RESEARCH PAPER

B-Caryophyllene: Pharmacological Profile, Mechanisms, And Emerging Therapeutic Applications

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ABSTRACT

Beta-caryophyllene (BCP), a bicyclic sesquiterpene widely distributed in medicinal and nutritional plants such as black pepper, clove, hops and cannabis. Due to its special chemical structure, BCP possesses a variety of pharmacological activities against inflammation, oxidation, immunity, microorganism infection and gastrointestinal damages as well as depressive and cancerous diseases. Interestingly, BCP is a selective agonist of the cannabinoid type-2 (CB2) receptor allowing its influence on the endocannabinoid system and increasing therapeutic potential. Experimental research has provided the evidence that BCP largely inhibits inflammation, oxidative stress and apoptosis in various tissues; restores immune system functions; and imparts protective effects to gastrointestinal and cardiovascular organs. There are also reports that BCP sensitizes several chemotherapeutic agents, such as cisplatin, doxorubicin, paclitaxel and sorafenib. Toxicological studies demonstrated that BCP induces no or mild reversible hepatic and hematological alterations up to doses several times higher than the usual dietary intake. Altogether, the data presented here demonstrate that beta-caryophyllene constitutes a promising multitargeting natural molecule with significant applicative perspective as pharmaceutical formulations, nutraceuticals, and functional food.

Keywords*:* β-Caryophyllene; CB2 receptor; Anti-inflammatory; Oxidative stress; Immunomodulatory; Anticancer

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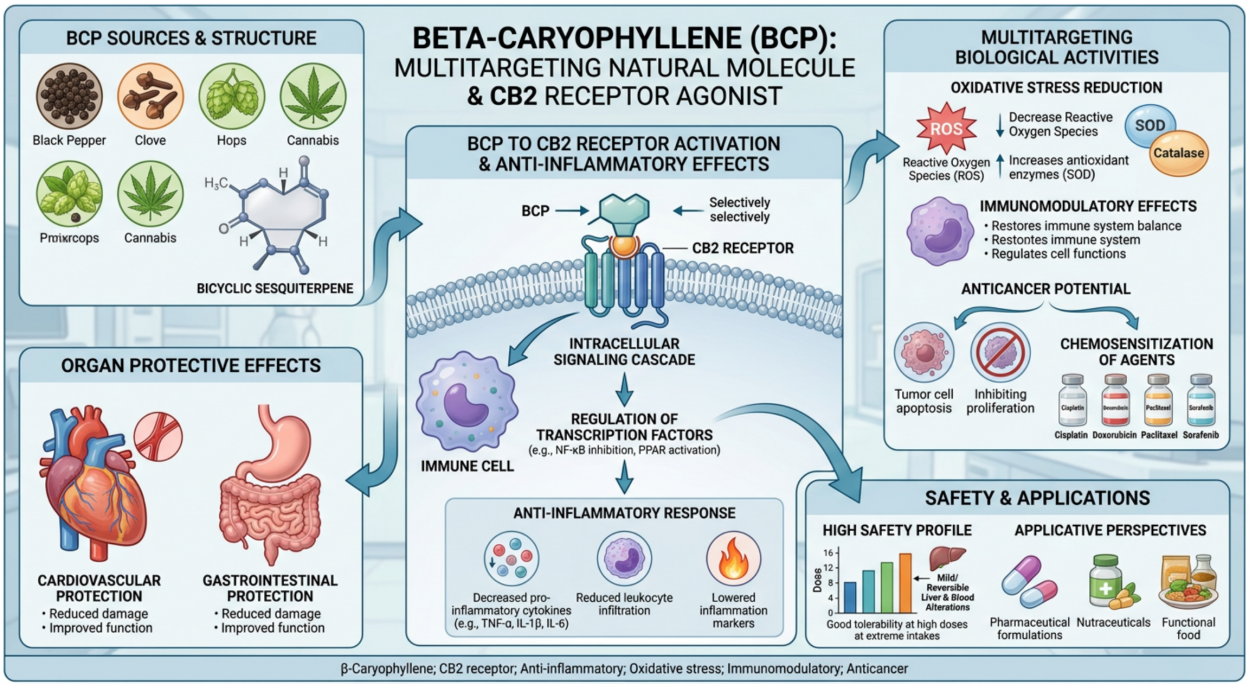
Graphical Abstract

