

The economic burden extends beyond medical expenses, affecting workforce efficiency and contributing to higher insurance premiums and public health expenditures. Additionally, the social and quality-of-life impacts are considerable, with affected individuals experiencing both physical and mental health challenges. This section explores the multifaceted impact and cost

[1] *Metabolic syndrome - Symptoms and causes - Mayo Clinic*, https://www.mayoclinic.org/diseases-conditions/metabolic-syndrome/symptoms-causes/syc-20351916%C2%A0.

of metabolic disorders on society, underscoring the urgent need for effective prevention and management strategies.

1. Healthcare Costs

- **Direct Costs:** Treatment of metabolic disorders involves significant direct healthcare costs, including hospitalizations, medications, surgeries, and outpatient care. For example, in the United States, the medical costs associated with obesity alone were estimated at $147 billion annually.
- **Indirect Costs:** These include loss of productivity due to illness, disability, and premature death. Obesity and T2DM result in substantial absenteeism and reduced workforce participation.

2. **Economic Burden**

- **Workforce Impact:** Metabolic disorders reduce workforce productivity due to increased absenteeism and presenteeism (reduced productivity while at work). This impacts overall economic output.
- **Insurance and Disability Costs:** Increased prevalence of these disorders drives up health insurance premiums and disability claims, placing a strain on both private insurers and public health systems.

3. **Quality of Life**

- **Physical Health:** Individuals with metabolic disorders often suffer from chronic pain, fatigue, and physical limitations, reducing their quality of life.
- **Mental Health:** These disorders are associated with higher rates of depression, anxiety, and other mental health issues, further impacting overall well-being and productivity.

4. Social Impact

- **Healthcare Disparities:** Metabolic disorders disproportionately affect low-income and minority populations, exacerbating existing healthcare disparities. These groups often have limited access to healthy foods, safe environments for physical activity, and healthcare services.
- **Public Health Challenges:** The rising prevalence of metabolic disorders presents significant public health challenges, necessitating large-scale preventive measures and public health campaigns.

Dysfunctional Endocannabinoid System and Its Relationship to Metabolic Disorders

The endocannabinoid system (ECS) is a complex network of receptors, endogenous ligands, and enzymes involved in a variety of physiological processes, including appetite regulation, energy balance, and glucose metabolism. Dysregulation of the ECS has been implicated in the pathogenesis of several metabolic disorders, including obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. This section explores how a dysfunctional ECS contributes to the development and progression of these metabolic conditions.

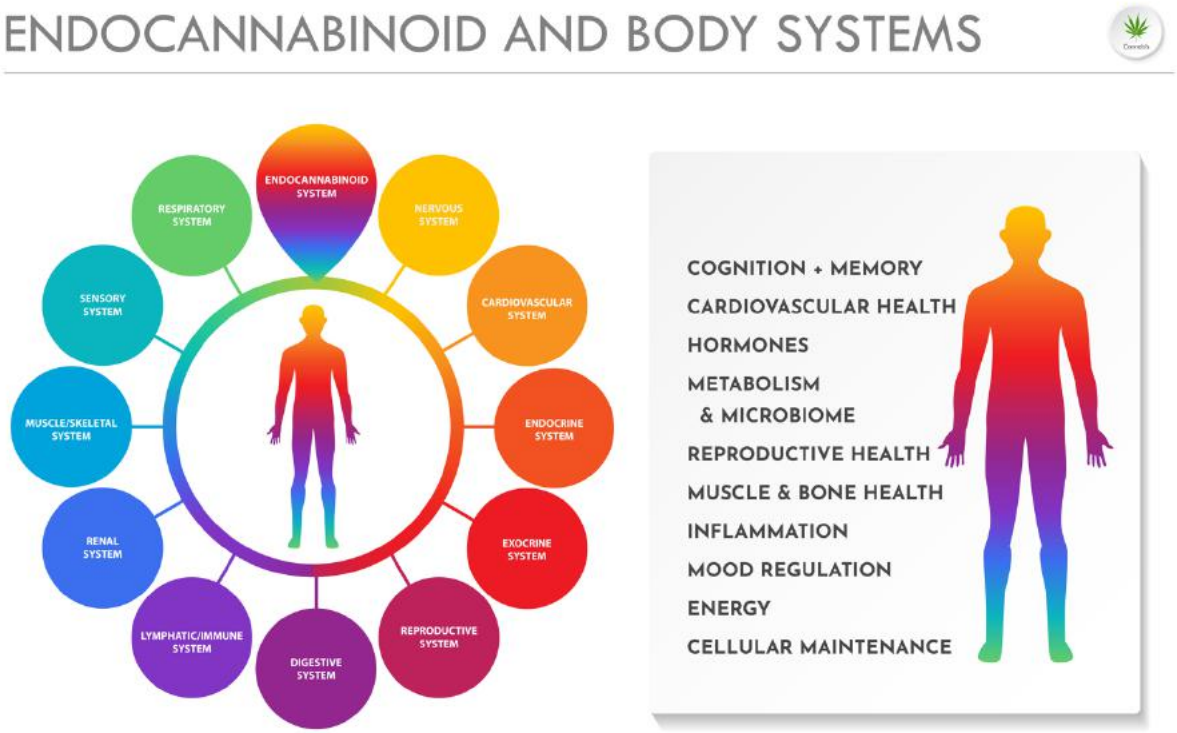


Figure 1: Endocannabinoid system plays a role in all body systems functions.[2]

Components of the Endocannabinoid System (ECS)

The Endocannabinoid System (ECS) consists of:

1. **Receptors:** The primary receptors are cannabinoid receptor type 1 (CB1) and type 2 (CB2). CB1 receptors are mainly found in the central nervous system but also in peripheral tissues such as adipose tissue and the liver. Similarly, CB2 receptors are also found throughout the central nervous system and peripheral tissues (including adipose tissue and liver) but also on every immune cell.

[2] Proprietary image owned by Blair Medical Group.

2. **Endocannabinoids:** The two main endocannabinoids made naturally by the body are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These endogenous ligands bind to and activate CB1 and CB2 receptors.
3. **Enzymes:** Enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are responsible for the degradation of AEA and 2-AG, respectively.

Dysregulation of the Endocannabinoid System

A dysfunctional endocannabinoid system plays a significant role in the development and progression of metabolic disorders through mechanisms involving appetite regulation, lipid metabolism, and insulin sensitivity. Targeting the ECS, particularly with CB1 antagonists and CB2 agonists such as beta-caryophyllene, offers promising therapeutic avenues for addressing these conditions. Further research is needed to develop effective and safe ECS-targeted therapies to combat the growing epidemic of metabolic disorders.

Dysregulation of the ECS, characterized by overactivation of CB1 receptors and altered levels of endocannabinoids, is associated with several metabolic disturbances:

Obesity

- **Mechanism:** CB1 receptor overactivation in the central nervous system leads to increased appetite and food intake. Peripherally, CB1 activation in adipose tissue promotes lipogenesis (fat storage) and reduces energy expenditure.
- **Evidence:** Studies have shown elevated levels of endocannabinoids in obese individuals, correlating with increased CB1 receptor activity. CB1 antagonists have been found to reduce appetite and body weight in both animal models and clinical trials.

Type 2 Diabetes Mellitus (T2DM)

- **Mechanism:** ECS dysregulation contributes to insulin resistance and impaired glucose homeostasis. CB1 receptor activation in the liver leads to increased gluconeogenesis and decreased insulin sensitivity.
- **Evidence:** Elevated endocannabinoid levels are observed in diabetic patients. Animal studies demonstrate that CB1 receptor blockade improves insulin sensitivity and reduces blood glucose levels.

Dyslipidemia

- **Mechanism:** Overactivation of CB1 receptors affects lipid metabolism, leading to increased triglyceride levels and altered cholesterol profiles. CB1 activation promotes lipogenesis in the liver and adipose tissue while inhibiting fatty acid oxidation.

- **Evidence:** Dyslipidemic patients often exhibit higher endocannabinoid levels. CB1 antagonists have shown to improve lipid profiles by reducing triglycerides and increasing high-density lipoprotein (HDL) cholesterol levels.

Therapeutic Implications

1. CB1 Receptor Antagonists: Targeting CB1 receptors with antagonists has shown promise in reducing obesity, improving insulin sensitivity, and normalizing lipid profiles. However, central side effects such as depression and anxiety have limited their clinical use.

2. Peripheral CB1 Antagonists: These agents aim to block CB1 receptors in peripheral tissues while minimizing central nervous system side effects. They represent a potential therapeutic approach for metabolic disorders without the adverse psychiatric effects.

3. CB2 Receptor Agonists: Activation of CB2 receptors, which are primarily anti-inflammatory, may help ameliorate metabolic inflammation and improve metabolic outcomes.

Beta-Caryophyllene and the Endocannabinoid System

Beta-caryophyllene (BCP) is a natural compound that selectively binds to CB2 receptors, providing anti-inflammatory effects without the psychoactive effects associated with CB1 receptor activation. By regulating the ECS, particularly through CB2 receptor activation, BCP shows potential in ameliorating inflammation and metabolic dysregulation seen in metabolic disorders.[3] [4] [5]

Beta-Caryophyllene: A Potential Therapeutic Agent?

