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SYSTEMATIC REVIEW: THE SYNERGISM OF CONVENTIONAL ANTI CANCER AGENTS WITH SECONDARY METABOLITE COMPOUNDS OF MEDICINAL PLANTS FOR AS ANTI BREAST CANCER

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ABSTRACT

Breast cancer (BC) is the leading cause of cancer-related deaths in women worldwide. Immediate treatment is required for this condition. However, undesirable side effects can occur during conventional cancer treatment. Secondary metabolite compounds derived from plants are the most popular alternative treatments for reducing side effects. Various medicinal plant compounds have been identified that exhibit anti-BC properties. This review aimed to summarize the research on the synergistic effects of secondary metabolite compounds of medicinal plants-drug interactions, with a focus on BC treatment. The method of this study was carried out systematically by searching articles from databases, such as PubMed, Scopus, and Science Direct for original research articles and using the keywords "drug synergism, herbal, and breast cancer treatment". The potential of combining herbal medicines or natural products with conventional drugs has been systematically explored in several studies. The screening results showed that 13 studies on the synergistic effect of chemical compounds from medicinal plants have a significant BC therapeutic effect when used with conventional drugs. Most studies have been conducted in vitro, but there is also one clinical trial in which treatment with the curcumin-paclitaxel combination was superior to paclitaxel monotherapy. Exploring the synergistic effects of combinations is technically demanding and complex, including in the context of drug or herb interactions, but is likely to provide significant progress in BC treatment. In conclusion, all secondary metabolites of medicinal plants listed in this review have synergistic effects with BC drugs.

Keywords: Synergism, conventional drugs, secondary metabolite compounds, BC treatment

INTRODUCTION

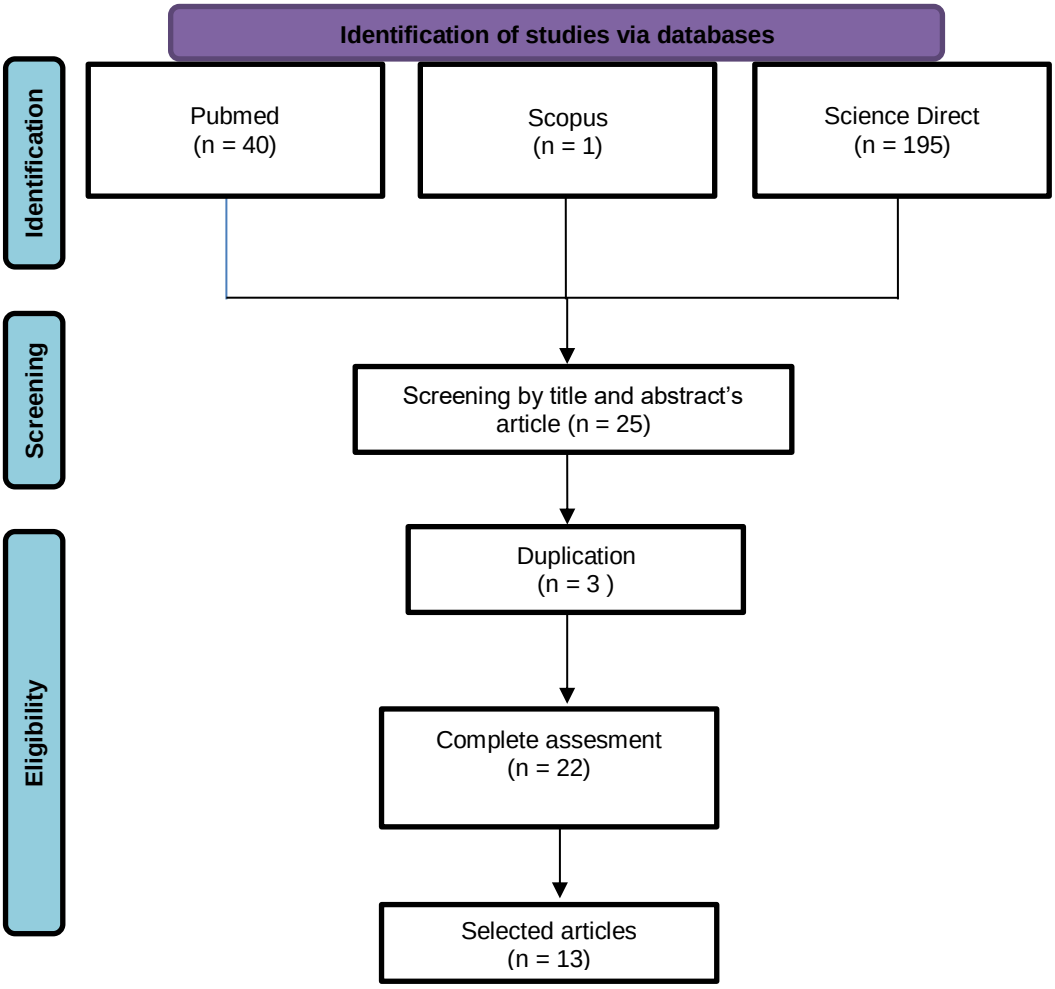
Cancer is a disease characterized by abnormal and uncontrolled cell growth and the ability to attack and move between cells and body tissues (Kementerian Kesehatan RI, 2024). Cancer is one of the leading causes of death worldwide. The globe reached a major milestone in 2021. Ten million people died from cancer, and an estimated 20 million were diagnosed with cancer. In the coming decades, this figure will continue to rise. However, all cancers can be prevented, treated, or cured. Cancer cases throughout the world are predicted by the World Health Organization (WHO) to soar by 77 percent or reach 35 million sufferers in 2050 (WHO, 2024). Breast cancer (BC) is a disease that often affects women, with a proportion of 30.8% of the total cases of other cancers (Setnasasean, 2021). According to the Global Cancer Observatory (GLOBOCAN) data in 2020, the number of new cases of BC in Indonesia reached 68,858 (16.6%) out of a total of 396,914 cases. The death toll exceeded 22, 000. In Indonesia, there were 3,404 cases of BC and 18,150 cases of breast tumors, from 38 provinces the highest was in Central Java Province with 3,206 cases, second in East Java Province with 3,077 cases, and third in DI Yogyakarta Province with 1,985 cases, while in Bengkulu Province there were as many as 44 cases of breast tumors and 13 suspected cases of BC (Kementerian Kesehatan RI, 2019).

