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# The synergistic anticancer effects of curcumin in combination with breast cancer chemotherapy drugs

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## ABSTRACT

Breast cancer has been steadily increasing in recent years, becoming a worldwide concern. Recent advancements in drug discovery and drug therapy have improved the survival rates of breast cancer patients. However, the long-term application of conventional chemotherapy drugs causes chemoresistance, and high dosage leads to adverse toxicity effects. At this point, curcumin, which exerts multiple beneficial effects, could be a potential novel agent in breast cancer treatment. Recent studies have found out that the combination of curcumin with chemotherapy drugs is effective in resensitising cancer cells towards chemotherapy drugs as well as reducing the chemotherapy dosage. Moreover, *in vitro*, and *in vivo* studies on different breast cancer cell lines as well as human clinical trials have shown the synergistic potential of curcumin in anticancer activities. Hence, this review summarises the synergistic anticancer effects of curcumin in combination with conventional chemotherapy drugs. This review also provides critical insights into the cellular and molecular effects of curcumin in combination with chemotherapy, particularly in relation to their modulation of key signalling pathways. Given curcumin's poor availability, recent advances in nanoformulations have shown promise in enhancing its therapeutic potential. Therefore, this review also highlights the nano-formulated curcumin in combination with nanopackaged chemotherapy drugs, laying the groundwork for future research. Finally, this review analyses the research gap and discusses the future prospects of breast cancer treatment. In short, the findings presented in this review provide remarkable insights into the mechanisms underlying novel curcumin-based combination therapies, with the hope of achieving significant improvements in breast cancer treatment in the near future.

***Keywords:*** *Curcumin; breast cancer; chemotherapy; mechanisms and outcomes*

## INTRODUCTION

The prevalence of breast cancer incidence is increasing at a fast rate, making it a global health burden. An estimated 7.8 million women have suffered from breast cancer in the past few years, resulting in about 685,000 deaths in 2020 (WHO, 2024). Breast cancer commonly originates from the lobules that produce milk and the ducts that deliver milk to the nipples.

Breast cancers are classified into *in situ* (at an early cancer stage) and invasive carcinomas. *In situ* types only grow in the lining of ducts and glands, while invasive types invade the surrounding connective tissues of the breast (Sharma et al., 2010). At the later advanced stage, invasive breast cancer is at a high risk of spreading to other body parts via blood and lymphatic vessels, resulting in highest mortality rate.

Over the years, conventional monotherapies including chemotherapy, radiation, surgery, and hormone therapy have effectively contributed to a reduction in the breast cancer mortality rates. Among these treatments, chemotherapy remains a primary treatment option, especially for aggressive type of breast cancer. Unfortunately, chemoresistance along with toxicity effects have been reported after the patients undergo repeated treatments (Gote et al., 2021). The cancer cells start to adapt to therapy and become resistant to drugs after prolonged treatment. As a result, higher doses of chemotherapy are often required to overcome resistance, resulting in increased toxicity (Senapati et al., 2018). Recent studies have demonstrated that curcumin possesses a range of pharmacological properties, particularly in enhancing synergistic anticancer effects. Compared to conventional chemotherapy, co-administration with curcumin can circumvent problems such as chemoresistance, high toxicity, and unwanted side effects. Curcumin also has chemopreventive, anticancer, anti-inflammatory, and antimicrobial properties (Kong et al., 2021; Ngai, 2020; Ramasamy et al., 2015). The main key takeaway regarding curcumin is its ability to target multiple cellular and molecular pathways, enabling it to more effectively suppress cancer growth, inhibit cancer proliferation, and ultimately induce apoptosis in cancer cells.

Therefore, this review highlights the cellular and molecular effects of curcumin when co-administered with various conventional chemotherapy drugs. It explores curcumin's anticancer effects through its ability to simultaneously target multiple signalling pathways. To validate its efficacy, findings from *in vitro*, *in vivo*, and clinical studies are analysed (Ganjali et al., 2014). Additionally, this review explores the potential of combining nanocurcumin with nanoformulated chemotherapy drugs to enhance breast cancer treatment outcomes in the near future.

## Monotherapy across different breast cancer subtypes and the development of chemoresistance

The risk of getting breast cancer is rising with age, and the peak of cases occurs in women over 40. While breast cancer is more common in postmenopausal women, there is also a growing number of cases being diagnosed in premenopausal women (Konat-Baska et al., 2020). The development of breast carcinoma is highly influenced by various risk factors, including genetics, hormone use, and the external environmental factors (Asudas et al., 2025). Due to the complexity of breast cancer biology, monotherapy remains one of the primary systemic approaches for treating early-stage and locally advanced cases (Burguin et al., 2021; Valero et al., 2002).

Therapeutic strategies are typically tailored according to specific breast cancer subtypes, which are mainly categorised into luminal A, luminal B, HER2-enriched, and basal-like (Dass et al., 2021). These classifications are primarily based on the expression of immunohistochemistry (IHC) markers, including hormonal receptors such as progesterone receptor (PR), oestrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2), as well as basal markers such as cytokeratin 5/6 (CK5/6), epidermal growth factor receptor (EGFR), and the Ki-67 proliferation index (Dass et al., 2021; Waks and Winer, 2019).

In this context, luminal A is characterised by the expression of PR and/or ER, but not HER2. Luminal B, on the other hand, is characterised by the expression of PR and/or ER as well as HER2. As both subtypes are hormone receptor-positive, they are commonly treated with endocrine therapies such as tamoxifen, anastrozole, or letrozole (Sebastian et al., 2023). For example, tamoxifen functions by binding to the ER and blocking its transcription activity, thereby inhibiting cancer cell proliferation (Yao et al., 2020). In contrast, HER2-enriched subtype is typically characterised by high levels of HER2 and a lack of PR and ER expression, making it unresponsive to hormone therapy. Instead, it is treated with anti-HER2 agents, such as monoclonal antibodies like trastuzumab or small-molecule inhibitors like lapatinib (Agostinetto et al., 2024).

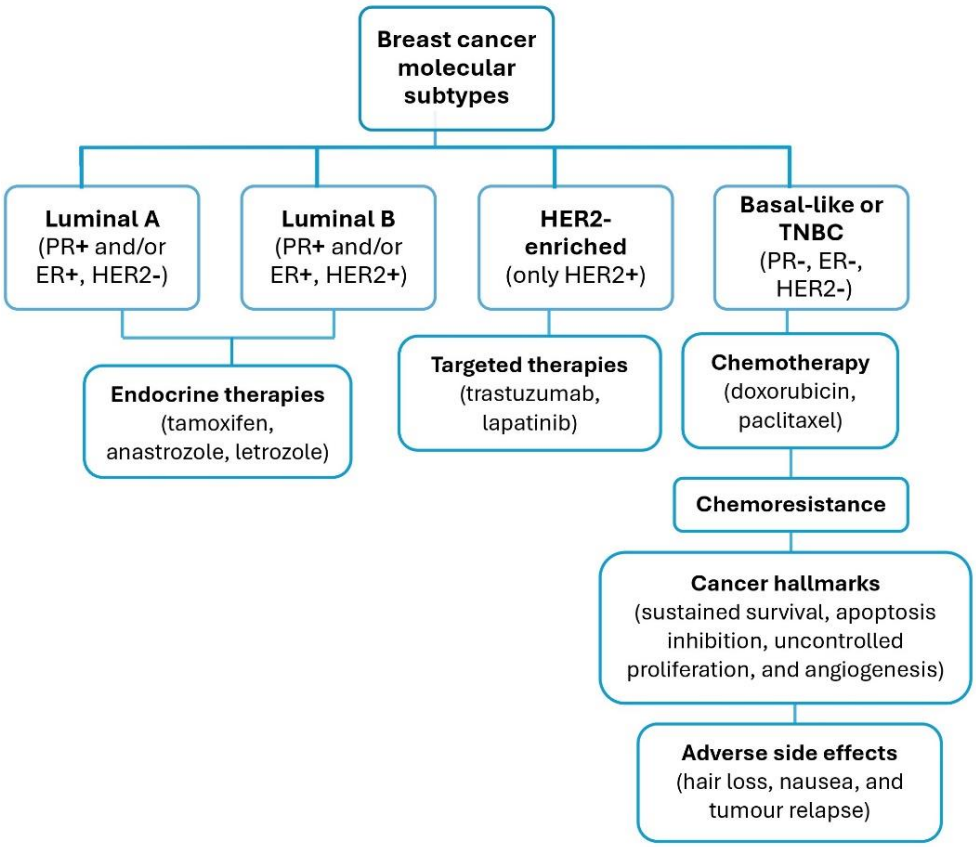
Finally, the basal-like subtype typically lacks expression of all three receptors and is often referred to as triple-negative breast cancer (TNBC). The term basal-like arises from the similarity in the expression of basal markers, including EGFR, CK5/6, CK14, and CK17 (Cheang et al., 2008; Dai et al., 2015; Pillar et al., 2012). However, not all TNBC cases are basal-like. Approximately 70-80% of TNBC fall into the basal-like molecular subtype (Dass et al., 2021; Lam et al., 2014). Moreover, TNBC, which accounts for 15-25% of all breast cancer cases, is notably aggressive and lacks targeted therapeutic options, making it a significant treatment challenge (Asudas et al., 2025; Dai et al., 2017; Newton et al., 2022). As a result, chemotherapy drugs such as doxorubicin or paclitaxel are commonly administered, either as single or in combination (Pont et al., 2024). These chemotherapeutic agents play a key role in eliminating the fast and vigorously growing cells, aiming to reduce the risk of cancer developing into an aggressive stage and decrease the mortality rate (Yao et al., 2020).

