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REVIEW

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Essential oils and their nanoformulations for breast cancer therapy

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Abstract

Breast Cancer (BC) is the most prevalent type of cancer in the world. Current treatments include surgery, radiation, and chemotherapy but often are associated with high toxicity to normal tissues, chemoresistance, and relapse. Thus, developing novel therapies which could combat these limitations is essential for effective treatment. In this context, phytochemicals are increasingly getting popular due to their safety profile, ability to efficiently target tumors, and circumvent limitations of existing treatments. Essential Oils (EOs) are mixtures of various phytochemicals which have shown potential anticancer activity in preclinical BC models. However, their clinical translation is limited by factors such as high volatility, low stability, and poor solubility. Nanotechnology has facilitated their encapsulation in a variety of nanostructures and proven to overcome these limitations. In this review, we have efficiently summarized the current knowledge on the anticancer effect of EOs and constituents in both in in vitro and in in vivo BC models. Further, we also provide a descriptive account on the potential of nanotechnology in enhancing the anti-BC activity of EOs and their constituents. The papers discussed in this review were selected using the keywords "antiproliferative Essential Oils in breast cancer," "anticancer activity of Essential Oil in breast cancer," and "cytotoxicity of Essential Oils in breast cancer" performed in PubMed and ScienceDirect databases.

KEYWORDS
breast cancer, chemosensitization, essential oil, monoterpenes, nanoformulation, nanoparticles, sesquiterpenes

1 | INTRODUCTION

Breast Cancer (BC) is the most common cancer globally and one of the leading causes of cancer-associated deaths in women (Łukasiewicz et al., 2021). Gene expression profiling has now delineated BC into four main subtypes, which are luminal A, luminal B, enriched with human epidermal growth factor receptor 2 (HER2), and triple negative (or basal-like) (Johnson et al., 2021). These subtypes show significant differences in terms of their molecular characteristics, prevalence, clinical implications, and response to treatments (Johnson et al., 2021). Luminal tumors are most common (60%–70%) and are characterized by the expression of hormonal receptors such as estrogen receptor and progesterone receptor (Johnson et al., 2021). Luminal A tumors tend to have a lower proliferation rate and a better prognosis, while luminal B is associated with a higher proliferation rate and a worse prognosis (Johnson et al., 2021). Further, 12%–20% of all

BCs belong to the HER2-enriched category. These tumors are identified by an increased activity of the Erb-B2 oncogene that results in aggressive tumor growth and a poor clinical prognosis (Johnson et al., 2021). The absence of these three receptors is the feature of the last category called Triple Negative BC (TNBC). TNBC accounts for about 10%–15% of BC cases (Zagami & Carey, 2022). TNBC tends to be more aggressive, associated with a higher recurrence, and often has limited treatment options due to the absence of targeted receptors (Zagami & Carey, 2022). Research is ongoing to identify new treatment approaches for TNBC, including immunotherapies and targeted therapies that focus on other molecular pathways.

The choice of treatment for BCs depends on the diagnosed subtype, the level of invasiveness, and metastasis. Primary treatment for BC in the nonmetastatic stage is lumpectomy often followed by mastectomy. However, adjuvant treatments such as radiation therapy and chemotherapy are imperative to avoid tumor relapse.

Currently, the treatments of BC were classified on the basis of their specific mechanism of action: interfering with DNA synthesis (e.g., 5-fluorouracil, methotrexate, and cytarabine), directly binding of DNA structure (e.g., cisplatin, dactinomycin, daunorubicin, and doxorubicin), interfering with the transcription process of RNA synthesis (e.g., dactinomycin, daunorubicin, and doxorubicin), inhibiting topoisomerase (e.g., etoposide), and blocking mitosis (e.g., paclitaxel and vinca alkaloids).

Highly aggressive and metastatic BCs such as TNBC are also being treated with various targeted therapies and immunotherapies.

