BLAIR MEDICAL GROUP

Research Summary

Cardiovascular Diseases (CVDs) and Beta-Caryophyllene

Potential Applications of Endocannabinoid Treatment Modalities

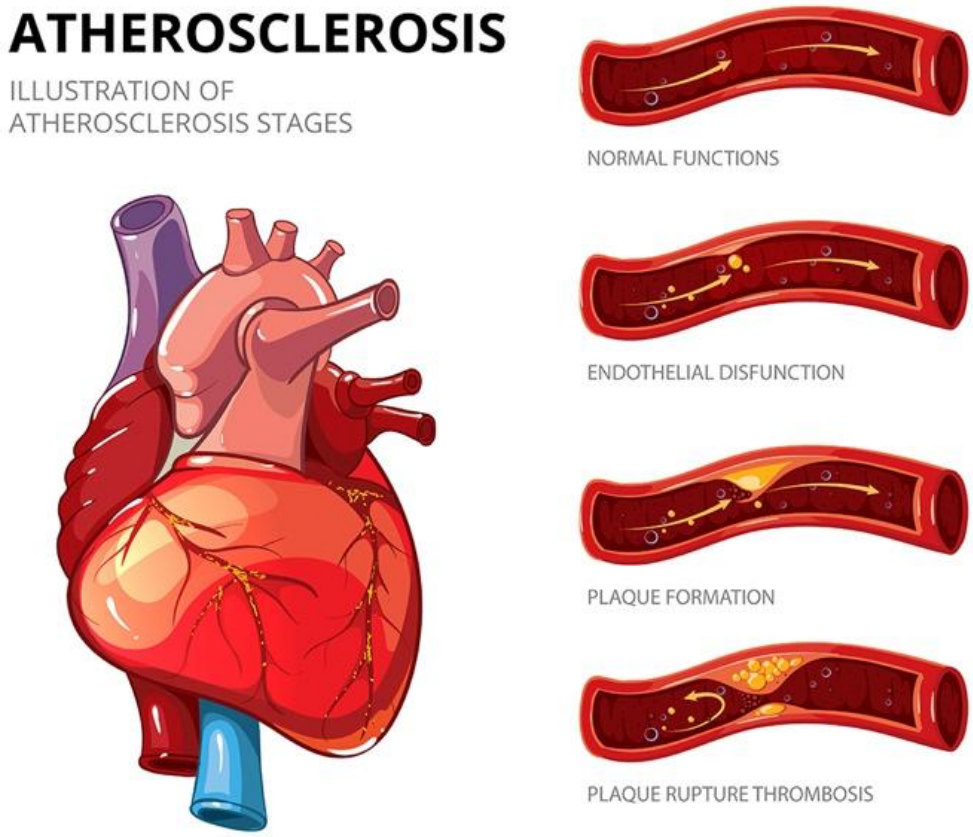
Presented by retired Colonel (Dr.) Philip Blair

Research Overview

Cardiovascular diseases (CVDs) are the leading cause of death globally. 17.9 million people die from CVDs, an estimated 32% of all deaths worldwide.[1] Cardiovascular diseases are disorders of the heart and blood vessels. They include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other related conditions.

Heart and blood vessel diseases are the leading causes of death for people in the United States. About 697,000 people in the United States died from heart disease in 2020—that's 1 in every 5 deaths.

Many of these disorders are related to the building up of plaque in the walls of the arteries, a process called atherosclerosis. This buildup of plaque narrows the arteries, making it more difficult for the blood to flow through. Plaque can also rupture (break open). When it does, a blood clot can form on the plaque, blocking the flow of blood, causing a heart attack or stroke.



Some risk factors for heart disease can't be controlled, such as your age or family history. But you can take control of other risk factors to reduce your risk, including:

- Track your blood pressure and cholesterol levels.
- Make healthy diet choices. Being overweight, obese, or having diabetes raises your risk of heart disease.
- Quit smoking.
- Get regular physical exercise.
- Manage your stress levels and find healthy ways to cope with stress.
- Get good-quality sleep.
- Limit alcoholic drinks.

Beta-Caryophyllene: Providing Additional Protection from Inflammation and Cardiovascular Disease

BCP activates the endocannabinoid type 2 receptor (CB2R) which regulates every immune cell in the body and produces a cardio-protective effect. It also activates many receptors throughout the body that regulate pain and metabolism including nuclear metabolic receptors PPAR-α & PPAR-γ, opioid receptors, TRPV1, serotonin 5-HT1a, nerve growth factor TrkA even as it inhibits inflammatory receptors TLR4 and NLRP3 inflammasome. BCP research experiments indicate potential protection against atherosclerosis and heart attacks.