Despite the widespread use of chemotherapy drugs in treating breast cancer, resistance after repeated treatment is still a predominant obstacle. Patients are found to have a decline in cancer cell sensitivity towards the drugs, leading to therapeutic tolerance. Cancer cells are capable of coping with the presence of therapeutic agents, preventing themselves from drug cytotoxicity effects (Yeldag et al., 2018). Subsequently, the cancer cells progress and generate remarkable cancer hallmark capabilities, including sustained survival, apoptosis inhibition, uncontrolled cell proliferation, and angiogenesis induction during metastasis (Figure 1). At the same time, cancer cells transport the drugs out of the cells, via adenosine triphosphate (ATP) energy-dependent efflux pumps.

Ultimately, the cancer cells evolve into a higher carcinogenic and aggressive grade, which is also known as malignant breast cancer (Hanahan and Weinberg, 2011). Moreover, chemotherapy is associated with adverse side effects, such as hair loss, nausea, and tumour relapse, subsequently affecting patient compliance (Asudas et al., 2025).

**Figure 1**

*Classification of breast cancer molecular subtypes, their corresponding subtype-specific monotherapies, and the development of chemoresistance*




*Note: +/- indicates the expression of hormone receptors on breast cancer. PR = progesterone receptor, ER = oestrogen receptor, HER2 = human epidermal growth factor receptor 2, and TNBC = triple negative breast cancer. Positive (+) indicates the presence of hormone receptor while negative (-) indicates the absence of hormone receptor on the breast tissues.*

## Curcumin as a therapeutic agent and its pharmacological properties

To overcome the challenges encountered in conventional monotherapy, recent studies have focused on the interaction of natural plant ingredients such as curcumin with breast cancer chemotherapy drugs. Compared to conventional cancer treatments, using natural plant ingredients has become an emerging approach, notably in improving treatment efficiency and lowering the financial burden of cancer treatment (Huang M et al., 2021; Wang et al., 2012). This is primarily due to the rich availability of resources, promising chemopreventive and therapeutic effects of natural plants. Therefore, curcumin, one of the excellent sources of natural bioactive components, has been extensively studied for cancer treatment. Curcumin is extracted from *Curcuma longa* and is classified as the turmeric species under the ginger family. Curcumin is also known as diferuloylmethane, significantly making up 2-5% of turmeric (Salehi et al., 2020). In recent years, curcumin has shown great potential in enhancing recovery outcomes for patients suffering from various adverse illnesses including excessive oxidative conditions, exercise-induced inflammation, muscle soreness, and anxiety (Hewlings and Kalman, 2017; Jabczyk et al., 2021; Peng et al., 2021).

In recent years, curcumin has demonstrated considerable anticancer potential due to its natural and pharmacological safety properties. Previous research has proved that curcumin exerts multiple pharmacological properties, including anti-inflammation, antioxidant, antimicrobial, and most importantly, anticancer effects. In the context of anticancer activity, curcumin inhibits tumour growth and invasion through multiple molecular

mechanisms, notably by inducing apoptosis and suppressing the cell proliferation cycle (Mansouri et al., 2020). Moreover, emerging research indicates that curcumin targets cancer cells specifically without harming normal cells, making it a more promising therapeutic agent for breast cancer treatment (Banik et al., 2017). The combination of anticancer drugs with curcumin exhibits lower side effects, overcoming the non-selectivity of chemotherapy that eliminates a high percentage of high proliferative healthy cells during treatment (Kooti et al., 2017; Tan and Norhaizan, 2019). Therefore, incorporating curcumin as a synergistic adjunct in breast cancer therapy presents a promising and innovative treatment strategy.

**The mechanisms of action of curcumin in anticancer activity**

The anticancer effects of curcumin have been reported in numerous cancers such as breast, colorectal, lung, pancreatic, and prostate cancers (Kong et al., 2021). Recent studies have shown the anticancer roles of curcumin in targeting different molecular targets and regulating the underlying signalling pathways. For instance, the interconnections between transcription factors (TFs), inflammatory cytokines, adhesion molecules, apoptosis-related factors, growth factors, and enzymes play a fundamental role in anticancer activity (Giordano and Tommonaro, 2019; Liu et al., 2018).

The main key cellular TFs involved in the formation of cancer are activating protein-1 (AP-1), cyclooxygenase-2 (COX-2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), specificity protein-1 (SP-1), and signal transducer and activator of transcription 3 (STAT3). Overexpression of TFs has been observed during cancer progression, and subsequently contributes to the development of chemoresistance in cancer cells. In recent studies, curcumin has been demonstrated to improve the synergistic anticancer effects by inhibiting the TFs activation, leading to downregulation of the underlying oncogenic kinases (Banerjee et al., 2017; Younes et al., 2022; Zoi et al., 2021).

For instance, curcumin downregulates the TFs, including NF-κB, STAT3, and COX-2, that are involved in cancer angiogenesis and metastasis. Firstly, NF-κB serves as a central mediator of inflammatory responses, play a role in regulating the survival of innate immune cells and inflammatory T cells (Liu et al., 2017). Previous studies have found that the curcumin analogues, such as 3,5-Bis(2-fluorobenzylidene)-4-piperidone (EF24), and the more recently developed 3,5-Bis(2-pyridinylmethylidene)-4-piperidone (EF31), inhibit NF-κB activity. Specifically, EF24 was shown to block IκB kinase (IKK) and prevent the phosphorylation of IκB, key upstream regulators of NF-κB activation (Esmaeazlzadeh et al., 2024; Olivera et al., 2012). This inhibition prevents the degradation of IκB, thereby retaining NF-κB in the cytoplasm and suppressing its nuclear translocation and oncogenic gene transcription. Similarly, curcumin has been shown to inhibit the phosphorylation of STAT3 directly or interfere with the interleukin-6 (IL-6)/STAT3 signalling axis, both of which block STAT3 nuclear translocation and DNA-binding activity (Golmohammadi et al., 2024). Regarding COX-2, curcumin was found to suppress its expression by inhibiting the phosphorylation of upstream regulators such as protein kinase C (PKC), p38 mitogen-activated protein kinase (MAPK), and cAMP response element-binding protein (CREB), all of which are required for COX-2 activation (Lee et al., 2020). Concurrently, curcumin suppresses the key stimulators in angiogenesis, such as vascular endothelial growth factor (VEGF) and EGFR. The primary role of EGFR in mediating angiogenesis is through promoting the expression of VEGF. When EGFR is activated, it triggers downstream signalling pathways, such as the phosphoinositide 3-kinase (PI3K) /protein kinase B (Akt) pathway. Subsequently, the mammalian target of rapamycin (mTOR) receives stimulatory signals via PI3K and is also phosphorylated by Akt (Wee and Wang, 2017). This activation of mTOR leads to increased expression of VEGF, which in turn, VEGF increases vascular permeability and stimulates the production of proteases. As a result, the proteases modify the extracellular membrane and aid the invasion of cancer cells into surrounding tissues (van Cruijsen et al., 2005). However, when curcumin inhibits EGFR, it indirectly suppresses VEGF expression as well, contributing to the inhibition of angiogenesis. Mechanistically, curcumin suppresses the activity of early growth response-1 (Egr-1) activity, which also functions as an upstream regulator of EGFR. Suppression of Egr-1 leads to reduced EGFR expression and consequently inhibits EGFR-mediated metastasis in cancer cells (Wong et al., 2019).

Moreover, suppression of the inflammatory cytokines is also one of the important mechanisms of curcumin's anticancer activity. Besides the main TFs such as NF-κB, STAT3, and COX-2, inflammatory cytokines also found to be involved in the development of cancers. During cancer progression, cytokines supply growth factors to the cancer cells continuously. Therefore, downregulation of inflammatory cytokines such as chemokine C-X-C motif ligand 1 (CXCL1) and CXCL2 prevents chronic inflammation, reducing breast cancer metastasis (Deng et al., 2016). In this context, curcumin-induced changes in microRNA (miRNA) expression have also been shown to affect inflammatory cytokine levels. For instance, curcumin upregulates miR-181b in breast cancer cells, which in turn leads to the downregulation of CXCL1 expression (Korbecki et al., 2022). Additionally, curcumin suppresses CXCL1 and CXCL2 through modulation of the NF-κB signalling pathway. As previously described, curcumin inhibits the phosphorylation of IκB, thereby preventing the nuclear translocation of NF-κB. This inhibition reduces NF-κB-mediated transcription of pro-inflammatory cytokines, including CXCL1 and CXCL2 (Bachmeier et al., 2008).

