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Essential Oils' Potential in Breast Cancer Treatment: An Overview

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Abstract

Essential oils are widely used in the pharmaceutical industry for their antimicrobial, antiviral, antifungal, antiparasitic, and insecticidal properties. Their anticancer activity has been increasingly explored as the natural constituents of essential oils play an important role in cancer prevention and treatment. The chemical composition of essential oils includes monoterpenes, sesquiterpenes, oxygenated monoterpenes, phenolic sesquiterpenes, and others. Several mechanisms of action such as antioxidant, antimutagenic, antiproliferative, enhancement of immune functions, modulation of multidrug resistance, and synergistic mechanism of volatile constituents are responsible for their chemotherapeutic properties. This review focuses on the activity of essential oils and their chemical composition in regard to breast cancer.

Keywords: essential oils, antitumor activity, chemical composition, antitumor mechanism, breast cancer

1. Introduction

Cancer is a disease in which normal cells change into a type of cell that can continuously proliferate and, by a process named metastasis, migrate to distant parts of the body [1]. Breast cancer (BC) is the most common cancer in women in the world, presenting high morbidity and mortality [2]. It causes a major public health problem, and the incidence is increasing all over the world [3].

The treatment used for cancer causes many side effects; besides, there are a large number of cases of resistance toward anticancer drugs [4]. These are the main causes that limit the success of treatment in aggressive BC cases. Thus, the need to have novel therapeutic agents is urgent [2].

Natural products, such as plants, may hold the future of BC treatment as the source for new drugs that can interfere with certain processes and ultimately result in clinical usage as an adjuvant therapy [1].

Essential oils (EOs) act as protective mechanism for plants against bacteria, viruses, insects, and even herbivores [5]. They are widely used by the population to treat cancer and can change the metabolism of cancer cells in very low doses, besides provide energy for synthetic processes [6]. This way, EOs are being considered as a promising agent opening venues for novel anticancer therapy as a way to defeat side

effects and the high cost of chemotherapy approaches in BC [7]. This review focuses on apoptosis as an action mechanism by EOs in breast cancer cells, antitumoral activity of EOs and their bioactive compounds, and optimization of EOs' use and their potential as an alternative for side effects reduction during breast cancer treatment.

2. Induction of apoptosis in breast cancer cells by essential oils

Apoptosis is a cellular process involved in physiological and pathological conditions. The mechanism of apoptosis plays an important role in the pathogenesis of many diseases, such as cancer, in which it can be reduced by the cells as a mechanism of survival so they can continue to proliferate, leading to metastasis and resistance to drugs. Caspases can act as initiators and executors of this process and can be activated in an intrinsic or extrinsic way. The intrinsic, or mitochondrial, pathway is controlled by proteins from the Bcl-2 family, which can be proapoptotic proteins such as Bax, Bak, Bad, Bcl-Xs, Bid, Bik, Bim, and Hrk, or antiapoptotic such as Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1 [8].

Collected from Kerman, Golestan, and East Azerbaijan provinces from Iran, EO from the seed of *Foeniculum vulgare* Mill, known as fennel (FN), increased the expression of a proapoptotic factor Bax and decreased antiapoptotic factor Bcl2 gene expression, which leads to cytotoxic effects on MCF7 [7]. FN also had action against MDA-MB [9]. But the FN from Tajikistan presented low cytotoxicity when compared to doxorubicin [10].

Another plant in Iran, *Oliveria decumbens*, is used as a vegetable and medicinal plant by the population to treat cancer-related symptoms. Its EO (OEO) inhibited viability of murine mammary carcinoma 4T1, promoting apoptosis in vitro and led to a TH1 anticancer response in 4T1 tumor-challenging mice [11]. OEO and its main component, thymol, also showed anticancer properties in MDA-MB-231 BC monolayers by activation of intrinsic and maybe extrinsic apoptosis [12]. Also, in Iran, all EOs obtained from the aerial parts of *Zhumeria majdae* collected from five different localities were active and did not show cytotoxicity variability for MCF7 [13].

