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# A Review of Potential Anti-Cancer Effect of Sesquiterpene Lactones in Breast Cancer

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**Abstract**

Despite significant advances in treatment, breast cancer remains a medical problem and the most common cancer leading to death among women worldwide. The most common breast cancer treatments, radiotherapy and chemotherapy are usually expensive and can cause severe side effects and low response rates due to drug resistance. To overcome these problems, medicinal plants can be the best alternative to chemotherapy drugs with fewer side effects and cost-effectiveness. Sesquiterpene lactones are compounds of the Asteraceae plant family that has significantly impacted various aspects of breast cancer cells. This review focused on the biological properties of Sesquiterpene lactones and their potential processes in breast cancer, leading to enhanced anticancer effects.

***Keywords:*** Breast Neoplasms [MeSH], Sesquiterpenes [MeSH] Lactones [MeSH]

## Introduction

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***Highlights***

- Sesquiterpenes from different species induce apoptosis in breast cancer cells by different mechanism.
- Sesquiterpenes have anticancer effects in breast cancer cells.

Breast lobules or ductal epithelial cells that are malignant are what give rise to breast cancer. Breast cancer is the most prevalent kind of cancer in women across the world, accounting for 25% of all cancer cases (1). According to the WHO report, 2.3 million women globally received a breast cancer diagnosis in 2020, and 685,000 of them passed away. By the year 2020, 7.8 million women who received a breast cancer diagnosis in the previous five years would still be living (2). According to doctors in Iran, eight thousand Iranians are diagnosed with breast cancer annually, and there are around 30 to 35 cases of the disease per 100,000 Iranian women (3). Because of the interaction of hereditary and environmental variables, breast cancer is a very diverse illness that gradually accumulates genetic and epigenetic alterations in breast cancer cells. Although epidemiological evidence points to unique factors like age, obesity, alcohol consumption, and dealing with estrogens, which are highlighted by early menstruation, late menopause, and lifelong infertility, the presence of family history is thought to be the disease's most vital contributing factor. Using a diet containing fiber, a low-fat diet, mobility, physical activity, weight control, not delaying marriage, not using alcohol, and breastfeeding are among the environmental factors of breast cancer control (4-6). The symptoms of this cancer can be in the form of a lump in the breast, its shape change, fluid secretion from the nipple, or skin abnormalities in the desired area, which usually at first appear as a small lump in the breast, but the bump grows over time and spreads to areas near the breast such as the skin and lymph nodes under the arm. The tumor may invade organs such as the liver, brain, lungs, and bones. If breast cancer is diagnosed in the early stages and before it progresses and spreads to the surrounding areas, it can be treated (7, 8). In the treatment of breast cancer, surgical methods such as mastectomy, lumpectomy, removal of the ovaries and radiation therapy, hormone therapy, and chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil, adriamycin, and paclitaxel) are used. Recently, methods such as a monoclonal antibody (Herceptin) and gene therapy have been used to treat this cancer (9-12). According to the progress made in the treatment field, the treatments mentioned above have limited effectiveness in many cases (13). Therefore, more efforts are needed to improve chemotherapy and develop treatment methods specific to breast cancer so that the standard of living can be improved. There are new treatment methods that deserve further studies. For this reason, analyzing the chemical compounds of plants and determining their biological activity is of great importance. Due to the reduction of toxicity and side effects of chemotherapy, traditional treatment methods can make massive progress in cancer treatment in the coming decades (14, 15). Herbal compounds are among the essential sources of anti-cancer drugs due to fewer side effects and better therapeutic effects. In general, plant-based anti-cancer medications may be divided based on their mode of action as inhibitors, antioxidants, and mitosis-interfering substances (vinca alkaloids, taxol) (16, 17), antioxidants (thymoquinone, vincristine) (18, 19), and inhibitors compounds that change DNA (such as camptothecin) (20) and agents that prevent angiogenesis (flavopiridol, epigallocatechin gallate) (21, 22). Sesquiterpene lactones, a novel class of chemicals with numerous anti-cancer effects, are produced from the Asteraceae (Compositae) family, which includes several significant medicinal herbs, including Artemisia annua, Arnica montana, and Tanacetum parthenium Astraceae family are considered one of the essential plant families for therapeutic purposes (23, 24). Many studies have been done in phytochemistry and the therapeutic effects of plants of this family. Various compounds with different biological effects have been isolated from these plants and introduced to