Emerging research also reported that curcumin can enhance cell adhesion activity by inhibiting SP-1 transcriptional activity and focal adhesion kinase (FAK) phosphorylation, ultimately contributing to cancer cell suppression. The inhibition of FAK activity enhances the extracellular matrix (ECM), which plays vital roles by providing anchorage for cell adhesion and maintaining the stiffness of cell membranes (Huang J et al., 2021).

Therefore, the downregulation of FAK signalling reduces primary tumour growth and cell invasion *in vitro* (Deng et al., 2016). Mechanistically, curcumin suppresses FAK activity by inhibiting its phosphorylation at key tyrosine (Tyr) residues, including Tyr397, Tyr407, Tyr576, Tyr577, Tyr861, and Tyr925, leading to cytoskeletal remodelling, which reduces cell adhesion required for migration (Chen et al., 2013). Moreover, curcumin has been shown to downregulate cluster of differentiation 24 (CD24), a cell surface glycoprotein known to promote FAK activation. By reducing CD24 expression, curcumin disrupts its interaction with the SP-1 and FAK, thereby impairing cell adhesion (Chen et al., 2013).

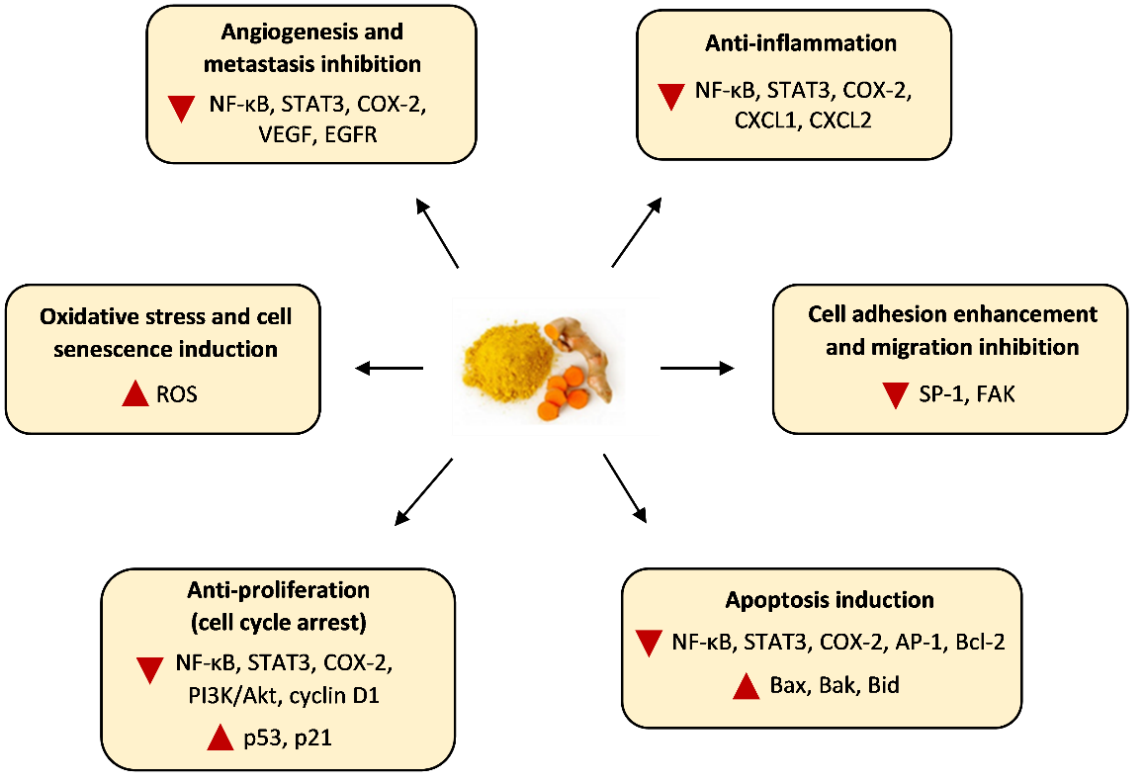
In addition, curcumin not only stimulates apoptosis induction by downregulating the main TFs, including NF-κB, STAT3, COX-2, but also by inhibiting AP-1. AP-1 is a transcription factor complex composed of Fos and Jun protein dimers, and although it has been associated with both pro- and anti-apoptotic roles depending on context, it is frequently linked to cancer progression (Ameyar et al., 2003). Curcumin has been shown to inhibit the binding of c-Jun and c-Fos to the promoter region of AP-1, mainly though suppressing the redox activity of apurinic/apyrimidinic endonuclease 1 (APE1). This redox function of APE1 is essential for maintaining the DNA-binding activity of AP-1, and its inhibition by curcumin reduces AP-1-mediated gene transcription, thereby attenuating pro-survival and pro-proliferation signalling pathways, as well as reducing oxidative stress (Li et al., 2019). Curcumin also suppresses the anti-apoptotic B-cell lymphoma 2 (Bcl-2), a well-known inhibitor of apoptosis. Downregulation of Bcl-2 by curcumin promotes mitochondrial outer membrane permeabilisation (MOMP), thereby triggering the intrinsic apoptotic pathway (Rao et al., 2011). Meanwhile, curcumin upregulates the apoptosis promoting factors BCL2 Associated X, Apoptosis Regulator (Bax) and Bcl-2 homologous antagonist killer (Bak) to enhance cellular apoptosis (Yang et al., 2015). Bax and Bak are essential, functionally interchangeable effectors of MOMP. Their activation leads to the release of mitochondrial intermembrane space proteins such as cytochrome *c*, which in turn activates the caspase cascade and amplifies the apoptotic response (Wong et al., 2019; Yamazaki and Galluzzi, 2022). Furthermore, curcumin promotes the cleavage of the BH3 interacting-domain death agonist (Bid), which facilitates Bax oligomerisation and accelerates cytochrome *c* release, ultimately leading to programmed cell death (Gogada et al., 2011).

Likewise, curcumin induces cell cycle arrest by downregulating the NF-κB, STAT3, COX-2, and most importantly, the PI3K/Akt pathway (Liu et al., 2018). The overexpression of PI3K/Akt pathway is implicated in cancer progression, leading to cancer hallmarks such as metastasis and cell survival. Mechanistically, activated PI3K transduces signals to the downstream effectors and recruits other oncogenic signalling proteins, including Akt. Following the activation of PI3K/Akt, the downstream substrates are recruited, resulting in the formation of protein complexes that promote cancer proliferation (He et al., 2021). Curcumin interferes with this pathway by directly targeting PI3K and Akt or by modulating their upstream regulators, such as IκB kinase β (IKKβ) and AMP-activated protein kinase (AMPK). Specifically, curcumin inhibits IKKβ and activates AMPK, both of which contribute to the downregulation of the mammalian target of rapamycin complex 1 (mTORC1), thereby suppressing the PI3K/Akt/mTOR signalling pathway (Zoi et al., 2024). Furthermore, curcumin has been found to downregulate cyclin D1, a proto-oncogene that is frequently overexpressed in various cancers. Notably, its gene (CCND1) is amplified in up to 20% of human breast cancers, and its protein is overexpressed in approximately 50% of cases (Mukhopadhyay et al., 2002). Cyclin D1 regulates the activity of Cyclin-Dependent Kinase 4 (CDK4), and together they form a complex that phosphorylates Rb. This phosphorylation event leads to the release of E2F, which promote the transcription of genes essential for G1 to S phase transition and DNA replication (Qie and Diehl, 2016). By downregulating cyclin D1, curcumin suppresses CDK4 activity, thereby preventing Rb phosphorylation and E2F activation, ultimately contributing to cell cycle arrest and the inhibition of cancer cell proliferation. Meanwhile, curcumin has been reported to resensitise cancer cells towards chemotherapy drugs by activating the tumour suppressor p53 and p21 genes (Liu et al., 2018). Both p53 and p21 tumour suppressors play a crucial role in regulating the cell cycle, allowing the cells to undergo cell cycle arrest. Once the p53 gene is activated, the p21 gene expression is upregulated. The high levels of p21 induce the formation of the retinoblastoma protein (Rb)-E2F protein complex, leading to the downregulation of cell cycle genes (Engeland, 2022). As a result, the reduced function of cell cycle genes leads to cell cycle arrest, conferring anticancer advantages.

Finally, curcumin has been shown to effectively induce oxidative stress in cancer cells, resulting in DNA damage. This process involves the upregulation of reactive oxygen species (ROS), and when ROS levels surpass the threshold concentration, cancer cell apoptosis is initiated, ultimately leading the cancer cell death (Qian et al., 2019). Larasati et al. (2018) also implied that curcumin exhibits a strong affinity for competing with the co-factors to bind to ROS-metabolic enzymes. This binding inhibits the catalysation of ROS, contributing to the upregulation of ROS levels and further suppressing cancer growth. The anticancer mechanisms mediated by curcumin are summarised in Figure 2.

