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B-CARYOPHYLLENE AS A PARTNER FOR DOXORUBICIN: EVIDENCE FOR CHEMOSENSITISATION, TISSUE PROTECTION AND LIPID-BASED CO-DELIVERY

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Abstract

Doxorubicin (DOX) is one of the most widely used anticancer drugs, but cumulative heart damage, bone marrow suppression and efflux-pump-mediated resistance limit how much of it patients can receive. β-Caryophyllene (BCP) is a bicyclic sesquiterpene found in the essential oils of several hundred plant species. It is a selective agonist of the cannabinoid type 2 (CB2) receptor, has low toxicity in rodents and is used as a food flavouring. This review brings together the evidence for using BCP alongside DOX. First, it outlines how DOX works and why it damages healthy tissue. It then summarises the sources, pharmacology and safety of BCP and its direct anticancer effects. Cell studies show that BCP and its oxide (β-caryophyllene oxide, BCPO) can increase DOX cytotoxicity in leukaemia, colon and liver cancer cells, mainly by limiting P-glycoprotein-mediated efflux. The effect is not universal, however: it was absent in at least one fully resistant cell line. Evidence that BCP protects the heart during DOX treatment is suggestive but still indirect in the sources reviewed here. Both drugs face delivery problems. DOX already has clinical liposomal forms, while BCP's poor solubility and volatility have been addressed with self-emulsifying drug delivery systems (SEDDS), which raised its peak plasma level 3.6-fold in healthy volunteers. Carrying both agents in one lipid system is an attractive idea, but it has not yet been tested in animals. We close by listing the experiments needed before the combination can move forward: checkerboard synergy studies, matched normal-cell controls, pharmacokinetic studies and in vivo cardiac safety testing.

1. INTRODUCTION

Chemotherapy remains central to cancer treatment despite the growth of targeted and immune-based therapies, and anthracyclines are among its most used agents. Doxorubicin (DOX) is active against a wide range of solid tumours and

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blood cancers (Kciuk et al., 2023). Its clinical value has always been held back by the same problem: the doses that kill tumour cells also damage the heart and bone marrow, and many tumours become resistant by pumping the drug out (Carvalho et al., 2009; Bhutani et al., 2025).

One response has been to pair chemotherapy drugs with plant-derived compounds that either add their own anticancer effect or protect normal tissue, so that the chemotherapy dose can be lowered (Choudhari et al., 2020; Gao et al., 2022). β-Caryophyllene (BCP) is a strong candidate for this role. It is common in edible plants, it acts on the CB2 receptor without psychoactive effects, and it has shown anticancer, anti-inflammatory and antioxidant activity in preclinical studies (Fidyt et al., 2016; Francomano et al., 2019). Several groups have tested it directly with DOX in cancer cells (Di Giacomo et al., 2017; Di Sotto et al., 2020).

Earlier reviews have covered BCP's pharmacology broadly (Fidyt et al., 2016; Francomano et al., 2019; Janadri et al., 2025) or its role as a chemosensitiser across many drugs (Ahmed, 2025). This review focuses on one pairing, BCP with DOX. It asks three questions. What is the cell-level evidence that BCP improves the effect of DOX? Is there evidence that BCP protects tissues that DOX harms? And can both compounds be delivered together, given that each has its own formulation problem?

2. Approach

This is a narrative review. [AUTHORS TO ADD: databases searched (e.g. Web of Science, Scopus, PubMed), date range, search terms (e.g. "β-caryophyllene" AND "doxorubicin"; "β-caryophyllene" AND "self-emulsifying"), language limits and how studies were selected. Many journals now ask for this even in narrative reviews.] Studies were included if they reported original data on BCP or BCPO combined with DOX, on the anticancer or protective effects of BCP, or on lipid-based delivery of either compound. Reviews were used for background on DOX toxicity and BCP pharmacology.

