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Systematic Review

Anti-Breast Cancer Activity of Essential Oil: A Systematic Review

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Abstract: Breast cancer is the second highest cancer-related death worldwide. The treatment for breast cancer is via chemotherapy; however, occurrences of multidrug resistance, unselective targets, and physicochemical problems suggest that chemotherapy treatment is ineffective. Therefore, there is a need to find better alternatives. Essential oil is a plant secondary metabolite having promising bioactivities and pharmacological effects, including anti-breast cancer capabilities. This review intends to discuss and summarize the effect of essential oils on anti-breast cancer from published journals using keywords in PubMed, Scopus, and Google Scholar databases. Our findings reveal that the compositions of essential oils, mainly terpenoids, have excellent anti-breast cancer pharmacological effects with an IC_{50} value of 0.195 µg/mL. Hence, essential oils have potential as anti-breast cancer drugs candidates with the highest efficacy and the fewest side effects.

Keywords: breast cancer; essential oils; terpenoids

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1. Introduction

Breast cancer is a complex condition triggered by abnormalities in the the proliferation of breast cells. Although the disease is present worldwide, there are regional variations in death and survival rates due to differences in the population structure, way-of-life, genetics, and the environment [1,2]. Breast cancer is the most common cancer and the leading cause of mortality among women [3,4]. In the United States, there were around 252,710 new instances of invasive breast cancer and 6341 new cases of ductal carcinoma. The Asia–Pacific area accounts for over 24% of all breast cancer cases, with China, Japan, Vietnam, and Indonesia having the greatest incidence rates [5,6]. The prevalence of this condition is still very high globally, and in Indonesia, and it is predicted that the incidence would rise to 85 per 100,000 women by 2022 [7–9]. Thus, the treatment of breast cancer is still receiving special attention. The treatment of breast cancer to date consists of three methods, namely, surgical therapy, radiation therapy, and chemotherapy [10]. However, these therapies cause a lot of tissue damage and other unwanted side effects [6,11]. Therefore, materials with low toxicity are needed as an alternative that can be taken for therapy. Besides the toxic effect produced being much smaller [12], the effectiveness is also not inferior to drugs used in chemotherapy. One of the natural ingredients widely used in the treatment of breast cancer is essential oil [13]. Essential oils are secondary metabolites in several plants with volatile properties and have many pharmacological effects, including the treatment of cancers [14],

such as lung cancer [15], colon cancer [16–18], prostate cancer [19,20], breast cancer [21,22], cervical cancer [23,24], and many more. Currently, many studies are regarding the activity of essential oil for the treatment of breast cancer which has also been summarized in review articles. However, a systematic review of the use of essential oil in the treatment of breast cancer has not been specifically carried out. Therefore, this review aims to summarize and discuss studies related to the use of essential oils for breast cancer therapy arranged based on the rules of a systematic review.

2. Methodology

The arrangement of this systematic review was based on the results of the collected journals and reviews using Scopus, Pubmed, and Google Scholar databases with the keywords "essential oil for breast cancer", "monoterpene for breast cancer", "sesquiterpene for breast cancer", and so on. The inclusion criteria were in the form of research articles and journals for the last 10 years (2011–2021), while the exclusion criteria were journals without identification of compounds (Figure 1).

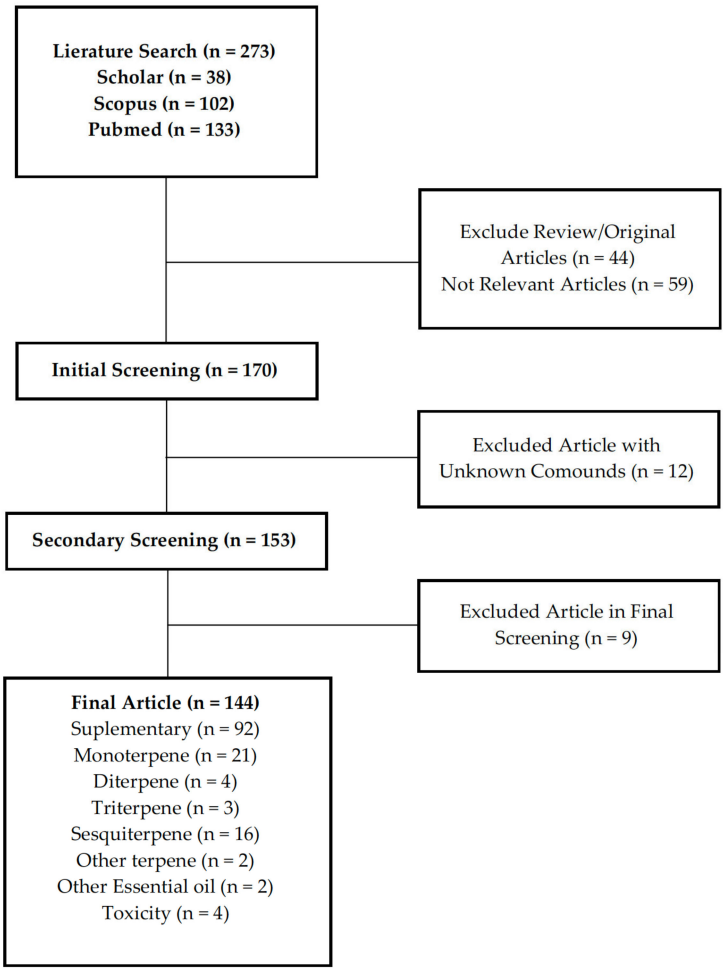

Figure 1. Flowchart of the methodology.

3. Result

In the literature search, 135 articles were listed. After screening the title and abstract, 48 articles were selected for a detailed study. Finally, 46 articles were chosen for this review.

3.1. Breast Cancer

Breast cancer is the most common cancer with a high mortality in women [3]. The malignant illness which causes this cancer starts in the breast cells. Factors including

the population structure, lifestyle, genetics, and the environment, can increase the risk of acquiring this cancer, similar to other malignant tumors [1,2,25].

According to breast cancer oncology, neoplastic cells are different from other normal body cells. Normal tissues in the body have limited growth regulation keeping their structure and function working as usual. Cancer cells, however, have prolonged and chronic proliferation without external stimulation [26]. A breast tumor usually begins with ductal hyperproliferation which will develop into a benign tumor or metastatic carcinoma if stimulated continuously by various carcinogenic factors. The tumor microenvironment, such as the influence of the stroma or macrophages, also plays an important role in the initiation and progression of breast cancer [27–29].

The two theories put forth as the basis for the initiation and progression of breast cancer are the cancer stem cell theory and the stochastic theory (Figure 2). According to the cancer stem cell theory, all tumor subtypes develop from the same stem cell or progenitor cell. Different phenotypes of a tumor are caused by genetic and epigenetic alterations that are acquired in stem cells or progenitor cells. The stochastic theory describes that each tumor subtype originates from a single type of cell (stem cells, progenitor cells, or differentiated cells). Any breast cell may progressively develop random mutations, and if these mutations result in malicious behavior, the breast cells are categorized as tumor cells.

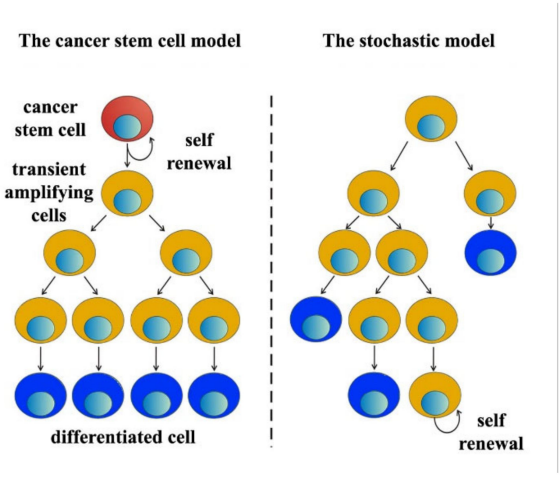

Figure 2. Stem cell and stochastic model.