**Figure 2**

*The main mechanisms of action of curcumin, targeting various molecular regulators implicated in cancer progression*




*Note: The arrows indicate the molecular regulators influenced by curcumin during its anticancer activities.* ▲ *shows upregulation while* ▼ *shows downregulation.*

## Cellular and molecular effects of curcumin in combination with breast cancer chemotherapy

The results based on the currently available evidence have proven the potential roles of curcumin in cancer treatment. In light of the pharmacological safety and efficacy of curcumin, its co-treatment with chemotherapeutic drugs may offer synergistic benefits, particularly in addressing key challenges such as chemoresistance and adverse side effects (Tan and Norhaizan, 2019; Younes et al., 2022). To date, there are various combinatorial treatments targeting different breast cancer molecular subtypes that have been demonstrated to exhibit effective results in enhancing the anticancer effects while minimising the side effects of chemotherapy drugs during treatment. This review explores the cellular and molecular effects of curcumin in combination with breast cancer therapies, highlighting its potential as a clinically effective anticancer treatment. The key findings from *in vitro* and *in vivo* studies are summarised in Table 1 and Table 2, respectively, with an overview provided in Figure 3.

### *Doxorubicin and curcumin*

Doxorubicin belongs to the Adriamycin family and is one of the most effective chemotherapy drugs used in treating different types of cancer, especially breast cancer. Doxorubicin mainly targets the mitotic cell cycle, associated with the production of free radicals to induce cellular apoptosis in carcinoma cells (Borghesi et al., 2020). Although doxorubicin works effectively in inducing apoptosis signalling, chemoresistance is still a predominant challenge. Due to the overactivation of MAPK and its interaction with the extracellular-signal-regulated kinase (ERK) pathway, this leads to poor cell death and sustained tumour growth in cancer cells (Christowitz et al., 2019). The activation of MAPK cascades is critical for promoting cancer proliferation, mainly by activating and phosphorylating the downstream proteins, including ERK1 and ERK2. Once the ERK cascades are hyperactivated, phosphorylated ERK1 and ERK2 translocate to the nucleus to regulate key cellular processes, including cancer cell proliferation (Guo et al., 2020). Notably, nuclear ERK is also able to activate various oncogenic TFs such as Ets-like kinase-1 (Elk-1), cellular-Fos (c-Fos), or cellular-MYC (c-Myc), further upregulating the oncogenic stimulation (Ebner et al., 2007). Moreover, doxorubicin treatment is a targeted therapy for TNBC, but epithelial-mesenchymal transition (EMT) was observed after long-term treatment. EMT triggers large-scale cancer cell movements and later invades other tissues, resulting in cancer metastasis (San & Ngai, 2024).

However, the addition of curcumin has been demonstrated to suppress the doxorubicin induced EMT. According to Chen et al. (2013), co-treatment of curcumin and doxorubicin significantly inhibited the EMT, transforming growth factor-β (TGF-β), and PI3K/Akt signalling, all of which promote cancer cell progression. The activation of PI3K leads to the conversion of PIP2 (Phosphatidylinositol 4,5-bisphosphate) to PIP3 (Phosphatidylinositol 3,4,5-trisphosphate), which acts as a docking site for Akt at the cell membrane. Once Akt is activated, it phosphorylates several downstream proteins, including Ras homologue enriched in the brain (RHEB), mammalian target of rapamycin (mTOR), and glycogen synthase kinase 3 (GSK3) (Arcaro and Guerreiro, 2007; He et al., 2021). Interestingly, GSK3 is typically active and suppresses cyclin D1 levels by phosphorylating it at threonine 286, marking it for degradation. However, when GSK3 is phosphorylated by Akt, it becomes inactive, leading to the stabilisation and accumulation of cyclin D1, which contributes to cell cycle progression (Hajka et al., 2021; Yang et al., 2006).

Moreover, EMT process is found to be modulated by Akt/mTOR pathway. The activation of mTOR by Akt phosphorylation leads to reorganisation of the actin cytoskeleton, mainly through altering the phosphorylation state of protein kinase C (PKC) (Jain and Basu, 2014; Roshan et al., 2019). This reorganisation of the actin cytoskeleton is a key step in the EMT process, as it allows for the migration and invasion of cells. Finally, the activation of Akt is also correlated with the thymidylate synthase (TS) activation, an enzyme essential for cell survival and often overexpressed in cancer cells (Dong et al., 2023). The TS pathway is regulated by Akt phosphorylation, ultimately leading to cell proliferation (Jiang et al., 2016).

Moreover, the addition of curcumin inhibited the doxorubicin-induced morphological changes and reduced the development of breast cancer into the aggressive stage. Based on the results of BT-20 (ER+) and MDA-MB-468 (TNBC) cell lines, the addition of curcumin inhibited the doxorubicin-induced downregulation of E-cadherin expression. The loss of E-cadherin at the primary tumour site promotes metastasis by allowing dissociation of epithelial cells to invade surrounding tissues (Na et al., 2020; San and Ngai, 2024). In normal epithelial cells, α-catenin links β-catenin to actin and links E-cadherin to the actin cytoskeleton, promoting the clustering of adherens junctions (AJs) (Tian et al., 2011). However, the loss of E-cadherin is often accompanied by the co-loss of catenins, leading to disrupted cell junctions and EMT (Borcheding et al., 2018). Therefore, by inhibiting the loss of E-cadherin expression, curcumin protects the cell junctions and controls epithelial cancer behaviour even after long-term exposure to doxorubicin. Furthermore, co-treatment of curcumin and doxorubicin enhanced the anti-proliferative effects on BT-20 cell lines. In short, the combination of curcumin and doxorubicin significantly reduced the cell viability, proving the efficacy of curcumin to resensitize breast cancer cells towards chemotherapy drugs (Chen et al., 2013).

To further confirm the synergistic potential of curcumin in combination with doxorubicin, an *in vivo* study on tumour-bearing mice has been conducted by Sen et al. (2011). Based on the results, curcumin reverted doxorubicin-induced resistance and provided a survival advantage to tumour-bearing mice. The combination of curcumin and doxorubicin partially prevented the reduction in viable immune cells caused by the tumour itself in the mice's spleen, bone marrow, and thymus, overall protecting the mice from immune suppression (Sen et al., 2011). Furthermore, the addition of curcumin was found to ameliorate the drug-induced systemic toxicity which causes severe liver and cardiovascular injuries. Compared to doxorubicin alone, the addition of curcumin has been reported to reduce toxicity and protect the functional immune cells of tumour-bearing mice.

*Paclitaxel and curcumin*

Paclitaxel (Taxol) is also one of the treatment options for primary and advanced breast cancers, particularly cancers that have started to spread to the lymph tissues. Paclitaxel binds to microtubule-associated proteins, thereby stabilising microtubules and disrupting their normal dynamic functions. This action induces mitotic arrest at the G2/M phase, inhibits spindle assembly and division, ultimately leading to the death of cancer cells (Schmidt et al., 2007). According to Quispe-Soto and Calaf (2016), co-treatment of curcumin and paclitaxel reduced the activation of NF-κB and Bcl-2 genes on MCF-7 (ER+ and PR+), and MDA-MB-231 (TNBC) cell lines. Meanwhile, the pro-apoptotic marker Bax was found to be upregulated in MDA-MB-231 cell lines, indicating that curcumin enhances mitochondria-dependent apoptosis by upregulating Bax while downregulating Bcl-2 gene expression. As a core regulator, Bax plays an important role in activating mitochondrial outer membrane (MOM) permeabilisation. The upregulation of Bax mediates mitochondrial permeabilisation and subsequently leads to the activation of downstream caspases, ultimately leading to programmed cell death (Peña-Blanco and García-Sáez, 2018; San et al., 2025).

In another experimental study, the results also implied that the addition of curcumin potentiated the paclitaxel effects in terms of growth inhibition and NF-κB suppression in the MDA-MB-231 cells. As aforementioned, NF-κB activation is essential for cancer progression and survival. However, the addition of curcumin has been shown to effectively suppress oncogenic NF-κB signalling while simultaneously inhibiting the stem-like properties of cancer cells. Notably, curcumin has been reported to downregulate the binding of NF-κB to DNA, reducing the functions of NF-κB in possessing chemoresistance and cancer proliferation (Wang et al., 2021). From the *in vitro* results, the addition of curcumin resensitised the cancer cells by reducing the matrix metalloproteinase-9 (MMP-9) expression that is involved in ECM remodelling and cancer progression (Kang et al., 2009). MMP-9 plays a critical role in facilitating cancer metastasis, mainly by modulating the ECM-related growth factors including VEGF,

fibroblast growth factor (FGF), and membrane-tethered EGF, as well as activating other oncogenic TFs like TGF-β (Juric et al., 2018). Altogether, MMP-9 upregulates the expression of pro-survival proteins, leading to sustained cancer survival. However, the combination of paclitaxel and curcumin effectively reduced MMP-9 expression, implying the synergistic potential of curcumin in breast cancer treatment.

An *in vivo* study on xenograft mouse models was also conducted by Kang et al. (2009) to further confirm the synergistic potential of curcumin in combination with paclitaxel. From the results, the addition of curcumin reduced the cell growth as well as the tumour size. Based on the tumour xenograft mouse model, the combination of curcumin and paclitaxel significantly inhibited tumour growth compared to control animals. Furthermore, MMP-9 expression which promotes tumour invasion was found to be weakly positive when the mouse was treated with curcumin and paclitaxel (Kang et al., 2009) The results further implied the synergistic potential of curcumin in reducing cell growth and cancer progression.