EO of *Decatropis bicolor* (Zucc.) Radlk, empirically used in Mexico for BC treatment, showed a selective cytotoxic effect toward MDA-MB-231 by activation of Bax and caspases 9 and 3 through intrinsic apoptosis pathway [14]. The apoptosis of MCF7 was stimulated by *Ocimum sanctum* EO with the regulation of apoptotic genes p53 and Bid and elevation of Bax/Bcl-2 [15]. Similar results were found with MCF7 apoptosis induction by *Tetradlinis articulata* [16] and *Myrtus communis* L., commonly used in Morocco for culinary purposes [17]. Carvacrol is the major ingredient of *Zataria Multiflora* EO and induced apoptosis in 2D and 3D cell cultures of MDA-MB-231, MCF7, and T47D with selectivity and increased reactive oxygen species (ROS) generation, loss of mitochondrial membrane potential ($\Delta\Psi_m$), caspase 3 activation, and DNA damage [18]. *Thymus vulgaris* L. EO was also proapoptotic to MCF7 and MDA-MB-231 cells [6].

Nuclear factor- κ B (NF- κ B) is involved in tumor development by regulation of cell proliferation, apoptosis, and cell migration, and its activation is associated with both inflammation and development of cancer, processes that seem to be linked [19]; therefore, its influence by components can be used as a target. Justified by the use already made by the local population, research has shown that *Cyphostemma juttae* (Dinter & Gilg) Desc. EO decreased NF- κ B activation with suppressive action on triple negative breast cancer cell lines (TNBCs) [20].

The inhibition effect of EO from *Erythrina corallodendron* L. (ECEO) seems to be mediated by the suppression of the epithelial-mesenchymal transition (EMT) process, implicated with metastasis in cancer progression. Another aspect that

points to it being a possible good target for a new chemotherapeutic agent is that ECEO had greater cytotoxicity to breast cancer cells MDA-MB-231 and MCF7 than to normal human mammary epithelial cells (HMLEs). Although it was not as good as the positive drugs, it may qualify as an adjuvant drug [21].

MCF7 cells treated with frankincense EO (FCO), pine needle, and geranium activated the 5'-adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signaling pathway, which controls cell growth, proliferation, and autophagy and is deregulated in cancer [22]. As a consequence, there was suppression of cell viability, proliferation, migration, and invasion activity. FCO was also effective in inhibiting tumor growth and inducing apoptosis in human BC mouse model [2].

Aquilaria spp. can provide agarwood, and its EO has proven to reduce the cell number of MCF7, suggesting an effect on cell death and attachment inhibition. Although there have not been any reports of its traditional use for cancer treatment, many reports show its use for inflammatory-associated diseases [23]. On the other hand, *Boswellia* sp. gum has proved to have anti-neoplastic effects and is very commonly used for aroma therapy. EO of *B. sacra* induced cell death in T47D, MCF7, and MDA-MB-231, and the EO hydrodistilled at 100°C was more potent than the one prepared at 78°C, which demonstrates the importance of the form of preparation in the effect of the EO [24].

3. Antitumoral activity of EOs and bioactive compounds

Terpenes (TPs) are usually part of EOs' constituents. Terpenoids (TPNs) are a modified class of terpenes that can be classified according to the number of units of isoprene. Monoterpenes (MTs) are the TPNs with only 2 isoprene units and 10 carbon atoms, sesquiterpenes (STs) have 3 isoprene units and 15 carbon atoms, diterpenes have 4 isoprene units and 20 carbon atoms, triterpenes (TTs) have 6 isoprene units and 30 carbon atoms, and tetraterpenes have 8 isoprene units and 40 carbon atoms [25]. The biosynthesis of terpenoids is shown in **Figure 1**.

Sesquiterpenes (STs) are produced in plants in a way to interact with other plants and as a response to herbivores. These compounds are widely distributed, have been exploited in research for their phytomedicinal potential [26], and are associated with decreasing progression of cancer.

Many plants have demonstrated antiproliferative activity on MCF7 cells and have MT as a major constituent of their EO composition, such as the following: *Schefflera heptaphylla* (β -pinene) [27]; *Heteropyxis dehniae* (linalool) [28]; *Schinus molle* and *Schinus terebinthifolius* (α -phellandrene) [29]; *Melaleuca alternifolia* (terpinen-4-ol) [30]; *Citrus limon*, *Citrus medica*, and *Citrus sinensis* (limonene) [31]; and *Cunila angustifolia* (pulegone and isomenthol) [32], *Satureja khuzistanica* Jamzad (carvacrol) [33], *Satureja intermedia* C.A. Mey (γ -terpinene, thymol, and p-cymene) [34], *Melaleuca armillaris* (Sol Ex Gateau) (1,8-cineole) [35], *Monodora myristica*, *Xylopia aethiopica*, *X. parviflora* [36], *Laurus nobilis*, *Origanum syriacum*, *O. vulgare*, *Salvia triloba* [37], and berries of *Schinus molle* L. and *S. terebinthifolius* Raddi (more active) (α -phellandrene, β -phellandrene, α -terpineol, α -pinene, β -pinene, and p-cymene) [29].

