

A SYSTEMATIC REVIEW ON THE GENETIC MODULATION AND THERAPEUTIC REPURPOSING POTENTIAL OF HINOKITOL IN THE TREATMENT OF BREAST CANCER

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ABSTRACT

Hinokitiol (β -thujaplicin) is a naturally occurring tropolone derivative was obtained from the wood of Cupressaceae family plants. Its numerous pharmacological characteristics, including antimicrobial, antioxidant, anti-inflammatory, and anticancer effects. Recent studies shows its potential in oncology, particularly for treating breast cancer (BC). Due to impaired DNA repair processes and tumor aggressiveness, breast cancer associated with BRCA1 and BRCA2 mutations often has a bleak outlook. Hinokitiol emerged as a promising candidate for drug repurposing in this scenario due to its remarkable ability to simultaneously modify multiple cellular pathways. Recent research indicates that hinokitiol activates caspase-dependent pathways which lead to apoptosis. Furthermore, it possesses chemosensitizing properties that enhance the efficacy of conventional anticancer drugs while reducing the dosage and associated sideeffects. Hinokitiol's anticancer effects are also backed by findings that it reduces metastasis, inhibits autophagy, and manages oxidative stress. Its therapeutic potential is additionally enhanced by its ability to bind metal ions and interfere with crucial enzymatic functions. In-silico research suggests that hinokitiol could be beneficial in personalized medicine for individuals with hereditary breast cancer, indicating its potential to directly engage with target BRCA1 and BRCA2 related molecular pathways. These findings indicate hinokitiol as a novel, safe (natural compound), and adaptable therapeutic option that could be utilized to develop targeted strategies for treating breast cancers associated with BRCA1 and BRCA2.

KEYWORDS: Hinokitiol, anticancer, Breast cancer, insilico study, BRCA1, BRCA2, repurposing, β - thujaplicin.

INTRODUCTION

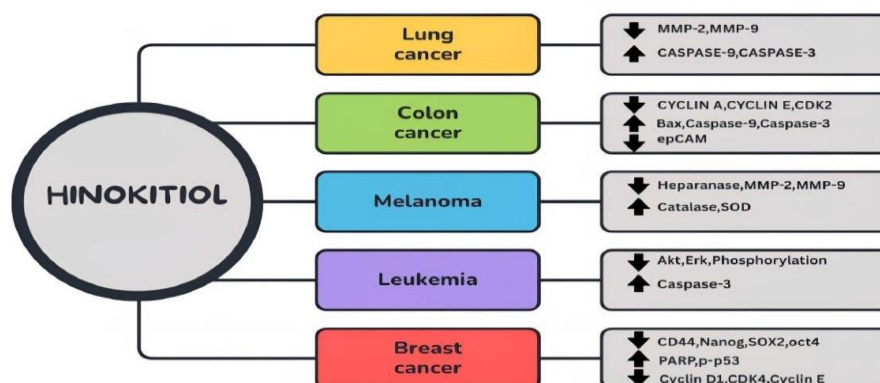
Breast cancer remains to be one of the most common and deadliest cancer affecting women in many parts of the world. The early identification, efficient treatment and prolonged management of breast cancer is a challenge due to genetic, molecular and clinical heterogeneity. Advances in surgical procedures, chemotherapy, radiation therapy, and targeted cell therapy have had minimal effects in terms of mortality and breast cancer is still one of the most leading causes of cancer deaths. The multifaceted nature of breast cancer is made even more complicated by the subtypes (HR+, HER2+, and TNBC) and variation in biological cancer characteristics and response to treatment.^[1]

Molecular pathways that are being opportunely investigated as potential therapeutic targets in breast cancer include the DNA damage response (e.g., BRCA1/2 mutations), hormonal pathways (e.g., estrogen receptor modulators), cell cycle regulation (e.g., CDK4/6 inhibitors), and properties of cancer stem cells. These insights into the molecules have helped to identify newer targets and rational development of therapeutic products that will be more specific and less toxic. In parallel, Tropolone derivatives, the compounds with seven-membered aromatic ring possessing an oxygen atom, have also become subjects of increased attention that could be explained by the variety of bioactivities the compounds could exert, namely, antimicrobial, anti-inflammatory and anticancer effects. Among the latter, the natural monoterpenoid hinokitiol (also referred to as β -thujaplicin), present in the heartwood of cupressaceous plants is of particular interest since it can potentially kill cancer cells both by inducing apoptosis, autophagy and by inhibiting their growth and stemness.² This existing review highlights how thorough research is much needed in order to discover and establish new therapeutic agents, repurposing drugs and natural agents to overcome breast cancer in a lasting manner.