*Cisplatin and curcumin*

Cisplatin is well-known for its DNA-intercalating properties and has been recognised as a potential therapeutic agent in treating TNBC, a high-grade carcinoma subtype. Cisplatin exerts its effect by cross-linking with DNA bases, thereby disrupting RNA transcription and DNA replication, ultimately hindering the DNA repair mechanisms of carcinoma cells (Hill et al., 2019). As a result, this induces damage to cancer cells and promotes apoptosis. Moreover, cisplatin also functions as an antineoplastic agent by inhibiting neoplasm formation during the progression of malignant tumours.

According to the study conducted by Zou et al. (2018), the co-treatment of curcumin and cisplatin increased cancer cell chemosensitivity and enhanced the anticancer effects by inhibiting the overexpression of Flap endonuclease (FEN1) which is involved in cisplatin resistance. During cancer cell proliferation, the FEN1 endonuclease facilitates DNA repair in carcinoma cells and counteracts cisplatin-induced DNA damage. Based on the findings, the combination of curcumin and cisplatin downregulated FEN1 expression, while simultaneously enhancing cellular apoptosis and inhibiting proliferation of MCF-7 and MDA-MB-231 cell lines (Zou et al., 2018).

Despite the success of cisplatin in treating aggressive cancers, its long-term use has been associated with nephrotoxicity, characterised by tubular damage and inflammation in the kidneys (Kumar et al., 2017). However, the nephrotoxicity response was significantly reduced when curcumin is in combination with cisplatin. Based on the *in vivo* results, the co-treatment of curcumin and cisplatin substantially reduced the tumour weights and restored the kidney weights of the treated rats. Curcumin has been reported to suppress the NF-κB and TNF-α pathways that produce excess inflammatory cytokines and cause renal damage (Kumar et al., 2017). Overall, the results demonstrate that curcumin restored renal function by mitigating cisplatin-induced toxicity following long-term use.

*5-Fluorouracil (5-FU) and curcumin*

5-Fluorouracil (5-FU) is widely used as a first-line chemotherapy drug in the treatment of solid breast cancer tumours. Its therapeutic efficacy is greatly associated to the induction of cellular apoptotic pathways. During its anticancer activity, 5-FU incorporates into the RNA and DNA building blocks, disrupting their synthesis. It also inhibits TS, a key enzyme involved in DNA replication and cancer cell proliferation (Dong et al., 2023; Ponce-Cusi and Calaf, 2015). The combination of curcumin and 5-FU was discovered to have great potential for overcoming the undesirable side effects of chemoresistance. Based on the study conducted by Haritha et al. (2021), curcumin exhibited a higher affinity to TS co-factors and downregulated the TS pathway more effectively than 5-FU alone. The results showed that the co-treatment of curcumin and 5-FU significantly increased the apoptosis in MDA-MB-231 and HCC 1937 (TNBC) as well as BT474 (HER2+) cell lines.

Another study also proved that the co-administration of curcumin and 5-FU has reduced the cell viability of the MDA-MB-231 cell lines by downregulating the NF-κB pathway and later led to apoptosis (Vinod et al., 2013). Concurrently, the normal immortalised MCF10A cell lines were not affected, revealing that the curcumin and 5-FU combination is not toxic and safe for clinical use. The addition of curcumin also resensitised SK-BR-3 (HER2+) and MCF-7 cell lines and at the same time completely silenced the TS pathway. Therefore, this study revealed that the combination of curcumin and 5-FU is synergistic in enhancing the cellular apoptosis effects.

An *in vivo* study on the xenograft mice was also conducted by Haritha et al. (2021) to further confirm the synergetic potential of curcumin in combination with 5-FU. The results showed that the pretreatment of curcumin with 5-FU enhanced 5-FU mediated apoptosis by increasing the cleavage of poly ADP-ribose polymerases (PARPs) in xenograft mouse models. PARPs have a variety of cellular functions, such as DNA repair and programmed cell death. Under pathological conditions, PARPs are activated and play their role in repairing the DNA of carcinoma, ultimately persisting the survival of cancer cells (Morales et al., 2016). To this extent, activated PARPs catalyse the transfer of ADP-ribose units from nicotinamide adenine dinucleotide (NAD+) to amino acid residues, building poly ADP-ribose (PAR) chains on these target proteins. This process, known as mono- or poly-ADP-ribosylation, is involved in various key cellular processes and is present in nearly all eukaryotic cells (Fehr et al., 2020). The addition of PAR chains can be reversed by poly-ADP-ribose glycohydrolase (PARG), an enzyme that breaks down the PAR chains, releasing free ADP-ribose units to reattach to other breaks in another location (Curtin and Szabo,

2020). This recycling of ADP-ribose units enables further PAR synthesis. In contrast, the cleavage of PARPs, which is associated with the activation of caspase-3, represents a successful induction of programmed cell death (Han et al., 2023). This cleavage inactivates PARPs and prevents it from carrying out its normal function in DNA repair, leading to cell death. Notably, the addition of curcumin was found to not only inhibit the PARPs-DNA repair activities but also increase the cleavage of PARPs. Altogether, the addition of curcumin improved the efficacy of 5-FU. Based on the results, the tumour size of the mice models was reduced when 5-FU was co-administered with curcumin, implying the synergistic potential of curcumin.

*Carboplatin and curcumin*

Carboplatin, well-known as a derivative drug of cisplatin, was initially developed to reduce the nephrotoxicity of cisplatin in cancer treatment (Lynce and Nunes, 2021). Hence, the mechanisms of action of carboplatin and cisplatin are similar, and both also target the higher-grade carcinoma such as TNBC. Although cisplatin is more effective in treating cancers, carboplatin has lower toxicity and side effects, making it a more favourable choice when considering the toxicity profiles (Sousa et al., 2014).

Previous research has demonstrated that the co-treatment of curcumin and carboplatin has improved the sensitivity of resistant TNBC cells to carboplatin, thus enhancing the anticancer effects. According to the findings, curcumin sensitised the TNBC-resistant CAL-51-R and MDA-MB-231 cell lines to carboplatin by suppressing cancer proliferation and increasing apoptosis (Wang G et al., 2022). The addition of curcumin also drastically reduced the colony numbers of both CAL-51-R and MDA-MB-231 cell lines, further implying the potential of curcumin in enhancing the cytotoxic effects of carboplatin. Mechanistically, curcumin was found to upregulate the ROS production, leading to oxidative stress and apoptosis in tumour cells. This effect successfully restored the sensitivity of CAL-51-R and MDA-MB-231 cell lines to carboplatin.

In a further assessment, the upregulated ROS by curcumin was found to attenuate the DNA repair protein RAD51 and, in contrast, upregulate the expression of the DNA damage marker γH2AX (Wang G et al., 2022). During cancer progression, the overexpression of the RAD51 plays a critical role in repairing damaged DNA that is induced by anticancer agents. However, the upregulated ROS reverses the function of RAD51, mainly by suppressing the DNA damage response (DDR) signalling of the RAD51 (Wang Z et al., 2022). As a result, the function of RAD51 to induce DNA repair is depleted, potentiating the inhibitory effect on cancer growth.

Moreover, an *in vivo* study on Ehrlich ascites carcinoma (EAC)-bearing mice has been conducted by El-Azab et al. (2011) to further validate the anti-angiogenic effects of carboplatin in combination with curcumin. EAC is a spontaneous murine mammary adenocarcinoma that originates from the ascites form. To generate EAC cell lines, serial intraperitoneal (i/p) passage in outbred mice was first carried out in the laboratory (Jaganathan et al., 2010). Next, the mouse model was inoculated with EAC cell suspension to produce EAC tumour-bearing mice. According to the study, the combination of carboplatin and curcumin significantly suppressed cancer angiogenesis, which was reflected in the reduction of micro vessel density (MVD). The MVD is measured by counting vessels in the most vascularised tumour region, reflecting the capacity of cancer cells to form new capillary blood vessels during angiogenesis (Kraby et al., 2018). Based on the results, the MVD was found to be greatly reduced due to the VEGF inhibitory effect of curcumin at the plasma level. As aforementioned, VEGF plays a critical role in promoting angiogenesis through increasing vascular permeability. The addition of curcumin suppressed VEGF expression and its receptor, leading to reduced vascular density and permeability in EAC-bearing mice (El-Azab et al., 2011). Moreover, the tumour weight of the mice model was greatly reduced when the carboplatin was co-administered with curcumin, further implying the synergistic potential of curcumin in cancer treatment.

*Gemcitabine and curcumin*

Gemcitabine is classified as an antimetabolite chemotherapy drug and has been widely used to treat multiple cancers. Recently, gemcitabine has demonstrated efficacy in treating metastatic breast cancer, primarily through the inhibition of DNA synthesis. Previous research has shown that gemcitabine incorporates into DNA, halting chain elongation and ultimately inducing apoptosis (Sun et al., 2020). At present, gemcitabine is commonly combined with other drugs such as paclitaxel, epirubicin, and 5-FU to treat the more advanced cancer stages.