BCPlus is beta-Caryophyllene (BCP), a natural essential oil extract found in many nutritious herbs such as black pepper, cloves, and hemp. FDA has approved BCP as safe food flavoring. BCPlus liposomal is tasty, water soluble and extremely bioavailable in concentrations of 30mg/mL with usual servings of 1/2mL twice daily. It is effective in adults and children with no significant side effects and offered in 60 mL bottles and sample sizes at http://www.blairmedicalgroup.shop

Phytocannabinoid: BCP is a full-fledged cannabinoid substance acting on several parts of the body's extended endocannabinoid system including nuclear receptors, enzymes, and transport molecules. BCP affects the endocannabinoid system by increasing the tissue levels of 2-Arachidonoylglycerol (2-AG), N-arachidonoylethanolamide (AEA), Palmitoylethanolamide (PEA), Oleoylethanolamide (OEA), and the expression of CB receptors, increases the expression of PPAR-α receptor, spares the basal tissue levels of docosahexaenoic acid (DHA), decreases the plasmatic levels of AEA and reverses the increase of plasmatic lipoperoxides. **Anti-Inflammatory Effect of Beta-Caryophyllene doi: 10.3390/ijms23073633.**

BCP is found in many vegetables and fruits and offers many health benefits augmenting the body's natural endocannabinoid system. **Therapeutic Potential of β-Caryophyllene: A Dietary Cannabinoid in Diabetes and Associated Complications. doi:10.3390/nu12102963**

Observed Therapeutic Effects of Beta-Caryophyllene

Because of its strong CB2R activating properties Beta-Caryophyllene (BCP) has been shown to be cardioprotective, hepatoprotective, neuroprotective, nephroprotective, gastroprotective, chemopreventive, antioxidant, anti-inflammatory and immuno-modulatory. The available evidence suggests that BCP can be an important candidate of plant origin endowed with CB2R selective properties that may provide a solid rationale for its pharmacotherapeutic application and development like a drug.

Additionally, BCP can be promoted as a nutraceutical and functional food for general health and well-being. A focused review on CB2 receptor-selective pharmacological properties and therapeutic potential of β-caryophyllene, a dietary cannabinoid. 2021. doi: 10.1016/j.biopha.2021.111639

Furthermore, given the wide availability in edible plants and dietary use, with safety, and no toxicity, BCP can be promoted as an effective alternative to Cannabis or Hemp-derived products.

ATHEROSCLEROSIS

BCP protects against atherosclerosis and myocardial damage by regulating endothelial vascular lining, monocyte & macrophage activation, and preserving intra-cellular mitochondria & endoplasmic reticulum function. In myocardial damage mitochondria are frequently compromised in function and numbers leading to heart failure. In addition, oxidative stress causes impairment of the endoplasmic reticulum that serves to detoxify breakdown proteins and fragments which otherwise become sources of inflammation.

BCP specifically inhibits receptors that are well known for stimulating the release of inflammatory cytokines from immune cells: NLRP3 inflammasomes and Toll-Like receptors. Inflammasomes play an important role in the induction of inflammatory cascades via the activation of pro-inflammatory cytokines and the induction of programmed cell death. NLRP3 inflammasome is activated by cholesterol crystals and induces IL-1β-production in the processes of atherosclerosis and diabetes. It also protects the body against congestive heart failure and hepatotoxicity from dietary causes. No toxicity was seen.

β-caryophyllene possesses antioxidant properties, preventing oxidative damage to fat molecules and maintaining high levels of glutathione, a key molecule that neutralizes reactive oxygen species (ROS) that stimulates excessive cholesterol synthesis. ROS are very toxic to mitochondria causing a breakdown in membrane and energy transfer. They're very toxic in the endoplasmic reticulum as well. Thus, this compound can be used as an attempt to prevent or reduce atherosclerosis in hypercholesterolemic rats. **β-caryophyllene reduces atherogenic index and coronary risk index in hypercholesterolemic rats. 2017 PMID 28411027**

β-caryophyllene inhibited cardiac hypertrophy, tachycardia, oxidative stress, apoptosis, and endothelial dysfunction and protected the heart in experimental MI. In this study BCP counteracted all the derogatory effects of high doses of an adrenaline like drug that causes heart attacks in many people because of multiple derangement of heart tissue particularly in blood.