According to the cancer sites, there are many types of breast cancer, including invasive and non-invasive cancer. When abnormal cells originating from milk ducts or lobules spread out closer to the breast tissue, invasive carcinoma develops [30]. These type of cancer cells can pass through the breast tissue and migrate to various parts of the body by the immune system or through systemic circulation [31]. The most frequent malignancy in women is invasive breast cancer. Non-invasive breast cancer, on the other hand, refers to cancer that has not spread from the lobules [32]. Atypical cells can form and progress into invasive breast cancer, even when they have not yet spread to other tissues outside of the lobules or ducts.

Treatment of breast cancer currently consists of three methods, including surgical therapy, radiation therapy, and chemotherapy. Every technique has positives and negatives aspects, starting with surgical therapy, which aims to prevent, diagnose, stage, and remove malignant tissue. In the case of radiation therapy, the irradiated rays can often kill more than 40% of cancer cells. If chemotherapy is used, it can lessen the quantity of cancer cells and stop them from spreading. However, each approach has a number of disadvantages, such as pain, infection, bleeding, blood clots, and gastrointestinal issues for surgical therapy. The mechanism of action for radiation is typically harmful to normal cells, which can occasionally be destroyed by the delivery of high radiation doses throughout the radiation process. Chemotherapy, on the other hand, is not selective and also has a negative effect

on healthy cells [6]. In addition, the limitations of chemotherapy are side effects and multiple drug resistance issues, prompting researchers to explore treatments utilizing natural compounds such as essential oils. Essential oils are plant-defense compounds (secondary metabolites), which contain active components with therapeutic action, one of which is anti-radical; hence, they can be used as an alternative cancer treatment.

3.2. Essential Oil

The original name of essential oil was Quinta Essential, given by Paracelsus von Hohenheim in the sixteenth century [33]. It is a combination of volatile secondary metabolites produced by plants, mostly used for pollinator attraction and self-defense against predators. Hydrocarbons and volatile terpenes make up most of the essential oils. Plant tissues' glandular cells produce essential oil, which is then accumulated in the resin vessel [34]. Ethereal oil and cooking oil are additional names for essential oil. Depending on the type of plant, the oil has a harsh flavor, is volatile at room temperature without decomposing, and often dissolves in organic solvents, though it is insoluble in water [35,36]. Essential oil can be extracted via distillation of plant extract. At high concentrations, essential oil can be used as local anesthetics. For example, clove oil is used to treat toothache, although it has the side effect of damaging mucous membranes [37]. Most essential oils have strong antibacterial and antifungal properties. Some of the most renewable activities of essential oils are controlling Alzheimer's disease, neurodegeneration, and anti-cancer activity [12,38–40].

Essential oils can be grouped based on several classifications and types. In this review, the oil is classified into two major parts: (1) based on the method of extraction and (2) based on the oil content.

3.2.1. Classification Based on the Method of Extraction

Several extraction methods have been reported and steam distillation is the most preferred method in producing essential oils at large quantities with well-maintained purity. However, the method is not suitable for all plant parts because it is not stable at high temperatures [41]. To overcome this problem, methods such as cold pressing and solvent extraction methods have been developed.

a. Steam Distillation

Steam distillation is a method that is often used for essential oil extraction [42]. The principle of steam distillation is using steam as a separation agent to separate the various component of the mixture [43], such as the separation of essential oil in the stems, leaves, and flowers. The flow of steam around these parts will cause the oil to be evaporated and carried away with the steam, which is then condensed and separated by decantation. This method is often used to make traditional or aromatherapy oils that are pure and free from impurities [44]. The quality and purity of the oil depend on various factors, such as the pressure of the steam passing through the plant material, the refrigerant used, the temperature of the closed system during oil production, as well as the skills of the distiller. The oil produced by steam distillation is of high value because of the high quality and purity of the extracts [37,45].

b. Cold Pressing Method

The cold pressing method is used to obtain high purity oils [46]. The principle of this method is applying pressure to extract the essential oil substances present in the plant. This method is mostly used by the citrus family to extract oil from fruit peels, such as tangerines, grapefruit, lemons, oranges, and others [47]. The oil is forced out of the plant parts by mechanical pressure, and the extracted results are in liquid form or mixed with water. Thus, a filtering or distillation step is required to separate the oil and the water [48–50].

c. Extraction Using Solvent

Some plant materials are unsuitable for steam distillation due to high temperatures (in the form of steam) or cold pressing. The resulting oils following this method can be

contaminated or have low purity. To avoid this, plants such as jasmine, rose, orange blossom (neroli), tuberose, and oak were extracted using solvents. This process works by passing plant materials through a hydrocarbon solvent, such as ethanol, ether, methanol, hexane, alcohol, and petroleum [38,51]. The solvent mixture is then filtered and distilled under low pressure to obtain the essential oils [52].

d. Microwave-Assisted Hydrodistillation (MAHD)

Microwave-assisted hydrodistillation (MAHD), a complex distillation technique that combines conventional hydrodistillation with microwave heating, has lately gained popularity for the extraction of essential oils from medicinal plants and herbs due to its cost-effectiveness and environmentally friendly nature. A method's efficiency can be increased by increasing the yield, among other factors, through optimization of its parameter conditions. Microwave-assisted hydrodistillation (MAHD) was developed and utilized to extract some plants' essential oils in an effort to make use of microwave heating with the traditional HD. Using the MAHD approach for this extraction has several benefits. Even though the distillation takes less time than the traditional extraction method, the oil yield is slightly higher, and this would help to meet the steadily rising demand for essential oil from medicinal plants. Less time is needed to complete the extraction, resulting in less electricity being used, which lowers operating costs as well. Furthermore, MAHD does not use any chemicals. Because of this, the essential oil obtained using this technique is virtually pure and secure. Given their widespread use in both food preparation and medicine, these requirements are crucial for medicinal essential oils [53].

e. Ohmic-Assisted Hydrodistillation (OAHD)

Ohmic-assisted hydrodistillation (OAHD) is a newly proposed extraction technique that has been utilized to separate essential oils and makes use of the benefits of ohmic heating. Over the past ten years, interest in ohmic hydrodistillation, which combines ohmic heating with hyrodistillation, has increased. In comparison to the traditional hydrodistillation procedure, ohmic-aided hydrodistillation (OAHD) has a shorter extraction time, uses less energy, and produces a greater yield. The extraction time for the OAHD method was 24.75 min, but the HD approach required 1 h to extract the thyme essential oil. In comparison to HD, there were no differences in the essential oil molecules derived by OAHD [54].

3.2.2. Classification Based on Contents

Most essential oils are composed of secondary metabolite components of the terpenoid group (monoterpenoids, triterpenoids, and sesquiterpenoids) and phenylpropanoids. Other names for essential oils are culinary oil and ethereal oil. The oil can have a strong flavor, be volatile at ambient temperature without disintegrating, and frequently dissolve in organic solvents, while being insoluble in water, depending on the plant species [55].

a. Terpenes

Terpenes are the main constituents of essential oils derived from various types of plants or flowers. They are naturally occurring, volatile, unsaturated or open-chain, or cyclic compounds. Terpenes can be classified according to the number of isoprene units, a 5-carbon compound that gives off a scent or taste as a defense mechanism [56]. Based on the isoprene, terpenes are divided into monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. Monoterpenes and sesquiterpenes are the largest components in essential oils [57].