Based on the study conducted by Serasanambati et al. (2013), curcumin enhanced the anticancer effect of gemcitabine in breast cancer treatment, primarily by suppressing NF-κB activity. The combination of curcumin and gemcitabine was found to significantly inhibit cell proliferation, reducing the survival rates of MCF-7 and MDA-MB-231 cell lines. Furthermore, the addition of curcumin increased the percentage of apoptotic cells, implying the potential of curcumin in enhancing the gemcitabine-induced cytotoxicity. It is well known that NF-κB plays a critical role in cancer cell survival and proliferation, which has been reported in many cancer cases. Similar to other drug combinations, curcumin mainly targets and suppresses the expression of NF-κB, enhancing the synergistic effects of gemcitabine.

To further confirm the synergistic potential of curcumin in enhancing the activity of gemcitabine, an *in vivo* study on tumour-bearing female Sprague-Dawley (SD) rats was conducted by Jain et al. (2014). Based on the results, the tumour volumes of SD rats were significantly reduced after the co-treatment of gemcitabine and

curcumin. The SD rats remained in good condition following the initial dose of treatment, suggesting that curcumin contributed to enhancing their survival (Jain et al., 2014). As compared to gemcitabine only, the SD rats co-treated with gemcitabine and curcumin exhibited lower oxidative stress with a reduction of aspartate transaminase (AST) and alanine transaminase (ALT) enzymes in the plasma. The treatment of gemcitabine is often associated with drug-induced hepatotoxicity, which causes liver injury and failure in patients (Robinson et al., 2003). Hence, the leakage of AST and ALT from damaged hepatocytes into the bloodstream resulted in high transaminase enzymes in the bloodstream during liver injury (Gao et al., 2016). However, curcumin plays its antioxidant role, reducing the gemcitabine-induced hepatotoxicity and helping to maintain liver function of SD rats.

**Table 1**

*In vitro research studies of curcumin in combination of breast cancer chemotherapy*

| Types of combination | Cell lines | Effects/Outcomes | Mechanisms | References |
|---|---|---|---|---|
| **Doxorubicin + Curcumin** | BT-20 (ER+)<br>MDA-MB-468 (TNBC) | 1. Anti-proliferation<br>2. Inhibition of drug-induced morphological changes<br>3. Resensitisation of cancer cells | 1. Inhibition of EMT<br>2. Suppression of TGF-β and PI3K/Akt<br>3. Inhibition of E-cadherin loss | Chen et al., 2013 |
| **Paclitaxel (Taxol) + Curcumin** | MCF-7 (ER+, PR+)<br>MDA-MB-231 (TNBC) | 1. Growth inhibition<br>2. Enhancement of cellular apoptosis<br>3. Resensitisation of cancer cells | 1. Suppression of NF-κB, Bcl-2<br>2. Upregulation of Bax<br>3. Reduction of MMP-9 expression | Kang et al., 2009<br>Quispe-Soto and Calaf, 2016 |
| **Cisplatin + Curcumin** | MCF-7 (ER+, PR+)<br>MDA-MB-231 (TNBC) | 1. Increase in cancer cell chemosensitivity<br>2. Anti-proliferation<br>3. Enhancement of cellular apoptosis | 1. Downregulation of FEN1 overexpression | Zou et al., 2018 |
| **5-Fluorouracil (5-FU) + Curcumin** | MDA-MB-231,<br>HCC 1937 (TNBC)<br>BT474, SK-BR-3 (HER-2+)<br>MCF-7 (ER+, PR+) | 1. Increase in apoptotic cells<br>2. Reduction of drug resistance<br>3. Reduction of cell viability | 1. Downregulation of TS pathway<br>2. Downregulation of NF-κB | Haritha et al., 2021<br>Vinod et al., 2013 |
| **Carboplatin + Curcumin** | MDA-MB-231 (TNBC)<br>CAL-51-R (TNBC resistant) | 1. Resensitisation of cancer cells<br>2. Anti-proliferation<br>3. Increase in apoptotic cells | 1. Upregulation of ROS production<br>2. Attenuation of the DNA repair protein (RAD51)<br>3. Upregulation of the DNA damage marker ( γH2AX) | Wang G et al., 2022 |
| **Gemcitabine + Curcumin** | MDA-MB-231 (TNBC)<br>MCF-7 (ER+, PR+) | 1. Anti-proliferation<br>2. Increase in apoptotic cells | 1. Suppression of NF-κB | Serasanambati et al., 2013 |

*Note: In vitro (cell lines) studies of the cellular and molecular effects, as well as the main mechanisms of action are summarised.*

**Table 2**

*In vivo research studies of curcumin in combination of breast cancer chemotherapy*

| Types of combination | Animal models | Effects/Outcomes | Mechanisms | References |
|---|---|---|---|---|
| **Doxorubicin + Curcumin** | Tumour-bearing mice | 1. Reduction of drug induced toxicity<br>2. Reduction of drug-indued resistance | 1. Protection from immune suppression<br>2. Partially prevention of the reduction in viable immune cells caused by the tumour itself in the mice's spleen, bone marrow, and thymus | Sen et al., 2011 |
| **Paclitaxel (Taxol) + Curcumin** | Xenograft mouse | 1. Reduction of tumour size<br>2. Suppression of tumour progression | 1. Suppression of MMP-9 expression | Kang et al., 2009 |
| **Cisplatin + Curcumin** | Tumour-bearing rats | 1. Reduction of nephrotoxicity<br>2. Restoration of renal function | 1. Suppression of NF-κB and TNF-α<br>2. Suppression of inflammation cytokines | Kumar et al., 2017 |
| **5-Fluorouracil (5-FU) + Curcumin** | Xenograft mice | 1. Reduction of tumour size<br>2. Downregulation of carcinoma's DNA repair | 1. Increase in PARPs cleavage | Haritha et al., 2021 |
| **Carboplatin + Curcumin** | EAC-bearing mice | 1. Anti-angiogenesis<br>2. Reduction of tumour weight | 1. Reduction of MVD<br>2. Inhibition of VEGF expression | El-Azab et al., 2011 |
| **Gemcitabine + Curcumin** | Tumour-bearing female SD rats | 1. Reduction of tumour volumes<br>2. Reduction of hepatotoxicity<br>3. Reduction of oxidative stress | 1. Antioxidative<br>2. Reduction of AST and ALT enzymes | Jain et al., 2014 |

*Note: In vivo (animal models) studies of the cellular and molecular effects, and the main mechanisms of action are summarised.*

## Clinical trials of curcumin in breast cancer treatments

Up to the present, clinical trials have confirmed the anticancer properties of curcumin such as chemopreventive, antioxidant, anticancer, and anti-inflammatory. Research into curcumin remains active, though only a limited number of clinical trials have been completed and documented to date.

*Monotherapy of curcumin*

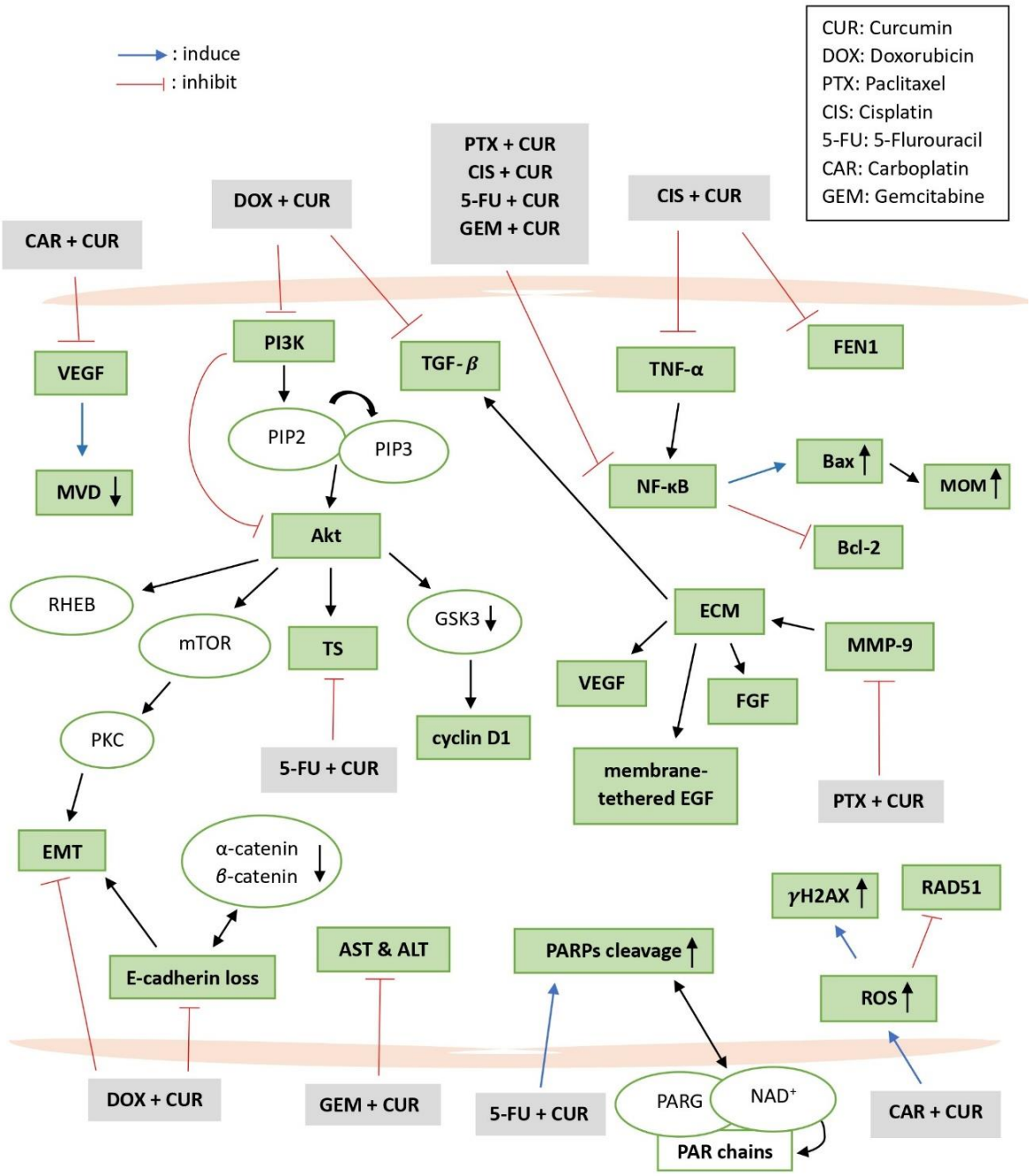
In a phase I clinical trial, 500 mg of curcumin was distributed to 20 breast cancer patients twice a day immediately after meals. According to the apoptosis and cell proliferation (Ki67 assay) research findings, a decline in cancer cell proliferation was observed in the time frame of 0 - 56 days (ClinicalTrials.gov, 2021).