METHODOLOGY

This review carried out an extensive search of the available scientific literature on hinokitiol and its role in cancer, with special focus on breast cancer. Research articles were collected from PubMed, Scopus, Web of Science, and Google Scholar using keywords such as "hinokitiol", " β -thujaplicin", "anticancer", "insilico study", "repurposing", "breast cancer", "BRCA1" and "BRCA2". Therefore, the study includes the anticancer effects of hinokitiol either in cell lines, animal models, or through molecular analyses, while works that did not provide mechanistic or cancer-related insights were excluded. The information gathered was carefully read and then organized into themes—such as hinokitiol's cytotoxic effects in different cancers and its role in breast cancer stemness, apoptosis, and autophagy, and its ability to overcome drug resistance. The information collected was carefully compared and summarized to highlight what is currently known about hinokitiol's potential in breast cancer therapy.

CYTOTOXICITY OF HINOKITIOLO IN VARIOUS CANCER TYPES



Hinokitiol has demonstrated potent cytotoxic effects across multiple cancer types by targeting diverse cellular pathways critical for tumor growth, survival, and metastasis. Its multi-targeted actions induce cell death, inhibit proliferation, and reduce metastatic potential, making it a promising anticancer agent. For instance, in oral squamous cell carcinoma (OSCC) cell lines, hinokitiol reduced cell viability by downregulating cell cycle mediators and promoting apoptosis, as evidenced by increased levels of cleaved caspase-3.

Cytotoxic Effects of Hinokitiol in Lung Cancer^[1,2,3]

In lung cancer involves several interconnected cellular pathways that hinder tumor growth, trigger cell death, and reduce metastasis. In lung cancer models, hinokitiol blocks the migration and invasion of cancer cells by lowering the levels of matrix metalloproteinases, specifically MMP-2 and MMP-9. These enzymes are essential for tissue re-modeling and spread of cancer. It activates apoptosis by stimulating caspase-9 and caspase-3 which increases the levels of the tumor suppressor protein p53 and the pro-apoptotic protein Bax and encourages the release of cytochrome c from mitochondria. Hinokitiol also shows its antioxidant effects by boosting the activities of catalase and superoxide dismutase, effectively reducing oxidative stress in cells and weakening the survival of tumor cells.

Moreover, hinokitiol causes significant DNA double-strand breaks in lung cancer cells, activating the ATM and γ -H2AX DNA damage response pathways. This leads to a halt in the S-phase of the cell cycle, stopping cancer cells from growing further, and promoting cellular senescence. Hinokitiol encourages autophagy which results in non-apoptotic cell death by breaking down damaged cellular structures.

Importantly, these mechanisms work not only in typical lung cancer cell lines but also in those with acquired resistance to EGFR-tyrosine kinase inhibitors, as hinokitiol disrupts both proliferation and colony formation in these resistant populations. Together this emphasizes hinokitiol's potential as a multi-targeted anticancer agent for lung cancer, indicating promise both as a standalone treatment and as an additional option to current therapies.

Mechanisms of Hinokitiol-Induced Cell Death in Colon Cancer^[4,5,6]

Hinokitiol also shows anticancer activity in colon cancer that reduces tumor growth, triggers cancer cell death and limits the metastatic activity. In colon cancer cell lines such as HCT-116 and SW-620, hinokitiol induces S-phase cell cycle arrest by lowering levels of cell cycle regulators like cyclin A, cyclin E, and Cdk2, while raising p21, which inhibits cyclin-dependent kinases. In addition to halting of the cell cycle, hinokitiol causes apoptosis by increasing the expression of the pro-apoptotic protein Bax and activating caspase-9 and caspase-3, which lead to programmed cell death. It also reduces the anti-apoptotic protein Bcl-2. These actions together trigger cell death through the intrinsic mitochondrial pathway.

Therefore, hinokitiol can induce cell death in colon cancer by decreasing the activity of the AKT/mTOR signaling pathways, which is also beneficial for cell growth and survival. Autophagy markers increase when exposed to hinokitiol, and blocking this pathway reduces its harmful effects, confirming the role of autophagy. Additionally, hinokitiol hinders migration and metastatic potential by blocking pathways like Akt/mTOR and reducing the expression of epithelial cell adhesion molecule (EpCAM), which is involved in the movement and lifespan of tumor cells. In vivo studies show that giving hinokitiol orally to mice with tumors significantly reduces both the volume and weight of tumors. This highlights its potential as a treatment for colon cancer by targeting cell growth, survival, and spread through various supporting molecular pathways.