Beta-caryophyllene (BCP) is a bicyclic sesquiterpene found in many familiar herbs such as cloves, hops, and allspice, as well as cannabis. It has gained interest for its diverse

[3] Li WY, Yang F, Chen JH, Ren GF. β-Caryophyllene Ameliorates MSU-Induced Gouty Arthritis and Inflammation Through Inhibiting NLRP3 and NF-κB Signal Pathway: In Silico and In Vivo. Front Pharmacol. 2021 Apr 23;12:651305. doi: 10.3389/fphar.2021.651305

[4] Jha et al. 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. Front Pharmacol. 2021 May 14;12:590201. PMID: 33967792, doi: 10.3389/fphar.2021.590201. PMID: 34054510

[5] Li H, Wang D, Chen Y, Yang M. β-Caryophyllene inhibits high glucose-induced oxidative stress, inflammation and extracellular matrix accumulation in mesangial cells. Int Immunopharmacol. 2020 Jul;84:106556. doi: 10.1016/j.intimp.2020.106556. PMID: 32416450.

pharmacological properties. Studies[6] suggest BCP may offer benefits for metabolic disorders by influencing several key pathways:

- **Anti-inflammatory:** BCP demonstrates anti-inflammatory activity by modulating the cannabinoid receptor 2 (CB2) and other inflammatory signaling pathways, potentially mitigating chronic low-grade inflammation associated with metabolic disorders.
- **Insulin sensitivity:** BCP may improve insulin sensitivity by increasing glucose uptake in muscle cells and reducing glucagon secretion from the pancreas.
- **Lipid metabolism:** BCP might influence fat storage and metabolism, potentially reducing the accumulation of fat in the liver and other tissues.
- **Oxidative stress:** BCP's antioxidant properties may help combat oxidative stress, protecting cells from damage.

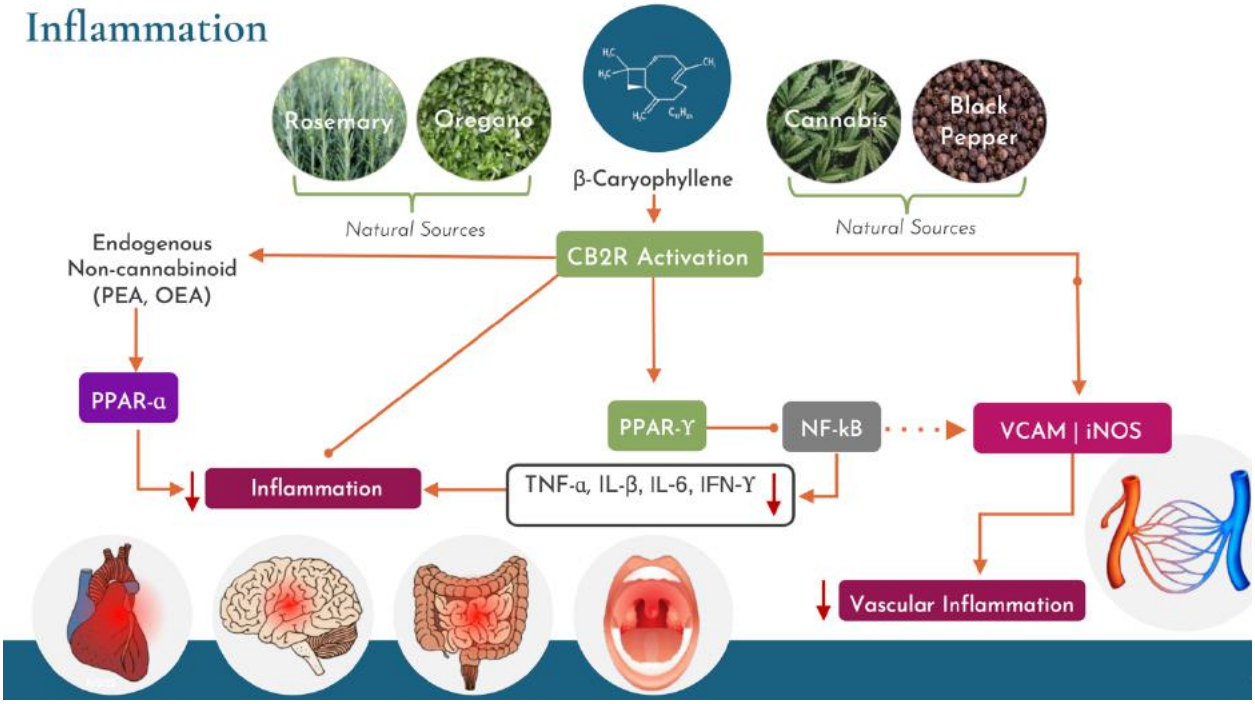


Figure 2: BCP from natural sources stimulates CB2 inducing broad anti-inflammatory effects.[7]

[6] Sharma et al. Polypharmacological Properties and Therapeutic Potential of Beta-Caryophyllene: A Dietary Phytocannabinoid of Pharmaceutical Promise. Current Pharmaceutical Design, 2016, 22, 3237-3264. doi: 10.2174/1381612822666160311115226. PMID: 26965491.

[7] Hashiesh et al. A focused review on CB2 receptor-selective pharmacological properties and therapeutic potential of β-caryophyllene, a dietary cannabinoid. Biomed Pharmacother. 2021 Aug;140:111639. doi: 10.1016/j.biopha.2021.111639. PMID: 34091179.

Research Studies on the Therapeutic Potential of Beta-Caryophyllene

Research on BCP and metabolic disorders is still in its early stages. Preclinical studies using cell and animal models have shown promising results. For example, BCP administration improved insulin sensitivity, reduced inflammation, and prevented fatty liver disease in animal models.[8] However, human clinical trials are limited. More research is needed to determine the optimal dosage, long-term safety, and efficacy of BCP in managing metabolic disorders in humans.

Scientific research exploring the therapeutic potential of beta-caryophyllene in managing metabolic disorders has yielded promising results, highlighting the compound's ability to regulate key metabolic pathways and improve metabolic health. Studies have shown that beta-caryophyllene can influence adipogenesis, the process by which fat cells develop and accumulate in the body, thereby potentially reducing obesity-related complications.

Additionally, beta-caryophyllene's interaction with CB2 receptors in the endocannabinoid system has been linked to improved insulin sensitivity, suggesting a role in managing diabetes and related metabolic conditions. The anti-inflammatory properties of beta-caryophyllene have also been shown to mitigate chronic inflammation associated with metabolic disorders, potentially reducing the risk of complications like cardiovascular disease.

Furthermore, research on beta-caryophyllene's antioxidant effects indicates its potential to combat oxidative stress, a common feature of metabolic disorders that contributes to cellular damage and disease progression. By targeting multiple aspects of metabolic dysfunction, beta-caryophyllene offers a comprehensive approach to managing these complex conditions and improving overall metabolic health.

[8] Scandiffio et al. Protective Effects of (E)-β-Caryophyllene (BCP) in Chronic Inflammation. Nutrients. 2020 Oct 26;12(11):3273. doi: 10.3390/nu12113273. PMID: 33114564

Disease	Main Metabolic Effect	Experimental Model	BCP Administration	References
Obesity and dyslipidemia	Decrease of visceral fat index. LDL and VLDL	Wistar rats fed with HFFD	30 mg/Kg b.w./day for 4 weeks by oral gavage	[10]
	Inhibition of adipogenesis	Bone marrow cells	0.1–100 μM for 3–4 days in differentiation medium	[85]
	Inhibition of lipid accumulation	Preadipocytes (3T3-L1 cells)	1 nM–10 μM for 9 days in differentiation medium	[133]
			5 or 10 μM for 6 days in differentiation medium	[134]
	Suppression of body weight gain	HFD-fed C57BL/6N mice	0.15% or 0.3% supplemented diets for 16 weeks	[134]
			0.02% or 0.2% supplemented diets for 4 and 8 weeks	[136]
	Reduction of total cholesterol, triglycerides, and LDL cholesterol levels	Hypercholesterolemic Wistar rats	1 mL/Kg b.w. for 3 days by oral gavage	[126]
			30 mg/Kg b.w./day for 4 weeks by oral gavage	[135]
Hepatic steatosis	Decrease of hepatic HMG-CoA reductase activity	Hypercholesterolemic Wistar rats	1 mL/Kg b.w. for 3 days by oral gavage	[126]
			30 mg/Kg b.w./day for 4 weeks by oral gavage	[135]
	Inhibition of palmitate-inducible lipid accumulation Downregulation of FAS and upregulation of ATGL Reduction of triglycerides. increase of FFA uptake and FFA oxidation	Human hepatocyte cell line (HepG2)	5 μM for 24h in serum free medium	[78]
			1, 10 or 100 μM for 24h	[23]
T2D	Increase of glucose uptake and GLUT4 translocation	Skeletal myotubes (C2C12 cells)	1, 10, 100 nM for 30 min in glucose and serum free medium	[133]
	Decrease of blood glucose levels and proinflammatory cytokines levels Increase of plasma insulin	Streptozotocin-Induced Diabetic rats	200 mg/Kg b.w. for 45 days by oral gavage	[138,139]
	Decrease of fasting blood glucose and fasting insulin	Wistar rats fed with a HFFD	30 mg/Kg b.w./day for 4 weeks by oral gavage	[10]
Cardiovascular disorders	Reduction of atherogenic and coronary risk index	Hypercholesterolemic Wistar rats	30 mg/Kg b.w./day for 4 weeks by oral gavage	[10]
	Protective role against isoproterenol-induced myocardial infarction	Male Sprague–Dawley rats	100 or 200 mg/Kg b.w/day for 21 days orally	[140]
	Protective effect against Doxorubicin-induced inflammation in the myocardium	Male Wistar Rats	25, 50, 100 mg/Kg b.w. for 5 days by intraperitoneal injection	[141]
			25 mg/Kg b.w. for 6 days a week for 5 weeks by intraperitoneal injection	[142]

HFFD: high fat/fructose diet; HFD: high fat diet; LDL: low density lipoprotein; HMG-CoA: Hydroxy methylglutaryl-Coenzyme A; FAS: fatty acid synthase; ATGL: adipose triglyceride lipase; GLUT4: glucose transporter 4; VLDL: very low density lipoprotein; FFA: free fatty acids.