Most types of terpenes, excluding clove oil, have a lower specific density than water and are soluble in organic solvents like ether and alcohol. It has a distinctive odor that characterizes the essential oils and high refractive index [57]. Terpenes play an important role in the taste, fragrance, and pigment of a plant. It has been reported that terpene possesses a variety of bioactivities, including anticancer, antibacterial, antihyperglycemic, antifungal, antiviral, analgesic, anti-inflammatory, and antiparasitic [56].

b. Monoterpenes

Almost all essential oils are monoterpenes, a 10 carbons compound with at least one double bond. Monoterpenes have a basic structure consisting of two linked isoprene units. These compounds can undergo cyclization and oxidation in various ways [58]. The high hydrocarbon content and fast reaction to air and heat sources making it not durable [34,59]. Due to their low molecular weight, many of these compounds exist in the form of essential oils. Examples of monoterpenes are geraniol, terpineol, limonene, myrcene, linalool and pinene [58].

It is reported that monoterpenes have antimicrobial, anti-inflammatory, antioxidant, antipruritic, hypotensive, and analgesic pharmacological properties [58].

c. Sesquiterpene

Sesquiterpene consists of 15 carbon atoms and has complex pharmacological action, such as that of chamazulene, which is found in German chamomile. The most prevalent kind of functional group identified in essential oils is the oxygenated groups. Similar to terpenes, it is vital to know the different classes of oxygenated compounds since each class has a distinct potential for health benefits [59–61].

Three linked isoprene units combine to form sesquiterpene lactones with one of the methanol groups oxidized to the lactone form. These sesquiterpenes are vital for plant defense since they are insecticides, antibacterial, antiviral, and antifungal agents. In addition, this compound can also provide biological activities, such as antibacterial, antiviral, antifungal, and anticancer [62].

3.3. Bioactivity of Essential Oils as Cancer Agents

Secondary metabolites found in essential oils can be used as active components in cancer treatments, such as the terpene group. Terpenes have been studied for anti-cancer activity. The following is the anti-cancer activity of essential oils:

3.3.1. Prostate Cancer

Prostate cancer is a cancer of the prostate gland that occurs in men [63]. A study of essential oils for anti-prostate cancer reported that essential oil containing jacaric acid selectively induces apoptosis in hormone-dependent (LN-CaP) and independent human prostate cancer cells (PC-3). The essential oil from *Solanum erianthum* and *Pinus wallichiana* has also been reported to exhibit significant anti-proliferative activity in prostate cancer [64]. The mechanism of essential oils in prostate cancer is to specifically inhibit ROS and have apoptotic activity in cancer cells [65]. In other research, the essential oil of Panax ginseng was shown to have saponins with antimutagenic and anti-tumor effects. *Guatteria pogonopus* leaves significantly inhibit PC-3M metastatic prostate malignancy both in vitro and in vivo [66]. Terpene essential oil has activity against three human cancer cells, one of which is prostate cancer cells. In addition, essential oil activity from the Mentha species was also reported in another prostate cancer cell line, namely LNCaP [67].

3.3.2. Glioblastoma

Glioblastoma multiforme (GBM) is a type of glioma (tumor of brain tissue) that grows and develops rapidly. These tumors are formed from star-shaped glial cells (astrocytes) that support nerve tissue in the brain [68]. Uncontrolled tumor development will lead to cancer [69]. Essential oil from *Hypericum hircinum* has antiproliferative activity on human glioblastoma tumor cells (T98G) [70]. Additionally, the cytosolic $Ca2^{+}$ content of T98G cells is increased by the essential oil from *Zanthoxylum tinguassuiba*, which contains bisabolol and sesquiterpenes, and the viability of human glioblastoma cells is altered by causing apoptosis. According to a recent study, glioblastoma cell line SF-767 was sensitive to *Ocimum basilicum* L. and *Lippia multiflora* EOs, whereas SF-763 cells were most responsive to *Ageratum conyzoides* L.'s essential oils with potent anti-tumor effects [71].

3.3.3. Colon Cancer

Colon cancer is cancer that develops in the large intestine or at the bottom of the large intestine connected to the anus (rectum) [72]. Several studies reported the activity of essential oils, mainly the terpene group for alternative colon cancer treatment. Geraniol, a monoterpene found in essential oils of various fruits and herbs has been proposed to represent a new class of cancer agents for chemoprevention, because it has significant antiproliferative activity on colon cancer cells (Caco-2) [73]. Essential oils from *Afrostyrax lepidophyllus*, *Scotonycteris zenkeri*, and *Athanasia brownii Hochr* showed a strong inhibitory effect on human colon carcinoma cell line HCT116 [74]. The essential oil of *Satureja khuzistanica* significantly reduced the viability of SW480 colon cancer cells in a dose-dependent manner [75]. The essential oil of *Artemisia campestris* exhibits significant antitumor activity against HT-29 colon cancer cells [76] while Thymoquinone inhibited the proliferation of a series of human colon cancer cells (Caco-2, HCT-116, LoVo, DLD-1, and HT-29) [77].

3.3.4. Liver Cancer

The aberrant growth of liver tissue that mutates and develops a tumor is known as liver cancer [78]. Essential oils from Thymus citriodorus, Artemisia indica, and Pituranthos tortuosus (Desf.) have substantial cytotoxic effects on HepG2 liver cancer cells when tested for anti-cancer activity [79]. The HepG2 liver cancer cell line undergoes apoptosis in response to zanthoxylum schinifolium essential oil, but not in response to caspase activation. [80]. Moreover, essential oil isolated from the leaves of *N. variabillima* also showed cytotoxic activity on human liver cancer cells [81].

3.3.5. Uterus and Cervix Cancer

Uterus cancer is a malignant tumor that develops commonly in the uterus in women with menopause or over 50 years of age [82]. Several studies have been reported on the activity of essential oils against uterus and cervix cancer. The uterine carcinoma cell line Siha and the cervical cancer cells HeLa, were both sensitive to the essential oils from the leaves of *Casearia sylvestris* and *Liquidambar styracifua* L. [83] The essential oil of *Aristolochia mollissima*'s rhizome and aerial increased the cytotoxicity of the human cervical cancer cell line HeLa [84]. Essential oil furanodiene from the rhizome of *Curcuma wenyujin* also demonstrated growth inhibition in an in vivo study in uterine cervical tumors (U14) of rats [85].

3.3.6. Lung Cancer

Lung cancer is a malignancy in the lung tissue originating from cells inside and outside of the lungs (metastasis) [85]. Essential oils from *Xylopia frutescens* leaves were reported to have a cytotoxic effect both in vitro and in vivo in NCI-H358M and PC-3M lung carcinoma cell lines [86]. The essential oil i n *Tridax procumbens* also showed a significant effect on preventing lung cancer cell metastasis on B16F-10 cell lines [87]. The essential oil obtained from *Litsea cubeba* seeds has activity on human NSCLC cells, A549, through the induction of apoptosis and cell cycle arrest [88], while the essential oil of *Solanium spirale* Roxb. showed significant cytotoxicity against NCI-H187 cells [89].

3.3.7. Leukimia

Leukemia is a health condition whereby the body produces excess white blood cells, also called abnormal leukocytes [90]. The THP-1 cell line showed concentration-dependent growth inhibition in the studies of *A. indica* essential oils in leukemia [91]. The cytotoxic efficacy of the essential oils of pine wood, *Cedrus libani, Juniperus excelsa*, and *Juniperus oxycedrus* against drug-sensitive CCRF-CEM and leukemia CEM/ADR5000 expressing multidrug-resistant P-glycoprotein was also demonstrated [92].

3.4. Bioactivity of Essential Oils as Anti-Breast Cancer Agents

Essential oils have been widely studied to treat breast cancer. From the articles collected, it is known that compounds that act as cancer agents are mostly terpene and its derivatives (Table 1).

Table 1. Bioactivity of Essential Oils as Anti-Breast Cancer Agent.