β-Caryophyllene inhibits Fas-receptor and caspase-mediated apoptosis signaling pathway and endothelial dysfunction in experimental myocardial infarction. 2021. PMID 34816538

MYOCARDIAL FUNCTION

It is well established that isoproterenol causes impaired cardiac function, elevated cardiac marker enzymes, and enhanced oxidative stress markers. This drug promoted lysosomal dysfunction along with activation of NLRP3 inflammasomes and toll-like receptor & NFκB thus raising proinflammatory cytokines. Mitochondrial dysfunction was followed by endoplasmic reticulum stress signaling and cardiac cell death as well as altered autophagy (waste product elimination). Isoproterenol also triggered dyslipidemia and homeostasis malfunction. BCP showed protective effects on all biochemical and molecular parameters analyzed including microscopic studies of preserved cardiomyocytes and cell organelles. **β-Caryophyllene, a natural bicyclic sesquiterpene attenuates β-adrenergic agonist-induced myocardial injury in a cannabinoid receptor-2 dependent and independent manner. 2021. doi: 10.1016/j.freeradbiomed.2021.01.046.**

The combined application of β-caryophyllene and another terpene, cineole, synergistically protected mice against structural and functional myocardial damage and cardiac hypertrophy caused by toxic doses of isoprenaline via the PI3K/AKT/mTOR pathway that controls cell cycling and metabolism. **Combination of 1,8-cineole and beta-caryophyllene synergistically reverses cardiac hypertrophy. doi: 10.1016/j.bioorg.2022.105823**

β-caryophyllene significantly reversed the infarct size, ECG, and blood pressure alterations, correcting for the isoproterenol (adrenaline-like) induced myocardial infarction; it also notably diminished inflammatory markers, such as TNF-α, IL-Iβ, and NFκB (controlling DNA transcription of cytokine production). Furthermore, BCP inhibited Toll-like receptors 2-4 and their adaptor proteins with a substantial reduction in inflammatory mediator levels. **β-Caryophyllene as a Potential Protective Agent Against Myocardial Injury: The Role of Toll-Like Receptors. Molecules 2019, doi: 10.3390/molecules24101929.**

CHOLESTEROL MANAGEMENT

It is widely thought that cholesterol is an important factor in cardiovascular disease. Dietary or lifestyle indiscretions may lead to distortions in the body's production of cholesterol containing lipid particles. These particles are at risk for oxidation reactions from ROS. And these oxidized particles have been implicated in atherosclerosis. β-Caryophyllene reduced total cholesterol, triglycerides, and LDL (low density lipoprotein) like the reference drug simvastatin. β-Caryophyllene treatment inhibited the HMG-CoA reductase activity, by preventing the increase in ROS and regulates the antioxidant system. β-caryophyllene could be used to treat high cholesterol disorders because it lowers cholesterol, triglycerides and LDL while protecting the liver against lipid damage and improving the hepatic antioxidant defense system. Furthermore, β-caryophyllene could avoid statin drug side effects like renal failure, muscle pain and memory disorders. **Hypolipidemic effect of β-caryophyllene to treat hyperlipidemic rats. [compared to simvastatin]. 2017. doi: 10.1007/s00210-016-1326-3.**

β-caryophyllene lowered serum total cholesterol, LDL and the atherogenic index and increased HDL. β-caryophyllene ameliorated liver injury as evidenced by decreasing hepatomegaly, intracellular fat droplet steatosis and hepatic marker enzymes ALT & AST (alanine aminotransferase and aspartate aminotransferase) while BCP increased the antioxidant enzyme superoxide dismutase (SOD). In addition, BCP showed inhibition of the activity of hepatic HMG-CoA which synthesizes cholesterol. **Hypocholesterolemic effect of β-caryophyllene in rats fed cholesterol and fat enriched diet. 2018. doi: 10.3164/jcbn.17-3.**

Trans-caryophyllene (TC) treatment prevented attachment of monocytic cells to blood vessel lining cells and macrophage infiltration to the aortic surface as well as reduced total serum levels of cholesterol and triglycerides. These monocytes invade the lining of coronary arteries, try to digest oxidized LDL cholesterol but fail and become foam cells as part of the obstructive plaques. TC inhibits the induction of vascular cell adhesion molecule-1 (VCAM-1) mediated by the JAK2/STAT1/IRF-1 pathway dependent on

activation of CB2R. By blocking these mechanisms TC prevents atherosclerosis. **Inhibitory effect of trans-caryophyllene (TC) on leukocyte-endothelial attachment. 2017. doi: 10.1016/j.taap.2017.06.016.**

CARDIO AND VASCULAR

Beta-Caryophyllene serves a protective function for heart and vascular systems.