B-Caryophyllene: Pharmacological Profile, Mechanisms, And Emerging Therapeutic Applications



INTRODUCTION

Beta-caryophyllene (BCP) also referred to as caryophyllene is a natural sesquiterpene found in more than 100 plant species. It is a major component of essential oils found in several herbs and spices, contributing to their biological activities and characteristic flavors. β-Caryophyllene (BCP) has attracted increasing scientific interest due to its potential therapeutic value, largely attributed to its unique chemical structure. This review highlights its origin, molecular properties, and broad biological significance.[1]

BCP is a plant-based hydrocarbon that occurs most abundantly in botanicals including hops, cannabis, cloves, black pepper and peppermint and is considered to be a key phytochemical. It is the same spicy, woody and pepper-like fragrance that makes it a treasure for flavorants and fragrances. BCP is an important constituent of black pepper and contributes to its characteristic odor and a wide range of biological activities, which are beneficial not only in the kitchen, but also commercially.

Structurally, beta-caryophyllene presents an unusual bicyclic framework in that a cyclobutene ring is fused with a cyclohexane ring. This rare architectural feature sets BCP apart from other sesquiterpenes, and is believed to be the principal reason why BCP has such a diverse spectrum of biological actions and molecular reactions within living systems.[2]

One of the most interesting facts about beta-caryophyllene is that it selectively interacts with the endocannabinoid system, specifically a high affinity binding to the cannabinoid type-2 (CB2) receptor. Stimulus-selective activity at the receptors may have particular theoretical significance as changes in CB2 receptor activation do not produce the psychotropic effects associated with cannabinoid type-1 receptor activation, leading to clinically interesting aspects (Pertwee et al.) [3]

BCP has widely been reported to possess a variety of pharmacological activities, such as antioxidant, anti-inflammatory, anticancer, cardiac-protective, hepatoprotective, gastroprotective and nephroprotective properties antimicrobial and immunomodulatory activities.[2] Taken together these characteristics make beta-caryophyllene a promising sesquiterpene and open new perspectives for its use as a biologically active compound in pharmaceuticals or as a flavoring agent. Due to its novel molecular structure and action on the endocannabinoid system, it is continuing to gain attention for both therapeutic and industrial applications. [4]

Table 1: Natural Sources of β-Caryophyllene and Their Distribution in Essential Oils

Plant Name	Family	Origin	B-Caryophyllene % (Essential oil)
Cannabis sativa	Cannabaceae	Central Asia	3.8–37.5%
Syzygium aromaticum (Clove)	Myrtaceae	Indonesia, Madagascar	1.7–19.5%
Humulus lupulus (Hops)	Cannabaceae	Europe	5.1–14.5%
Ocimum gratissimum	Lamiaceae	Africa / Asia	5.3–10.5%
Ocimum micranthum	Lamiaceae	Central & South America	4.0–19.8%
Origanum vulgare (Oregano)	Lamiaceae	Europe / Mediterranean	4.9–15.7%
Piper nigrum (Black Pepper)	Piperaceae	South India	~7.3%
Lavandula angustifolia (Lavender)	Lamiaceae	Mediterranean	4.6–7.6%
Cinnamomum verum	Lauraceae	Sri Lanka	6.9–11.1%
Cinnamomum tamala	Lauraceae	India / Nepal	25.3%
Cananga odorata (Ylang-ylang)	Annonaceae	Southeast Asia	3.1–10.7%
Lantana camara	Verbenaceae	India (Leaf oil)	23.3%