Combinations of these therapies are often administered simultaneously to improve the overall outcome (Waks & Winer, 2019). Despite the advent of novel targeted therapies or immunotherapy, chemotherapy is still the inevitable cornerstone in the BC treatment regime.

Unfortunately, the efficacy of existing chemotherapy drugs has decreased due to increasing challenges such as molecular heterogeneity, high metastasis, and the emergence of chemoresistance (Waks & Winer, 2019). Chemoresistance refers to the ability of cancer cells to resist or subvert the activity of chemotherapeutic drugs (Cao et al., 2021). Studies have shown that chemotherapy drugs induce feedback activation of oncogenic signaling pathways and promote chemoresistance in BC (Kholodenko et al., 2021). For instance, upregulation of STAT3 activation by doxorubicin promotes chemoresistance in highly aggressive TNBC cell line, MDA-MB-231 (Gariboldi et al., 2007). Likewise, resistance to Trastuzumab in HER2-positive BC cells has also been associated with a positive feedback loop mechanism involving STAT3 activation mediated by upstream mediators such as fibronectin, EGF, and IL-6, as well as downstream effectors such as mucins (MUC1/4) (Li et al., 2014). Furthermore, emerging studies suggest that BC stem cells, a small subset of cancer cells with self-renewal and redifferentiation properties also contribute to chemoresistance (De Angelis et al., 2019). Interestingly, studies have also found that chemotherapeutic drugs can enrich BC stem cells and promote chemoresistance (Lu et al., 2017; Martins-Neves et al., 2018).

Essential oils (EOs) are phytocomplex secondary metabolites produced by various aromatic plants that are extensively used in traditional medicine for thousands of years for their therapeutic properties. In recent decades, numerous studies have proven that EOs possess several biological activities, including antimicrobial and anticancer effects (Adorjan & Buchbauer, 2010). As previously reviewed by Lesgards et al. (2014), growing body of evidence suggest the effectiveness of EOs in overcoming chemoresistance, mitigating cancer stemness, and combating metastasis in highly invasive and metastatic cancer models including BC. Several EOs and their components also exhibit chemo-sensitizing and synergistic effects when administered in combination with chemotherapeutic drugs (Lesgards et al., 2014).

Despite abundant evidence supporting promising anti-BC effects, limitations like high volatility and poor aqueous solubility pose major challenges to the successful translation of EOs to clinical stage (Cimino et al., 2021). Nanoformulation of EOs and their components have been extensively utilized as a strategy to overcome their limitations and improve their therapeutic effectiveness. A recently published review discusses the scope of nanomedicine strategies to foster the application of anticancer EOs (AbouAitah & Lojkowski, 2022).

In this Review, we are attempting to give a comprehensive summary of literature on the effectiveness of EOs and components against BC, the challenges to their clinical translation, and the scope of nanotechnology to improve their therapeutic efficacy. We have conducted an extensive literature search to compile EOs and EO nanoformulations proposed for BC therapy. The search strategy was executed using PubMed and ScienceDirect databases using keywords such as "antiproliferative Essential Oils in breast cancer," "anticancer activity of Essential Oil in breast cancer," and "cytotoxicity of Essential Oils in breast cancer." Articles on specific of essential oil compounds discussed in the manuscript such as "Terpenes, Sesquiterpenes, and Phenylpropanoid" were also searched utilizing similar combinations of keywords. For finding articles on EO nanoformulations, keywords including "encapsulated Essential Oil cytotoxicity in breast cancer" and "Essential Oil nanoemulsion in breast cancer" were used. Articles published in English language and after the year 2010 were selected for the final analysis. For uniformity, articles used units other than μg/mL (for EOs) and μM (for EO compounds) are excluded. Whenever only cytotoxicity is reported, EOs having IC_{50} values >100 μg/mL are excluded from further analysis.