In another phase II clinical trial, daily dosages of 1,125 to 2500 mg of curcumin were given to 30 breast cancer patients. The results have confirmed the efficacy of curcumin in decreasing inflammation in breast tissues. Additionally, Meriva type (formulated curcumin with lecithin) was given at 500 mg twice a day to the patients.

The results showed that the formulated curcumin is effective in inhibiting NF-κB activity as well as reducing the fatigue side effects caused by excessive NF-κB signalling (ClinicalTrials.gov, 2019). NF-κB plays a crucial role in mediating cancer progression, and it is well-known for its role in regulating inflammation, cell proliferation, and cell death. Previous research has highlighted the pivotal role of NF-κB in cancer survival, demonstrating its ability to interact with other TFs to activate genes that promote cell proliferative and pro-inflammatory cytokines production, resulting in sustained cancer proliferation accompanied by chronic inflammation (Taniguchi and Karin, 2018). Furthermore, excessive NF-κB activation has been demonstrated to protect cancer cells from necrosis factor-alpha (TNF-α)-induced apoptosis, leading to uncontrolled cell proliferation and insensitivity to cell death (Zinatizadeh et al., 2021). However, the use of curcumin has been reported to effectively downregulate NF-κB activation and reduce the unwanted side effects, implying the clinical benefits of curcumin in cancer treatments.

**Figure 3**

*The underlying mechanisms of curcumin in combination with various breast cancer chemotherapy drugs*




*Note: The cellular and molecular pathways regulated by the curcumin combinational treatments are summarised. Green box: Molecular targets regulated by curcumin during anticancer activity. Blue arrows: Upregulation of the molecular targets. Red lines: Suppression and inhibition of the molecular targets.*

In addition, clinical trials have evaluated the role of curcumin in mitigating treatment-related side effects in breast cancer patients. In a randomised, double-blind phase II clinical trial involving 30 breast cancer patients, oral curcumin at a dose of 6 g/day (2 g, three times daily) was administered during postoperative radiotherapy (ClinicalTrials.gov, 2012). Patients were randomly assigned to receive either Curcumin C3 Complex—a standardised extract containing 95% curcuminoids, or a matching placebo to ensure unbiased comparison. The findings revealed that curcumin significantly reduced the severity of radiation-induced dermatitis and decreased the incidence of moist desquamation, indicating its potent anti-inflammatory properties and potential to improve treatment tolerability (Ryan et al., 2013). In another randomised phase II clinical trial involving 191 breast cancer patients, the therapeutic potential of a topical curcumin gel was assessed for the prevention of radiation-induced skin toxicity (Abdeahad et al., 2024). Patients applied either a curcumin-based gel, HPR Plus™ (a commonly used moisturising agent), or a placebo gel approximately every 4–6 hours throughout their radiotherapy course and for one week after completion. The results demonstrated that curcumin gel effectively reduced the severity of radiation-induced dermatitis, particularly skin redness and discomfort, further supporting its role in improving the tolerability of conventional cancer treatments (ClinicalTrials.gov, 2017).

Collectively, this evidence supports the role of curcumin as a potent anticancer agent with a great potential for enhancing anticancer effects in combination with conventional therapies such as chemotherapy, notably by targeting molecular pathways like NF-κB and its downstream signalling cascades. Curcumin also has been demonstrated its significant effects in reducing the hallmarks of cancer, including inflammation and undesirable side effects. In parallel, clinical evidence has shown the potential of curcumin in alleviating treatment-related toxicities, such as radiation-induced dermatitis and associated discomfort. These findings further highlight curcumin's role in improving treatment tolerability as part of supportive care in breast cancer management.

While curcumin alone has demonstrated clinical benefits, its therapeutic efficacy as a monotherapy remains modest. The absence of significant tumour regression or long-term disease control in clinical settings has prompted growing interest in combination strategies that pair curcumin with conventional chemotherapeutic agents. Such approaches aim to enhance overall treatment efficacy, reduce toxicity, and overcome resistance. Therefore, the following section highlights the anticancer effects of curcumin in combination with conventional chemotherapeutic drugs in the completed clinical trials, highlighting their effects on treatment efficacy, safety, and tolerability.

*Curcumin in combination with breast cancer chemotherapy*

Building upon the promising research findings from both *in vitro* and *in vivo* studies, as well as clinical evidence reviewed in this study, curcumin demonstrates its synergistic effects in enhancing the cytotoxicity effects of breast cancer chemotherapy drugs. These findings have sparked growing interest in combination therapies, with clinical trials offering further evidence of their therapeutic potential.

Currently, two clinical trials evaluating curcumin in combination with breast cancer chemotherapy have been completed, summarised in Table 3.0. In a phase I clinical trial, docetaxel (100 mg/m2) was given as an intravenous (IV) infusion every 3 weeks for 6 cycles in combination with the oral administration of 500 mg curcumin for 7 consecutive days to 14 patients. Docetaxel is one of the new antineoplastic agents, widely used to treat patients with metastatic breast cancer. The mechanism of action of docetaxel is similar to that of paclitaxel, also targeting microtubule assembly. Remarkably, docetaxel is categorised as a tubulin-stabilising agent that enhances the stability of microtubules, primarily by preventing their depolymerisation (Shimoyama et al., 2001). The depolymerisation of microtubules disrupts the function of cell cycle, hindering the cancer cells from division. As a result, docetaxel leads to cell cycle arrest in G2/M phase and apoptosis in cancer cells (Imran et al., 2020). Previous research has showed that the co-treatment of curcumin and docetaxel was synergistic in enhancing the anticancer effects. According to the results, improvements in biological markers were observed in the patients. Specifically, the carcinoembryonic antigen (CEA) tumour and VEGF markers were significantly reduced from the third cycle (Bayet-Robert et al., 2010). Further investigation on the maximal tolerated dose of curcumin in combination with docetaxel was performed. At the highest curcumin dosage level (8000 mg), 3 out of 14 patients were found to experience dose-limiting toxicities, and 2 out of the 3 patients at this dosage level declined further treatment. Therefore, the maximal tolerated dose of curcumin was determined to be 8000 mg.

Another phase II clinical trial randomly assigned 150 patients with metastatic breast cancer to receive either weekly paclitaxel (80 mg/m2) plus placebo, or weekly paclitaxel (80 mg/m2) in combination with curcumin (300 mg solution IV injection) for 12 weeks. Based on the primary results, the objective response rate (ORR) of paclitaxel in combination with curcumin was higher than the paclitaxel plus placebo at the 4th week of follow up. A significant difference was detected in both groups for the patients who had completed the treatment for 3 months. Moreover, the higher ORR in the curcumin group was maintained for 3 months after treatment was completed, implying the lasting additive effects of curcumin when in combination with paclitaxel. Furthermore, the secondary results after 24 weeks of the treatment also showed improvement. The progression-free survival (PFS) of cancer in the curcumin group was 2.4 weeks longer compared to paclitaxel alone (Saghatelyan et al., 2020). The physical condition of the paclitaxel group in combination with the curcumin group was also improved, proving that curcumin is pharmacologically safe and well-tolerated when in used with chemotherapy drugs.