BIOSYNTHESIS

Formation of β-caryophyllene in biosynthesis is mainly via the classical mevalonate (MVA) pathway which governs production of terpenoid compounds in e.g. plants and yeast. In this pathway, mevalonate is further enzymatically converted into vital isoprenoid precursors. First, mevalonate is converted to IPP, which in turn switches to DMAPP. These active C5 units are successively used in condensation with others (C5) on the way to geranyl diphosphate (GPP). Continuing elongation results in the formation of FPP, which is a common precursor during sesquiterpenes biosynthesis. Conversion of FPP via cyclization with certain terpene synthases leads to the synthesis of β-caryophyllene, as illustrated by Fig. 1

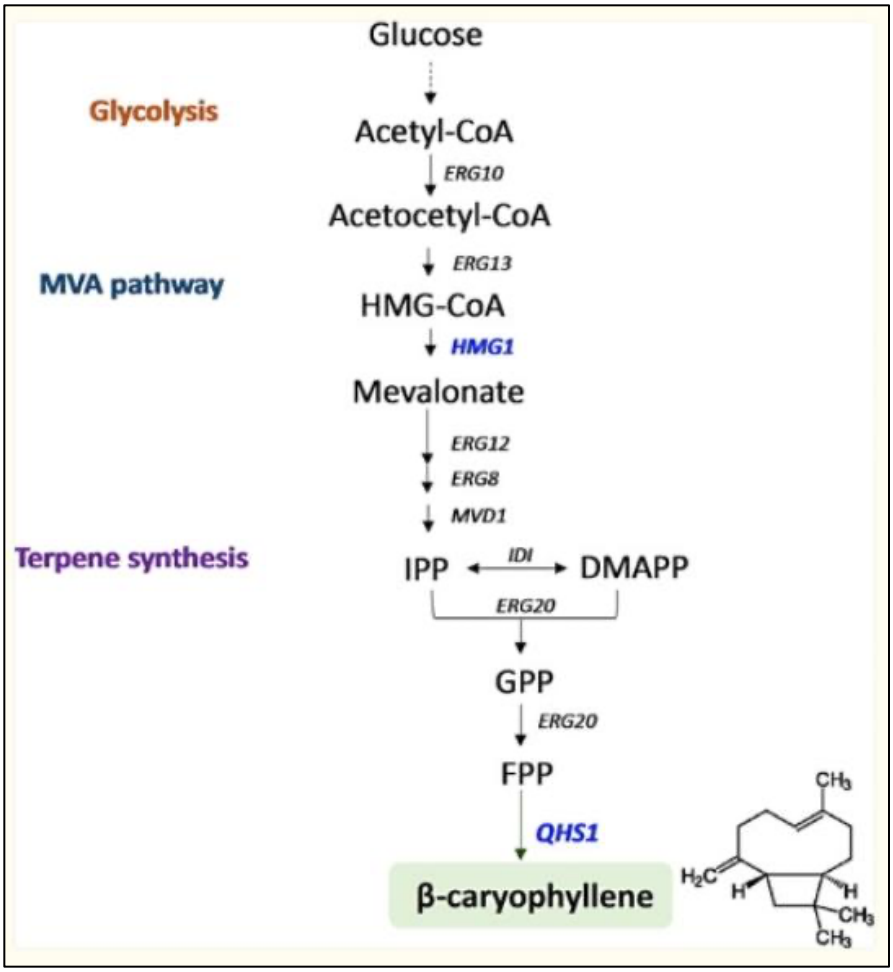


Fig. 1. Biosynthesis pathway of β-caryophyllene

BIOLOGICAL PROPERTIES

1. Anti-inflammatory activity of β-caryophyllene (BCP)

Inhibition of multiple key inflammatory molecules accounts for the anti-inflammatory properties of β-caryophyllene. In experimental studies, BCP has been shown to strongly inhibit the generation and activity of major inflammatory mediators including proteins, enzymes and pathways. In the animal model of gouty arthritis, treatment with BCP significantly inhibits joint swelling and enhances functional recovery through suppressing inflammasome-associated proteins (NLRP3 and ASC, caspase-1) as well as upstream signal molecules (TLR4, MyD88, IL-1β and NF-κB) in synovial tissues. These metabolic alterations are associated with a pronounced reduction in systemic pro-inflammatory cytokines. The inflammatory signaling was also attenuated in the context of lipopolysaccharide (LPS)-induced systemic inflammations.[5]

BCP exerts uniform activity in diverse experimental models of inflammation. Additionally, it aids in the wound healing process by suppressing IL-6 and TNF-α production, inhibiting mast cell infiltration and alleviating inflammatory cell aggregation at the injury site. In vitro studies with LPS-stimulated gingival fibroblasts and oral epithelial cells demonstrate that BCP causes a marked reduction of inflammation-related gene expression. In addition, BCP is able to suppress the expression of IL-1β, NF-κB1 and matrix metalloproteinase (MMP)-13 in human monocytes through decreasing intracellular ROS production.