3. Doxorubicin: action and limitations

3.1. How DOX kills cancer cells

DOX is an anthracycline antibiotic originally obtained from Streptomyces peucetius. It inserts between DNA base pairs and traps topoisomerase II on DNA, which leads to double-strand breaks and cell death. It also undergoes redox cycling of its quinone ring, producing reactive oxygen species (ROS), and it affects chromatin structure, ceramide signalling and immune responses to dying tumour cells (Kciuk et al., 2023). This mix of mechanisms explains its broad activity across tumour types.

3.2. Toxicity to healthy tissue

The best-known adverse effect of DOX is cardiotoxicity. It can appear as acute arrhythmia during treatment or as a chronic, dose-dependent cardiomyopathy that may lead to heart failure years later (Carvalho et al., 2009; Bhutani et al., 2025). Risk rises with cumulative dose and is higher in children, older adults and patients with existing heart disease or prior chest radiation (Belger et al., 2024). Several mechanisms are involved: ROS generated by DOX in cardiac mitochondria, disturbed iron handling that feeds iron-dependent oxidative damage (Ye et al., 2024), ferroptosis (Yi et al., 2024), other forms of programmed cell death (Li et al., 2024), and disrupted autophagy (Tan et al., 2025). Bone marrow suppression, mucositis, hair loss and nausea are also common (Carvalho et al., 2009).

These mechanisms matter for this review because several of them involve oxidative stress and inflammation, which are processes BCP is reported to influence (Section 4.2).

3.3. Resistance through efflux pumps

Many tumours become resistant to DOX by overexpressing ATP-binding cassette (ABC) transporters, especially P-glycoprotein (P-gp, ABCB1), which pump the drug out of the cell before it reaches DNA. P-gp-mediated resistance is a recognised problem in haematological cancers and has been a target for drug development for decades, with limited clinical success so far (Alvarez-Carrasco et al., 2025). A non-toxic natural compound that reduces P-gp function would

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therefore be useful, and this is where most of the BCP–DOX evidence lies (Section 5).

4. β-Caryophyllene: sources, pharmacology and safety

4.1. Sources and chemistry

BCP is a bicyclic sesquiterpene ($C_{15}H_{24}$) with an unusual cyclobutane ring and a trans double bond. A systematic analysis of the literature found about 300 plant species from 51 families whose essential oils contain more than 10% BCP, with reported contents ranging from 9.8% to 75.6% (Maffei, 2020). Well-known sources include clove, black pepper, copaiba and cannabis. Among pines, BCP is the main component of Pinus halepensis oil (Hamzaoui et al., 2024). In Pinus wallichiana, published analyses of needle oil show mainly α-pinene and β-pinene, with BCP absent or present at only about 2% (Yousuf Dar et al., 2012; Sharma et al., 2019; Sinha, 2019). Plant species and plant part therefore matter a great deal when choosing a natural source. Microbial production of BCP in engineered yeast and bacteria is being developed as an alternative to plant extraction (Tsigoriyna et al., 2024).

BCP oxidises easily in air to β-caryophyllene oxide (BCPO), which has its own biological activity. Several of the studies discussed below tested both compounds.

4.2. Pharmacology

The main known target of BCP is the CB2 receptor, for which it is a selective agonist. It does not bind the CB1 receptor responsible for the psychoactive effects of cannabis (Fidyt et al., 2016; Ricardi et al., 2024). CB2 is found mostly on immune cells and in peripheral tissues, and its activation reduces the release of inflammatory mediators. BCP also acts on peroxisome proliferator-activated receptors α and γ (Hashiesh et al., 2020). Through these targets it has shown anti-inflammatory, antioxidant, analgesic and neuroprotective effects in animal models (Francomano et al., 2019; Ricardi et al., 2025).

Of particular relevance to DOX is a study in which BCP protected the rat heart against cyclophosphamide, another cytotoxic drug. The effect was linked to suppression of the TLR4/NF-κB inflammatory pathway and activation of the Nrf2/HO-1/NQO1 antioxidant pathway (Younis, 2022). BCP has also protected the stomach lining against chemical injury (Tambe et al., 1996).