Table 1: Evidence of a role of BCP on metabolic diseases.[9]

Obesity

Obesity, a common metabolic disorder, is characterized by an excessive accumulation of body fat and is associated with various health risks, including heart disease, stroke, and type 2 diabetes. Insulin resistance, another hallmark of metabolic disorders, impairs the body's ability to regulate blood sugar levels, leading to elevated glucose levels and increased risk of diabetes. Dyslipidemia, characterized by abnormal lipid levels in the blood, can contribute to atherosclerosis and cardiovascular disease.

Obesity is defined as an abnormal or excessive accumulation of fat in the body that affects overall health. Excess adiposity is a risk factor for mortality and its deleterious effects increase susceptibility to chronic diseases. Obesity remains a significant health problem worldwide.

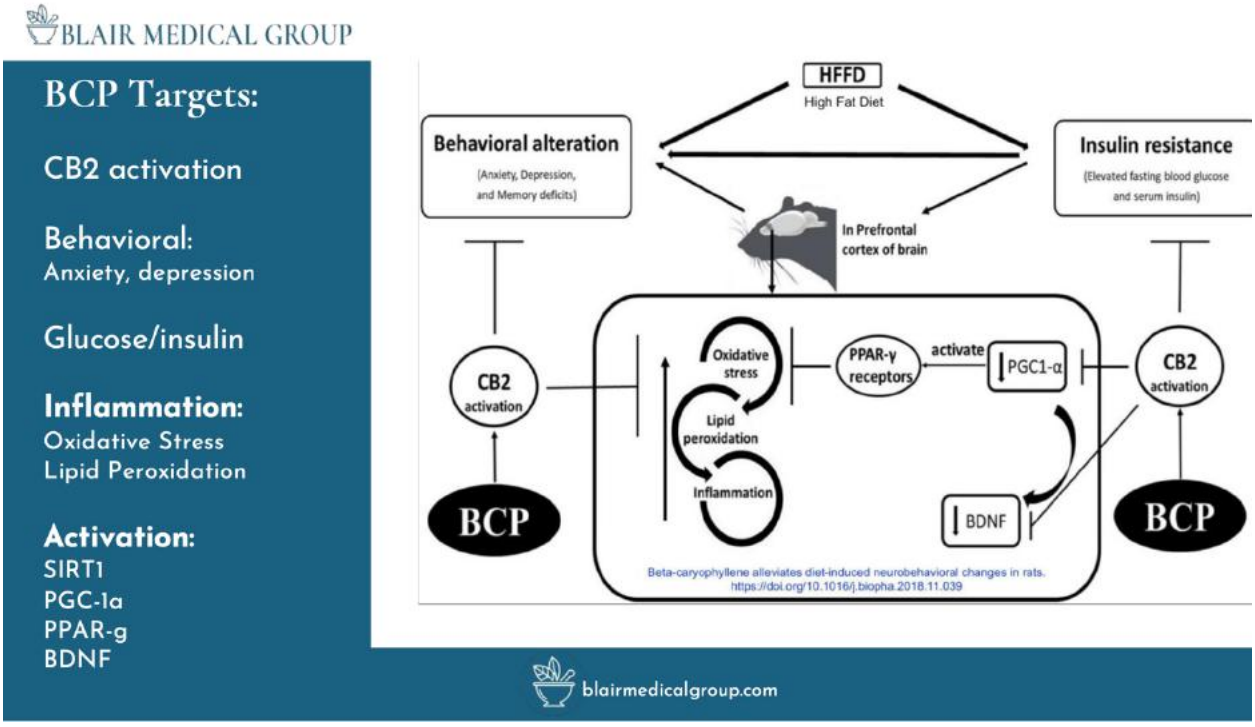
Nutraceuticals have attracted attention as they contain a wide variety of molecules with therapeutic properties against this disease. The CB2 receptor has been described as an anti-obesity target. BCP is a dietary cannabinoid and a natural agonist for the CB2 receptors of the endocannabinoid system. Several studies provide insight into the pharmacological and therapeutic potential of BCP. Recent studies reveal that BCP treatment modulates inflammation

[9] Scandiffio et al. Protective Effects of (E)-β-Caryophyllene (BCP) in Chronic Inflammation. Nutrients. 2020 Oct 26;12(11):3273. doi: 10.3390/nu12113273. PMID: 33114564

through crosstalk between cannabinoid receptor type 2 (CB2) and peroxisome proliferator-activated receptor gamma (PPAR-γ).[10]

BCP treatment protects against eWATs adipocytes (white fat) from hypertrophy during HFD consumption (high fat diet), which is relevant considering that hypertrophy is a trigger for inflammatory signals that sustain obesity. Furthermore, we found that BCP protected against the development of macrovesicular steatosis. Activation of CB2 is highly related to the control of hepatic steatosis.

Obesity and metabolic diseases are associated with a loss of metabolic homeostasis and an increase in the inflammatory response. BCP consumption promotes a shift between the activation of anti-inflammatory pathways, such as those related to PPAR-g mediated by CB2R, and the inhibition of proinflammatory pathways that involve NF-kB signaling, which may be amplified through inhibition of the Toll receptor pathway. These mechanisms are redundant in tissues of metabolic importance, where BCP acts locally and at a systemic level to reduce metaflammation, known as a chronic, low-grade inflammatory state originating from metabolic cells in response to excess of nutrients.



[10] Irrera et al. β-Caryophyllene Mitigates Collagen Antibody Induced Arthritis (CAIA) in Mice Through a Cross-Talk between CB2 and PPAR-γ Receptors. Biomolecules. 2019 Jul 31;9(8):326. doi: 10.3390/biom9080326. PMID: 31370242

Figure 3: BCP improves behavior, insulin resistance, and neuroprotection by activating CB2R that counteracts high-fat-fructose-diet induced inflammation and depletion of BDNF and PGC1a to activate PPAR-γ nuclear receptors in the prefrontal cortex of the brain.[11]

How β-Caryophyllene Works in Appetite Regulation

The Three Mechanisms of Appetite Involve:

- Physiologic pathway (homeostatic)
- Reward pathway (addictive)
- Inflammatory pathway

Beta-caryophyllene addresses all three pathways.

Physiologic Pathway of Appetite – Gut hormones involved in appetite

- GLP1
- CB2R
- Adiponectin
- Leptin
- Pro-opio-melanocortin (POMC)
- TLR4 inhibition

β-caryophyllene Regulates Appetite Hormones

Obesity incites airway resistance in asthmatic subjects by up-regulating macrophages causing the release of pro-inflammatory cytokines from white adipose tissue into the general circulation thereby promoting oxidative stress in the respiratory tract. In a study of fattened mice and human visceral adipose tissue, BCP was found to inhibit macrophage polarization (M2 to M1) by up-regulating adiponectin, GLP-1 and down-regulating leptin with several cytokines. In addition, thermogenesis and activation of the melanocortin pathway stimulated the browning of adipose tissue which plays a crucial role in energy homeostasis. It does this by generating heat from the hydrolysis of triglycerides by means of the uncoupling protein (UCP-1) in mitochondria. In lean subjects, brown adipose tissue (BAT) plays a crucial role in energy homeostasis by thermogenesis.

[11] Youssef DA, El-Fayoumi HM, Mahmoud MF. Beta-caryophyllene alleviates diet-induced neurobehavioral changes in rats: The role of CB2 and PPAR-γ receptors. Biomed Pharmacother. 2019 Feb;110:145-154. doi: 10.1016/j.biopha.2018.11.039. PMID: 30469079.

BCP treated groups experienced a weight loss effect within a few days of treatment and thereafter until termination of the study. It was suggested that this effect was due to an elevated expression of POMC (proopiomelanocortin), a pituitary polypeptide precursor for normal energy homeostasis. Under BCP influence, this hormone was elevated in a dose dependent manner reducing the daily food intake in subject mice and correlating with POMC levels. Furthermore, GLP-1 was found to be significantly elevated in the BCP treaty groups, along with energy, expenditure and oxygen production, implying considerable functional mitochondrial up regulation.[12]

Appetite Effects of BCP

- Up-regulates GLP-1, UCP-1 & Adiponectin
- Up-regulates POMC (pro-opio-melanocortin) reducing food intake
- Down-regulates inflammatory nuclear receptor NFkβ, TNFa, IL-1b, IL-6
- Down-regulates leptin
- Shifts macrophage from M1 to M2 [anti-inflammatory] in adipose

Reward Pathway of Appetite

CB2R Agonists Inhibit Reward Pathway

- Opioids, Cocaine, Nicotine, Meth
- Alcohol
- Benzodiazepine (valium like)
- THC
- Food (sugar)

[12] Jiayao et al. Mechanisms of weight-loss effect in obese mice by the endogenous cannabinoid receptor 2 agonist beta-caryophyllene. Obes Res Clin Pract. 2023 Nov-Dec;17(6):499-510. doi: 10.1016/j.orcp.2023.10.004. PMID: 37919194.