modern pharmaceutical science, which has anti-malarial, anti-insect, anti-cancer, antioxidant, anti-fungal, anti-bacterial, and anti-viral effects (25-27). Artemisia contains essential components such as terpenoids, alkaloids, phenolics, and coumarins, making it a significant genus in both biochemical and pharmacological fields (27, 28). Among the biological compounds isolated from this genus are sesquiterpene lactones which are recognized as apoptosis inducers and cell proliferation inhibitors in a variety of malignancies, including breast cancer (24, 29-32). Using substances that can induce the apoptotic death of cancerous cells is now one of the critical methods in cancer treatment (33, 34). There are many mechanisms through which apoptosis is induced in the cell whose anti-cancer effects have been identified in various types of research (24, 30, 31, 35). The search strategy was via PubMed, SCOPUS and Google scholar for identifying studies published on effect Sesquiterpene lactones in breast cancer.

### *Sesquiterpenes*

Sesquiterpenes are a family of terpenoids built by connecting three isoprene units. Each isoprene unit consists of 5 carbon and eight hydrogen atoms (36). The primary terpene suppression unit is Farnesyl Diphosphate (FPP), which is synthesized from the head-to-tail condensation of an isoprene unit to a geranyl diphosphate group (37). Sesquiterpenes are one of the most diverse groups of secondary metabolites produced mainly in higher plants and invertebrates, and fungi (37, 38). These compounds are represented by acyclic, single, two, three, and four-ring systems (Figure 1) (37). Although sesquiterpenes can be found in human food, they are primarily used in dietary supplements and traditional medicines. Additionally, due to the fascinating biological actions of some sesquiterpenes and their derivatives, sesquiterpenes can develop into a rich source of candidate molecules for drug development (39). As a result of recent research in the field of producing new drugs derived from natural substances, sesquiterpenes have shown anti-inflammatory, antibacterial, anti-parasitic, anti-tumor, anti-malarial, and anti-cancer effects (37, 39, 40). Sesquiterpenes and their derivatives have been studied for their high potential to fight cancer, including breast cancer. The main methods used to achieve this include modifying nuclear factor kappa (NF-kB), inhibiting lipid peroxidation, and delaying the production of reactive oxygen and nitrogen species (ROS&RNS) (41-45).

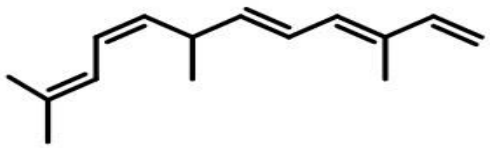

**Figure 1.** The general structure of sesquiterpene.

### *Type of sesquiterpene lactone*

Sesquiterpene lactones, which differ from other sesquiterpenoids in the presence of a lactone ring in their structure. More than 100 families of flowering plants include a wide variety of natural compounds known as sesquiterpene lactones, the majority of which are sourced from the Compositae (Asteraceae) family and are mainly extracted from the leaves or blooming heads of the plant (46). Based on the lactone rings, it is possible to divide these molecules into two groups: 6, 12- (e.g., parthenolide, costenolide, artabsin, santonin, matricin, etc.) and 8, 12-olides (e.g., inonolide, helenaline, inonolide, thapsigargin, and alantolactone) (47). Sesquiterpene lactones are colorless lipophilic, and in addition to being chemically and chemotaxonomically interesting, many have anti-tumor, anti-leukemia, cytotoxic and antimicrobial properties. The presence of valuable medicinal structures in this group of compounds, such as artemisinin, costunolide, parthenolide, britannin, and nardosinen, has attracted the attention of many researchers in the field of inflammatory diseases and types of cancer. One of the structural features of all these compounds is the inclusion of unsaturated gamma lactones (α-methylene-Y-lactones). The unsaturated, carbonyl system that underlies their high chemical reactivity allows for

the production of covalent adducts with nucleophilic residues on a variety of biological molecules (29, 48). The six main groups of sesquiterpene lactones are Germacranolid: with a 10-sided ring connected to a 5-sided lactone ring, Eudesmanolice, and Eremophilanolide: with two 6-sided rings connected and a 5-sided lactone ring, Pseudoguaianolide, and Guaianolide with a 5-sided ring attached to a 7-sided ring. Connected to a 5-sided lactone ring and Xartarodide or a 7-sided ring attached to a 5-sided lactone ring (Figure 2), some types of sesquiterpene lactones also have unusual structures like artemisinin and are not classified in a specific category (29, 47-50).