4.3. Safety

BCP is approved as a food flavouring and has a favourable safety record in animals. In a 90-day study, Wistar rats given BCP oil by mouth at 150, 450 or 700 mg/kg/day showed no adverse effects, and the highest dose was taken as the no-observed-adverse-effect level (Schmitt et al., 2016). In female Swiss mice, single doses of 300 and 2000 mg/kg and repeated doses over 28 days caused no toxicity, which places its acute toxicity above 2000 mg/kg (da Silva Oliveira et al., 2018). Human safety data at the doses that might be needed for anticancer use are still lacking.

4.4. Pharmacokinetic limits

BCP is volatile, almost insoluble in water and prone to oxidation, and its oral bioavailability from simple oil preparations is low (Francomano et al., 2019). This is a practical barrier to any therapeutic use and is the reason delivery systems are discussed in Section 7.

5. Direct anticancer effects of BCP

Apart from its interaction with DOX, BCP has its own antiproliferative activity. In colorectal cancer models it induced apoptosis and inhibited angiogenesis (Dahham et al., 2021). In multiple myeloma cells, including lines resistant to dexamethasone, it reduced survival by inducing apoptosis and blocking cell-cycle progression (Mannino et al., 2021). BCP and BCPO isolated from Aegle marmelos caused apoptosis in lymphoma (Jurkat) and neuroblastoma cells through effects on 15-lipoxygenase (Sain et al., 2014). Essential oils rich in BCP or BCPO have also shown cytotoxicity. An oregano oil containing 8.18% BCP and 13.36% BCPO killed about 60% of HeLa cells at 2 µL/mL (Moghrovyan et al., 2022). A microwave-extracted P. halepensis oil, dominated by BCP, gave IC_{50} values of 14.55–25.70 µg/mL against prostate and cervical cancer cells and arrested the cell cycle at G0/G1 (Hamzaoui et al., 2024). The anti-angiogenic

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action of BCP and its potential as a chemosensitiser have recently been reviewed (Ahmed, 2025).

The concentrations needed for these effects are generally in the micromolar range, higher than plasma levels reached after normal dietary intake. This is one reason why BCP is better seen as a companion to chemotherapy than as a stand-alone treatment.

6. BCP and BCPO as chemosensitisers for doxorubicin

Four cell-based studies have tested BCP or BCPO directly with DOX (Table 1).

Table 1. Studies of BCP or BCPO combined with doxorubicin in cancer cells.

Study	Compound(s)	Cell lines	Main finding	Proposed mechanism
Di Giacomo et al. (2017)	BCP, BCPO	Caco-2 (colon), CCRF/CEM (leukaemia), CEM/ADR5000 (DOX-resistant leukaemia)	Both had low cytotoxicity alone but increased DOX cytotoxicity in all three lines; BCPO was the stronger sensitiser	Higher intracellular rhodamine 123, indicating inhibition of ABC efflux transporters
Di Sotto et al. (2020)	BCP, BCPO	HepG2 (liver)	Both increased the cytotoxicity of low-dose, repeated (metronomic) DOX	More intracellular DOX and rhodamine 123, lower P-gp expression; docking near the ATP-binding site of P-gp
Ambrož et al. (2017)	BCPO (with α-humulene, trans-nerolidol, valencene)	A2780, SKOV3 (ovarian), CCRF/CEM, CEM/ADR (leukaemia)	BCPO acted synergistically with DOX in SKOV3 and CCRF/CEM, but no compound improved DOX effect in resistant CEM/ADR cells	Intracellular DOX rose up to about 10-fold, yet resistant cells were not sensitised
Helal & Jaradat (2024)	BCPO	HepG2	BCPO IC_{50} 45.79 µg/mL at 48 h; increased DOX cytotoxicity by about 20%	DNA binding proposed, through the epoxide group

Taken together, these studies point in the same direction. BCP and BCPO are weakly toxic on their own but can make cancer cells more sensitive to DOX, and the most consistent explanation is reduced drug efflux through P-gp and related transporters. Two studies measured this directly, through accumulation of the P-gp substrate rhodamine 123 and of DOX itself (Di Giacomo et al., 2017; Di Sotto et al., 2020).