In vivo studies further confirm the anti-inflammatory activity of BCP. BCP has also been demonstrated to reduce inflammatory macrophage infiltration in benign prostatic hyperplasia and protect the liver from alcoholic steatohepatitis while reducing dermal inflammation through MAPK, EGR1, and TSLP pathways. BCP from essential oils of Senecio flammeus and Croton campestris present an anti-inflammatory activity using classical models of inflammation, such as TPA-induced ear edema, carrageenan add foot edema, granuloma formation, peritonitis and chemically induced pain.[6]

In the setting of infectious and immune-mediated respiratory inflammation, BCP dramatically attenuated pulmonary inflammation, bacterial burden and lung injury in Mycoplasma pneumoniae-induced pneumonia largely mediated by modulation of NF-κB-dependent pathways. Furthermore, BCP was found to increase the anti-inflammatory effects when combined with other compounds, such as curcumin in particular in human chondrocyte cells, and could be applied for combinatorial therapies. Altogether, a great body of molecular, cellular and in vivo evidence have demonstrated β-caryophyllene as strong and versatile anti-inflammatory agent.[7]

2.Antioxidant activity of β-caryophyllene

β-Caryophyllene has been found to have strong antioxidant potential making an important part of its therapeutic profile mainly because of its capability for tissue protection against oxidative damage. Studies involving wound healing have demonstrated that the cutaneous application of β-caryophyllene significantly improved endogenous antioxidant enzymatic defense mechanism. This might be attributed to the up-regulation of major antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT), and that is highly responsible for reduced glutathione (GSH). In concert, these enzymes function to detoxify the over accumulation of reactive oxygen species (ROS) that is produced in the early inflammatory response to tissue damage and so prevent oxidative damage to cellular lipids, proteins and nucleic acids.

By up-regulating enzymatic antioxidants, β-caryophyllene contributes to the maintenance of redox status in damaged organs and prevents aggravation of oxidative stress associated tissue damage. Its capacity to balance the oxidative milieu plays a key role in its tissue protectant and healing features.[8]

In addition to local tissue repair, β-caryophyllene has been widely investigated as a natural antioxidant with systemic protective effects. Its ability to scavenge reactive oxygen species and decrease oxidative stress have been related with cardioprotection. A research team led by Hebaallah Mamdouh Hashiesh reported that β-caryophyllene ameliorates diabetes-induced pathological changes of the myocardium in mice. The protective effect was due to lower oxidative cellular damage and decrease of inflammation as a consequence of activation of CB2 receptors. [9]

3.Immunomodulatory properties of β-caryophyllene (BCP)

β-Caryophyllene has been shown to display marked immunomodulatory activity by modulating the function of several immune cell types, such as mononuclear phagocytes and T lymphocytes, as well as natural killer (NK) cells. Besides, BCP could modulate immune cell functions and control the expression of certain pro-inflammatory or anti-inflammatory cytokines, which is involved in general immune responses regulation. [10]

As important effector cells in innate immunity by pathogen clearing and inflammatory mediator releasing, macrophages exhibit significant decrease of pro-inflammatory cytokines production after BCP exposure. In particular, BCP inhibits the production of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) to inhibit downstream inflammatory signaling.