There are several risk factors associated with BC, including excessive weight gain, especially after menopause; rapid increase in height during puberty; fast food that contains a

lot of saturated fat and eating too sweet foods; alcoholic drinks; the influence of hormones and reproductive factors, such as menarche or first menstruation at a young age (less than 12 years); giving birth to the first child at an older age (above 35 years); menopause at an older age (above 50 years); long-term use of oral contraceptives (> 7 years old); infertility or barrenness; not being married; not breastfeeding children; exposure to ionizing radiation during breast growth; genetic or hereditary factors; and having ever suffered from benign breast tumors. There are several other important factors that cause BC, such as progesterone or estrogen intake, lifestyle and endocrine aspects including exogenous and endogenous, and women with high mammographic density (Kurniasih, 2014).

The first course of treatment for breast cancer usually includes surgical excision (such as lumpectomy or mastectomy), followed by adjuvant therapies, including radiation therapy or chemotherapy. The standard for non-metastatic breast cancer is surgery-based local therapy, with adjuvant systemic treatments (chemotherapy, radiotherapy, endocrine therapy, or targeted therapy) advised to lower recurrence and increase survival, according to a number of clinical guidelines and reviews that support this strategy (J. Wang & Wu, 2023). However, chemotherapy can pose a risk of long-term toxicity and side effects and is relatively expensive compared to other treatments. The active ingredients of medicinal plants are expected to work synergistically and complement each other with chemotherapy to form certain bonds, thus increasing the effectiveness of treatment, reducing side effects, and minimizing drug resistance (Dona et al., 2019). According to earlier studies, doxorubicin intercalates into DNA, inhibits topoisomerase II, and generates reactive oxygen species (ROS), which leads to DNA damage, activation of apoptotic pathways, and ultimately cancer cell death. In breast cancer cells, doxorubicin induces apoptosis by upregulating pro-apoptotic proteins (BAX), caspases, and downregulating anti-apoptotic proteins (BCL-2), while also increasing ROS and activating JNK signaling pathways (Kciuk et al., 2023). Regarding side effects, doxorubicin is known to cause cardiotoxicity (heart damage), myelosuppression (reduced blood cell production), nausea, vomiting, hair loss, and fatigue (Thorn et al., 2011). For example, doxorubicin was combined with peiminine in in vitro and in vivo studies. The results showed that the combined effects of doxorubicin and peiminine on DNA damage and cell survival were reduced by ZEB1 knockdown. Tumor growth was significantly suppressed by in vivo test (Xu et al., 2024). This review summarizes the synergism between BC drugs and plant-derived secondary metabolites. The author hopes that this study can be used as a reference to develop more research on the synergism of BC drugs and other secondary metabolites from medicinal plants to develop an effective strategy for BC treatment.