Bisabolene isomers are the main constituents of opoponax (*Commiphora guidotti*); therefore, a ST named β -bisabolene and an alcoholic analogue, α -bisabolol, were tested for their in vitro and in vivo influence on BC. Only β -bisabolene exhibited selective cytotoxic activity for mouse cells MG1361 and human BC cells MCF7, MDA-MB-231, SKBR3, and BT474 with a 37.5% reduction of the growth of transplanted 4T1 mammary tumors [38].

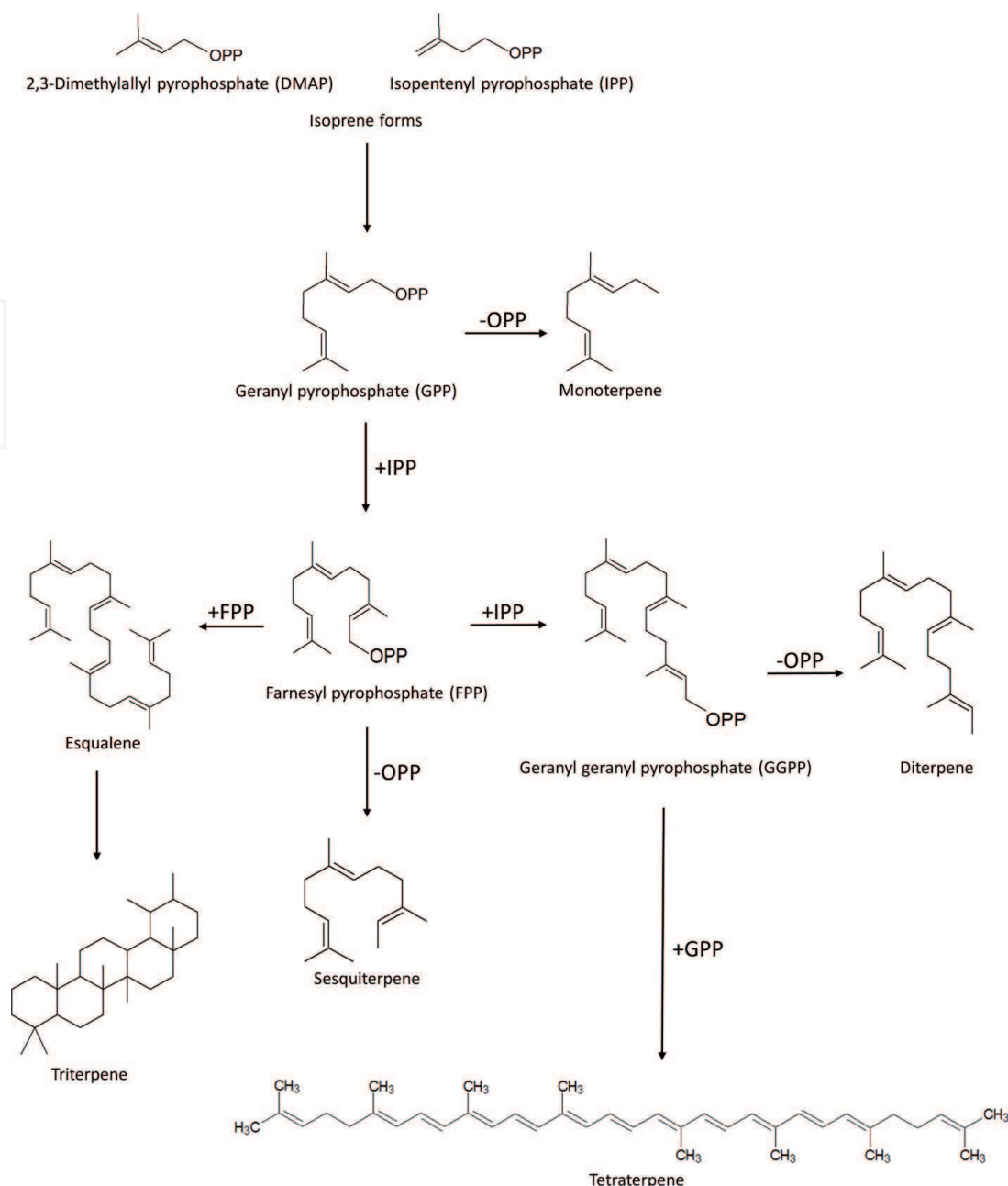


Figure 1.
Terpenoids' biosynthesis.