No	Plant Name	Compounds	Methods	Activities	Ref.
1	*Zataria multiflora*	Monoterpenes and triterpenes	MCF-7 and MDA-MB-231 cells	Triggers apoptosis by inducing ROS, mitochondrial membrane potential (MMP) loss, DNA damage, G2 and S-phase arrest in MDA-MB-231 cells and spheroids.	[93]
2	*Zataria multiflora*	Monoterpenes	In vitro using 4T1 cells	Inhibition of proliferation and apoptosis of 4T1 and TC1 cells.	[94]
3	*Cymbopogon citratus*	Monoterpenes	In vivo using 54 Holtzman female rats	Shows tumor reduction as well as necrosis and mitosis.	[95]
4	*Oliveria decumbens*	Monoterpenes	In vitro using 4T1 cells	Induces apoptosis through ROS generation, mitochondrial membrane potential disruption, caspase-3 activation, and DNA damage.	[38]
5	*Pinus sylvetris*	Monoterpenes	In vitro using MCF-7 cells	Inhibits the growth of MCF-7 cells by 45.3% and 99.7%.	[96]
6	*Erythrina corallodendron* L.	MonotMonoterpenes erpen	In vitro using MDA-MB-231, MCF-7 and HMLE cells	Inhibits the proliferation, migration, and invasion of breast cancer cells in a dose-dependent manner.	[97]
7	*Cyphostemma juttae*	Diterpenes	In vitro using MDA-MB 231 and SUM 149 cells	*C. juttae* oil substantially reduces the activation of NF-κB transcription factors, resulting in a significant decrease in several NF-κB target genes.	[98]
8	*Juniperus oxycedrus* L.	Monoterpenes	In vitro using MCF-7 cells	ALEO shows an IC_{50} value of 31% (v/v) against MCF-7 cells after 36 h of treatment.	[99]
9	*Pallines spinosa*	Monoterpenes and triterpenes	In vitro using MCF-7 and MDA-MB-231 cells	Induces apoptosis in MCF-7 and MDA-MB-231 cell lines, and alters Bcl-2 and Bax protein levels.	[60]
10	oleo-gum-resin and its essential oil of *Ferula assa-foetida* and ferulic acid	Monoterpenes	In vitro 4T1 cells	The results show that the three constituents can inhibit the proliferation of 4T1 cells. Our MTT assay results demonstrated a significant cytotoxicity effect in a time and concentration-dependent manner.	[100]
11	*Decatropis bicolor* (Zucc.)	Monoterpenes	In vitro using MDA MB 231 cells	Cytotoxic effect on MDA-MB-231 cells in a dose- and time-dependent manner with an IC_{50} of 53.81 ± 1.691 μg/mL, but independent of the breast epithelial cell line MCF10A (207.51 ± 3.26 μg/mL).	[101]
12	*Cinnamomum longepaniculatum*	Monoterpenes	A549 and MCf-7 cells	The essential oil derived from C. longepaniculatum with the main compounds of terpinen-4-ol, α-terpineol, and safrole induces apoptosis or substantial necrosis in human A549 lung cancer and MCF-7 breast cancer cells.	[61]

Table 1. *Cont.*

No	Plant Name	Compounds	Methods	Activities	Ref.
13	*Nigela sativa*	Thymoquinone (p-benzoquinones)	In vitro using MCF-7 cells	*Nigela sativa* essential oil significantly reduced breast cancer cell survival (MCF-7). The nucleo-cytoplasmic morphological features of NSEO-NE-treated cells were cell membrane blistering, cytoplasmic vacuolation, chromatin marginalization, and nuclear fragmentation. The results demonstrated that NSEO-NE induces apoptosis in MCF-7 cells.	[102]
14	*Opoponax (Commiphora guidottii)*	Sesquiterpenes	MCF-7 cells	The loss of viability was due to the induction of apoptosis as demonstrated by the Annexin V-propidium iodide and caspase-3/7 activity assays/test.	[103]
15	*Hypericum perforatum*	Sesquiterpenes	MCF-7 cells	The essential oil of Hypericum perforatum also showed anticancer activity against MCF-7 cells. The IC_{50} values of essential oil, MTX, and MTX essential oil were 0.78, 6.25, and 0.195 µg/mL, respectively. However, Hypericum perforatum essential oil was found to be non-cytotoxic for MDBK cells.	[104]
16	*Pinus corainensis*	Monoterpens	MDA-MB-231 cells (TNBC)	Inhibits TNF α-induced MDA-MB-231 cell invasion as determined by a three-dimensional spheroid invasion assay.	[105]
17	*Chenopodium ambrosioides* L.	Monoterpenes	MCF-7 cells	Inhibits the growth of MCF-7 cells within 24 h ($p < 0.05$), which is consistent with the results of fluorescent staining of live/dead cells.	[106]
18	*Boswelia sacra*	Triterpenes	MDA-MB-231 cells (TNBC)	Induces cancer cell death, prevent the formation of cellular tissue (MDA-MB-231) cells in Matrigel, and cause multicellular tumor spheroid damage (T47D cells), and regulates molecules involved in apoptosis, signal transduction, and cell cycle development.	[107]
20	*Syzigium aromaticum*	Diterpenes	BSLT (brine shrimp lethality test) method	Tests on BSLT and MTT showed essential oils had the highest cytotoxic effect, followed by ethanol and water extracts. The LD_{50} concentration of essential oil in 24 h of BSLT was 37 µg/mL.	[108, 109]
21	*Laurus nobilis* L.	Monoterpenes	MCF-7 and T47D cells	Shows a strong antiproliferative activity for both leaves and fruit; however, the fruit remained more potent against both breast cancer cell models (MCF7 and T47D).	[110]
22	*Lycopus lucidus Turcz. var. hirtus Regel*	Sesquiterpenes	MCF-7 cells	The essential oil can induce apoptosis of carcinoma cell lines and decrease the level of intracellular GSH.	[111]
23	*Cordia africana* Lam.	Sesquiterpenes	MCF-7 cells	Has an apoptotic mechanism with IC_{50} inhibition of 4.55 µg/mL.	[112]
24	*Lemon volatile oil*	Monoterpenes	MCF-7 cells	Oil derived from lime leaves shows cytotoxic activity against breast cancer cells (MCF-7) at IC_{50} 10% (v/v).	[113]

Table 1. *Cont.*

No	Plant Name	Compounds	Methods	Activities	Ref.
25	*Murraya koenigii*	Sesquiterpenes	MCF-7 cells	Essential oil in particular exhibits strong antibacterial and cytotoxic effects with a dose-dependent trend ($\leq$5.0 µg/mL).	[114]
26	*Cedrelopsis grevei*	Sesquiterpenes	MCF-7 cells	The main constituents are (E)-β-farnesene (27.61%), δ-cadinene (14.48%), α-copaene (7.65%), and β-elemene (6.96%). Grevei essential oil is active against MCF-7 cells (IC_{50} = 21.5 mg/L).	[115]
27	*Asteraceae family*	Sesquiterpenes	MCF-7 and MDA-MB-468 cells	*Britannin* can induce apoptosis in MCF-7 and MDA-MB-468 cells. Western blot analysis shows that Bcl-2 expression markedly decreased in response to *Britannin* treatment, whereas Bax protein expression increased, which is positively correlated with increased p53 expression.	[116]
28	*Tanacetum polycephalum* L. *Schultz-Bip*	Sesquiterpenes	In vivo (white rats)	Histopathological examination showed that TPHE significantly suppressed the carcinogenic effect of LA7 tumor cells. Tumor sections from TPHE-treated mice showed a significantly decreased expression of Ki67 and PCNA compared to the control group.	[117]
29	*Gaillardin, was isolated from the chloroform extract of Inula oculus-christi aerial*	Sesquiterpenes	MCF-7 cells	Gaillardin is able to induce apoptosis in the breast cancer cell lines of MCF-7 and MDA-MB-468 and determine the mechanism underlying their anticancer effects. Induction of apoptosis with Gaillardin treatment is confirmed by annexin V-FITC/PI staining, and activation of caspase-3, -6, and -9.	[118]
30	*Opoponax (Commiphora guidottii)*	Sesquiterpenes	In vivo (white rats)	Opoponax essential oil shows specific cytotoxicity for mammary tumor cells of humans and mice in vitro and in vivo, and this warrants further investigation into the use of β-bisabolene in medicine.	[103]
31	*Eupatorium lindleyanum DC.*	Sesquiterpenes	MDA-MB-231 cells (TNBC)	Inhibits migration, invasion, and motility of MDA-MB-231 cells in a concentration-dependent manner by invasion and apoptosis.	[119]
32	*Eupatorium lindleyanum DC.*	Sesquiterpenes	MDA-MB-468 cells (TNBC)	EO-induced cytotoxicity is mediated by the induction of apoptosis.	[120]
33	*Ulva fasciata*	Sesquiterpenes	MDA-MB 231cells (TNBC)	Computational study shows the interaction of guai-2-en-10α-ol with the Asp855 residue of the EGFR kinase domain in the active conformation. All these results suggest the anticancer potential of guai-2-en-10α-ol via the EGFR/PI3K/Akt pathway.	[121]
34	Plants such as *Inula helenium*	Sesquiterpenes	MDA-MB 231cells (TNBC)	ALA can inhibit the proliferation, motility, migration, and tube formation of human umbilical vein endothelial cells. ALA also inhibits angiogenesis at the chorioallantoic membrane of chicken embryos and slows the growth of the xenograft of human breast cancer of MDA-MB-231.	[61]