RESEARCH METHOD



Tools and Materials

The article review was carried out systematically by searching databases from PubMed, Scopus, and Science Direct for original research articles with a combination of keywords in English: "drug synergism, herbal, and breast cancer treatment." Article searches were not limited by date but included all relevant publications available in English.

Article Selection Criteria

The inclusion criteria were full-text articles in English and articles discussing combination treatments that have a synergistic effect between conventional drugs and secondary metabolites from medicinal plants for BC treatment, in vitro, in vivo, and clinical tests. The articles were not limited by date. The exclusion criteria were articles discussing the synergism of breast cancer drugs and medicinal plants with complex metabolite compounds.

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Research Procedure

Data from the selected articles were manually extracted. The key features of this study include the combination of traditional medications with secondary metabolites, their synergistic impact mechanisms, cancer cell types, techniques, and data-displaying tables. Additionally, details about the author and year of release are provided. Following the search procedure, 236

items were identified in the full database. All article titles pertaining to the use of secondary metabolites in conjunction with conventional medications for the treatment of BC were sent to Mendeley for reprocessing. Abstract-based article screening. The inclusion criteria comprised 25 studies that examined the use of secondary metabolites in conjunction with conventional medications for the treatment of BC. Sorting the Mendeley application eliminated duplicate articles, leaving 13 entries. Every selected article had full text. Thirteen articles were still being debated in the literature review.

RESULTS AND DISCUSSION

Table I. Synergistic Effect Between Conventional Drugs And Secondary Metabolite Compounds Of Medicinal Plants As BC Therapy

Conventional drugs	Secondary metabolite compounds	Study design	Object	Results	Reference
Doxorubicin	Peiminine	In vitro and in vivo	MDAMB-231 cells and mouse	In vitro: reduce cell viability (50%), comet assay (Induce DNA damage) In vivo: suppress tumor growth	(Xu et al., 2024)
	Furanodiene	In vitro	MDA-MB-231	Reduce cell viability (35.29%)	(Z. F. Zhong et al., 2016)
	Forskolin	In vitro	MDA-MB-231 and MDA-MB-468 cells	Reduce cell viability (±50%), cell cycle profile	(Illiano et al., 2018)
	Evodiamin	In vitro	MCF-7 cells	Reduce cell viability (±40%), increase apoptotic cell (30.05%)	(S. Wang et al., 2014)
	Erianin	In vitro	MDA-MB-231 and MCF-7 cells	Reduce cell viability MDA-MB-231 (28.14%), MCF-7 (43.17%)	(Xie et al., 2021)
	Ursolic acid	In vitro	MCF-7 cells	Combination index (0.5)	(Zong et al., 2019)
Paclitaxel	Curcumin	Clinical test	Patients with metastatic and advanced BC	Superior efficacy. ORR 50.7%	(Saghatelyan et al., 2020)
	Curcumin	In vitro and in vivo	MCF-7 cells and mouse	Reduce cell viability (±60%), suppress tumor growth	(Yang et al., 2017)
	Acetoxyeugenol acetate (AEA)	In vitro	MCF-7 cells	Combination index (0.51 – 0.66)	(Aun et al., 2011)
Metformin	Formononetin	In vitro	MCF-7 cells	Combination index 0.760	(Xin et al., 2019)
Celecoxib	Asetilbritannilakton (ABL)	In vitro	MDA-MB-231, MDA-MB-468, and MCF-7 cells	Combination index < 1	(B. Liu et al., 2011)
Conventional drugs	**Secondary metabolite compounds**	**Study design**	**Object**	**Results**	**Reference**
5-fluorouracil (5-FU)	Proanthocyanidins	In vitro	MDA-MB-231 cells	Combination index 0.5	(Chen et al., 2017)