EO of *Myrcia splendens* (Sw.) DC. (Myrtaceae) from Amazonian Ecuador has its anticancer activity in MCF7 attributed to α -bisabolol in its composition [39], and EO from leaves of *Anaxagorea* mainly composed of β -eudesmol, α -eudesmol, and β -bisabolene showed similar effect [40].

EO from leaves of *Schinus terebinthifolius* Raddi (Anacardiaceae) collected in Brazil, with germacrene D as one of the major compounds, and fractions were tested in vitro against MCF7. All of them had anticancer activity and that may be due to α - and β -pinene structures [41]. EO of *S. molle* made in Costa Rica was active in breast carcinoma EMT-6 cell line and also had beta-pinene and alpha-pinene as major components [42]. Similar results were not found in EO from leaves of *Porcelia macrocarpa* R. E. Fries (Annonaceae), with main compounds germacrene D and bicyclogermacrene, which did not have significant effect on human breast adenocarcinoma SKBr [43].

β -Elemene is the major active component of the EO from a traditional plant from China, *Curcuma wenyujin* Y.H. Chen et C. Ling, and showed significant cytotoxicity in multidrug-resistant cell line MCF7/adriamycin through inhibition of mTOR

activity, related with cell proliferation and cancer, with the presence of autophagy. However, it only showed effects at high concentrations and the EO had problems regarding stability [44].

Different parts of the same plant can have different chemical constitution and biological activity. For example, the EO of *Garcinia atroviridis* Griff. ex T. Anders showed different results when different parts of plants were used. The essential oil from stem bark (EO-SB) had 79.8% of fatty acid including palmitoleic acid and palmitic acid, and the leaf oil (EO-L) had 86.3% of STs. While EO-SB did not induce cytotoxic effect, the EO-L stimulated the growth of BEAS-2B normal cells, but not in MCF7 cancerous cells, proving the medicinal effects of STs. But the best result was noticed when EO-L was associated with tamoxifen, which demonstrated better activity than the treatment with the drug alone [45]. The EO of *Pallines spinose* flower (F-PSEO) showed different composition than the leaf EO (L-PSEO). F-PSEO contained 96.39% of STs with 78.63% of the oil as oxygenated derivatives such as acorenone B, α -muurolol, and α -cadinol. The L-PSEO was composed of 51.60% of oxygenated STs and 34.06% of SQ hydrocarbons. F-PSEO had stronger anticancer results for MCF7 and MDA-MB-231 and both EOs induced a caspase-dependent and caspase-independent apoptosis and altered the levels of Bcl-2 and Bax proteins [46].

A component that can optimize the anticancer effects when combined with chemotherapy or reduce side effects of the current treatment is a target for many researches. *Rhizoma curcumae* is a plant known to possess activity against different types of cancer cells [47] and is common in Chinese medicine for the treatment of cancer [48]. Curcumol, a guaiane type ST lactone, is the major component of *R. curcumae* and, in combination with doxorubicin, made MDA-MB-231 cells more sensible to the action of doxorubicin through the activation of transcription factor NFAT1 and through the bind of the promoter region of miR-181b-2-3p, which is implicated in motility of BC [49] and less survival in breast cancer patients [50]. Curcumol also demonstrated in vivo suppress of tumor growth [49].

EO of *Blepharocalyx salicifolius* was cytotoxic against the MDA-MB-231 cell not by mechanisms related to apoptosis but by preventing cell metabolism reactions. Its main constituents identified were STs bicyclogermacrene, globulol, viridiflorol, γ -eudesmol, and α -eudesmol [51].

Leaves of *Garcinia celebica* L, popularly used in Malaysia and known as “mangishutan,” provide an ST-rich EO composed of α -copaene (61.25%), germacrene D (6.72%), and β -caryophyllene (5.85%) with antiproliferative action to MCF7 cells [52]. A similar result was found with the leaf of *Phoebe bournei* (Hemsl.) Yang, which is also composed mainly of STs such as α -copaene, α -muurolene, α -cadinene, and 1s-calamenene [53].