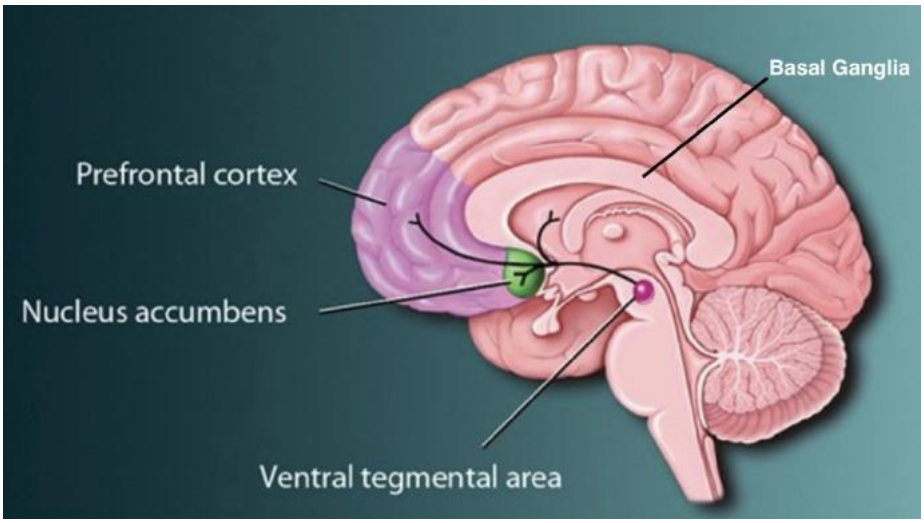


Figure 4: Major brain areas involved in addiction.[13]

In the reward pathway, the ventral tegmental area of the mid-brain is stimulated by addictive substance, sends a signal (release of dopamine) to the Nucleus accumbens, and then, through the process of dopamine reuptake, ends this signal. The signal also connects with the prefrontal lobe and the basil ganglia. The prefrontal lobe uses executive functions to decide whether to inhibit or accept the pleasurable impulse. This can lead to motivation for repeating the experience or acquiring more of the substance that represents addiction. Furthermore, a tolerance to the substance or activity can develop leading to higher or more frequent dosing.

BCP activates the CB2R expression that occurs in the cell bodies of dopaminergic neurons. The CB2R counteracts the dopamine release in the nucleus accumbens induced by drugs, prevent drug reward and reduces the reinforcing effects of abused substances. However, direct antagonism of dopaminergic receptors did not show promising results for addiction treatment. The ability of BCP to target different receptors able to modulate dopaminergic tonus on VTA provides a rationale for the development of addiction pharmacotherapy based on this unique terpene. Plus, CB2R agonists do not induce the psychiatric side effects related to the blockade of CB1R. Thus, CB2R activation by BCP could represent a novel mechanism for drug addiction treatment.[14]

[13] https://biobunch.blogspot.com/2016/03/biology-behind-addiction.html
[14] Asth et al. Effects of β -caryophyllene, A Dietary Cannabinoid, in Animal Models of Drug Addiction. Curr Neuropharmacol. 2023;21(2):213-218. doi: 10.2174/1570159X20666220927115811. PMID: 36173065

Prefrontal Lobe – Executive function:

- Inhibition of impulse
- Weighing consequences
- Reflective decision

Imbalances in the brain reward system are commonly shared across food and drug addiction. CB2R overexpression decreased CB1 and opioid receptor activity in the ventral tegmental area (VTA), a key component of the reward pathway in addiction physiology. Remarkably, BCP prevented or reversed behavioral changes resulting from drug exposure. But CB2 alone is insufficient to inhibit this process and it requires other signaling molecules in combination: PPARα & PPAR-γ. CB2R is a potential therapeutic target for eating control and the comorbid emotional effects associated with food addiction. Through its pleiotropic mechanisms BCP decreases reward and drug-seeking pathways, reduces anxiety and sensitivity to other drugs of abuse like alcohol, opioids, nicotine, and THC. It can be used as a substitute or alternative intervention to cannabis.[15]

Inflammatory pathway

Beta-caryophyllene regulates appetite by reducing inflammation, promoting a healthy gut microbiota, and enhancing adiponectin activity. These actions collectively support balanced hunger signals and healthy eating patterns. One of the keyways BCP helps in appetite regulation is through its anti-inflammatory properties. Chronic inflammation is often linked to metabolic disturbances and altered appetite control. By reducing inflammation, BCP can help normalize appetite and improve overall metabolic health. Moreover, BCP's influence on gut health contributes to appetite regulation. It promotes a healthy balance of gut microbiota, which plays a crucial role in the body's ability to regulate hunger and satiety signals. A balanced gut microbiome can improve the production of hormones like ghrelin and leptin, which are essential for hunger regulation. Additionally, BCP has been shown to enhance the activity of adiponectin, a hormone that regulates glucose levels and fatty acid breakdown. Increased adiponectin levels can lead to improved energy balance and reduced appetite.

Obesity is associated with a low-grade inflammatory state and adipocyte hyperplasia/hypertrophy. Inflammation inhibits the “browning” of white adipose tissue. CB2R agonists counteract inflammation by inhibiting pro-inflammatory cytokine while

[15] Galaj et al. Beta-caryophyllene inhibits cocaine addiction-related behavior by activation of PPARα and PPARγ: repurposing a FDA-approved food additive for cocaine use disorder. Neuropsychopharmacology. 2021 Mar;46(4):860-870. PMID: 33069159.

stimulating the release of anti-inflammatory cytokines (IL-4, IL-8, IL-10, IL-13) and suppressing macrophage and their migration to adipose tissue proving the potential use of these agents in the treatment of obesity.[16] Furthermore, CB2R activation stimulates reduced food intake and induces an anti-obesity effect in mice potentially reversing all the obesity-related effects.[17]

In a comprehensive study of obesity β-caryophyllene, a well-established CB2 agonist, improved total body weight, fasting glucose levels, oral-glucose tolerance, insulin tolerance and fasting triglycerides. At the same time BCP prevents adipocyte hypertrophy and liver steatosis. BCP also modulated the levels and expression of immune response factors including adiponectin, leptin, insulin, interleukin-6, tumor necrosis factor-a, and Toll-like receptor-4.

TLR4 is a transmembrane protein expressed in immune cells mainly of myeloid origin, including monocytes, macrophages and dendritic cells representative of the pattern recognition receptors (PRR), so named for their ability to recognize evolutionarily conserved components of microorganisms. The main ligands for TLR4 are lipopolysaccharides (LPS), the major components of the outer membrane of Gram-negative bacteria and some Gram-positive bacteria. The fact that BCP counteracts the inflammatory impact of TLR4 provides significant potential for BCP therapeutic potential.[18]

Diabetes

Epidemiological Evidence of a Dysregulated Endocannabinoid System in Diabetes Mellitus

The presence of such a complex signaling system comprising the expanded Endocannabinoid System and their many metabolic enzymes and targets together, and several endocannabinoid system-related lipid mediators considerably complicates the development of selective pharmacological and genetic tools to understanding the metabolism controls of the endocannabinoid system. Even more complicated are its exploitation towards new therapies against metabolic disorders.

Increasing evidence suggests that an overactive endocannabinoid system (ECS) contributes to the development of diabetes. By promoting energy intake and storage while impairing both

[16] Wu et al. CB2R agonist JWH-133 attenuates chronic inflammation by restraining M1 macrophage polarization via Nrf2/HO-1 pathway in diet-induced obese mice. Life Sci. 2020 Nov 1;260:118424. doi: 10.1016/j.lfs.2020.118424.
[17] Rossi et al. Cannabinoid Receptor 2 as Ant obesity Target: Inflammation, Fat Storage, and Browning Modulation. J Clin Endocrinol Metab. 2016 Sep;101(9):3469-78. doi: 10.1210/jc.2015-4381. PMID: 27294325.
[18] Franco-Arroyo et al. β-Caryophyllene, a Dietary Cannabinoid, Protects Against Metabolic and Immune Dysregulation in a Diet-Induced Obesity Mouse Model. J Med Food. 2022 Oct;25(10):993-1002. doi: 10.1089/jmf.2021.0166. PMID: 35792574.

glucose and lipid metabolism the ECS facilitates inflammation and exerts pro-apoptotic effects leading to pancreatic islets damage. The ECS also indirectly participates in beta cell failure through activation of the Nlrp3 inflammasome in infiltrating macrophages, resulting in beta cell apoptosis. Furthermore, hyperglycemia triggers additional ECS up regulation culminating in a vicious circle. The ECS also controls diabetes-induced oxidative stress, inflammation, fibrosis and subsequent tissue injury in target organs for diabetic complications.

Specifically, CB1 in the CNS, signals reward circuits leading to a craving for highly palatable food. In peripheral organs CB1 activates anabolic metabolic pathways that favor fat storage. CB1 receptor activation induces endoplasmic reticulum stress resulting in elevated hepatic levels of long-chain ceramides that in turn inhibit insulin signaling. In white adipocytes, CB1 receptor activation increases fatty acid synthesis, enhances triglyceride accumulation and blocks lipolysis, whereas in brown adipose tissue, or healthy fat, the CB1 receptor counteracts the mitochondrial uncoupling protein that burns ATP for heat.

In addition, the CB1 receptor increases hepatic lipogenesis and impairs mitochondrial oxidative phosphorylation in skeletal muscle. In cardiometabolic diseases, increased plasma levels of the endocannabinoids AEA and 2-AG along with increased CB1 receptor expression were seen in obesity and diabetes that strongly correlated with adverse coronary circulatory events. Furthermore, in a secondary action CB1 receptor can form a heteromeric complex with the insulin receptor and inhibits insulin signaling by blocking insulin receptor kinase activity. Thus, the ECS in diabetes is a nightmare of dysfunction but with some hope of reversal with the activation of CB2R that show equal and opposite effects.[19]

[19] Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol. 2016 Apr;173(7):1116-27. doi: 10.1111/bph.13226. PMID: 26076890