Digitoxin	Actein	In vitro	MDA-MB-453 and BT474 cells	Combination index 0.6	(Einbond et al., 2008)

Combination Index (CI) <1, =1, and >1 indicated synergism, additive effect, and antagonism, respectively
Lower cell viability after treatment with anticancer agents is typically regarded as a good result
Note: The efficacy result in a clinical trial is typically reported as the degree to which a treatment or intervention achieves its intended therapeutic effect under controlled conditions. Common efficacy results include the objective response rate (ORR), which is the percentage of patients whose tumors shrink or disappear after treatment.

The results of these studies show the synergistic effect of conventional drugs and secondary metabolites from medicinal plants for BC treatment. Conventional drugs such as doxorubicin, paclitaxel, metformin, celecoxib, 5-fluorouracil (5-FU), and digitoxin are often used with secondary metabolites from medicinal plants. Synergistic combinations require the use of two compounds together, combining a chemotherapeutic agent and secondary metabolites from medicinal plants.

Doxorubicin

Doxorubicin intercalates into DNA, disrupting DNA replication and transcription. This interference prevents cancer cells from dividing and causes them to die through apoptosis (Christowitz et al., 2019). Doxorubicin exhibited a synergistic effect when combined with peiminine, furanodiene, forskolin, evodiamine, erianine, and ursolic acid.

Peiminine triggers ferroptosis, a form of regulated cell death distinct from apoptosis, contributing to its anticancer effects. This mechanism involves the activation of Nrf2 signaling pathways that help combat oxidative stress within cancer cells (Yi et al., 2024). Peiminine and doxorubicin were taken in vitro and in vivo study. In vitro testing induced a significant decrease in colony formation. By blocking MAPK signaling pathways, it successfully prevented. Additionally, the combined effects of doxorubicin and peiminine on DNA damage and cell survival were reduced by ZEB1 knockdown. The combined effect of Peiminine and Doxorubicin reduced cell viability; doxorubicin 1µM (80%), doxorubicin 1µM + Peiminine 2µM (50%). Tumor growth was significantly suppressed in the in vivo test (Xu et al., 2024).

Furanodiene inhibited the adhesion, migration, and invasion of BC cells without inducing cytotoxicity. It achieves this by down-regulating integrin αV, β-catenin expression, and inhibiting focal adhesion kinase (FAK) phosphorylation, which are critical for metastatic processes(Z. Zhong et al., 2014; Z. F. Zhong et al., 2016). Furanodiene enhances the anti-cancer effect of doxorubicin on ERα-negative MDA-MB-231 BC cells and ERα-low expression 4T1 cells through suppressing cell viability through inducing mitochondria-caspases-dependent apoptosis. Furanodiene suppresses cell viability by causing mitochondrial apoptosis, which amplifies the anti-cancer effects of doxorubicin in ERα-negative BC cells independent of reactive oxygen species and dependent on caspases. Combined treatments of furanodiene (20 µM) and doxorubicin (2 µM) could significantly inhibit cell viability with a value of 35.29% (Z. F. Zhong et al., 2016).

Forskolin, a natural compound derived from the roots of the plant *Coleus forskohlii*, has garnered attention for its potential anticancer properties. Forskolin activates adenylate cyclase, which converts ATP to cAMP. This increase in cAMP is crucial as it influences various cellular functions and is associated with inhibiting cancer cell growth and enhancing sensitivity to chemotherapy. Specifically, cAMP signaling can induce mesenchymal-to-epithelial transition, inhibit cell migration, and promote apoptosis in cancer cells through both protein kinase A (PKA)-dependent and independent pathways (Sapio et al., 2017). In both triple-negative breast cancer (TNBC) cell lines, forskolin significantly increased the anti-proliferative effects of doxorubicin in every combination. The combination of forskolin and doxorubicin caused a significant, time-dependent increase in the number of dying cells. Forskolin sensitizes TNBC cells to doxorubicin via cAMP/PKA-dependent ERK inhibition. The result of viability cells on MDA-MB-231 cells: Viability decreases to approximately 50% with the combination, compared to ≈80% with doxorubicin alone, on MDA-MB-468 cells:

Viability decreases to approximately 40% with the combination, compared to ≈90% with doxorubicin alone (Illiano et al., 2018).