A ST isolated from the EO of *Rhizoma curcumae* named Furanodiene (FD) is associated with anticancer activities in various types of cancers in humans. FD also showed action on chemo-resistant breast cancer cells [54]. EO of *R. curcumae* and the main bioactive component FD were assessed on doxorubicin-resistant MCF7 cell line; although it showed inhibitory effects on cell viability it did not work on ABC transporters [47], which promote the efflux of chemotherapeutic compounds from cells leading to reduction of drug levels inside the cancer cells and insensitivity to the treatment associated with resistance [55]. Furthermore, FD induced apoptosis via intrinsic/extrinsic-dependent and NF- κ B-independent pathways [54].

Multidrug-resistant human BC cells MCF7/ADR were treated with EO of *Inula japonica* (IJO) or its ST component isoalantolactone (ISO) or *Angelicae dahuricae* EO (ADO). IJO, ISO, and ADO may reverse the cancer cell by down-regulating ABCB1 expression [56]. This gene encodes a transporter that changes the phenotype of the cells into a multidrug resistance type associated with worse prognosis in BC patients [57].

EO of *Lycopus lucidus* Turcz. var. *hirtus* Regel was mainly composed of STs α -humulene, β -caryophyllene, and humulene epoxide II, which resulted in a significant dose-dependent inhibition of cell growth human BC cell lines MDA-MB-435S and ZR-75-30, possibly due to the presence of STs in its composition [58].

A primary alcohol named 2-phenylethanol was the main constituent in the EO of *Magnolia virginiana*, while in *M. grandiflora* oil sample the main compounds were ST alcohol (E,E)-farnesol (18%) and 2-phenylethanol (10%). Both EOs were active against MDA-MB231 cell [59]. Similar action was found with EO of *Eryngium campestre* and *E. amethystinum* from central Italy, rich in ST hydrocarbons like germacrene D, allo-aromadendrene, β -elemene, spathulenol, and ledol against human breast adenocarcinoma cells [60].

In the Amazon Rain Forest, climate changes seem to influence *Iryanthera polyneura* Ducke trees. EOs obtained from leaves collected in the rainy season were more active against MCF7. STs spathulenol, α -cadinol, and τ -muurolol were identified as the main compounds [61]. Some seasonal variation was also found in EO of *Mentha* species, *M. arvensis*, *M. piperita*, *M. longifolia*, and *M. spicata*, and they all stimulated the decrease of MCF7 proliferation. Their major compounds were MTs such as menthol, menthone, piperitenone oxide, and carvone, respectively [62].

STs represent 88.57% of all the compounds detected in *Hedyosmum sprucei* EO (Chloranthaceae), collected in the Amazonian region of Pastaza, which led to cytotoxic effects on MCF7 [63]. Similar effect was observed in STs from EO of *Ballota undulata*, *B. saxatilis*, *B. nigra* [64], *Convolvulus althaeoides* [65], *Talauma gloriensis* [66], *Cedrelopsis grevei* [67] and *Feronia elephantum* Correa [68].

Pinus roxburghii Sarg. is a Nepal pine used for skin injuries. Its needle EO can inhibit up to 70% of MCF7 cells due to high concentrations of STs such as (E)-caryophyllene and α -humulene and of MT alcohols terpinen-4-ol and α -terpineol [69]. *P. sylvestris* showed cytotoxic selectivity to ER-negative BC cells MDA-MB-231 compared to ER-positive cell line (MCF7) but its chemical composition was not elucidated [70].

Volatile oil from *Saussurea lappa* root (VOSL) showed better anti-breast cancer efficacy and lower side effects than its isolated STs named costunolide (Cos) and dehydrocostuslactone (Dehy), although when combined Cos and Dehy induced apoptosis with regulation of the c-Myc/p53 and AKT/14-3-3 signaling pathways in MCF7 cells or MDA-MB-231 [71].