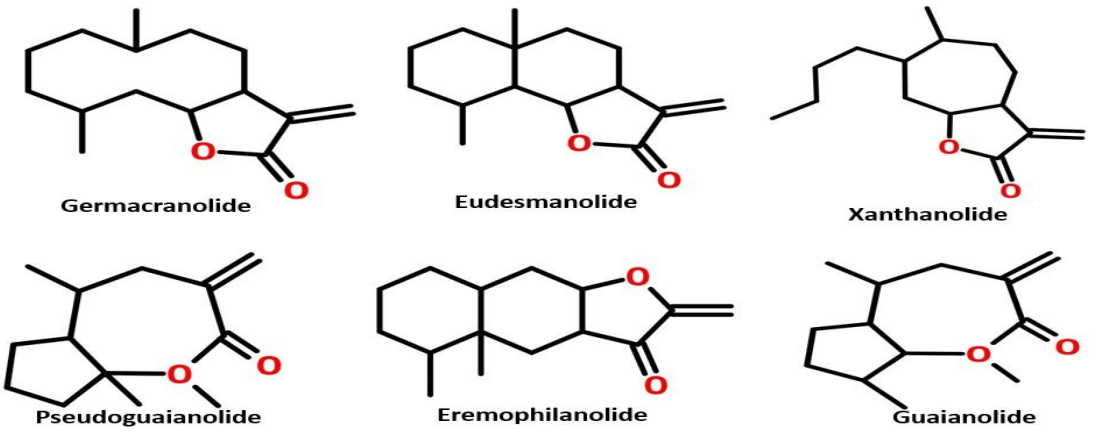


**Figure 2.** Chemical structures of main groups of sesquiterpene lactones.

**Table 1.** The main types of sesquiterpenes.

| ***Types of sesquiterpene lactones*** | ***Number and type of rings*** |
|---|---|
| Germacranolid | One 10-sided ring connected to a 5-sided lactone ring. |
| Eudesmanolice | Two 6-sided rings connected to each other and a 5-sided lactone ring. |
| Eremophilanolide | Two 6-sided rings connected to each other and a 5-sided lactone ring. |
| Pseudoguaianolide | One 5-sided ring connected to a 7-sided ring. |
| Guaianolide | One 5-sided ring connected to a 7-sided ring. |
| Xartarodide | One 7-sided ring connected to a 5-sided lactone ring. |

***Sesquiterpene lactone in breast cancer***

Sesquiterpene lactones have been shown to suppress breast cancer cell growth and trigger apoptosis in a variety of cancer forms (29). The molecular mechanisms of these substances' actions and their anticancer characteristics have been extensively investigated on several cell lines in recent years. A study was conducted on cacalol, a sesquiterpene lactone isolated from Cacalia delphiniifolia. It was found that this compound inhibits growth and induces apoptosis in MDA-MB231 and MCF-7 cell lines. This investigation assessed cell survival and apoptotic rates in the previously described cancer cell lines using various cacalol doses. The findings of this study demonstrated that cacalol has an anti-tumor effect via inhibiting the FAS expression pathway and modifying the Akt-SREBP pathway in cancer cells since it dramatically slows the development of cancer cells while being less hazardous for healthy HBL100 and MCF10A cells (51). The sesquiterpene lactone molecule Gaillardin, isolated from the chloroform extract of the aerial portions of the Inula oculus-Christi plant, has been demonstrated in studies to suppress the growth of the MCF-7 and MDA-MB-468 breast cancer cell lines via inducing the mitochondrial pathway. Western blot analysis revealed that the