Evodiamine, an alkaloid derived from *Evodia rutaecarpa*, has shown promising potential in BC. Evodiamine inhibits the growth of both estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) BC cell lines in a concentration-dependent manner. It achieves this by mediating degradation of estrogen receptors (ER) and activating caspase-dependent apoptotic pathways, leading to increased cell death (K.-L. Wang et al., 2013). When doxorubicin and evodiamine were administered together, the viability of MCF-7 and MCF-7/ADR cells was significantly reduced. In MCF-7/ADR cells, the combination of doxorubicin and evodiamine produced a noticeably greater percentage of apoptotic cells. Individual treatment with doxorubicin (2 mM) or evodiamine (1 mM) induced apoptosis in 11.27% and 11.77% of cells, respectively. In contrast, concurrent treatment with doxorubicin and evodiamine increased the apoptotic cell population to 30.05%. Evodiamine enhances the apoptotic action of doxorubicin by inhibiting the Ras/MEK/ERK cascade and IAP expression without inhibiting P-glycoprotein (P-gp) expression and activity (S. Wang et al., 2014).

Erianin, a natural biphenyl compound extracted from Dendrobium species, has shown significant potential in BC treatment, particularly in targeting TNBC. Erianin promoted apoptosis in BC cells by activating caspase-dependent pathways. Studies have shown that it increases the expression of pro-apoptotic proteins, such as cleaved-caspase-3, caspase-7, and caspase-9, while decreasing the expression of anti-apoptotic proteins, such as Bcl-2. This dual action leads to both early and late apoptosis in BC cells (Yan et al., 2022; Y. Zhang et al., 2019). ER and DOX·HCl significantly inhibited the viability of BC cell lines (MDA-MB-231, MCF-7, and MCF-10A). The combination of erianin with doxorubicin in small amounts significantly reduces the survival rate of cancer cells, with little effect on normal cells (Xie et al., 2021).

Previous studies have demonstrated that ursolic acid can suppress the metastatic potential of BC cells. It impairs glycolytic metabolism and mitochondrial respiration in these cells, which are vital for their energy production and invasive capabilities. This suppression is mediated through the activation of Caveolin-1 signaling, which is essential for regulating cellular metabolism (S. Wang et al., 2021). Ursolic acid can increase the amount of doxorubicin entering cells to accumulate in the nuclei, decreasing the digoxin efflux ratio (Zong et al., 2019).

Paclitaxel

Paclitaxel (PTX) stabilizes microtubules, preventing their normal breakdown and reformation, which is necessary for cell division. This action blocks cells from progressing through mitosis, leading to apoptosis (programmed cell death) (Lu et al., 2022). The mechanisms of PTX action represent several ways in which PTX affects cellular processes, resulting in programmed cell death. PTX is frequently used as the first-line treatment drug in BC (Abu Samaan et al., 2019). Paclitaxel exhibited synergistic effects when combined with curcumin and acetoxyeugenol acetate.

Curcumin inhibits the proliferation of BC cells and promotes apoptosis. Specifically, it induces cell cycle arrest at the G2/M phase, which helps prevent unchecked cell division characteristic of cancerous tissues (S. Hu et al., 2018; D. Liu & Chen, 2013). The combination of paclitaxel and curcumin inhibits breast tumor growth by eliminating BC stem cells and non-stem BC cells simultaneously. The higher inhibitory effect of paclitaxel combined with curcumin was attributable to synergism and the enhanced cellular internalization of paclitaxel and curcumin. It was also done by in vivo study showed that this combination had tumor inhibition effect because tumor necrosis appeared in most areas of tumor species (Z. Yang et al., 2017). For the treatment of advanced and metastatic BC, curcumin and paclitaxel work well together. After 12 weeks of treatment and a brief follow-up, this treatment outperformed the paclitaxel-placebo combination in terms of ORR and physical performance. The clinical trial reported that the combination of curcumin and paclitaxel showed significantly better efficacy compared to paclitaxel with placebo in patients with advanced, metastatic breast

cancer. The objective response rate (ORR) was 50.7% in the curcumin group versus 33.3% in the placebo group (p = 0.0145), and this difference was even more pronounced in patients who completed the full treatment (61.3% vs. 38.5%, p = 0.0041) (Saghatelyan et al., 2020).