Thymoquinone (TQ) is a MT and the main constituent of the EO from the seed of *Nigella sativa*. It can optimize chemotherapeutic agents and reduce its toxic side effects, proving to affect the modulation of signaling pathways and molecules with important participation in oncogenic processes such as initiation, progression, invasion, metastasis, and angiogenesis [1]. TQ encapsulated in poly(D,L-lactide-co-glycolide) nanoparticles inhibits the proliferation of MDA-MB-231 cells [72], and same effect was obtained with TQ loaded with liposomes in MCF7 and T47D [73]. TQ derivatives decreased the growth of MCF-7/Topo [74]. TQ improved the growth inhibition of reference drug doxorubicin in multidrug-resistant MCF-7/TOPO cells, which may be a good source for a booster in the treatment [75]. TQ also showed apoptotic effect in BC cell line (T47D) in combination with gemcitabine as well as alone [76].

TQ was not only active in BC cells but also in vivo by reduction of tumor cell growth, invasion, and migration. These actions seem to be related to the activation of peroxisome proliferator-activated receptor (PPAR)- γ , which acts to inhibit cell growth and proliferation. It also increases ROS, leading to the phosphorylation of p38, a mitogen-activated protein kinase (MAPK), which leads to an antiproliferative and proapoptotic efficacy of TQ in BC [77].

In breast tumor xenograft mouse model, TQ was able to reduce the tumor growth and act synergistically with doxorubicin with antiproliferative and pro-apoptotic effects [78]. Similar result was found with mice injected with triple negative BC (MDA-MB-231 and MDA-MB-436 cells), probably due to the inhibition of eukaryotic elongation factor 2 kinase (EEF2K) signaling [79], which downregulates steps in protein synthesis and increases solid tumor size in vivo [80]. On mice transplanted with breast cancer with EMT6/P cells, the synergic action of TQ and resveratrol decreased the tumor size and led to the cure of 60% animals with no liver or kidney toxicity. The combination also induced apoptosis in EMT6/p and human epithelial BC cell lines MCF7 and T47D [81]. In the xenograft mouse model, TQ increased expression of p-p38 protein in tumors, and led to a decrease in the XIAP, survivin, Bcl-xL, and Bcl-2 antiapoptotic proteins [78].

Eugenol (Eu), an oxygenated MT, is an important volatile constituent of clove EO mainly obtained from *Syzygium*, which has promising results in vitro for the prevention of the progression of BC, with alteration in cellular energy metabolism of MCF10A-ras [82]. For MCF-7 cell, there were cytotoxicity of cinnamon, thyme, chamomile, and jasmine EOs. MT eugenol seems to play an important role in cinnamon action [83].

EO rich in MT eucalyptol from *Cinnamomum glanduliferum* from Egypt and *Nepeta menthoides* from Iran inhibited respectively, MCF7 [84] and MCF7, T47D and MDA-MB-231 [85].

The EO from *Hedychium spicatum* from different regions of western Himalaya where collected and the samples from Almora, Binsar and Uttarakhand were rich in MT and ST and showed cytotoxicity action in MCF7 [86]. Similar effect was observed with EOs obtained from mint (*Mentha spicata*), ginger (*Zingiber officinale*), lemon (*Citrus limonum*), grapefruit (*Citrus paradisi*), jasmine (*Jasminum grandiflora*), lavender (*Lavandula stoechas*), chamomile (*Anthemis nobilis*), thyme (*Thymus vulgaris*), rose (*Rosa centifolia*) and cinnamon (*C. zeylanicum*) from a commercial source in China, composed by elements such as MTs limonene and menthol [83].

Protium heptaphyllum (Aubl.) EO was collected during 3 years and did not exhibit significant cytotoxicity against MCF7 cancer cells, with no change in caspase-3 and TNF- α levels. The major compounds were MT such as terpinolene and p-cymene-8-ol, and p-cymene. However, the EO had antimutagenic activity, which might provide a chemo-preventive effect [87].

The fruit of *Angelica archangelica* L. growing in Iceland provides MT-rich α -pinene EOs differing mainly in the absence or presence of the MT β -phellandrene. However the cytotoxic activity in Crl mouse-BC-cells was independent of the quantity of their main components [88].

The method of preparation affected the composition of EO from *Pituranthos tortuosus* (Desf.) Benth and Hook (Apiaceae). The EO was rich in MT and the major components of the sample prepared by hydrodistillation (HD) were MT β -myrcene, MT sabinene, phenylpropanoids trans-iso-elemicin and MT alcohol terpinen-4-ol. The mayor components from the sample prepared by simultaneous hydrodistillation solvent (n-pentane) (DE) were MTs terpinen-4-ol, sabinene, gamma-terpinene and beta-myrcene. And the mayor components from the sample prepared by conventional-volatile-solvent extraction (SE) were MT terpinen-4-ol, phenylpropanoid dillapiole, and MT allo-ocimene. The DE sample was the most potent against MCF7 [89].