3.4.1. Monoterpenes

Nearly all essential oils contain monoterpenes, which have a structure of 10 carbon atoms with at least one double bond [59]. Monoterpene has been linked to breast cancer in numerous studies. The oxygenated monoterpene 1,8-cineole is a major component of the oil from *L. nobilis* fruits and leaves. The leaves and fruits' crude ethanol fractions, including solvent extracts, show strong antiproliferative activity. However, the fruits are more potent against both breast cancer cell models (MCF7 and T47D). At the IC_{50} value, the mechanisms of apoptosis are different when the proapoptotic efficacy of *L. nobilis* fruits is not regulated by p53 or p21, and the component of the leaves extract substantially increased p53 level. In both extracts, apoptosis is independent of caspase-8 or Fas ligand [110].

Essential oils derived from *Zataria multiflora* were investigated using MCF-7 and MDA-MB-231 cells. It is known that the main component of these essential oils are monoterpenes. The mechanism of monoterpenes is apoptosis by inducing reactive oxygen species (ROS), mitochondrial membrane potential (MMP) disruption, DNA damage, G2 and S-phase [122]. The essential oils were also investigated in vitro using cell lines of 4T1 and TC1 and tested on white winstar mice. As compared to controls, the results showed that the tested essential oils were effective at reducing tumor weight and inhibiting 4T1 and TC1 cell growth and death. They also enhanced the secretion of TNF-, IFN-, and IL-2 while decreasing IL-4. During the treatment with *Zataria multiflora* oil, the biochemical factors of mice did not change significantly [94].

In addition, *Cymbopogon citratus* essential oils include monoterpenes which reduce tumors, necrosis, and mitosis. Carvacrol-treated test animals did not exhibit necrosis, mitosis, or infiltration. The cumulative tumor volume was significantly reduced by carvacrol at a dose of 100 mg/kg/day BW, dropping to 0.11–0.05 cm^3 from 0.38–0.04 cm^3 in the DMBA group (p 0.01). Thus, it may be concluded that carvacrol and *Cymbopogon citratus* extracts exhibited antitumor effects on female rats having DMBA-induced breast cancer [95].

Anti-breast cancer activity was also analyzed by in vitro and in vivo for *Oliveria decumbens* essential oils by enhancing apoptotic and immunomodulatory effects. Based on the MTT test, *Oliveria decumbens* essential oils inhibit viability on 4T1 cancer cells without significant effects on normal cells L929 in 2D analysis, as well as the anti-proliferative effect on 4T1 spheroid (3D analysis). The results showed that *Oliveria decumbens* essential oils induce apoptosis through ROS generation, mitochondrial membrane potential disruption, caspase-3 activations, and DNA damage. On in vivo testing, the effectiveness of *Oliveria decumbens* essential oils were evaluated in tumor-induced 4T1 mice and cytokine to confirm the antitumor effect and development of immune response associated with Th1 expansion [38].

The monoterpene of *Pinus sylvestris*' essential oils demonstrated minimal inhibitory doses of 0.125, 0.1, 3.0, and 10.0 μg/mL, against *B. subtilis*, *S. cerevisiae*, *S. aureus*, and *E. coli*, respectively. The proliferation of MCF-7 cells was decreased by 45.3% and 99.7% by the oils at 50 μg/mL and 100 μg/mL, respectively, and 14,36 ± 0.28 μg/mL was the inhibitory concentration of DPPH (2,2-diphenyl-1-picrylhydrazyl) for radical scavenging [96].

Additionally, the essential oils from the leaves of *Erythrina corallodendron* L. reduced the growth, migration, and invasion of breast cancer cells in a dose-dependent manner. Further research on the essential oils from leaves of *E. corallodendron* should be performed to elucidate their potential as a clinical drug or adjuvant to treat migration and invasion of breast cancer [97].

Moreover, essential oils from the *Oxycedrus* L. fruit showed higher efficacy against MCF-7 cells as compared to the extract derived from the leaves. According to reports, *Oxycedrus* L. triggered caspase-9 activation and mitochondrial potential loss in ER + breast cancer cells, indicating that the fruit oils activated the intrinsic mechanism of death in these cells [99].

According to a different study, the essential oils of *Pallines spinosa*'s flowers were substantially more effective than those of the oil leaves against MCF-7 (IC_{50} 0.25 ± 0.03 μg/mL) and MDA-MB-231 (IC_{50} 0.21 ± 0.03 μg/mL), respectively. When compared to breast cancer

and cell hematology, the toxicity of flower oils was five to eight times lower in normal MCF-10-2A (IC_{50} 1.3 ± 0.2 µg/mL) and blood mononuclear cells (2.80 ± 0.45 µg/mL), respectively. Both oils change the levels of the proteins Bcl-2 and Bax and cause caspase-dependent and MCF-7 and MDA-MB-231 cell-dependent apoptosis. Additionally, the oils control the production of cyclin D1, CDK4, and p21 proteins to suppress the cell cycle in both cancer cell lines at the G0/G1 phase [60].

Ferula assa-foetida and *Decatropis bicolor* (Zucc.) also contain monoterpenes having anti-breast cancer effectiveness. The cytotoxic impact on MDA-MB-231 cells is dosage- and time-dependent, with an IC_{50} of 53.81 ± 1.691 µg/mL, but is independent of the breast epithelial cell line MCF10A (207.51 ± 3.26 µg/mL). However, ferulic acid did not show any significant effect until 500 µg/mL [100,101].

The essential oils from *Cinnamomum longepaniculatum* were mainly terpinen-4-ol, α-terpineol, and safrole, which are known to induces apoptosis or substantial necrosis in human A549 lung cancer and MCF-7 breast cancer cells [106]. Among the four main components of Korean pine essential oils, d-limonene, 3-carene, α-pinene, and β-myrcene demonstrated the highest suppression of nuclear factor κB (NF-κB) triggered by the tumor necrosis factor (TNFα) [105]. The active substance in the essential oils could inhibit the growth of MCF-7 cells within 24 h ($p < 0.05$), which is consistent with the results of live/dead cell fluorescent staining.

Chenopodium ambrosioides L. inhibited essential oils by 58.98%, 1-isopropyl-4-methylbenzene by 37.8%, and α-terpinene by 32.09%. In comparison to the control, the relative MDA content increased considerably (p 0.05) up to concentrations of 1.25, 0.21, and 0.17 µg/mL for essential oils 1-isopropyl-4-methylbenzene, and α-terpinene, respectively, and subsequently declined ($p < 0.05$) [61].