AEA induces apoptosis in MCF-7 human BC cells through a caspase-dependent pathway. Studies have demonstrated that treatment with AEA leads to increased activation of caspases-3 and -9, which are critical mediators of the apoptotic process. The compound also enhances intracellular levels of reactive oxygen species (ROS), contributing to its pro-apoptotic effects (Hasima et al., 2010). From the result of MTT assay isobologram-illustrated conclude that AEA was able to significantly lower the viability levels of MCF-7 cells when paired with paclitaxel. CI analysis indicated that synergistic effects (CI=0.51–0.66) were observed for all combinations of paclitaxel and AEA for 24 h. AEA synergistically with paclitaxel enhances the proapoptotic effect on MCF-7 cells, due to its chemosensitization role (Aun et al., 2011).

Metformin

Metformin exerts its anticancer effects through several pathways. Metformin activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis. The mammalian target of rapamycin (mTOR) pathway, which is essential for cell division and growth, is inhibited as a result of this activation. By inhibiting mTOR, metformin reduces protein synthesis and cell growth, thereby exerting antiproliferative effects on cancer cells. Metformin inhibits mitochondrial complex I of the respiratory chain, leading to reduced ATP production and increased AMP levels. This shift in energy metabolism can trigger autophagy and apoptosis in cancer cells (Lord & Harris, 2023; O. H. Y. Yu & Suissa, 2023).

Metformin have a synergistic effect when combined with Formononetin. Some human foods and plants contain the isoflavonoid phytoestrogen formononetin (FM). FM has been extensively researched. FM has strong antioxidant and anti-tumor properties, according to earlier research (W. Hu & Xiao, 2015; Mu et al., 2009; X. Zhang et al., 2014). Formononetin has been reported to enhance the chemosensitivity of TNBC by activating pathways related to mitophagy and apoptosis. Specifically, it increases the expression of the BTB domain and CNC homolog 1 (BACH1), which plays a critical role in tumor aggressiveness. The combination of formononetin with other therapies has been shown to suppress TNBC metastasis and improve overall survival rates in patients (Li et al., 2023). Formonenetin 40 μM and metformin 150 μM combination dramatically decreased the proliferation of MCF-7 cells (CI= 0.760). The combination also enhances inhibition of cell growth, and induction of apoptosis in MCF-7 cells mediated by the ERK1/2 signaling pathway (Xin et al., 2019).

Celecoxib

Celecoxib inhibit COX-2. Overexpressed in many cancers, COX-2 contributes to tumorigenesis and poor prognosis. Celecoxib selectively inhibits COX-2, which can reduce tumor cell proliferation and induce apoptosis. Celecoxib as antiangiogenic effect, by suppressing vascular endothelial growth factor (VEGF) and other pro-angiogenic signals, celecoxib can hinder the formation of new blood vessels necessary for tumor growth. Celecoxib have a synergistic effect when combined with acetyl britannilacton (ABL). In China, bronchitis and inflammation are frequently treated using acetylbritannilactone (ABL), a novel active extract extracted from the traditional Chinese medicinal herb Inula britannica L. ABL has strong anticancer properties against colon, breast, ovarian, leukemia, and prostate cancer cells, according to earlier research (Bai et al., 2006; Pan et al., 2007; Rafi et al., 2005). By activating the mitochondrial apoptotic pathway, ABL causes BC cells to undergo apoptosis. Reactive oxygen species (ROS), which are essential in causing cell death, are produced during this process calculated as described (Bailly, 2021).