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The evidence also has clear limits. The study by Ambrož et al. (2017) is a useful warning. Even when intracellular DOX rose substantially, fully resistant CEM/ADR cells were not sensitised, which suggests that efflux is not the only resistance mechanism at work in those cells. BCPO appeared more active than BCP in two of the studies, so formulations that let BCP oxidise may behave differently from those that protect it. All four studies used cancer cell lines only. None tested whether BCP also increases DOX toxicity in normal cells, which would cancel the benefit. None used formal synergy analysis across a full matrix of doses in every cell line. Finally, the effective concentrations in vitro have not been compared with achievable plasma levels.

Similar sensitisation has been reported for other natural agents combined with DOX, such as Zataria multiflora essential oil in prostate cancer cells (Zare et al., 2021) and the drug metformin across several cancer models (Jalali et al., 2024). The principle of using a low-toxicity partner to lower the DOX dose is therefore not unique to BCP. What makes BCP interesting is that it may also act on the tissue damage DOX causes.

7. Can BCP protect healthy tissue from doxorubicin?

The case for cardioprotection rests on overlapping mechanisms. DOX damages the heart through oxidative stress, inflammation, iron-dependent injury and cell death (Section 3.2). BCP reduces inflammatory signalling through CB2 and activates the Nrf2 antioxidant pathway, and it protected the rat heart against cyclophosphamide through exactly these routes (Younis, 2022). Reviews of BCP describe similar protective effects in other organs (Francomano et al., 2019; Ricardi et al., 2025).

Within the sources considered here, however, this evidence is indirect. It shows that BCP can protect the heart against a different cytotoxic drug and can act on pathways that DOX disturbs. It does not show that BCP protects the heart during DOX treatment without also protecting the tumour. That second point is important. An antioxidant that reduces DOX-induced ROS in the heart might, in principle, reduce DOX's ROS-dependent killing of cancer cells too. The cell studies in Table 1 suggest the net effect on tumour cells is positive, but no study reviewed here has measured tumour response and cardiac injury in the same animals. This is the most important gap in the field. [AUTHORS: consider adding direct in vivo studies of BCP against DOX cardiotoxicity, if any are published; none were among the thesis sources this review was built from.]

8. Delivery strategies

8.1. Established DOX formulations

DOX was one of the first drugs to be reformulated as a nanomedicine. Pegylated liposomal DOX (Doxil/Caelyx) was approved by the US Food and Drug Administration in 1995. Its long-circulating liposomes reduce peak plasma levels and cardiac exposure, at the cost of other side effects such as hand–foot syndrome (Abraham et al., 2005; Gabizon et al., 2025). Non-pegylated liposomal DOX (Myocet) offers a different pharmacokinetic profile (Ngan & Gupta, 2016). Polymeric micelles have also been tested. In a phase I trial of NK911, a micelle-encapsulated DOX, 23 patients with refractory solid tumours received 6–67 mg/m^2. Neutropenia was dose-limiting, the recommended phase II dose was 50 mg/m^2 every three weeks, and one partial response was seen, in metastatic pancreatic cancer (Matsumura et al., 2004). Cyclodextrin-based carriers are another option under study (Payamifar et al., 2025).