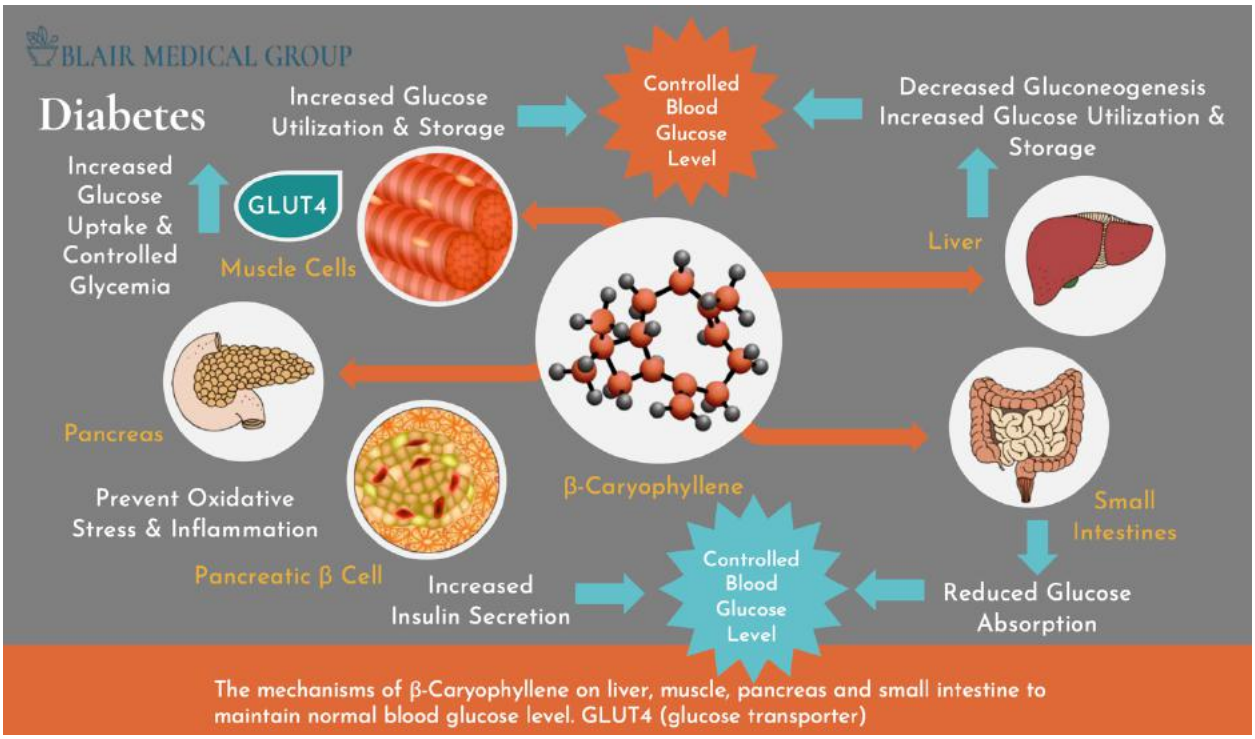


Figure 5: Beta-caryophyllene acts on liver, muscle, pancreas, and small intestine to maintain normal blood glucose level.[20]

Enzymes

BCP enhances secretion of insulin and restores glucose homeostasis by modulating the most important enzymes involved in glucose utilization and production in target tissues. Oral BCP in diabetic rats reduced carbohydrate metabolic enzymes including hexokinase, pyruvate kinase, glucose-6-phosphate dehydrogenase, gluconeogenic enzymes, stimulating glycogen synthase and inhibiting glycogen phosphorylase which is the key regulatory enzymes that catalyze glycogen synthesis. BCP brought all enzymes to near normal levels along with reducing blood glucose and improving insulin levels in plasma.[21]

Insulin Sensitivity

Insulin resistance (IR) and obesity predispose diseases such as diabetes, retinopathy, nephropathy, cardiovascular and neuropathy disorders. Beta-caryophyllene (BCP), a natural

[20] Hashiesh et al. Therapeutic Potential of β-Caryophyllene: A Dietary Cannabinoid in Diabetes and Associated Complications. Nutrients. 2020 Sep 28;12(10):2963. doi: 10.3390/nu12102963. PMID: 32998300
[21] IBID

sesquiterpene, exerts neuroprotective, anxiolytic and antidepressant effects via its selective agonism to cannabinoid receptor 2 (CB2R). This study was designed to examine the role of BCP

in improving diet-induced metabolic (insulin resistance), neurobehavioral (anxiety, depression and memory deficit), and neurochemical (oxidative, inflammatory and neurotrophic factor) variations in the prefrontal cortex of obese rat brains. BCP alleviated HFFD-induced IR, oxidative-stress, neuroinflammation and behavioral abnormalities. BCP corrected for the anxiolytic, antioxidant and anti-inflammatory effects, glycemic parameters, antidepressant and memory disturbances via CB2R & PPAR-γ.[22]

The primary defect for T2DM before the β-cell dysfunction and hyperglycemia is hyperinsulinemia induced by insulin resistance. Insulin activates the receptor (IR), which in turn recruits insulin receptor substrate (IRS) proteins that stimulate the transport of intracellular GLUT4 to the plasma membrane for glucose transport intracellularly. High levels of insulin over time creates a tolerance effect requiring greater amounts of insulin in response to hyperglycemia. During insulin resistance conditions such obesity, hypertension, and type 2 diabetes, insulin-mediated glucose transport is reduced in the skeletal muscle. In the present study, rats fed a high fat and fructose diet with induced diabetes showed impairment in glucose utilization. BCP significantly increased the glucose uptake and oxidation in muscle due to restored insulin signaling mechanisms thereby increasing GLUT4 availability and function. BCP also corrected the altered levels of blood glucose and serum insulin levels as well as the lipid parameters, oxidative stress markers, and antioxidant enzymes.[23]

Metabolism

BCP's anti-inflammatory properties are crucial for metabolic health. Chronic inflammation is a significant factor in metabolic disorders such as obesity and type 2 diabetes. By reducing inflammation, BCP helps mitigate the metabolic disturbances associated with these conditions.

Moreover, BCP influences lipid metabolism. Research indicates that BCP can enhance the activity of adiponectin, a hormone that regulates glucose levels and fatty acid breakdown.[24]

---

[22] Youssef DA, El-Fayoumi HM, Mahmoud MF. Beta-caryophyllene alleviates diet-induced neurobehavioral changes in rats: The role of CB2 and PPAR-γ receptors. Biomed Pharmacother. 2019 Feb;110:145-154. doi: 10.1016/j.biopha.2018.11.039. PMID: 30469079.

[23] Bandaru et al. Effect of β-Caryophyllene on oxidative stress, glucose metabolism in the skeletal muscle of high fat diet and fructose-induced type-2 diabetic adult male rats. Bioinformation. 2023 Apr 30;19(4):417-422. doi: 10.6026/97320630019417. PMID: 37822828.

[24] β-caryophyllene ameliorated obesity-associated airway hyperresponsiveness. 2021. https://doi.org/10.1016/j.phymed.2021.153610

Elevated adiponectin levels promote better lipid metabolism, energy expenditure, and reduced fat accumulation, thus supporting metabolic health.

In the pancreas CB1R, but not CB2R, mRNA is found in human β-cells whereas CB2R transcripts were found only in α-, δ-, and ε-cells but more so than CB1R transcripts. In this organ, CB2R has a yin-yang relationship with CB1R structurally and functionally in the context of cell types. While activation of CB2R has general anti-inflammation effects, cell type specific CB1R deletion in β-cells, myocytes, and hepatocytes has anti-inflammatory effects in mice. CB2R activation in the immune system is also thought to be anti-inflammatory and pro-tolerance and therefore may aid in preventing autoimmune-mediated self-destruction as in pre-symptomatic or honeymoon phase of T1DM.[25] In fact, activation of CB2R has been shown to reduce formation of leukocyte diapedesis by downregulation of integrins and selectins that promote adhesion, trans-endothelium migration and protect from tissue damage by reducing infiltration CD4+ T-lymphocyte subset of T helper 17 (Th17) cells. Furthermore, CB2R appears to promote immune tolerance by a pro-autophagy function. In this process excessive insulin is mispresented in the endosome-lysosome pathway. CB2R suppresses regulatory T cells that block self-reactivating T cells from exiting into the circulation.[26]

Anti-Hyperglycemic Oxidative Effects

Chronic hyperglycemia induces advanced glycation end products that link with advanced glycation end products-receptors (AGE-RAGE) causing oxidative stress, inflammasome activation (NLRP3), and tissue fibrosis. This process plays an important part in the development and progression of diabetic cardiomyopathy (DCM). The present study aimed to investigate the role of CB2 receptor activation in the murine model of DCM by BCP, as a dietary phyto-cannabinoid. BCP significantly improved glucose tolerance, reduced insulin resistance and enhanced serum insulin level. BCP restored phosphorylation of the diabetes caused dysfunctional cardiac contractile protein troponin I.

BCP increased PI3K/AKT phosphorylation, decreased expression of Keap1 which upregulated antioxidant enzymes (HO1, SOD2) that was mediated by stimulation of Nrf2 signaling. The AGE-RAGE signaling pathway in the heart of DCM mice was greatly modified by BCP based on evidence of decreased levels of AGEs, RAGE and NOX4. Additionally, NLRP3 inflammasome activation was downregulated along with the inflammatory cytokines: IL-1b and IL-18

[25] Liu et al. Anti-Inflammatory and Pro-Autophagy Effects of the Cannabinoid Receptor CB2R: Possibility of Modulation in Type 1 Diabetes. Front Pharmacol. 2022 Jan 18;12:809965. doi: 10.3389/fphar.2021.809965. PMID: 35115945

[26] IBID

expression. Collectively, these results demonstrate that inhibition of AGE-RAGE by BCP rescued diabetic mice from DCM.