**Table 3**

*Completed clinical trials of curcumin in combination with breast cancer chemotherapy*

| Trial | Main goals | Methods | Final outcomes | References |
|---|---|---|---|---|
| **Phase I Docetaxel and curcumin in advanced and metastatic breast cancer** | 1. Determine the maximal tolerated dose of curcumin<br>2. Confirm the synergistic potential of curcumin | 14 patients:<br>1. Docetaxel (100 mg/m$^2$), IV infusion every 3 weeks for 6 cycles<br>2. Oral administration of 500 mg curcumin for 7 consecutive days | 1. Limited 3 toxicities out of 14 patients<br>2. Maximal tolerated dose of curcumin is 8000 mg<br>3. CEA markers were significantly decreased from the 3$^{rd}$ cycle<br>4. VEGF markers were decreased by 30% between baseline and 3$^{rd}$ cycle, while -21% between baseline and 6$^{th}$ cycle | Bayet-Robert et al., 2010 |
| **Phase II Paclitaxel and curcumin compared to paclitaxel placebo in advanced and metastatic breast cancer** | 1. Identify the significance difference between combination and paclitaxel placebo<br>2. Study the pharmacokinetic effects of curcumin in this combination | 150 patients:<br>1. Phase I-random assignment of weekly paclitaxel (80 mg/m$^2$) plus placebo or weekly paclitaxel (80 mg/m$^2$) and curcumin 300 mg IV injection for 12 weeks<br>2. Phase II-continuous treatment for 24 weeks | Phase I<br>1. ORR of paclitaxel in combination with curcumin was significantly higher than paclitaxel plus placebo<br>2. High ORR in curcumin group was maintained for 3 months after treatment<br>Phase II<br>1. PFS of curcumin group was 2.4 weeks longer than paclitaxel group<br>2. Physical condition was improved in curcumin group | Saghatelyan et al., 2020 |

*Note: The main goals, methods, and final outcomes of the human clinical trials are summarised.*

**Nanoformulation of curcumin in combination with breast cancer chemotherapy**

Despite the achievements of curcumin in enhancing the synergistic anticancer effects, the low oral bioavailability of curcumin is a major limitation. The main reasons for this circumstance are due to its chemical instability, poor aqueous solubility, and rapid degradation. Consequently, this causes a minimally effective response, and the concentrations of curcumin in blood plasma and tissue are extremely low, or even undetectable (Lopresti, 2018). To overcome this limitation, nanoparticle formulation of curcumin is an alternative treatment, and recent studies have proven the efficiency of nanocurcumin in enhancing drug absorption in the body. The mechanisms underlying this nanoformulation are mainly attributed to its physicochemical properties, particularly particle size and surface characteristics. Overall, the nanoparticles with small sizes are more stable and contribute to the increase in surface area to volume ratio, ultimately enhancing the reactivity and distribution of curcumin among tissues (Gera et al., 2017). Additionally, the hydrophilic surface properties of curcumin enhance its accumulation at the target site, contributing to improved oral bioavailability.

Therefore, recent breast cancer research has focused on nanocurcumin in combination with nanopackaged chemotherapy drugs to enhance treatment efficacy. Previous research has suggested that the encapsulation of chemotherapy drugs by nanomaterials might be an innovative solution to mitigate the limitations of conventional chemotherapy. For instance, one of the major advantages of nanopackaged chemotherapy drugs is targeted site delivery. Due to the smaller size of nanoparticles, they target specific cells by enhancing cell permeability and thus achieving a higher retention rate (Cheng et al., 2021). Compared to traditional drugs, targeted delivery allows the drugs to be released in a controlled pathway, protecting normal tissues from cytotoxicity.

Based on an *in vitro* study, cisplatin was nanoformulated and co-delivered with nanocurcumin into MCF-7 cell lines. The results showed that the combination of both curcumin and nanoformulated cisplatin is effective in improving the synergistic anticancer effects. The cancer growth of MCF-7 cells was significantly suppressed, implying the great potential of nanoformulation in enhancing the efficacy of therapeutic regimens (Nguyen et al., 2018). In another *in vitro* study, the nanocurcumin in combination with nanopackaged doxorubicin also showed

a significant suppression of the cell viability in MCF-7 cell lines. It was reported that the drugs accumulated at the greatest level and efficiently eliminated the cancer cells when they were nanopackaged (Motevalli et al., 2019). Collectively, both studies showed that the co-administration of nanocurcumin and nanopackaged chemotherapy drugs has the potential to enhance the anticancer effects.

### Research gap and future direction

Despite the achievements of curcumin in reducing the chemoresistance and adverse toxicity of breast cancer combination therapy, minimal side effects such as diarrhoea, headache, rash, and yellow stool occur when the high doses of curcumin are used (Hewlings and Kalman, 2017; Hsu et al., 2023). Therefore, future studies should examine curcumin preparations with high absorption rates, such as nanoformulations, which potentially reduce the dosages of curcumin.

Furthermore, future studies should focus more on the synergistic effects of combining curcumin with other natural plant ingredients to enhance the efficacy of cancer treatment. A combination of plant derived natural compounds is safer, not toxic, more cost-effective, and nutritionally beneficial compared to chemotherapy drugs. For instance, the combination of curcumin with berberine (root derived from *Rhizoma coptidis*) has demonstrated synergistic chemopreventive effects by inducing cellular apoptosis in breast cancer cell lines. Natural ingredients have been demonstrated to be the potential alternatives to chemotherapy drugs, which modulate multiple cellular targets and induce caspase-dependent apoptosis signalling pathways (Wang et al., 2016). Furthermore, a combination of natural compounds has shown a higher cumulative effect for breast cancer treatment. According to earlier research, the combination of curcumin and citral (*Cymbopogon citratus*) was effective in inducing cell cycle arrest and apoptosis in breast cancer cell lines. Moreover, the co-treatment of phytonutrients not only shows chemopreventive but also has the potential to overcome the systemic toxicity of chemotherapy drugs, suggesting that the combination of phytonutrients may be a sustainable alternative for breast cancer treatment (Patel et al., 2015). Therefore, future research should focus on combining curcumin with a variety of natural compounds and prioritising comprehensive clinical studies to further validate its therapeutic potential.

To date, only two human clinical trials on the curcumin combinational therapies have been completed as summarised in Table 3.0. Additional clinical trials are essential to establish an appropriate starting-dose, assess potential toxicity side effects, and confirm the validity of findings from *in vitro* and *in vivo* studies. Notably, clinical trials remain the gold standard for evaluating new treatments, as their outcomes provide robust and reliable evidence to determine whether novel treatments can effectively address the limitations of the conventional therapies (Heneghan et al., 2017). However, current clinical trials show a lack of diversity in outcomes, which limits their ability to provide a more validated and consistent result. To ensure broader representation, future studies should recruit participants from underrepresented populations, including individuals with genetic variations, older adults, and those living with illnesses or disabilities. This approach enables the research outcomes to more effectively confirm the safety and efficacy of new drugs, maximising their benefits across diverse communities (Hindorff et al., 2018). Furthermore, clinical trials are essential to generate comprehensive and informative outcomes to support the efficacy of curcumin in breast cancer treatment. However, to date, only one combination therapy involving curcumin has been successfully completed a phase II clinical trial, highlighting the need for additional studies to produce more validated clinical evidence.

## CONCLUSION

The combination of natural plant ingredients like curcumin and chemotherapy drugs is an innovative treatment to overcome the chemoresistance of conventional breast cancer therapy. The co-treatment of curcumin and chemotherapy drugs not only enhances the resensitisation of cancer cells to treatment but also helps to mitigate the adverse toxic effects commonly induced by these drugs. Curcumin is also well-tolerated in animal studies, and the clinical outcomes showed significant improvements in recovering from chemoresistance side effects. Moreover, the underlying mechanisms of curcumin primarily involve the regulation of various molecular targets and the underlying signalling pathways, which are implicated in cell proliferation, metastasis, inflammation, and apoptosis. As a result, the regulation of the molecular targets effectively inhibits cancer progression into an aggressive stage. Furthermore, the *in vitro*, *in vivo*, and human clinical trials of the various combinational therapies shown in this review implied the synergistic potential of curcumin in enhancing the cytotoxicity effects of the drugs.

Nanocurcumin, on the other hand, demonstrated a significant impact in mitigating low oral bioavailability and systemic drug toxicity when combined with nanopackaged chemotherapy drugs. *In vitro* studies have demonstrated the effectiveness of nanoformulations in overcoming the limited therapeutic response of conventional treatments, suggesting that incorporating nanoformulated curcumin into combination drug therapies could be a promising strategy for future breast cancer treatment. In short, curcumin-based combination therapy shows significant potential as an effective approach for breast cancer treatment. However, further human clinical trials are essential to validate the clinical reliability of curcumin in breast cancer treatment.

## AUTHOR CONTRIBUTIONS

Ser Hui San was responsible for the acquisition and analysis of data, as well as manuscript writing. Siew Ching Ngai, as the supervisor, contributed to the conception and design of the study, critically revised the manuscript, and approved the final version for publication.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest in this work.

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