ABL synergistically enhances celecoxib-induced growth inhibition in MDAMB-231 cells, MDA-MB-468, and MCF-7 cell lines, the CI values of the concentration were less than 1, indicating that ABL synergistically enhances celecoxib-induced growth inhibition in MDAMB-231 cells. ABL enhances the apoptotic effect of celecoxib on COX-2 expressing

cells but has little effect on COX-2 negative cells. Thus, celecoxib and ABL may be an effective combination for cell growth inhibition due to their synergistic efficacy. (B. Liu et al., 2011).

5-fluorouracil (5-FU)

5-FU acts as an antimetabolite, interfering with DNA and RNA synthesis. Its primary mechanism involves the inhibition of thymidylate synthase (TS)24, an enzyme crucial for synthesizing thymidine monophosphate (dTMP), a nucleotide required for DNA replication. By interrupting this process, 5-FU causes a scarcity of dTMP, leading to "thymineless death" in rapidly dividing cancer cells. Additionally, 5-FU incorporates itself into RNA and DNA, causing disruptions in transcription and translation processes, further hindering cancer cell growth and viability (Longley et al., 2003). 5-fluorouracil (5-FU) have a synergistic effect when combined with Proanthocyanidins.

Proanthocyanidins from *Uncaria rhynchophylla* show promising anti-breast cancer effects, particularly against MDA-MB-231 cells, by inducing apoptosis and enhancing chemotherapy. *Uncaria rhynchophylla* trigger apoptosis through reactive oxygen species (ROS) production, cell cycle arrest, and modulation of pathways like PI3K/Akt. They inhibit proliferation and survival in triple-negative breast cancer cells (Chen et al., 2017). Proanthocyanidins have been shown to induce apoptosis in BC cell lines such as MCF-7 and MDA-MB-231. This process is mediated by altering the balance of pro-apoptotic and anti-apoptotic proteins, specifically increasing the expression of Bax while decreasing Bcl-2 levels, leading to enhanced cell death (Gao & Tollefsbol, 2018). The combination of Proanthocyanidins and 5-FU for 48 hours produces a synergistic cytotoxic effect on MDA-MB-231 cells, CI = 0.5 indicated synergism (Chen et al., 2017).

Digitoxin

A member of the cardiac glycoside class, digitoxin has been investigated for possible anticancer effects. Digitoxin has been demonstrated to cause apoptosis in a number of human cancer cell lines, including those from the breast, pancreatic, and other tissues. The apoptosis-inducing effect is more pronounced at higher concentrations of digitoxin, demonstrating a dose-response pattern (Haux et al., 2001). Digitoxin interferes with cellular processes critical for tumor growth and survival. It inhibits glycolysis and affects the expression of sodium pumps, which are overexpressed in cancer cells (Dasari & Bernard Tchounwou, 2014; Minerva et al., 2023).

Digitoxin have a synergistic effect when combined with Actein. Actein is a triterpene glycoside isolated from the rhizomes of Cimicifuga foetida (known as "shengma" in traditional Chinese medicine) and other related species. It is known for its pharmacological properties, including the ability to suppress cell proliferation, induce autophagy and apoptosis, and inhibit the growth of cancer cells, particularly breast cancer cells, due to its anti-angiogenic and immunomodulatory effects. Actein significantly inhibits the migration and adhesion of BC cells, critical factors in metastasis. It reduces the expression of matrix metalloproteinases (MMPs) and integrins, which are involved in cell adhesion and movement (Wu et al., 2018, 2020). Digitoxin's inhibitory effect on Na+-K+-ATPase activity and MDAMB-453 BC cell proliferation is amplified by actein. The fact that actein and digitoxin inhibit distinct stages of the cell cycle—actein causes G1 arrest, whilst digitoxin causes G2 arrest—may also contribute to the synergistic effects on growth inhibition. Actein may change other targets that digitoxin does not change. The combination of Actein and digitoxin produces a synergistic cytotoxic effect on MDA-MB-453 cells, CI = 0.6 indicated synergism (Einbond et al., 2008).