Anticancer Actions of Hinokitiol in Melanoma^[7,8,2]

By impacting several cellular pathways crucial for tumor growth and spread, hinokitiol shows strong anticancer effects against melanoma. It reduces the invasion and movement of cancer cells in melanoma models by blocking key pro-metastatic enzymes such as heparanase, MMP-2, and MMP-9. Hinokitiol triggers apoptosis through the intrinsic mitochondrial pathway, which features higher levels of pro-apoptotic proteins and caspase activation. It also inhibits the Akt and Erk signaling cascades pathways, which promotes the growth, survival and the ability to spread are often overactive in melanoma. Moreover, hinokitiol lowers oxidative stress and weakens cellular defenses by boosting antioxidant enzymes such as catalase. Therefore, these effects of hinokitiol lead to reduced tumor growth and better tissue structure which suggest hinokitiol could be a useful natural treatment for melanoma.

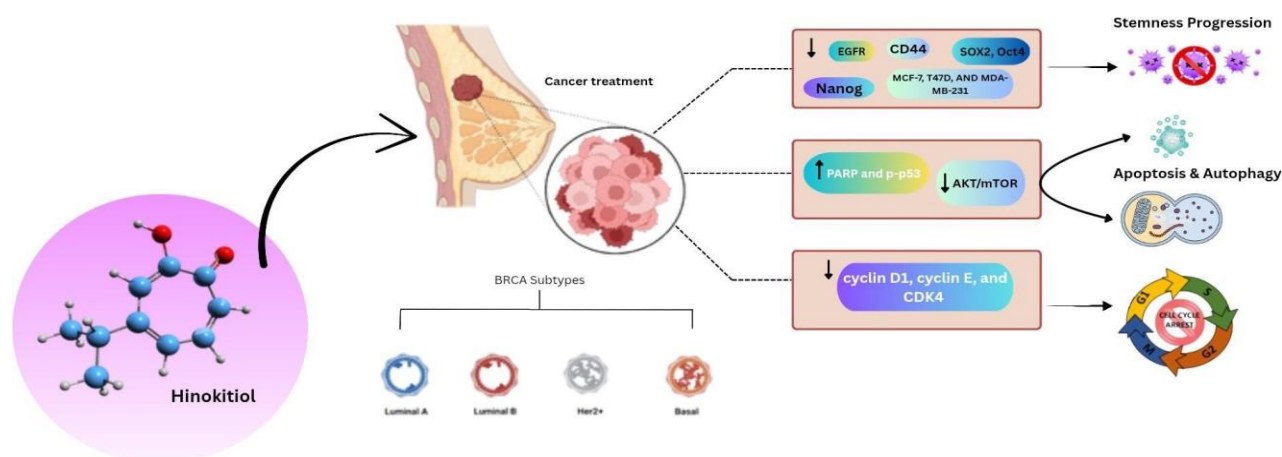
Hinokitiol's Role in Targeting Leukemia Cells^[9,10]

Hinokitiol exhibits diverse anticancer activities towards leukemia by inhibiting major signaling pathways like Akt and Erk pathways leading to decreased phosphorylation levels of these kinases. Additionally, This results in decreased heparanase production of an enzyme associated with the spread of tumor. In turn, migration and invasion of leukemia cells are lowered. Additionally, hinokitiol induces apoptosis in leukemia cells by activating caspase-3 and other pro-apoptotic proteins. It interferes with iron metabolism, a critical process required for the synthesis of DNA and maintains rapidly proliferating cancer cells which leads to cell death. Hinokitiol also affects several critical cellular signaling pathways such as NF- κ B, MAPK, and HIF-1. These impacts highlight the potential for hinokitiol as an important option for the treatment of leukemia, targeting several pathways critical to tumor growth, persistence, and metastasis.

Repurposing Hinokitiol for Breast Cancer Treatment

Among these various cancers, breast cancer (BC) stands out where hinokitiol shows remarkable therapeutic potential. It effectively reduces breast cancer cell viability in a dose-dependent manner and inhibits breast cancer stemness progression by modulating key stemness, apoptosis, and autophagy-related proteins.