Solanum erianthum leaf volatile oil demonstrated potent inhibitory activity against Hs 578T characterized by the abundance of MT α -terpinolene (17.8%), MT α -phellandrene (17.5%), MT p-cymene (15.7%), and MT β -pinene (11.7%) in the leaves [90].

The EO from *Myristica fragrans* (nutmeg) was composed of MT, oxygenated MT, SQ, phenolic ether, and phenylpropanoids, while *Morinda citrifolia* (mengkudu) had mostly carboxylic acids, esters, and isothiocyanate. Both Eos decreased MCF7 cells

[91]. Similar effect was obtained with EO from leaves of *Solanum spirale* Roxb containing 48.10% of diterpene alcohol (E)-Phytol [92], with EO from leaf, stem, stem bark, and root of *Uvariadendron angustifolium* with the presence of citral (a mixture of terpenoids) [93] and with EO from *Syzygium aromaticum*, a source of TT [4].

Litsea cubeba, composed by 68.9% of MT citral, and *Cinnamomum zeylanicum*, mainly composed by (E)-cinnamaldehyde, also had inhibitory action on BC cells MCF7, T47D and MDA-MB-231 [94].

EO from *Erigeron acris* root showed higher antiproliferative activity for MCF7 and MDA-MB-231 than *E. annuus*, which may be due to polyacetylenic compounds, matricaria and lachnophyllum ester [95], while *Waldheimia glabra* from the Himalayan Mountains, composed mainly of ST spathulenol and thujopsene, fatty alcohol 9-tetradecenol, MT α -thujone, santolina alcohol, and MT tertiary alcohols terpinen-4-ol only had mild action [96].

EO obtained from the seeds of onion *Afro styrax lepidophyllus* and garlic tree *Scorodophloeus zenkeri* are usually used as spices in Africa. It exhibited a strong inhibitory effect on MDA-MB 231. The predominant compound in both oils was the terpenoid 2,4,5,7-tetrathiaoctane [97]. EO of aerial parts, branches and leaves, of *Glandora rosmarinifolia* (Ten.) D.C. Thomas is composed mostly of aliphatic alkanes and diterpene hydrocarbons; it induces cell growth inhibition at triple negative-breast cancer-cell lines SUM 149 and MDA-MB-231 in part due to a pro-oxidant mechanism [5].

4. Optimization of the EOs' use against BC

Nanoemulsions (NEs) can work as an ally to reduce some problems associated with Eos such as sensibility and lability. That is what happened with the use of *Zataria multiflora* EO loaded into chitosan (CS) nanoparticles. This combination improved the proliferation inhibition rate of BC cells as well as apoptosis, generation of ROS, trigger of mitochondrial membrane permeabilization and DNA damage, with high selectivity to human cancer cells of breast adenocarcinoma MCF7, T47D, and MDA-MB-231 [98].

Another study made with CS and N,N,N-trimethyl chitosan (TMC) also increased the toxicity of another EO from *Ocimum gratissimum*, when loaded with TNC nanoparticles on MDA-MB-231 BC cell lines [99]. A similar result was found using *Cyperus articulatus* EO loaded with CS nanoparticles [100].

Nigella sativa L. has been used in traditional medicine for about 1400 years and it grows in countries bordering the Mediterranean Sea and India [101]. Its EO has properties such as anti-inflammatory and anticancer. *N. sativa*-EO-NE increased the apoptosis of MCF7 [102].

Mitomycin C (MTC) was solubilized in NEs of EO from ginger (EOG) and from frankincense, which was shown to increase the toxicity for MCF7 cells when compared with the use of MMC alone. EOG had the strongest apoptotic effect [103]. The same effect was seen when MTC was combined with chamomile NE oil [104].

Sandal wood EO (SEO), extracted from *Santalum* trees, was encapsulated into liposomes composed of 15% SEO, 78.5% water, 4% enzyme modified lecithin, and 2.5% polysorbate. This combination provoked DNA damage and cytotoxicity and genotoxicity against MCF7 cells [105].