β-caryophyllene considerably ameliorated all biochemical, transmission electron microscopic, molecular, and histological parameters evaluated in myocardial infarcted rats. Thus, β-caryophyllene inhibited oxidative stress and lysosomal leakage, preserved the heart, and heart lysosomal structure, and prevented the intrinsic pathway of myocardial cell death. Moreover, β-caryophyllene exhibited anti-oxidative stress, anti-lysosomal damage, anti-apoptotic, and myocardial infarct size limiting effects. **β-caryophyllene modulates isoproterenol-induced myocardial infarcted rats. DOI: 10.1016/j.ejphar.2022.175181**

β-Caryophyllene modulates numerous molecular targets by altering their gene expression, signaling pathways or through direct interaction. Various pharmacological activities such as cardioprotective, hepatoprotective, gastroprotective, neuroprotective, nephroprotective, antioxidant, anti-inflammatory, antimicrobial and immune modulator have been reported in experimental studies. It has shown potent therapeutic promise in neuropathic pain, neurodegenerative and metabolic diseases. **Polypharmacological Properties and Therapeutic Potential of Dietary Phytocannabinoid of Pharmaceutical Promise. DOI: 10.2174/1381612822666160311115226**

INFLAMMATION

Beta-Caryophyllene is proven to help relieve and mitigate chronic inflammation.

Information is the final common pathway for most pathologic diseases. Controlling inflammation is of paramount importance for the protection of all body systems. Experimental results show the ability of β-Caryophyllene to reduce pro-inflammatory mediators thus improving or making better chronic pathologies characterized by inflammation and oxidative stress, in particular metabolic and neurological diseases. On the other hand, this substance actually increases anti-inflammatory cytokines such as IL-10 & IL-4 in regulating the immune cells. β-Caryophyllene shows beneficial effects on obesity, non-alcoholic fatty liver disease/nonalcoholic steatohepatitis liver diseases, diabetes, cardiovascular diseases, pain, and other nervous system disorders. **Chronic Inflammation: Protective Effects of (E)-β-Caryophyllene in chronic Inflammation. (2020). doi: 10.3390/ nu12113273**

1. Cardiovascular Diseases – World Health Organization https://www.who.int/health-topics/cardiovascular-diseases

Additional references:

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- Women's Heart Health Part 2: Keys to Preventing Heart Disease and Managing Heart Health for Women
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Research summaries courtesy of Dr. Philip Blair, MD; BlairMedicalGroup.shop; 360.991.4791

ABOUT DR. PHILIP BLAIR

Retired Colonel (Dr.) Philip Blair 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.

After retiring from the Army in 1996 he managed workers injuries and provided primary care above the Arctic Circle in Alaska. He also provided services in Kodiak Island and Newfoundland, Canada.

In 2000 he became Vice President for Disease Management at AWAC, Inc., a medical management company, where he co-developed a highly successful interventional approach to chronic kidney disease. In 2011 he formed his own company consulting for employer-based health insurers and providing a revolutionary style of chronic disease management achieving success in over 75% of patients with diabetes, kidney disease, heart disease and metabolic syndrome. Now, he is developing products to support health.

About Blair Medical Group

Dr. Philip Blair has been providing healthcare consulting as the "AbleDoc" for years.

When Blair Medical Group developed our 'Abledoc's Apothecary' product line, we wanted to convey the trust and familiarity of the corner drugstore/apothecary, where the pharmacist knew everyone by name, and personally cared about their health. Blair Medical Group and our "Abledoc's Apothecary" brand is proud to build on this community tradition.

We are dedicated to supporting our partners and healthcare communities around the world.

We follow our core values in all aspects of our work:

Integrity – Compassion – Reliability – Quality – Commitment

Our vision is to make our nutritional supplements, products, and programs universally accessible, creating a healthier, revitalized world for everyone.

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