T lymphocytes are key mediators of immune responses in the adaptive immune system. In the animal model of EAE, BCP has been found to diminish disease severity by down-regulating microglia activation, dampening CD4(+) helper and CD8(+) cytotoxic T cell response and reducing pro-inflammatory cytokines production. Together, these effects conspire to induce an immune phenotype that is anti-inflammatory. [11,12]

BCP has also an effect on NK cells playing a key role in the early defense against virus-infected and tumor cells. Augmented NK cell cytotoxicity was also observed when GCP was present, especially against YAC-1 and Ehrlich ascites carcinoma.[13,14]

In addition to controlling immune cells at the individual level, BCP regulates their migration and infiltration into tissues, thus further extending its usefulness against sepsis, neurodegenerative disease, asthma pleurisy and cancer. In a sepsis model of Staphylococcus aureus infection, BCP and docosahexaenoic acid coadministration decreased neutrophil infiltration with elevation in IL-4/IL-5 levels.[15]

BCP prevented EAE in mice, an expression of multiple sclerosis through demyelination prevention and Th1/Treg ratio restoration through stimulation of the CB2 receptor. They were correlated with reduction in the clinical appearance and in NO, H2O2, IFN-γ, TNF-α and IL-17 concentrations. [13]

In addition, BCP improved neutrophilic asthma via increasing the expression of Tregs markers and repressing Th17-related ones as well as enhancing Treg/Th17 ratio through CB2-meditated STAT5 and JNK1/2 phosphorylation.[16] It was also able to suppress neutrophil migration during pleurisy and in BCG-induced pulmonary inflammation, and that it suppressed glioblastoma cell multiplication via CB2-dependent mechanisms.[17] Although the exact immune mechanisms are not yet well characterized, it is becoming increasingly evident that BCP has a strong therapeutic value in immune-mediated diseases.[18]

4.Antimicrobial properties of β-caryophyllene

β-Caryophyllene obtained from essential oil of Aquilaria crassna showed remarkable and broad-spectrum antimicrobial activity. Strong inhibitory activity against bacteria and fungi is demonstrated by the experimental findings. Of interest, Gram-positive bacteria including Staphylococcus aureus proved to be more susceptible to BCP than the other microorganisms tested with growth inhibitions at strikingly low minimum inhibitory concentrations (MICs), while effectiveness against Gram-negative bacteria was observed at moderate higher MIC values. The study also revealed potent antifungal activity and gave the initial indication of fungicidal nature of β-caryophyllene. The antimicrobial effects of this polyphenol have been ascribed to the disruption of microbial membranes integrity from a disease resistance and innate antioxidant perspective.[19]

Moreover, β-caryophyllene has been recently demonstrated to exhibit strong antibacterial activity toward Bacillus cereus (a common foodborne pathogen). It was found that the MIC value of the tested compound was 2.5% (v/v) and it could kill bacterial cells after exposure for 2 h. β-caryophyllene reduced bacterial surface charge and promoted membrane permeabilisation at sub-inhibitory doses, causing release of intracellular contents in the absence of efflux pump activity. These findings suggest that membrane destruction was the major cause for its antibacterial activity, and thus S-B can be considered as a natural antimicrobial in food preservation and safety applications.[20]

5.Gastroprotective properties of β-caryophyllene

β-Caryophyllene is a natural sesquiterpene that exists in dietary and medicinal plants like cloves, black pepper, and cannabis, which has become of interest because of its protective activity on gastrointestinal tract. Its gastroprotective effects are mainly related to the CB2 receptors that are also found in higher concentrations in gastrointestinal tissues and are a key element of the endocannabinoid system.[21]

BCP has been proved to possess remarkable anti-Helicobacter pylori activity in the culturing and animal models. In vitro tests, including disc diffusion and MIC analysis, demonstrated potent inhibition of bacterial growth. Mechanistic studies demonstrated that BCP inhibits bacterial DNA replication by suppressing the expression of crucial genes including dnaE, dnaN, holB, and gyrA. Furthermore, BCP down regulates major virulence factors such as cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA) and secretin A (SecA) and inhibits the type IV secretion system to facilitate toxin entry into gastric epithelial cells. Thus, BCP suppresses H. pylori-stimulated host cell damage in turn leading to the inhibition of apoptosis, vacuolating and morphological changes.