The molecular profile of lemon essential oils against breast cancer was examined using GC/MS analysis. Limonene (47.24% and 55.23%), geranial (14.48% and 7.94%), and neral (12.1% and 6.1%) made up most of the mixture. At an IC_{50} of 10% (v/v), the oils from the leaves exhibited cytotoxic action against breast cancer cells (MCF-7). According to the results (compared to untreated cells; $p < 0.05$), there was a significant increase in the expression level of the apoptotic protein caspase-8, a significant decrease in the expression level of the anti-apoptotic protein BcL-2, and a significant increase in the expression level of the proliferative marker Ki-67 [113,123].

Another test conducted on red algae *Plocamium* extract with monoterpenes as the dominant compound was against MDA-MB-231 triple-negative breast cancer cells. The results showed that it is able to disrupt mitochondria, activate caspase-3/7, externalize phosphatidylserine, reduce the number of polyploid cells, and is DNA fragmentation consistent with the induction of apoptosis with an IC_{50} value of 16 ± 2.2 µM, 7.3 ± 0.4 µM, and 3.3 ± 0.5 µM after 24 h, 48 h, dan 72 h, respectively [124].

3.4.2. Sesquiterpene

Sesquiterpenes have been widely studied for their activity against breast cancer. Yoe et al. reported that β-Bisabolene and α-Bisabolene from opoponax (*Commiphora guidottii)* showed specific cytotoxicity for mammary tumor cells of humans and mice both In vitro and In vivo. In addition, this compound also showed good selectivity in human cancer cells of MCF-7, MDA-MB-231, and SKBR3 [103]. Therefore, further investigation into the use of β-bisabolene in medicine is needed [103].

Additionally, *Hypericum perforatum essential* oil demonstrated that sesquiterpene such as germacrene D, δ-cadinene, γ-muurolene, germacrene B, α-copaene, bicyclogermacrene, and (E)-caryophyllene was the dominant compound. Cytotoxic activity of the essential oils on MCF7 breast cancer cells resulted in the suppression of cancer growth with an IC_{50} of 0.78 µg/mL. However in normal MDBK cells no cytotoxic activity was observed [125].

Essential oils of *Lycopus lucidus* Turcz. var. hirtus Regel was also reported to contain sesquiterpene; -Humulene (15.97%) was the dominant compound. These essential oils are reported to exhibit cytotoxic activity by reducing the cell viability of breast cancer [111].

Essential oils from *Cordia africana* Lam. contain 32.0% of β-caryophyllene having inhibition on MCF7 breast cancer cells with an IC_{50} of 4.55 μg/mL. In addition, this essential oils also exhibit apoptotic activity by the increase in protein caspase-8 which induces apoptosis in cells [112].

Essential oils from *Murraya koenigii* are also reported to be sesquiterpenes as the dominant compounds [114]. The essential oils inhibit the growth of MCF7 breast cancer cells. Essential oils from *Cedrelopsis grevei* leaves contained (E)-β-farnesene (27.61%), α-copaene (7.65%), δ-cadinene (14.48%), and β-elemene (6.96%) also inhibits the proliferation of MCF7 breast cancer cells with an IC_{50} value of 21.5 mg/L [115].

Herbal medicine derived from *Chloranthus serratus* essential oils was reported to suppress LIM kinase-1 (LIMK1) which plays an important role in invasion and metastasis of tumor cells by regulating actin cytoskeleton architecture, cofilin1 phosphorylation, F-actin polymerization and the cell migration of human breast cancer MDA-MB-468 and MDA-MB-231 cells with IC_{50} values of 4.64 μM and 3.14 μM respectively [126].

Another study reported that sesquiterpene from the *Pimpinella haussknechtii* fruit increased protein aggregation and mRNA expression of ATF-4, CHOP, GADD34, and TRIB3 in MCF7 breast cancer cells, with IC_{50} values of 45 and 25 μM [127]. Alantolactone, a sesquiterpene compound, were reported to inhibit angiogenesis, suppress phosphorylation of vascular endothelial growth factor receptor 2 and its downstream protein kinases including PLC-γ1, FAK, Src, and Akt in endothelial cells, and delay the growth of human breast cancer MDA MB 231 xenografts in mice. When tested on MDA MB 231 cells, the antiangiogenic activity of this chemical indicated that alantolactone is a prospective therapeutic candidate for antiangiogenic cancer therapy, with an IC_{50} of 40.4 μM [128].

Based on these In vitro and In vivo studies, sesquiterpenes were active against breast anticancer cells. In vitro studies on anti-breast cancer activity using MCF-7, MDA MB 231 and MDA MB 468 cells [60,120] shows significant results in inhibiting breast cancer [61,116,120,121]. In addition, the histopathological In vivo studies performed on white mice showed that sesquiterpenes significantly suppressed the carcinogenic effect of LA7 tumor cells in mice [103].

The mechanism of the sesquiterpenes is to inhibit the migration, invasion, and motility of MDA-MB-231 cells in a concentration-dependent manner by invasion and apoptosis [119]. Moreover, studies on the inhibition of the Akt pathway in MDA-MB-468 cells showed that it might stop the growth of those cells, by causing a cell cycle arrest in the G2/M phase and inducing caspase-dependent death [120].

According to a recent study, allantoin can prevent human umbilical vein endothelial cells from proliferating, migrating, moving, and forming tubes. Additionally, allantoin inhibited angiogenesis at the chorioallantoic membrane of chicken embryos and, via blocking angiogenesis, reduced the growth of the breast cancer xenograft MDA-MB-231 in mice [128].

3.4.3. Triterpenes

Triterpene has been reported to be active against breast cancer cells [129,130]. In comparison to the essential oils from the leaf (IC_{50} 2.4 ± 0.5 μg/mL and 1.5 ± 0.1 μg/mL), triterpenes from *Pallines spinosa* demonstrated a considerable cytotoxic effect on MCF-7 (IC_{50} 0.25 ± 0.03 μg/mL) and MDA-MB-231 (IC_{50} 0.21 ± 0.03 μg/mL) cells. When evaluated on normal MCF-10-2A (IC_{50} 1.3 ± 0.2 μg/mL) and blood mononuclear cells (2.80 ± 0.45 μg/mL) as opposed to breast cancer cell hematology, flower essential oils' toxicity was five to eight times lower. Both essential oils change the levels of the proteins Bcl-2 and Bax and cause caspase-dependent apoptosis in MCF-7 and MDA-MB-231 cells. Additionally, via modifying the expression of cyclin D1, CDK4, and p21 proteins in both cancer cell lines, essential oils suppressed the cell cycle at the G0/G1 phase [60].

Boswellia sacra essential oils which were distilled at 100 °C were more effective than essential oils prepared at 78 °C. This is because the extract has higher triterpene content. These compounds have the ability to cause the death of cancer cells, stop the growth of

MDA-MB-231 cells in Matrigel, harm multicellular tumor spheroids (T47D cells), and control molecules that control apoptosis, signal transduction, and cell cycle progression [107].

Xue et al. reported that the ethanolic extract of *Pleurotus eryngii* inhibits MCF7 cells. Three triterpene components, 2,3,6,23-tetrahydroxy-urs-12-en-28 oic acid, 2,3,23-trihydroxyurs-12-en-28 oic acid, and lupeol, make up most of this extract's composition. The ability of these substances to stop the growth of breast cancer cells was demonstrated by their respective IC_{50} values of 15.71, 48, and 66.89 μM, repsectively [131].