8.2. Lipid-based delivery of BCP

For BCP, the main aim of formulation is to improve solubility, protect against oxidation and raise oral absorption. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oil, surfactant and sometimes co-solvent that form fine droplets on contact with gastrointestinal fluid. In a randomised, double-blind, crossover study in 24 healthy adults, a single 100 mg dose of BCP in a VESIsorb® SEDDS gave a 3.6-fold higher Cmax, 2.2-fold higher $AUC_{0–12}$h and 2.0-fold higher $AUC_{0–24}$h than BCP in plain oil (Mödinger et al., 2022). The same technology raised the Cmax of cannabidiol 4.4-fold and shortened Tmax from 3.0 h to 1.0 h compared with a medium-chain triglyceride reference (Knaub et al., 2019). Lipid

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vesicles have also been used for BCPO: a transethosomal gel delivered it through the skin and produced 80.5% of maximum possible analgesia in an animal pain model (Natsheh et al., 2025).

8.3. Co-delivery of a phytochemical and a chemotherapeutic

Loading a natural compound and a chemotherapy drug into one carrier ensures that both reach the same tissue at a fixed ratio, which is harder to achieve when the two are given separately (Gao et al., 2022). For BCP and DOX, this is not simple. BCP is highly lipophilic and suits the oil core of a SEDDS or nanoemulsion. DOX hydrochloride is water-soluble and is usually loaded into the aqueous core of liposomes. A single carrier must therefore hold two molecules with opposite solubility, keep BCP from evaporating or oxidising, and release both at useful rates. The choice of route also matters. SEDDS are designed for oral use, while DOX is given intravenously in current practice, and the oral bioavailability of DOX itself is low. Early formulation work combining the two in a self-emulsifying system has been reported in thesis form, but to our knowledge no peer-reviewed study has yet tested such a system in animals.

9. Gaps and future directions

The evidence reviewed here supports further work on BCP as a partner for DOX, but several questions have to be answered first.

Synergy must be shown properly. Future cell studies should test DOX, BCP and their combination across a full dose matrix and report combination indices, rather than testing one fixed ratio. Formulated systems need blank-carrier controls, because surfactants and co-solvents can be cytotoxic in their own right.

Normal cells must be included. Every sensitisation experiment should include a matched non-cancer cell line, ideally cardiomyocytes such as H9c2 cells or stem-cell-derived human cardiomyocytes, to show that BCP sensitises tumours without sensitising the heart.

Resistance mechanisms beyond P-gp need attention. The lack of effect in fully resistant cells (Ambrož et al., 2017) shows that BCP will not overcome all forms of resistance. Studies should check which transporters and which other resistance pathways are involved in each model.

BCP versus BCPO. Because BCPO was the stronger sensitiser in two studies, and because BCP oxidises readily, formulations should report the BCP-to-BCPO ratio at the start and end of storage.

In vivo evidence is the main gap. Tumour-bearing animal studies that measure tumour growth and cardiac function (echocardiography, troponin, histology) in the same animals are needed before any clinical step.

Pharmacokinetics and drug interactions. Plasma and tissue levels of both drugs after co-administration, and any effect of BCP on DOX metabolism and clearance, have not been measured.

Source standardisation. Natural BCP-rich oils vary widely by species, plant part and extraction method. Studies should report the full composition of any oil used, or use purified BCP of known purity.

10. Conclusions

BCP is a safe, inexpensive and widely available sesquiterpene with a plausible role alongside DOX. Cell studies show that BCP and its oxide can increase DOX cytotoxicity, mainly by reducing drug efflux, although not in every resistant line. BCP also acts on inflammatory and oxidative pathways involved in DOX heart damage, but direct evidence that it protects the heart without protecting the tumour is still missing from the literature reviewed here. Lipid-based systems, especially SEDDS, solve much of BCP's bioavailability problem, and co-delivery with DOX in one carrier is a logical next step. Work on this combination should now move from single-ratio cell experiments to properly controlled synergy studies and to animal models that measure tumour response and cardiac safety together.

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Suggested figures: (1) chemical structures of DOX, BCP and BCPO; (2) a schematic of the proposed interaction: BCP/BCPO limiting P-gp efflux in tumour cells, and CB2/Nrf2-mediated protection in cardiomyocytes, with the unresolved question of tumour protection marked. Redraw the thesis schematic rather than reusing it, and do not show mechanisms that the cited studies did not test.

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