Moreover, in vivo investigations performed with H. pylori-infected Mongolian gerbils confirmed the gastroprotective effect of BCP. These treated animals had a low bacterial load, and after 6–12 weeks of treatment there was no detectable H. pylori 16S rRNA presented in the study. Histopathological examination showed reduction in gastric inflammation and better tissue architecture in BCP-treated groups, whereas hematological studies exhibited normalization of leukocyte patterns. These results indicate that BCP

may have potential as an anti-H. pylori natural agent or dietary intervention against H. pylori-inflicted gastric diseases, especially considering the increasing emergence of antibiotic resistance.[22]

6.Antidepressant properties of β-caryophyllene

Antidepressant-like activity of β-caryophyllene in stress induced model of depression. In a maternal separation model mimicking ELS, treatment with β-caryophyllene resulted in robust amelioration of depression-like behavior in mice. These results indicate a potential for BCP to mitigate the long-term behavioral consequences of early life stress, likely by effecting neurochemical and inflammatory pathways in brain.[23]

These observations have been further supported by studies using chronic stress paradigms. In another study, animals that were restrained for 28 days and exposed to other stress received BCP treatment daily. The compound also resulted in notable antidepressive effect, as compared to dendritic atrophy reserve the drug reduced behavioral despair tail suspension test and in forced swim test. At the molecular level, BCP restored stress-induced changes in hippocampal markers such as brain-derived neurotrophic factor (BDNF), cyclooxygenase-2 (COX-2) and CB2 receptor expression. In addition, BCP suppressed lipopolysaccharide (LPS)-enhanced induction of long-term depression in hippocampal slice preparations. Taken together, all these results show that β-caryophyllene reverses the behavioral and molecular alterations induced by chronic stress, highlighting its potential for therapeutic use in depression and stress-related disorders.[24]

7.Anticancer properties of β-caryophyllene

Notably, it has been found that β-caryophyllene exerts a strong antiproliferative effect on several cancer cell lines, such as HT-29 and HCT-116 colon cancer cells and PANC-1 pancreatic cancer cells, while almost having no effects on the CaCo-2 intestinal cancer cells. In comparison, its isomer α-humulene shows a more general activity in this sense. BCP also potentiates the cytotoxicity of isocaryophyllene and α-humulene in MCF-7 human breast cancer cells.

The anticancer activity of BCP is also demonstrated by animal studies. In C57BL/6N mice with high-fat diet (HFD)-induced obesity and melanoma carcinoma, BCP abrogated HFD-induced tumour-promoting effects. Pamburus missionis (Burm.f.) and 25% of BCP induced a synergistic anti-tumor effect with phytol and aromadendrene oxide ((GC/MS) for A431 inhibitor, causing cell-cycle arrest at G0/G1 or sub-G1 phase in A431 and HaCaT cells.

The anticancer effect of BCP is mediated through increased intracellular reactive oxygen species generation and mitochondrial membrane potential disruption. Bax/Bak pore formation to release cytochrome c into the cytoplasm, and is also characterized by upregulation of the pro-apoptotic protein Bax and down regulation of antiapoptotic protein Bcl-2. Cytochrome c when released initiates the formation of apoptosome and acts as an activator for caspase-9 which results in the activation of downstream effector caspases. BCP has been also shown to activate caspase-3 and facilitate nuclear fragmentation in BS-24-1 lymphoma cells [19] and MoFir Epstein–Barr virus-transformed T cells.

Indeed, BCP is likely to be responsible for the antiproliferative effect of C. gileadensis essential oil evidenced by MTT assays as well as inducing apoptosis by DNA fragmentation and caspase-3 activation, while leaving normal fibroblast cells unaffected. In addition, BCP increases the sensitivities of common anticancer drugs, especially paclitaxel, in MCF-7 2, L-929 and DLD-1 cells probably through elevating membrane penetration and intracellular drug uptake.