Through a CB2 receptor dependent mechanism complication caused by reducing oxidative damage, fibrosis, and inflammasome activation attributed to upregulation of PI3K/AKT/Nrf2 signaling, repression of EndMT transition, and inhibition of NLRP3 inflammasome activation were entirely mitigated.[27]

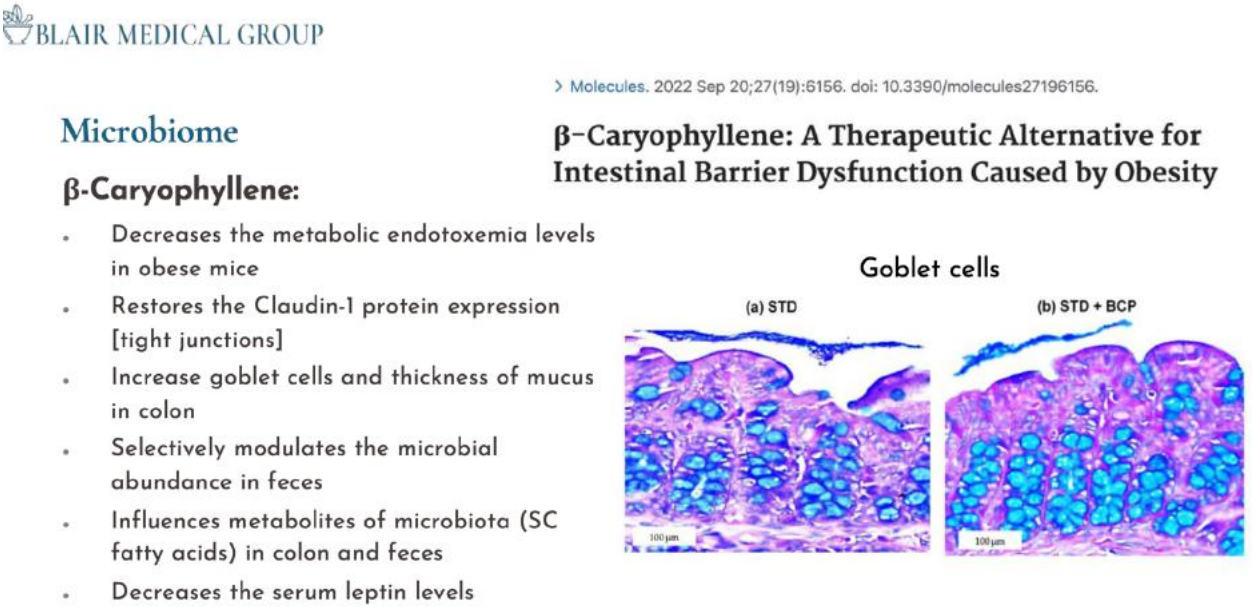


Figure 6: BCP enhances intestinal barrier function by promoting mucus, tight junctions, hormones, and microbiome modification.[28]

Microbiome

BCP also affects the gut microbiota, which plays an essential role in metabolic processes. It helps maintain a healthy gut microbiome balance, improving gut barrier function and reducing systemic inflammation.[29] This gut health improvement is directly linked to better metabolic outcomes, as a healthy microbiome supports efficient nutrient absorption and energy balance.

[27] HEBAALLAH et al. β-caryophyllene, a CB2 Receptor Agonist Alleviates Diabetic Cardiomyopathy via Inhibiting AGE/RAGE-Induced Oxidative Stress, Fibrosis, and Inflammasome Activation. Journal of Pharmacology and Experimental Therapeutics June 1, 2023, 385 (S3) 303; DOI: https://doi.org/10.1124/jpet.122.146170
[28] Rodríguez-Mejía et al. β-Caryophyllene: A Therapeutic Alternative for Intestinal Barrier Dysfunction Caused by Obesity. Molecules. 2022 Sep 20;27(19):6156. doi: 10.3390/molecules27196156. PMID: 36234691
[29] IBID

In a comprehensive study of intestinal barrier dysfunction caused by obesity the authors evaluated BCP at the mucosal layer, the basement membrane and the microbiome under dietary variations. In this case, obesity was induced with a high fat diet leading to exacerbation of metabolic and inflammatory processes in the gut. β-Caryophyllene Increased the number of goblet cells and the thickness of mucus in the colon of mice thereby increasing protection of the first line of gut defense. BCP induced the tight junction protein Claudin-1 restoring intestinal barrier function that was depleted by the high fat diet (HFD).

In the metabolic endotoxemia caused by increased amounts of lipopolysaccharide BCP decreased the levels to near normal. BCP also significantly increased acetic, propionic, and total fatty acid concentrations in the feces of HFD rats while showing a tendency for increasing butyrate. The fermentation metabolites (acetic, propionic, and butyric acid) from dietary fibers, is associated with various benefits by stimulating multiple hormonal and neural pathways, appetite control, energy homeostasis, reduction of body weight, among others.

In addition, butyrate upregulates tight junction proteins, regulates gut mucus barrier repair, and maintains Th17/Treg balance that is key immune ratio in food/protein sensitivities. Finally, BCP restored the phyla Akkermansia and Bacteroidetes that have decreased the high fat diet group as well as in dysbiosis. Metabolites released by Akkermansia promoted the proliferation of Firmicutes, which convert acetate and lactate into butyrate and co-exist in the mucosa decreasing the symptoms in inflammatory bowel disease.

Mitochondria

Another key factor in BCP metabolic effects are found in mitochondria. This study comparing BCP to a GLP-1 drug, liraglutide, for weight loss used high-sugar and high-fat diets with propylthiouracil (T3/T4 hormone inhibitor) to establish hyperlipidemic obese mice. BCP was found to activate CNR2, SIRT1/PGC-1α/PPARγ signaling pathway, and SIRT1/AMPK signaling pathway, and participate in lipid and energy metabolism to exert its dyslipidemia-improving and weight-loss effect.

BCP showed a superior weight-lowering effect than liraglutide (10% vs 3%) when administered for 4 weeks along with a host of other benefits.[30]

And, with respect to energy metabolism, BCP's stimulation of SIRT1 and PGC-1a enhanced mitochondrial biogenesis and function. Sirtuin-1 (SIRT1) stimulates downstream targets

[30] Jiayao et al. Mechanisms of weight-loss effect in obese mice by the endogenous cannabinoid receptor 2 agonist beta-caryophyllene. Obes Res Clin Pract. 2023 Nov-Dec;17(6):499-510. doi: 10.1016/j.orcp.2023.10.004. PMID: 37919194

involved in biogenesis of mitochondria and antioxidant defense. SIRT1 also suppresses inflammatory responses by inhibiting the NLRP3 inflammasome in vascular endothelial cells. SIRT1 activation is neuroprotective in diabetic neuropathy in part by enhancing mitochondrial bioenergetics and autophagy.

Additional studies have also demonstrated that AMPK and SIRT1 improves mitochondrial function through the PGC-1α and Nrf2 axis. Thus, BCP by its pleiotropic targets counteracts appetite (GLP-1), inflammation (NLRP3), neuropathy (SIRT1), and mitochondrial dysfunction (PGC-1a & Nrf2).[31]

Uniquely, the authors of the following study suggest BCP contributes to both an insulin-mimetic and physical exercise-mimetic role on muscular glucose metabolism. BCP displayed a stimulatory role also for PDH (pyruvate dehydrogenase) and the TCA cycle (tricarboxylic acid cycle) enzyme activity. Impaired PDH activity and reduced TCA cycle flux in skeletal muscle have been associated with obesity and type II diabetes. Skeletal muscle is the primary site of glycolytic products (lactate, pyruvate, alanine), which are biomarkers of chronic metabolic disease.

While CB1 in skeletal muscle has been associated with a reduction in glucose uptake and fatty acid oxidation, CB2 receptor stimulation in myotubes by BCP promoted lipid oxidation through SIRT1/PGC1α pathway that plays a major role in lipid metabolism, obesity and insulin resistance. BCP-CB2 receptor enhances all the steps of glucose metabolism in skeletal myotubes. Stimulatory effects were evidenced in glucose uptake, glycolytic enzymes activity, PDH, and TCA cycle enzyme activity, electron transport chain, and ATP synthesis.

Thus, BCP can be said to match the physiological signaling properties of insulin and exercise muscle stimulation accurately and effectively with possible restoration of considerable health in obesity and diabetes.[32]

In a 2020 study on mast cell activation and hyper responsive airways in obesity, it was found that BCP had a dramatic effect on metabolic hormones and inflammatory signaling. Obesity was induced with a high fat and fructose diet and systemic and cutaneous anaphylactic-like shock

[31] Khan et al. Cannabidiol and Beta-Caryophyllene Combination Attenuates Diabetic Neuropathy by Inhibiting NLRP3 Inflammasome/NFκB through the AMPK/sirT3/Nrf2 Axis. Biomedicines 12, no. 7: 1442. https://doi.org/10.3390/biomedicines12071442

[32] Geddo et al. Plant-Derived Trans-β-Caryophyllene Boosts Glucose Metabolism and ATP Synthesis in Skeletal Muscle Cells through Cannabinoid Type 2 Receptor Stimulation. Nutrients. 2021 Mar 12;13(3):916. doi: 10.3390/nu13030916. PMID: 33809114

was induced with a special compound. A broad range of inflammatory and anti-inflammatory substances were evaluated as well as hormones.