sesquiterpene lactone compound Gaillardin induces apoptosis through mitochondria through the loss of mitochondrial membrane potential as a result of the overexpression of p53 and the increase in the ratio of Bax/Bcl2, which suggests that the combination may be a suitable candidate for the treatment of breast cancer (52). The effect of this compound on the survival of cancer cells was investigated using the MTT test, and the results showed that a 40 micromolar dose of the Costunolide compound led to the arrest of the cell cycle in the G2/M phase. Apoptosis induction by increasing the expression of caspase 3 and 9 in vitro and MDA-MB231 and MCF-7 cancer cell lines was reported in this study (53). Britannin, a sesquiterpene molecule discovered in the plant Inula aucheriana, was tested on the cell lines MCF-7 and MDA-MB-468 and shown to trigger apoptosis. The outcomes of this investigation demonstrated that britannin is less hazardous in regular human fibroblast cell lines AGO1522 (35). The MDA-MB-468 cell line was used in a study by Bo Yang et al. to examine the effects of the sesquiterpene lactone Eupalinolide O compound, which was derived from the Eupatorium lindleyanum DC plant. The sesquiterpene molecule Eupalinolide O was demonstrated in this study to kill cells in various cell lines in a concentration- and time-dependent manner. Combining these two factors causes the cell cycle to stop in the G2/M phase and the expression of proteins involved in the cell cycle (cyclin B1 and cdc2) to decrease in the MDA-MB-468 cell line. By boosting the expression of caspases 3, 8, and 9, this substance also causes apoptosis (54). Another sesquiterpene lactone is Alantolactone, which is isolated from the plant Inula helenium L. Investigation of the anti-tumor effect of Alantolactone showed that this compound induces apoptosis in MCF-7 cell line without adverse effects in normal cell lines. It was also found that treatment of cells with Alantolactone significantly decreases the expression of Bcl2 and increases the expression of Bax and p53 compared to control cells. Alantolactone also reduced the expression of caspase 3 and 12 precursors and significantly increased the expression of caspase three and caspase 12 (55). Deoxyelephantopin (DET) and Isodeoxyelephantopin (IDET) are two compounds isolated from Elephantopus scaber plant. These sesquiterpene lactone compounds can cause cell cycle arrest in G1 and G2/M phases in the MDA-MB-231 cell line. Also, two compounds can increase the expression of cleaved caspase seven and caspase nine and decrease the expression of anti-apoptotic proteins Bcl-xL and Bcl2 (56). Drug-resistant breast cancer cells respond to the ambrosin compound's anticancer properties (MDA-MB231). Data analysis revealed that this sesquiterpene lactone dramatically causes apoptosis in MDA-MB231 cell lines while having minimal impact on MCF-12A, which are normal breast cells. According to the results of the Western blot, the increase in the ratio of Bax/Bcl2 (57).

Parthenolide is another sesquiterpene lactone compound that induces apoptosis in the MDA-MB-231 cell line by inducing Bid phosphorylation, TRAIL-dependent Bid cleavage without affecting caspase eight activity and increasing caspase three activity (58).

The chemical action of parthenolide was examined in an experiment by Sweerey C using MDA-MB-231 xenograft-derived cells as a breast cancer metastasis model and in vitro. The in vitro anticancer activity and chemosensitivity of parthenolide was assessed using MDA-MB-231 cells. In vitro, colony formation was effectively reduced, apoptosis was induced, and the expression of prometastatic genes IL-8 and anti-apoptotic gene GADD45beta1 was decreased by parthenolide alone or in combination with docetaxel. Animals treated with parthenolide and docetaxel together in an adjuvant setting showed significantly higher survival rates than untreated animals or animals treated with either drug alone (59).

Another substance that was initially isolated from the seeds of Centratherum anthelminticum is vernodalin. Vernodalin reduced the development of human breast cancer cells MCF-7 and MDA-MB-231 by causing cell cycle arrest and

apoptosis. Cytochrome c was released from both human breast cancer cells as a result of reduced Mitochondrial Membrane Potential (MMP), increased Reactive Oxygen Species (ROS) generation, and decreased anti-apoptotic molecules (Bcl-2, Bcl-xL). Caspase cascade activation, PARP cleavage, DNA damage, and ultimately cell death was brought on by the release of cytochrome c from the mitochondria to the cytosol (60).

In the study done by Nakagawa-Goto et al. on the cytotoxic effects of the sesquiterpene lactone isolated from the Elephantopus scaber plant (belonging to the Kasti family), called deoxyelephantopin and its semi-synthetic derivatives, on MCF-7 and MDA-MB 231 cell lines, it was determined it was found that these compounds reduced metastatic breast tumors in mice and, together with paclitaxel, have synergism against Triple-negative breast cancer (61).

Inula britannica, a medicinal plant, yields eupatolide, a sesquiterpene lactone that was shown to sensitize human breast cancer cells to TRAIL-induced apoptosis in 2010. Treating breast cancer cells MCF-7, MDA-MB-231, and MDA-MB-453 with TRAIL plus subtoxic quantities of eupatolide increased the cytotoxicity that TRAIL induced, whereas each drug alone only moderately caused cell death. The expression of cellular FLICE inhibitory protein (c-FLIP) in MCF-7 cells was reduced by induced eupatolide exposure alone. Eupatolide was shown to suppress AKT phosphorylation in a dose- and time-dependent manner (62).