Molecular Mechanisms of Hinokitiol in Breast Cancer



Inhibition of Breast Cancer Stem/Progenitor Cells (BCSCs) and Stemness Progression

Effect of Hinokitiol on breast cancer cell viability

The anti-cancer properties of hinokitiol on three different breast cancer cell lines—MCF-7, T47D, and MDA-MB-231, the latter representing the aggressive triple-negative subtype was investigated. The findings demonstrated that

hinokitiol significantly reduced the viability of cancer cells in both a dose- and time- dependent manner, while showing low cytotoxicity up to 200 μ M in normal cell line, indicating selective action against tumor cells. At the molecular level, hinokitiol inhibited key regulators of stemness. CD44 expression, a surface glycoprotein that controls cell adhesion, migration and stem cell survival, was strongly reduced. In addition, transcription factors essential for maintaining stemness — **Nanog, SOX2, and Oct4** — were downregulated in all three cancer cell lines. Since these factors constitute a central regulatory network that supports the pluripotency and tumorigenic potential of BCSCs, which further reinforces the fact that hinokitiol interferes with the very foundation of tumor relapse and progression.^[11]

Hinokitiol inhibits VM activity of (BCSCs)

Breast cancer stem (BCSCs) are a small but powerful group of cells inside tumors. They can drive cancer growth, resist treatments, spread to other parts of the body, and even create “fake blood vessels” through a process called vasculogenic mimicry (VM). Anti-angiogenic agents like bevacizumab have shown limited success in breast cancer, partly because VM allows tumors to circumvent angiogenesis inhibition. The authors showed that in mammosphere cultures enriched in BCSCs, hinokitiol even at sub-toxic concentration below its half maximal inhibitory concentration (IC 50) markedly inhibited the ability of these cells to form VM networks.

This inhibition was attributed to the suppression of a protein, called epidermal growth factor receptor (EGFR) which is vital in the regulation of tumor growth, metastasis, and stemness. Interestingly, hinokitiol did not change the expression of EGFR mRNA, and this implied that its effect was post-transcriptional. Further mechanistic studies demonstrated that hinokitiol enhances proteasome-degradation of EGFR protein to decrease its cellular levels and activity. The down-regulation of the EGFR and the anti-VM effect of hinokitiol was blocked when the proteasome inhibitor MG132 was present, suggesting that hinokitiol mediates down-regulation of the EGFR through proteasomal degradation. By down regulating EGFR, hinokitiol not only inhibited VM formation but also interfered with a major survival pathway in breast cancer stem-like cells.^[12]

Hinokitiol promotes the upregulation of miR-494-3p, which in turn inhibits BMI1 expression

Hinokitiol significantly reduced BMI1, which is the prime oncogene related to stemness to maintain the survival of breast cancer stem cells, their self-renewal, and tumor initiation. Depression in BMI1 was recorded consistently in both in vitro cultured breast cancer cells and tumor tissues in treated mice. The analysis identified miR-494-3p as a breast cancer suppressor microRNA. This miRNA is normally downregulated in cancer thereby enabling the oncogenes such as BMI1 to be active. Restoration of miR-494- 3p expression elevated cancer stemness features, showing its importance as an anti-cancer regulator. Hinokitiol increased miR-494-3p, which in turn led to the suppression of BMI1. Functional experiments proved that the inhibition of miR-494-3p ameliorated the inhibitory activity of hinokitiol on BMI1 and cancer stem cell self-renewal. This indicates that in addition to reversing the changes in miR-494-3p, hinokitiol also relaxes cancer stemness by downregulating BMI1.^[13]

Induction of Apoptosis and Autophagy in Breast Cancer Cells

Apoptosis is a programmed cell death process, a natural mechanism for removing abnormal cells, preventing the proliferation of potentially cancerous cells. Investigation of the pathways of anti-proliferative effect of hinokitiol on cancer cells was performed with breast tumor cell lines MCF-7, T47D, and MDA-MB- 231 incubating with hinokitiol during the 48 hours. The treatment resulted in significant elevation of cleaved PARP level and the percentages of apoptosis in all three lines. The enhanced apoptotic effects in the TNBC cell line were further confirmed using flow

cytometry. As p53 activation has been reported to cause apoptosis in breast cancer, we examined the p-p53 levels and found them significantly increased after hinokitiol treatment. Collectively, these findings are evidence that hinokitiol induces apoptosis by increasing the expression of cleaved PARP and p-p53, thus its application as a promoter of programmed cell death in breast cancer cells.^[11,14]

Earlier studies have shown that hinokitiol suppresses tumor growth through apoptosis. However, it can also occur via autophagy. The study demonstrated that hinokitiol induces autophagy in a dose-dependent manner. The use of the autophagy inhibitor 3-methyladenine confirmed that cell death was mediated via this pathway. Treatment of tumor cells with hinokitiol led to elevation of the autophagy markers.