DISCUSSION

Studies that assessed whether the combined use of natural items and anticancer medications for BC improved anti-BC efficacy were included in the systematic review. There are 13 studies retrieved, 12 studies included were conducted in vitro, while 2 of them were also conducted in vivo. There is only one clinical trial is the combination of paclitaxel and curcumin. In vitro test was done by MTT Assay. It measured metabolic activity, including cell viability, cytotocixity, and proliferation. In order to determine mitochondrial activity, this test depends on living cells converting MTT into formazan crystals. This test is used to evaluate the cytotoxic effects of medications on cell lines or primary patient cells in vitro since total mitochondrial activity is typically connected with the number of viability cells in the population (Konuk, 2024). In vivo investigations should be carried out later since efficacy and safety studies in animal models are necessary prior to clinical trials. In vivo investigations should be carried out later since clinical trials must be preceded by effectiveness and safety studies in animal models (Chapman et al., 2013).

The majority of research focuses on single compound. These single compound of herbals are mostly of interest in some East Asian countries, which reflects their culture, predominantly uses herbal materials for treatment (Farzaei et al., 2020). Multicomponent medications that target several different targets are becoming more and more popular these days. Furthermore, a single natural product's complete extract and compound prescription include a variety of components, making multi-target cancer treatment feasible (Chang et al., 2020). As a result, natural product-based cancer treatment needs to receive greater attention.

The most commonly used cell line was MCF-7, followed by MDAMB-231, MDA-MB-468, MDAMB-453, and BT474 cells. MCF-7 is a common model for studying hormone response because of its sensitivity to hormones through the expression of the estrogen receptor (ER) (C.-Y. Zhang et al., 2015). The MDA-MB-231 cell line is a widely used tool in BC research due to its triple-negative characteristics and high metastatic potential. Derived from a 51-year-old woman with metastatic BC in 1976, these cells do not express estrogen or progesterone receptors, nor do they overexpress HER2 protein, representing an aggressive form of BC with limited treatment options (Neve et al., 2006).

The MDA-MB-468 cell line has been used to perform metabolic characterization to understand the metabolic adaptations of TNBC, potentially revealing improved treatment regimens (Wojtowicz et al., 2020). MDA-MB-453 cells are a suggested model for apocrine breast cancer research since they are androgen receptor-positive and triple-negative for estrogen receptor-α, progesterone receptor, and Her-2/neu protein expression. The usefulness of the MDA-MB-453 cell line as a model for studies on human apocrine breast cancer is limited, though, since one study discovered that while it differs from patient tissues in a number of important ways, it shares some traits with apocrine breast cancer (Vranic Semir et al., 2011). BT-474 cells are estrogen receptor positive and overexpress c-ErbB-2 protein (HER2), making them a powerful model for hormone-dependent BC and immune therapy (van Slooten et al., 1995).

The combined anticancer drugs were doxorubicin in eight studies, paclitaxel in five studies, tamoxifen in two studies, docetaxel, metformin, rapamycin, celecoxib, 5-FU, digitoxin, and cisplatin in one study. In this review, the most used chemotherapy drugs for the combination treatment of BC are doxorubicin. However, the long-term therapy benefits for people with BC are limited when doxorubicin resistance develops (Wen et al., 2019). This suggests that there is a lot of need for in vivo test and clinical trial on natural products combined with doxorubicin for BC treatment in the future.

Research on combining natural products for a wider range of treatments is needed in the future. Second, the search terms did not contain the names of specific medications or natural products due to the large range of interventions. Even though a thorough search has been done to the best, some research combining natural items and anticancer medications may still be lacking. Despite the limitations, this study will contribute to the proposal of a natural product combination therapy for BC in the future because it gathers data showing the synergistic effects of combining natural products with anticancer agents, which are mainly taken into consideration for the treatment of BC.

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CONCLUSION

In recent decades, ethnopharmacology and phytomedicine have grown in popularity, particularly when taking into account their use in the broad area of human diseases. According to the findings of the systematic reviews mentioned above, chemical compounds from plants have a significant therapeutic effect when used with conventional drugs. Therefore, evidence-based phytotherapy need to be regarded as a legitimate alternative for the treatment of human diseases, including more complicated conditions like BC, as well as low- or mild-grade diseases. Indeed, strong clinical studies (randomized double-blind) are required to validate the pre-clinical data presented in this review, and there were one clinical trial have been shown. At the moment, free database of herb–drug interactions is becoming a concrete need for clinicians to treat BC. In conclusion, all secondary metabolites of medicinal plants listed in this review have synergistic effects with BC drugs.

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