Two naturally occurring sesquiterpene lactones, hydroxyisocostic acid and 5-hydroxycostic acid were found in the herb Laggera alata. They have anti-inflammatory properties that prevent Vascular Endothelial Growth Factor (VEGF)-induced proliferation in HUVECs (human umbilical vein endothelial cells) and suppress the development of blood vessels in zebrafish embryos. Additionally, they prevent the migration of HUVECs, the development of stress fibers, and the creation of tubes when VEGF is activated. Protein immunoblot examination demonstrated that these two substances activated downstream molecules (p38, FAK, Src/AKT/eNOS, and PLC/ERK1/2) and decreased VEGF-induced VEGFR2 phosphorylation. Additionally, it reduces the migration of MCF-7 cells brought on by angiopoietin-2 (63).

In vitro research was done on the anti-migratory, anti-invasive, and underlying processes of ivalin, an odesman-type sesquiterpene compound from the Chinese herb Carpesium divaricatum, in breast cancer cells. Wound healing and transwell techniques were used to gauge Ivalin's anti-migratory and anti-invasive properties. Ivalin treatment, in this regard, reduced N-cadherin, vimentin, and ZEB1 mRNA and protein expression in several breast cancer cells. Ivalin reduced the epithelial-to-mesenchymal transition process by increasing E-cadherin expression in the same cells, according to this study (EMT). The outcomes demonstrated that, in laboratory settings, Evalin effectively suppresses breast cancer cell migration, invasion, and cell proliferation in a dose-dependent manner (64).

Centipeda minima is the source of the natural sesquiterpene lactone known as arenicolide D. Arenicolide D dramatically lowers cell viability in the MDA-MB-231 cell line causing G2/M cell cycle arrest and apoptosis, according to laboratory tests on the substance. The Akt/mTOR and STAT3 signaling pathways were also suppressed by arenicolide D (65).

Brevilin A (Brv-A), a sesquiterpene lactone molecule from Centipeda minimum, has been shown in another research to have antiproliferative properties in breast cancer. In MCF-7 cells, Brv-A causes apoptosis and facilitates mitotic arrest in the G2/M phase of the cell cycle. This compound showed a dose-dependent antiproliferative effect by targeting NOX2 and NOX3, mitochondrial dysfunction (loss of MMP and modification of Bcl-2 family proteins), activation of MAPK, JNK, and p38, and induction of apoptosis. In addition, this compound enhanced the expression of Bip/GRP78, ATF4, and CHOP proteins and prevented STAT3

activation by reducing JAK2 and SRC phosphorylation (66).

Vernolactone, a novel sesquiterpene lactone isolated from the plant Vernonia zeylanica (L), was shown to have considerable cytotoxic effects on the breast cancer cells SKBR-3 and MDA-MB-231 but very modest effects on MCF-7 and normal mammary epithelium MCF-10A. Morphological alterations validated the pro-apoptotic results of the substance, DNA fragmentation, enhanced caspase 3/7 activities, up-regulation of p53, Bax, and down-regulation of Survivin (67).

Atractylenolide II (ATR II) is a sesquiterpene lactone that has recently been identified to suppress the development of breast cancer cells by inducing apoptosis, mainly by stopping the G2/M phase of the cell cycle. Additionally, the cytotoxicity of ATTR II on breast cancer was linked to the control of androgen receptors and potential anti-inflammatory effects via blocking NF-B signaling pathways (68).

A substance derived from Artemisia annua is called artemisinin. Since the turn of the century, semi-synthetic derivatives like Artesunate (ART), artemether, and their active metabolite Dihydroartemisinin (DHA) have been the first-line combination therapies for malaria (69). Additionally, substantial anticancer effects of ART and DHA were demonstrated in vivo and in vitro in breast cancer cell lines (70). An evaluation of the safety and tolerability of oral ART as an additional form of treatment for four years was done in the first phase through a clinical study. Twenty-three patients with advanced breast cancer received 100, 150, or 200 mg of oral ART once weekly in addition to conventional oncology care. According to this study, the highest tested daily dose of 200 mg/day (2.2 to 3.9 mg/kg/day) was safe and well-tolerated. It was advised to utilize 200 mg/day (2.2-3.9 mg/kg/d) for phase II/III studies with regular monitoring of reticulocytes, NTproBNP, and neurological and audiological exams because safety and tolerability were not demonstrated in this investigation (71).