Immunoblotting further revealed that hinokitiol reduced the expression of phosphorylated AKT, mTOR, and p70S6K. These indicate inhibition of the AKT/mTOR pathway. The overall evidence indicates that hinokitiol has anti-tumor effects via the activation of autophagic signaling mediated by the down-regulation of AKT/mTOR.^[15]

Cell Cycle Arrest and Inhibition of Proliferation

In this study, β -Thujaplicin was found to block the growth of luminal breast cancer cells (MCF-7 and T47D). It does so by suppressing cell proliferation by causing cell cycle arrest at the G1 to S phase. This was accompanied by downregulation of cell cycle regulators cyclin D1 and CDK4. It also decreases estrogen receptor α (ER- α) via enhanced protein breakdown by ubiquitination. Collectively, these findings suggest that β -thujaplicin may be useful in controlling hormone-sensitive breast cancer growth.^[16]

This study evaluated the in vitro cell culture and an in vivo xenograft mouse model to study its impact on ER- negative basal-like breast cancer and it was observed that β -Thujaplicin induced G0/G1- cell cycle arrest through regulation of key mediators, including cyclin D1, cyclin E, and CDK4 and activation of the important cell-cycle regulatory pathway led to suppress the proliferation of human breast cancer cells.

Further, it regulated the phosphorylation of AKT and GSK-3 β and protein level of beta-catenin, suggesting an influence on the GSK-3 β /beta-catenin signaling pathway. In the xenograft model, β -thujaplicin considerably diminished the development and weight of the tumors. however, the recognizable impacts on cell cycle and the AKT/GSK-3 β /beta-catenin pathway were affected by the tumor tissues. Taken together, it can be concluded that β - thujaplicin inhibits the development of basal-like mammary tumors through a GSK- 3 β / beta -catenin pathway and can be used as a potential agent in the chemoprevention of the basal-like subtype of breast cancer.^[17]

Overcoming Drug Resistance and Enhancing Chemotherapy Efficacy

The most serious obstacle to treatment of breast cancer is its chemoresistance, which is frequently mediated through overexpression of drug efflux transporters, including P-glycoprotein (P-gp). Hinokitiol has been demonstrated to inhibit the expression of P-gp and reduce efflux activity in a dose-dependent fashion increasing intracellular retention of other chemotherapeutic agents such as 5-Fluorouracil (5-FU). This is attributed to the suppression of the AKT/mTOR/p70S6K signaling pathway which is involved in the regulation of the P-gp. The combination of hinokitiol with 5-FU in mouse tumor models induced more apoptosis and tumor inhibition, suggesting the possibility of synergetic effects to overcome 5-FU resistant cancer cells and reduce the dosage of drugs used and associated side

effects. The ability of Hinokitiol to reverse drug resistance by targeting important survival and drug transporter signaling pathways shows the immense potential of Hinokitiol as an adjuvant to breast cancer treatment, particularly in multidrug-resistant cancer tumors.^[18]

CONCLUSION

Drug development can be an expensive, long and high risk process, typically taking 10 to 15 years on average to bring a drug to market. At the center of this process is the requirement to understand the protein-ligand interactions, which form the basis for developing new therapeutic targets. Natural herbal compounds are becoming the focus in this regard as safer and better performing alternatives. The current study is based on the analysis of one such natural compound, hinokitiol. It demonstrates significant cytotoxic activity among various cancers and also shows its possible interactions with target genes linked to breast cancer. Through insilico modeling, hinokitiol is expected to promote cancer cell death and reduce tumor spread, suggesting its value as a lead molecule in drug development. Computational use of natural bioproducts can be less time consuming and costly than the use of conventional methods.

Results underline the fact that computational models have potential but need to be followed up with clinical trials and validation wet-lab to verify efficacy. With increasing global interest in herbal compounds, particularly for cancer therapy, evidence supports that phytochemicals like hinokitiol may provide a promising avenue for breast cancer treatment and prevention. However, further research is needed to fully explore their potential and turn these ideas into applicable clinical practices.

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