β-caryophyllene Regulates Metabolism:

- Increases mitochondria numbers and performance
- Stimulates mitochondrial ATP production but decreases ROS
- Up-regulates mito-UCP-1 (uncoupling protein-1)
- Stimulates lipolysis (fat release for oxidative phosphorylation)
- Increased energy expenditure (weight loss)
- Up-regulates GLP-1 & Adiponectin
- Browning of white adipose tissue (eWAT -> BAT)

In this study BCP inhibited mast cell degranulation and key cytokines including TNFa, IL-b1, IL-6 while stimulating the anti-inflammatory cascade of neurotrophic factor two (NRF2) and heme oxygenase-1 (HO-1). Remarkably BCP inhibited the polarization of macrophages from the dormant M2 to the inflammatory M1 phase. In addition, BCP accelerated the browning of fat by stimulating mitochondrial uncoupling protein (UCP-1). Furthermore, BCP inhibited oxidative stress, cytokines, adipokines, and reactive oxygen species. Hormonally, BCP regulated the proopiomelanocortin (POMC) pathway, that regulates glucose homeostasis, appetite, and inhibits tumor necrosis factor production. Furthermore, BCP infiltrated through the cell membrane and stimulated NRF2, a well recognized anti-inflammatory signaling molecule. And finally, BCP inhibited the allergic reaction and airway hyper-responsiveness characterized in this obesity model. The authors suggest that by suppressing the IgE-independent pathway towards allergic response BCP may be used in case of pseudo-allergic reactions.[33]

Beta-caryophyllene also suppressed pseudo-allergic reactions – activation of Adiponectin and Nrf2/HO-1 signal pathways:

- Increased anti-inflammatory cytokines
- Inhibited anaphylaxis-like shock
- Inhibited mast cell degranulation and histamine release

[33] Pathak et al. Crosstalk between AdipoR1/AdipoR2 and Nrf2/HO-1 signal pathways activated by β-caryophyllene suppressed the compound 48/80 induced pseudo-allergic reactions. Clin Exp Pharmacol Physiol. 2021 Nov;48(11):1523-1536. doi: 10.1111/1440-1681.13555. PMID: 34314522

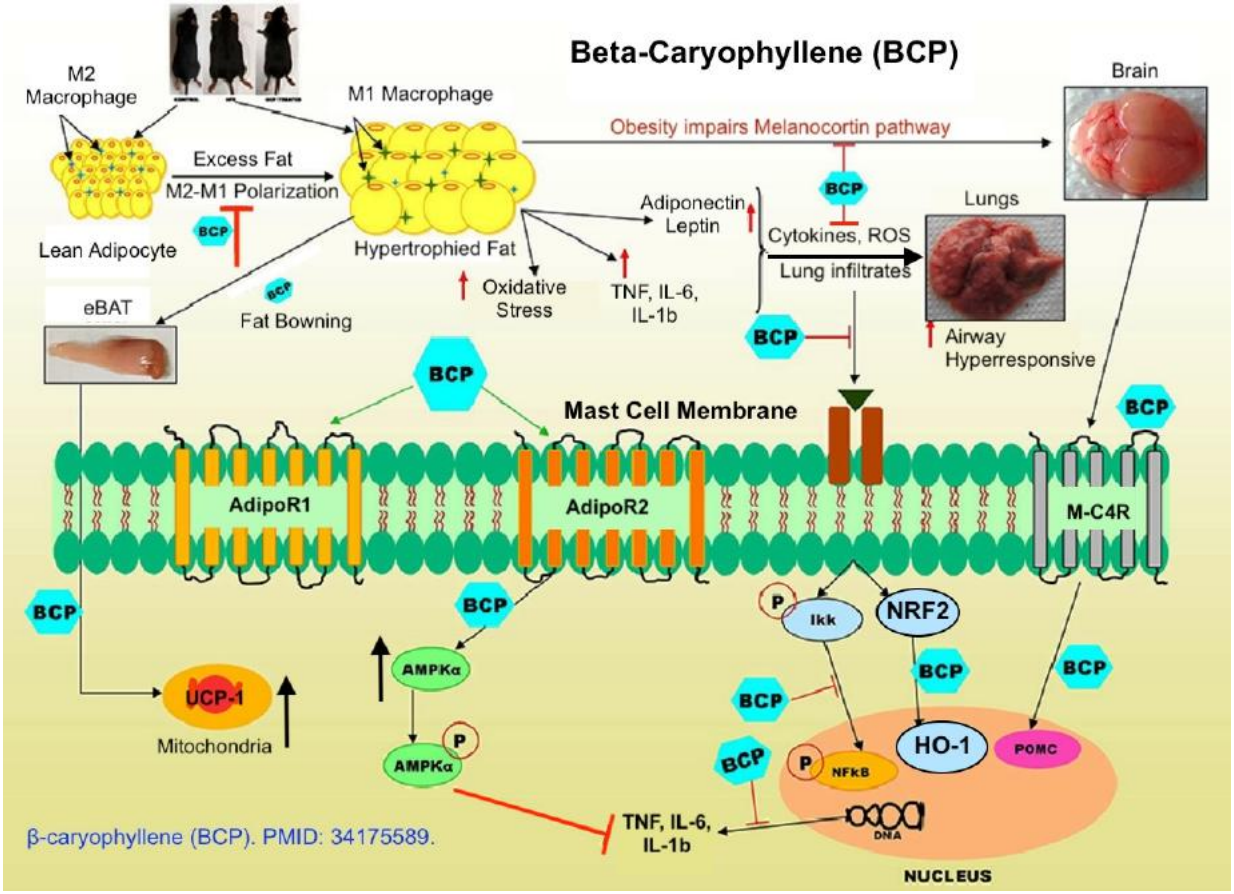


Figure 7: BCP regulates metabolism through multiple mechanisms and inhibits allergic response from mast cells.[34]

Weight Loss

BCP has been shown to influence lipid metabolism. Studies indicate that BCP can enhance the activity of adiponectin, a hormone involved in regulating glucose levels and fatty acid breakdown. Increased adiponectin levels promote energy expenditure and reduce fat accumulation.

Additionally, BCP exhibits potential in modulating gut microbiota, which plays a crucial role in maintaining metabolic health. By promoting a healthier balance of gut bacteria, BCP can improve gut barrier function and reduce systemic inflammation, thereby supporting weight management.

[34] IBID

In summary, beta-caryophyllene supports weight loss through anti-inflammatory effects, modulation of lipid metabolism, and improvement of gut microbiota composition.[35] These multifaceted actions make BCP a promising compound for further exploration in the context of weight management and metabolic health.

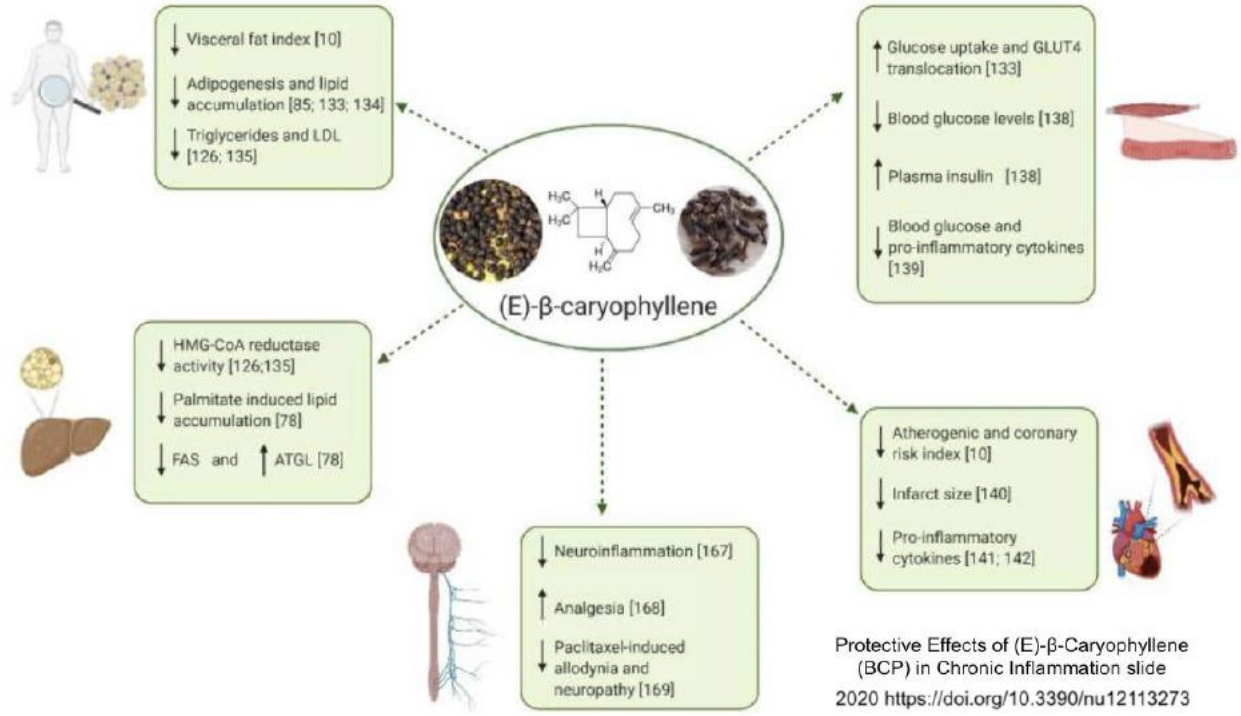


Figure 8: BCP protects against chronic inflammation.[36]

β-caryophyllene and appetite regulation:

- Decrease in food craving
- Improved energy
- Decreases body fat
- Increases fat breakdown
- Increases mitochondria, reduces dysfunction
- Modulates hormones adiponectin, leptin, GLP-1

Fasting Mimicry

Many of the metabolic effects of fasting are mimicked by BCP. Fasting is a tried-and-true method for weight loss and metabolic change. It does so by restricting calories, stimulating glycogen release, and mobilizing fat stores for metabolic action. In addition, fasting is

[35] Scandiffio et al. Protective Effects of (E)-β-Caryophyllene (BCP) in Chronic Inflammation. Nutrients. 2020 Oct 26;12(11):3273. doi: 10.3390/nu12113273. PMID: 33114564

[36] IBID

associated with appetite suppression, lipolysis, anti-inflammatory effects, and gut rest leading to improvements in digestive health. After a short period of time fasting generates ketone bodies in the form of β-hydroxybutyrate (BHB), acetoacetate and acetone, with BHB being most significant. BHB offers a host of modulation properties to the microbiome, enterocytes of the gut, hormones, neurological signaling, immunity and even DNA changes. BCP, although it does not directly stimulate production of BHB, has been shown to modulate all the same body systems by similar mechanisms.