BCP also shows combined anticancer/hypoglycemic activity in BALB/c mice with CT26 colorectal tumors under the condition of hyperglycemia. ART1-dependent NF-κB activation, which amplifies a deleterious paradigm associated with type 2 diabetes, namely glycolysis with an Akt/mTOR/c-Myc route, was suppressed by TCL. The current findings indicate that β-caryophyllene and its oxide can effectively attenuate glycolysis-reliant CRC, which may be valuable therapeutic agents in the treatment of glycolysis-dependent colorectal tumors.[25]

COMBINATION THERAPY

1.β-Caryophyllene (BCP) in Combination with Cisplatin

The anticancer effect of cisplatin can be increased by β-caryophyllene in lung cancer cell lines. BCP single drug treatment resulted in moderate inhibition of tumor cell growth, whereas significant antiproliferative effect was observed with the combination of BCP and cisplatin. The effect of two drugs in combination was significantly and synergistically stronger than either drug; alone the results showed a clear inhibition of cancer cells viability.

Mechanistic studies demonstrated that this increased antitumor effect is attributed to the BCP-mediated alteration of cell-cycle core and apoptotic sensitive genes. Co-treatment led to more enhanced cell-cycle arrest in a cell-type–specific manner, as well as increased induction of apoptosis signaling by upregulation of pro-apoptotic markers (eg, Bax and caspases) combined with down regulation of antiapoptotic protein Bcl-2. Moreover, BCP enhanced cisplatin-induced DNA damage responses, and subsequently increased programmed cell death. Altogether, these data indicated that β-caryophyllene can be a chemosensitizer to enhance the anticancer activity of cisplatin in lung cancer cells.[26]

2.β-Caryophyllene in combination with Doxorubicin

Cardioprotective Effect of β-Caryophyllene on Doxorubicin-Induced Chronic Cardiotoxicity in Experimental Rats. Doxorubicin is one of the most potent inducers of myocardial damage that induces intense oxidative and inflammatory stress. Therapy with BCP markedly ameliorated structural and functional cardiac injury of doxorubicin-treated rats.

These beneficial effects were considered to be due to the inhibition of reactive oxygen species formation, down-regulation of inflammatory mediators and upregulation of endogenous antioxidant systems in the heart. Additional molecular studies revealed that induction of cardiac CB2 receptors is an essential mechanism underlying these effects. By activating the CB2 receptor, β-caryophyllene suppressed inflammatory signaling and decreased oxidative damage, protecting myocardial cellular integrity. On a therapeutic standpoint, these results reinforce the recently emerging evidence that CB2 receptor agonists (in particular ß-caryophyllene) could prove to be useful adjuvant compounds for chemotherapy-induced cardiotoxicity prevention by modulating inflammation and oxidative stress signaling pathways.[27]

3.β-Caryophyllene in combination with Paclitaxel

Peripheral neuropathy is a common and dose-limiting side effect of paclitaxel (PTX) chemotherapy that typically presents as mechanical allodynia. Pain-relieving effect of β-caryophyllene in the IKWT mouse model of Paclitaxel-induced peripheral neuropathy To investigate whether β-caryophyllene ameliorates PTX-induced neuropathic pain, murine models were used. Paclitaxel was given concomitantly with BCP to prevent neuropathy, or after the development of neuropathy.

BCP significantly attenuated PTX-evoked mechanical allodynia in both prophylactic and therapeutic schedules. Notably, this anti-allodynic effect of BCP was suppressed by the CB2 receptor antagonist, demonstrating that selective activation of the CB2 receptor is mainly responsible for BCP-mediated protection. Further mechanism studies showed that BCP inhibited the paclitaxel-induced neuro inflammation in spinal cord by attenuation of p-p38 MAPK and NF-κB signaling, down-regulation of microglial activation markers (Iba-1) and pro-inflammatory cytokine IL-1β.

These results suggest that β-caryophyllene ameliorates chemotherapy-evoked neuropathic pain through suppression of neuro inflammatory responses and glial activation. In conclusion, the study emphasizes BCP as a non-psychoactive phyto cannabinoid with potential therapeutic value for the treatment of paclitaxel-induced peripheral neuropathy.[28]

4.β-Caryophyllene in combination with Sorafenib

The ability of caryophyllane sesquiterpenes, and in particular β-caryophyllene and β-caryophyllene oxide, to potentiate the anticancer effect of sorafenib has been investigated with liver, biliary and Panc-1 pancreatic cancer cell lines. Experiments in HepG2, Mz-ChA-1 and Bx-PC3 cells showed that the co-treatment of these sesquiterpenes led to a synergistic increase of cancer cell killing, particularly in pancreatic Bx-PC3 cells.