3.4.4. Diterpenes

Diterpenes are a group of hydrocarbons that are widely present in essential oils. Several studies reported that diterpenes are good anti-breast-cancer agents. Zito et al. [98] reported that the essential oils of *Cyphostemma juttae* have a dominant diterpene content, which is phytol compound (30%) tested against triple negative breast cancer cells (MDA-MB-231, SUM 149). Phytol substantially reduces the activation of NF-κB transcription factors, resulting in a significant decrease in several NF-κB target genes.

The extract of *Tinospora cordifolia* also contains diterpenes with breast anticancer activity against MCF7 cells. The results showed that the IC_{50} values at 24 and 48 h were 3.2 mM and 2.4 mM respectively. The cytotoxicity of this compound was specific for MCF-7 cells and had no toxic effect on normal Vero cells and V79 cells. This compound also significantly stimulated the formation of intracellular ROS, even at lower doses of 0.6 and 1.2 mM. Thus, it can be concluded that the diterpene compounds from this extract are effective and selective against cancer cells, especially breast cancer cells [132]. The diterpene myrsinol compound J196-10-1, derived from the roots of *Euphorbia prolifera*, can reverse multidrug resistance, namely daunorubicin, vincristine, and topotecan, with the IC_{50} value of daunorubicin from 29.65 μM to 0.55 μM, vincristine from 13.85 μM to 0.063 μM, and topotecan from 4.61 μM to 0.65 μM [106].

Myrsinane-type diterpenes, such as 3,7,10,14,15-tetraacetyl-5-propanoyl-13,17-epoxy-8,10,18-myrsinadiene and 3,7,10,14,15-pentaacetyl-5-butanoyl-13,17-epoxy-8-myrsinane, are present in *Euphorbia connata* Boiss. acetone:chloroform extracts. In MDA-MB cells, these compounds had an IC_{50} value of 24.53 ± 3.39 and 26.67 ± 1.41 μM, while in MCF-7 cells, the value was 37.73 ± 3.41 and 34.57 ± 2.12 μM, respectively, indicating a moderately inhibitory effect on breast cancer. Other diterpenes, such as 5,6-epoxy-8,9,15-triacetyl-3-benzoyl-14-oxo-jatropha-11 (E)-ene (3), exhibited weak cytotoxicity in MDA-MB cells (IC_{50} = 55.67 ± 7.09 μM) and moderate cytotoxicity in MCF7 cells (IC_{50} = 24.33 ± 3.21 μM) [133].

3.4.5. Other Terpenes

Essential oils from *Nepeta cataria* L. have also been tested on PC3 and MCF7 breast cancer cells. The largest content of these essential oils is the stereoisomer of nepetalactone, a class of terpene compounds. Essential oils of *N. cataria* were more effective against PC3 triple negative breast cancer than other breast cancer cells. In addition, western blot also showed the expression of apoptosis-inducing proteins. Therefore, it can be postulated that these plant compounds have the mechanism to treat cancer by inducing cell apoptosis [134]. The dominant compounds in essential oils from *Achillea fragrantissima* comprise 1-terpinen-4-Ol (30.90%) and p-cymen-3-Ol (21.22%), and these essential oils were effective against MCF7 breast cancer cells, with an IC_{50} value of 0.51 μg/mL extracted via hydrodistillation and 0.80 μg/mL extracted via volatile solvent extraction [135].

3.5. Types of Cells Used in Cytotoxic Studies

Cytotoxic studies of essential oils were performed on several types of breast cancer cell lines (Figure 3). Throughout this review, MCF-7 and MDA-MB-231 are the most common cancer cells used in cytotoxic studies, with 19 studies on MCF-7 and 11 on MDA-MB-231. (Figures 3 and 4) The breast cancer cell line MCF-7 contains glucocorticoid, progesterone, and estrogen receptors. The pleural effusion of a 69-year-old Caucasian woman with metastatic breast cancer (adenocarcinoma) was used as the source of this substance in 1970

by Dr. Soule of the Michigan Cancer Foundation in Detroit, Michigan. Because MCF-7 cells still possessed several desirable traits unique to the mammary epithelium, such as the ability to process estrogen in the form of estradiol via estrogen receptors (ER) in the cell cytoplasm, it is valuable for in vitro breast cancer investigations. It is the first hormone to react to a breast cancer cell line. Its special qualities are advantageous for experimental therapies, and the cells are also cytokeratin-sensitive. The epithelial-like cells develop in monolayers when cultured in vitro, and the cells have the ability to form domes.

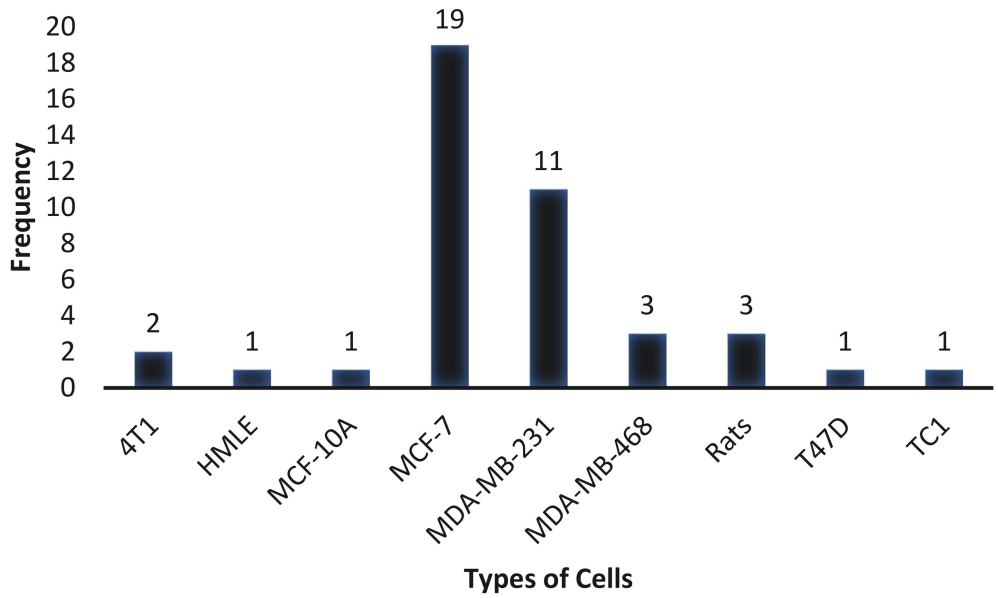

Figure 3. Types of cells used in the cytotoxicity study.

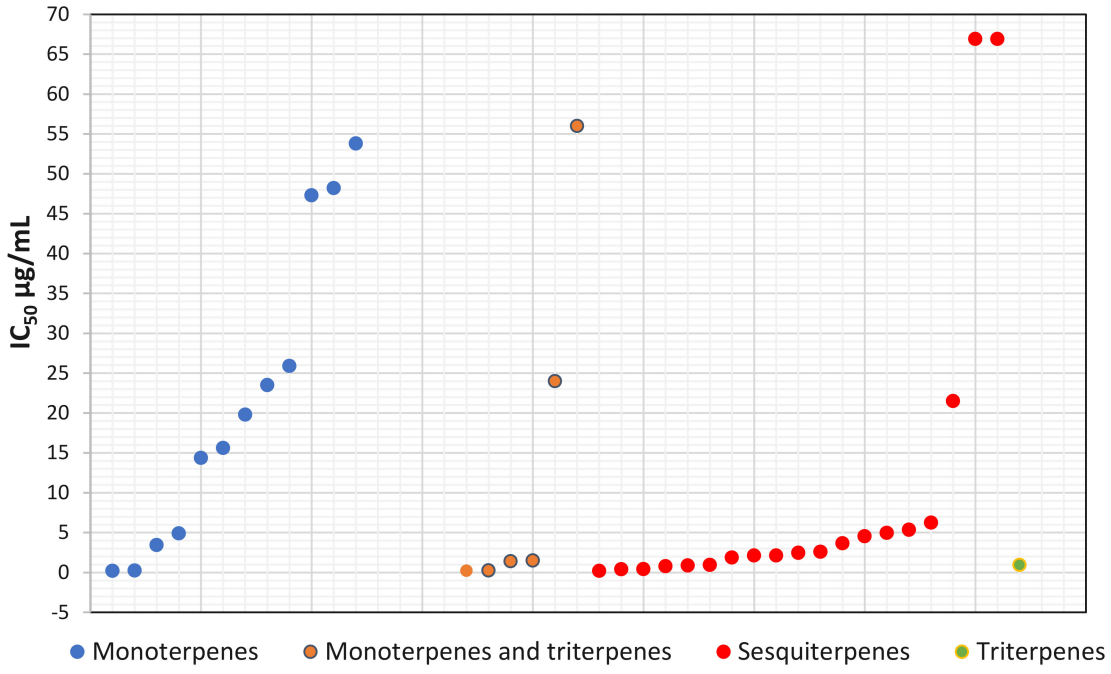

Figure 4. IC_{50} Value of essential oils in breast cancer cells.