5. EOs as an alternative for side effects reduction during BC treatment

Chemotherapy-induced nausea and emesis are one of the most common problems in BC patients and they can be inappropriately managed due to low

affordability of new medications [106]. Women suffering from BC received 5-day aroma therapy treatment using either ginger EO or a placebo. Nausea score was significantly lower after ginger EO inhalation but was not sustained for the overall treatment effect. Overall, the EO improved health-related quality of life [107].

Symptoms of urogenital atrophy (UA) are common in BC survivors [108]. The cause is due to systemic treatments as a side effect of endocrine therapies and topical estrogen is usually used to reduce the symptoms. Other alternatives are being sought and could be valid to improve life quality of the patients with BC. EO of *Cymbopogon martini* and *Pelargonium graveolens* affected the cell grown in hormone-dependent MCF7 and hormone-independent MDA-MB-231 cell lines with pronounced estrogenicity, but clinical trials are necessary to better understand these effects [109].

Reaction on the skin can happen in BC patients under radiotherapy treatment. Twenty four patients received an EO mixture with 32.5% of jojoba (*Simmondsia chinensis*), 30% *Aloe vera* (*Aloe barbadensis*), 10% of Tamanu (*Calophyllum inophyllum*), 10% primrose *Oenothera biennis*, 5% frankincense (*Boswellia carteri*), 5% geranium (*Pelargonium graveolens*), 5% lavender (*Lavandula angustifolia*), and 2.5% helichrysum (*Helichrysum angustifolium*) this EO mixture had a similar result as a medication used for treating this side effect and therefore can be used as an alternative treatment [110].

6. Unsatisfactory EOs results for BC

Some EOs used in research were not able to have satisfactory in vitro anticancer effects on MCF7 as EO from *Sideritis perfoliata*, *Satureja thymbra*, *Salvia officinalis*, *Laurus nobilis*, *Pistacia palaestina* [111], *Nepeta cataria* L. [112], *Nectandra leucantha* [113], *Laurus nobilis* L, *Origanum syriacum* L, *Origanum vulgare* L, *Salvia triloba* L. [37], *Salvia officinalis* [114], grapefruit (*Citrus paradisi*), ginger (*Zingiber officinale*) [83], and *Anemopsis californica* [115].

Origanum vulgare EO, composed mostly of 4-terpineol, induced cell proliferation of MCF7, although at the concentration of 50 mg/mL opposite effect was found, but still with minor effect when compared to the result in other cancer cells [116]. *Aloysia citriodora*, *Boswellia sacra*, *Boswellia serrata*, *Cistus ladanifer*, *Citrus × aurantium*, *Citrus limon*, *Citrus sinensis*, *Cymbopogon citratus*, *Foeniculum vulgar*, *Illicium verum*, *Satureja montana*, *Syzygium aromaticum*, *Thymus capitatus*, and *Thymus vulgaris* presented minor effects in MCF7, T47D, and MDA-MB-231 [94].

EO of *Semenovia suffruticosa* grown in Kerman, Iran, induced cell death in MCF7, but it also had the same effect on normal cell line [117]. EO from the leaves of *Solanum macranthum* did not show anticancer properties in Hs578T [90].

This information is helpful to elucidate some effects of EOs that are used by the population. Some EOs may not have any effect for BC or can even help stimulate BC cells or have toxic action. Due to this, it is important to determinate if they are safe for common use. Furthermore, it is worth mentioning that the results show unsatisfactory effects in regard to concentrations used, which does not prevent the use of these EOs in other researches with different outcomes.

7. Conclusions

Sesquiterpenes and monoterpenes are part of the main components of essential oils, some of them already being isolated and with actions described, although it is important to establish the force of the use of multiple compounds together.

A large number of essential oils from different plants have been described in the literature with promising in vitro effect in a variety of breast cancer cells and even

with in vivo effects in murine model; it is important to continue this research and take it to the next level with clinical trials.

The articles found in the literature and their results encourage the use of essential oils. The importance of plant research and the production of these oils demonstrated the difference they can make as a supporting anticancer agent or as a reducer of the side effects of breast cancer, which shows its power in the fight against breast cancer.

Acknowledgements

The authors would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel), Brazil (CAPES) [Finance Code 001] and Instituto Oswaldo Cruz for financial support.

Conflict of interest

The authors declare no conflict of interest.

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