**Table 2.** Anti-breast cancer effect of different sesquiterpene lactones

| ***Composition*** | ***Anti-breast cancer effect*** |
|---|---|
| Cacalol | Inhibiting the FAS expression pathway and modifying the Akt-SREBP pathway in cancer cells. |
| Gaillardin | Apoptosis induction by overexpression of p53 and the increase in the ratio of Bax/Bcl2. |
| Costunolide | Apoptosis induction by increasing the expression of caspase 3 and 9. |
| Britannin | Apoptosis induction by increasing the expression of caspase 3. |
| Eupalinolide O | Reducing the expression of proteins involved in the cell cycle (cyclin B1 and cdc2) and inducing apoptosis through increasing the expression of caspases 3, 8, and 9. |
| Alantolactone | Apoptosis induction by decreases the expression of Bcl2 and increases the expression of Bax,p53, and caspase 3 and 12. |
| Isodeoxyelephantopin, Deoxyelephantopin | Apoptosis induction by decreases the expression of Bcl2, and Bcl-xL and increases the expression of caspase 7 and 9. |
| Ambrosin | Apoptosis induction by the increase in the ratio of Bax/Bcl2. |
| Parthenolide | Apoptosis induction by inducing Bid phosphorylation, TRAIL-dependent Bid cleavage, and increasing caspase 3 activity. |
| Vernodalin | Reduced mitochondrial membrane potential (MMP), increased reactive oxygen species (ROS) generation and decreased anti-apoptotic molecules Bcl-2, Bcl-Xl. |
| Eupatolide | Decreased expression of cellular FLICE inhibitory protein (c-FLIP) and dose- and time-dependent suppression of AKT phosphorylation. |
| hydroxyisocostic acid, 5-hydroxycostic acid | Inhibition of HUVECs migration upon activation of VEGF and activation of downstream molecules (p38, FAK, Src/AKT/eNOS, and PLC/ERK1/2), reduction of VEGFR2 phosphorylation. |
| Ivalin | Decreased expression of N-cadherin, vimentin, and ZEB1 and increased expression of E-cadherin. |

| | |
|---|---|
| Arenicolide D | Increased induction of apoptosis and suppression of Akt/mTOR and STAT3 signaling pathways. |
| Brevilin A | Induction of apoptosis by targeting NOX2 and NOX3, mitochondrial dysfunction (loss of MMP and modification of Bcl-2 family proteins), activation of MAPK, JNK, and p38, increased expression of Bip/GRP78, ATF4, and CHOP proteins and decreased JAK2 phosphorylation. and SRC and prevent STAT3 activation. |
| Vernolactone | Increased activities of caspase 3/7, up-regulation of p53, Bax, and down-regulation of Survivin. |
| Atractylenolide II | Controlling androgen receptors and blocking related NF-B signaling pathways. |

## Conclusion

Different types of sesquiterpene lactones have been discovered, and these compounds have anticancer effects on breast cancer cell lines and animal models. These substances' reactions to breast cancer cell lines are influenced differently by their various structural differences. Sesquiterpenes are promising compounds to treat breast cancer and reduce side effects and are considered attractive for producing anti-breast cancer drugs. The change of expression of the anti-apoptotic proteins Bcl-xL and Bcl2, as well as the upregulation of p53, Bax proteins, and other caspases, including executive caspases, are potential ways by which different sesquiterpene substances may effect on breast cancer cells. These actions result in a decrease in cell cycle-related factors, an increase in apoptosis-related factors, and a reduction in metastasis and cell invasion-related factors. For the creation of novel active terpenoids that may be helpful in the treatment of cancer, the lactone core of sesquiterpenes is essential and which one is the best for breast cancer depends on the characteristics of this core. Sesquiterpene lactones have disadvantages despite their advantages: their isolation is restricted to natural product sources, and they have high bioavailability due to extensive plasma protein contacts. Also, have off-target and sensitizing characteristics. Due to the properties of this compound, the creation of biological sesquiterpenes requires a strong collaboration between biochemists, chemists, pharmacologists, cancer researchers, and doctors.

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