Both BCP and BHB: [37] [38]

- Suppress appetite
- Activate metabolic nuclear receptors PPAR-γ coactivator-1α (PGC-1α) & PPARα
- Promote uncoupling protein 1 (UCP1) in mitochondria for generating heat energy
- Stimulate glucagon-like peptide-1 (GLP-1, think Ozempic) & adiponectin (weight-reduction effects)
- Promote mitochondrial biogenesis, energy production, decrease oxidation by produces (ROS, SOD, Catalase, HO-1, Nrf2)
- Decrease Glycolytic flux (Insulin, Glycation, K* channels)
- Decrease neurologic excitement Glutamate/GABA ratio (GAD65, GAD67)
- Suppress Inflammation by inhibiting key receptors (NF-KB, NLRP3)
- Modulate Epigenetic: DNA acetylation/deacetylation
- Changes in Gut Microbiome (Akkermansia muciniphila)
- Upregulation of autophagy pathways for longevity: SIRT2, FOXOs, PGC1α

BCP can achieve these benefits without fasting, although results appear to be enhanced with a low carbohydrate or ketogenic diet. Furthermore, BCP protects against muscle loss by increasing glucose absorption through GLUT4 receptors and stimulating mitochondria glycolysis in muscle tissue. In muscle cells glycolysis promotes mTORC1 signaling and protein synthesis, improving skeletal muscle mass.[39] Thus, BCP appears to navigate the maze of metabolic disease complexities with particularly dexterity but without adverse effects.

---

[37] BHB: Amiri et al. The effects of sodium butyrate supplementation on the expression levels of PGC-1α, PPARα, and UCP-1 genes, serum level of GLP-1, metabolic parameters, and anthropometric indices in obese individuals on weight loss diet: a study protocol for a triple-blind, randomized, placebo-controlled clinical trial. Trials 24, 489 (2023). https://doi.org/10.1186/s13063-022-06891-9

[38] BCP: Youssef DA, El-Fayoumi HM, Mahmoud MF. Beta-caryophyllene protects against diet-induced dyslipidemia and vascular inflammation in rats: Involvement of CB2 and PPAR-γ receptors. Chem Biol Interact. 2019 Jan 5;297:16-24. doi: 10.1016/j.cbi.2018.10.010. Epub 2018 Oct 19. PMID: 30343038

[39] Geddo et al. Plant-Derived Trans-β-Caryophyllene Boosts Glucose Metabolism and ATP Synthesis in Skeletal Muscle Cells through Cannabinoid Type 2 Receptor Stimulation. Nutrients 2021, 13, 916. https://doi.org/10.3390/nu13030916

Future Research and Developments in the Field of Beta-Caryophyllene and Metabolic Disorders

As research on beta-caryophyllene and its effects on metabolic disorders continues to advance, future developments hold the potential to uncover new therapeutic applications and enhance our understanding of this natural compound. Ongoing studies exploring the molecular mechanisms by which beta-caryophyllene interacts with metabolic pathways can provide insights into novel treatment strategies and targeted interventions for metabolic disorders.

Moreover, clinical trials investigating the efficacy of beta-caryophyllene in managing specific metabolic conditions, such as diabetes or dyslipidemia, may offer valuable data on its safety and effectiveness in diverse populations. Collaborative research efforts between scientists, healthcare professionals, and manufacturers can accelerate the translation of research findings into practical solutions for individuals struggling with metabolic disorders.

In addition, advancements in technology and formulation techniques may lead to the development of innovative beta-caryophyllene delivery systems that enhance bioavailability and therapeutic efficacy. Nanoparticle-based formulations, controlled-release mechanisms, and combination therapies incorporating beta-caryophyllene with other bioactive compounds could revolutionize the treatment landscape for metabolic disorders and improve patient outcomes.

By staying informed about the latest research findings and emerging trends in the field of beta-caryophyllene and metabolic disorders, individuals can make informed decisions about incorporating this natural compound into their health and wellness routines. The future holds great promise for beta-caryophyllene as a key component in the management and prevention of metabolic disorders, paving the way for a healthier and more vibrant future for individuals seeking natural solutions to support their metabolic health.

Incorporating Beta-Caryophyllene into Your Diet and Lifestyle

Integrating beta-caryophyllene into your diet and lifestyle can be a simple yet effective way to leverage its metabolic health benefits. Adding beta-caryophyllene-rich foods like cloves, black pepper, and basil to your meals can introduce this compound into your daily nutrition. Incorporating these flavorful ingredients into recipes not only enhances the taste of your dishes but also provides a natural source of beta-caryophyllene to support metabolic function.

In addition to dietary sources, essential oils containing beta-caryophyllene can be used aromatically or topically to experience its therapeutic effects. Diffusing essential oils with beta-caryophyllene or applying them to the skin with a carrier oil can promote relaxation, reduce

stress, and potentially support metabolic health. These aromatic and topical applications offer convenient ways to enjoy the benefits of beta-caryophyllene in your daily routine.

Supplements containing beta-caryophyllene are another option for individuals looking to increase their intake of this beneficial compound. Beta-caryophyllene supplements, available in various forms like capsules or tinctures, offer a concentrated dose of the terpene for targeted support. When choosing supplements, it is essential to consult with a healthcare provider to determine the appropriate dosage and ensure compatibility with your overall health and wellness goals.

Tips for Managing Metabolic Disorders Naturally with Beta-Caryophyllene

When incorporating beta-caryophyllene into your routine to manage metabolic disorders naturally, consider the following tips to optimize its benefits and support your overall health:

1. **Balanced Diet**: Focus on a balanced diet rich in whole foods, fruits, vegetables, and lean proteins with the avoidance of refined carbohydrates and seed oil to support metabolic function and provide essential nutrients for overall health.
2. **Regular Exercise**: Engage in regular physical activity, such as cardio, strength training, or yoga, to promote metabolism, improve insulin sensitivity, and maintain a healthy musculature.
3. **Stress Management**: Practice stress-reducing activities like meditation, deep breathing, or mindfulness to lower cortisol levels, reduce inflammation, and support metabolic health.
4. **Adequate Sleep**: Prioritize quality sleep to regulate hormones, promote cellular repair, and enhance metabolic function for overall well-being.
5. **Hydration**: Stay hydrated by drinking an adequate amount of water daily to support digestion, metabolism, and detoxification processes in the body.

By incorporating these lifestyle strategies alongside beta-caryophyllene supplementation or dietary sources, individuals can take a holistic approach to managing metabolic disorders and promoting long-term metabolic health naturally.

Case Studies

Case Study #1: 55 yo woman with anxiety, depression, and PTSD weighed 297 lbs at the beginning of therapy with BCP. Her anxiety was so bad that her throat would close and no sound would come out. Over the period of 4 weeks she had significant relief of her anxiety and could now speak about her PTSD trauma and ask for help. She was not dieting but reported that

she was now able to avoid “sweets” and carbohydrates. She also reported she had lost 21 pounds during this period saying that “BCP is going to make all the difference in the world”.

Case Study #2: 64 yo construction worker from Florida had chronic neuropathic pain from shingles infection for 2 years. He was using gabapentin, oxycodone and benzodiazepines to alleviate his symptoms. He weighed 309 lbs at the beginning of BCP therapy. His pain was relieved immediately and over the course of two weeks he discontinued all pain medication. In efforts to lose weight prior to starting BCP he performed intermittent fasting with marginal success. However, within the first month of treatment he lost 30 pounds and during the 6 months following he has reduced his weight by over 75 pounds taking BCP twice daily with a vigorous work schedule. He has found that his appetite is well-controlled and his energy is high. Furthermore, his neuropathic pain has significantly subsided even when he skips BCP doses.

Conclusion: Unlocking the Potential of Beta-Caryophyllene in Managing Metabolic Disorders

In conclusion, beta-caryophyllene emerges as a promising natural compound with significant potential for managing metabolic disorders like obesity, diabetes, and dyslipidemia. Through its interactions with the endocannabinoid system and modulation of key metabolic pathways, beta-caryophyllene offers a holistic approach to improving metabolic health and addressing the root causes of these complex conditions.

By incorporating beta-caryophyllene-rich foods, essential oils, or supplements into one's daily routine and adopting healthy lifestyle practices, individuals can harness the therapeutic benefits of this terpene to support their metabolic well-being. While further research and clinical studies are needed to elucidate the full extent of beta-caryophyllene's effects on metabolic disorders, the current evidence suggests a promising future for this natural compound in revolutionizing the treatment and prevention of metabolic conditions.

MEDICAL DISCLAIMER

The information contained in this article is for educational purposes only. This content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Always consult with a qualified and licensed physician or other medical care provider and follow their advice without delay regardless of anything read in this white paper.

Read our blog article about BCPlus Immunity Blend at http://bit.ly/3GEvl6b

Townsend newsletter readers can get 10% off their purchase of BCPlus Immunity Blend capsules. Use code TOWNSEND at blairmedicalgroup.shop

About the author Dr. Philip Blair

Retired Colonel (Dr.) Philip Blair, MD, is a board-certified Family Physician licensed in Washington State. He graduated from West Point in 1972 and attended University of Miami School of Medicine and trained as a family physician. He had assignments in Georgia, Louisiana, Washington, Oklahoma, Texas, Hawaii, Kansas, Italy, Korea, Germany, and the Gulf War.

In 2014 he was introduced to cannabidiol. Since then, he has treated several thousand patients with non-psychoactive cannabinoids in his clinical practice. Currently he is researching the terpene β-Caryophyllene as an alternative to medicinal cannabis. Blair Medical Group SPC provides physician-formulated BCP products that everyone can use to support, restore, and activate the endocannabinoid system as well as addressing chronic pain and inflammation-related conditions. BCPlus products are available at blairmedicalgroup.shop. Dr. Blair is also available for private consultations and speaking engagements. Please contact him at DrBlairMD@icloud.com and (360) 991-4791.