Mechanistic study demonstrated that sesquiterpenes suppressed the activity and expression of ATP-binding cassette (ABC) drug efflux transporters, such

as P-glycoprotein (MDR1) or MRP1/2. This effect was associated with the inhibition of STAT3 signaling that resulted in enhanced intracellular accumulation of sorafenib. In the enhancing cytotoxicity, the combined therapy significantly decreased migration of the cancer cells, hinting an anti-metastatic effect. And more importantly, relatively low cytotoxicity to normal cholangiocytes was found. Our results suggest that caryophyllane sesquiterpenes can act as potential chemosensitizers to enhance the effectiveness of sorafenib and reverse the resistance in hepato-biliary-pancreatic tumours, which need to be validated further in vivo.[29]

TOXICOLOGICAL EVALUATION OF B-CARYOPHYLLENE

The available toxicological data suggest that β-caryophyllene is safe and has a low/wide safety margin. No deaths, behavioural changes, or clinically relevant alterations in body weight, food consumption, haematological parameters, serum biochemistry or organ morphology were observed in single (including up to 2000 mg/kg body weight) and 28-day repeat-dose studies with oral gavage administration of the test item by limit dose (2000 mg/kg body weight) to mice. Subchronic toxicological studies performed in rats for 90 days with feeding up to concentrations of 56,000 ppm also showed negative effects or mortality. At the highest exposure levels, dose-dependant hepatic changes including hepatocellular hypertrophy, increased liver weight and mild changes on blood parameters could be detected. These effects were considered non-adaptive and reversible with the no-observed-adverse-effect level (NOAEL) being around 222 mg/kg/day in male rats.

Supplementary safety assessments (genotoxicity, reproductive toxicity, sensitization and phototoxicity studies) are also consistent with the overall good safety profile of β-caryophyllene. There was no evidence of genotoxicity, sensitisation or photoxicicity and a wide safety margin was shown on repeated dose and reproductive parameters. Some renal alterations in male rats were determined to be species-specific and not pertinent for human risk assessment. In summary, the evidence presented here supports the safety of ß-caryophyllene at normal dietary exposures and extremely high (in excess of normal human consumption) doses may cause mild and reversible liver and blood related effects.[30]

CONCLUSION

β-Caryophyllene (BCP) is a naturally occurring bicyclic sesquiterpene that has gained significant attention due to its broad spectrum of pharmacological activities and unique mechanism of action as a selective CB2 receptor agonist. The available scientific evidence highlights its potent anti-inflammatory, antioxidant, immunomodulatory, antimicrobial, gastroprotective, antidepressant, and anticancer properties, making it a promising multi-target therapeutic agent. Its ability to modulate key molecular pathways involved in oxidative stress, inflammation, and immune responses further strengthens its potential in the management of various chronic and degenerative diseases.

In addition to its standalone effects, β-caryophyllene has demonstrated a remarkable ability to enhance the efficacy of conventional chemotherapeutic agents such as cisplatin, doxorubicin, paclitaxel, and sorafenib, indicating its role as a potential chemosensitizer in combination therapy. Toxicological studies also support its safety profile, with minimal adverse effects observed even at higher doses, reinforcing its suitability for pharmaceutical and nutraceutical applications.

Overall, β-caryophyllene represents a promising natural compound with significant therapeutic potential. However, further clinical studies and formulation-based research are required to fully explore its pharmacokinetic properties, optimize delivery systems, and establish its clinical efficacy and safety in human populations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Declarations

Ethical Approval and Consent to Participate

Not applicable. This study did not involve human participants or animals.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. Additional data may be obtained from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Authors' Contributions

All authors contributed equally to the conception, design, experimental work, data analysis, and manuscript preparation. All authors have read and approved the final manuscript.

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