The triple-negative breast cancer cell line MDA-MB-231 exhibits an indicative epithelial to mesenchymal transition (EMT), which is linked to BC metastasis. One of the most popular breast cancer cell lines in medical research labs is the MDA-MB-231 epithelial cell line. It was developed from a pleural effusion of a 51-year-old Caucasian woman with metastatic

mammary adenocarcinoma1. Based on the IC_{50} results, sesquiterpenes have the lowest IC_{50} value of 0.19 µg/mL in MCF-7 cancer cell line. In addition, from the 19 anticancer studies of sesquitepenes, 17 showed an IC_{50} below 20 µg/mL, indicating strong activity, as compared to monoterpenes with 7 out of 12 anticancer studies below 20 µg/mL. From this, it can be concluded that sesquiterpenes have the best potential anticancer activity compared to other compounds (Figure 4).

3.6. Clinical Trials of Essential Oils for Breast Cancer

Clinical trials for the use of essential oils as a breast cancer treatment on breast cancer patients are currently being conducted. Peppermint essential oil has undergone clinical testing on 100 breast cancer patients receiving outpatient care at the Imam Khomeini Hospital cancer center. Patients were randomized into interventions with control groups. The intervention group received aromatherapy with peppermint essential oil, whereas the control group received saline solution. From this study, it is suggested that the use of anti-nausea medications in combination with aromatherapy using peppermint essential oil can lessen nausea and vomiting during acute phase drug use [136]. The impact of inhaling ginger aromatherapy on patients with breast cancer symptoms, such as nausea, vomiting, and poor health-related quality of life (HRQoL), has also been investigated. In the acute period, essential oil inhalation significantly reduced visual analog scale (VAS) nausea scores when compared to the placebo [137]. The findings of recent clinical trials for the treatment of nausea and vomiting brought on by medication are generally positive. It is postulated that specific medicines using the components of essential oils would be developed to treat cancer in the future.

3.7. Toxicity and Side Effect of Essential Oils

The largest and most diversified collection of naturally occurring substances is comprised of terpenes, also referred to as terpenoids. They are mostly present in plants and make up the bulk of essential oils made from plants. Terpenes have numerous bioactive and pharmacological properties, as well as a variety of medical applications. Terpenes also provide for flexibility in the route of administration and the reduction of side effects in addition to these qualities. Terpenes are natural substances that are unlikely to harm healthy cells or have any negative side effects, which attracts many researchers to explore their potential as a cancer treatment [138]. Castilhos et al. conducted toxicity research of essential oils in 2017, and the findings show that these compounds exhibit relative selectivity to the predator *Chrysoperla externa*; nevertheless, some compounds also showed sublethal effects on reproduction. Carvacrol and thymol, two phenolic monoterpenoids, were less toxic than natural pyrethrins (the toxicity standard) in these bioassays, but they were more acutely lethal than other terpenoids screened, with an LD_{50} of 20,000 g/g. R-(+)-limonene was found to have sublethal impacts on fecundity and fertility, whereas oregano oil merely had a fecundity-related effect [139].

On laboratory animals, usually rats, the potential toxicity of various essential oils and their constituents was studied. The median lethal dose (LDso) test was used to assess acute toxicity in rats, and the results showed that most essential oils have an LDso of 1–20 g/kg, indicating low toxicity. Some essential oils, such as lemon oil, have an LDso of greater than 5 g/kg in humans. Therefore, the deadly dose for an adult weighing 70 kg would be 350 g, which is difficult to achieve under normal circumstances. The EOs from Boldo leaf, Chenopodium, Mentha pulegium (pennyroyal), Satureja hortensis (savory), and Thuja are a few notable outliers; they showed an LDsp between 0.1 and 1 g/kg in rats, signaling a high toxicity and recommending the need for necessary care while using them. Since some of the resultant compounds, such as the oxidation products of limonene, are potentially skin sensitizers, essential oils are subject to oxidative deterioration. Alipanah et al. (2021) formulated *Citrus sinensis* and *Citrus limon* essential oils using chitosan nanoparticles to improve the anti-breast cancer. This idea is also a solution to protect the instability of limonen and keep them from being easily oxidized [140]. Additionally, in

order to boost activity against breast cancer cells, Valizadeh et al. (2021) used chitosan to create na-noparticles of Syzygium aromaticum essential oils with the predominant amount of egeunol (MDA-MB-468) [109]. Therefore, proper essential oil storage is required to maintain their potency and lower the likelihood of negative responses. Essential oils should be kept in tightly sealed containers in a refrigerator or in a cool, dark location (brown bottles). Although the Flavor and Extract Manufacturers Association (FEMA) awarded most essential oils the GRAS (generally recognized as safe) certification, it should be noted that these oils were only tested as flavors with very low concentrations in the tested goods. Particular hazardous consequences, either local or systemic, for a concentrated essential oil, could manifest under certain conditions [141,142].

4. Author Perspective

Essential oils are plant-made active metabolites that serve as the plants' internal defense mechanisms. The active metabolites found in essential oils are potent antioxidants that aid in blocking ROS [143,144], and hence have medicinal efficacy to treat a variety of ailments. Due to their antioxidant properties, various research reviews claim that the mechanism of essential oils which inhibit ROS can be used in anti-cancer therapy. The molecular mechanism of anti-cancer essential oils as has been studied extensively due to the high prevalence of cancer patients, particularly breast cancer. From the studies, the terpene group is effective in inducing apoptosis and inhibiting the growth of breast cancer cells, such as the MCF-7 and MDA-MB231 cell lines. Despite extensive preclinical and clinical research using cancer cells and patients, the advantages of essential oils as a treatment for chemotherapy side effects, such as nausea and vomiting, have recently been revealed. In the fight against breast cancer, the outcomes of essential oils against cancer or cancer's side effects are highly substantial. It is envisaged that the physicochemical qualities of essential oils, such as stability in varied environments, can be improved in the future. It is also hoped that the active substance of essential oils will be incorporated into drug development for breast cancer.

5. Conclusions

As potential anti-breast cancer medicines, essential oils have demonstrated promising bioactivity and pharmacological characteristics in vitro and in vivo. Terpenoids, primarily monoterpenes, sesquiterpenes, diterpenes, and triterpenes, make up the majority of the essential oils' chemical composition. According to this review, essential oils from 18 out of 28 sesquiterpenes with IC_{50} values $\leq$ 20 μg/mL were reported in 17 out of the 19 anti-breast cancer investigations. This demonstrated that sesquiterpenes are the most effective anti-breast cancer agent, with an IC_{50} on the MCF-7 627 cancer cells line of 0.19 μg/mL. We believe that essential oils might eventually be employed as a primary or adjuvant therapy for the treatment of breast cancer, since they are highly effective and rarely exhibit side effects.

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