2 | OVERVIEW OF EOs

EOs are complex mixtures of distinctive plant secondary metabolites produced by specialized secretory structures called glandular trichomes dispersed on the surface of plant organs, mainly flowers, and leaves (Bunse et al., 2022; Sadgrove et al., 2022). EOs have been used in food and beverage industry, in cosmetic and personal care and aromatherapy. Moreover, abundant evidence validates promising therapeutic effects of EOs including antimicrobial, anti-inflammatory, and anticancer effects (Adorjan & Buchbauer, 2010). Several methods have been devised to extract EOs from the plant sources, like steam distillation, solvent extraction, supercritical fluid extraction, expression or cold pressing, and microwave-assisted extraction (El Asbahani et al., 2015).

Composition of the EO are determined mainly by employing gas chromatography–mass spectrometry (GC–MS). GC separates EO components based on their different affinities for the stationary and mobile phases in the chromatographic column. Each component gets eluted from the column at a specific retention time. The flame ionization detector with GC provides retention time and peak data. Eluted compounds enter the mass spectrometer, identifying them by mass-to-charge ratios (*m*/*z*) and generating unique mass spectra. These spectra are compared to a reference library of known compounds (Stashenko & Martinez, 2017).

Even though conventional GC–MS remains the foundation of EO analysis, it grapples with specific challenges. For instance, multitude of compounds in EOs that share similar retention times, might result in coelution within the same column. Moreover, some constituents in EOs showcase comparable mass spectra, diminishing the effectiveness of mass-fragmentograms in achieving proper separation (Cagliero et al., 2022; Stashenko & Martinez, 2017). To overcome these constraints, innovative approaches have emerged, such as the utilization of two columns with varying polarities, giving rise to multidimensional GC. Furthermore, the integration of ionic liquids as stationary phases has helped enhancing separation capabilities by eliminating the need for two complementary (a polar and non-polar) columns to fully characterize an EO's chemical profile (Cagliero et al., 2022; Stashenko & Martinez, 2017). On average, EOs are constituted by 20–60 various compounds belonging to various chemical groups mainly monoterpenes, sesquiterpenes, and phenylpropanoids (Louw, 2021; Sadgrove et al., 2022).

EO compounds are highly volatile, lipophilic, and have low molecular weights, which allow them to easily penetrate cell membranes of rapidly dividing cancer cells while sparing the normal cells unharmed (Sharma et al., 2022). Structural diversity of EOs allow them to simultaneously mediate multiple molecular mechanisms including inhibition of cell proliferation, alteration of pH gradient, enhancement of mitochondrial damage, induction of endoplasmic reticulum stress and activation of apoptotic pathways. In addition, EOs and their components have been reported to modulate several oncogenic signaling pathways involved in the initiation, progression, and metastasis of BC, which include the PI3K/pAKT, AMPK, mTOR, NF-κB, and STAT3 pathways (Bunse et al., 2022; Garzoli et al., 2022; Sharma et al., 2022).

Despite the fact that many EOs and EO compounds have a generally recognized as safe (GRAS) status, it would be necessary to validate the safety profile of the EO in accordance with the specific experimental conditions (Dosoky & Setzer, 2021). Multiple efforts have been dedicated to assessing the safety of EOs in animal models. Notably, Lulekal E. et al. observed that EOs from Cymbopogon citratus and Lavandula angustifolia showed no skin irritation and exhibited no acute or subacute toxicity in mice and rabbits (Lulekal et al., 2019; Mekonnen et al., 2019). Although, most of the EOs show low toxicity based on median lethal dose tests in animals (LD_{50} of 1–20 g/kg), exceptions like Satureja hortensis EO exhibit higher toxicity (LD_{50} 0.1–1 g/kg) cannot be overlooked (Vostinaru et al., 2020). Further, most of the EO compounds are typically small (<400 Da) with high lipophilicity, and they can easily cross the blood brain barrier (Bahr et al., 2019). Consequently, some EOs, particularly those rich in monoterpenes like α-pinene, limonene, and linalool, demonstrate anticonvulsive and neuroprotective properties in in vitro and in in vivo (Bahr et al., 2019). Conversely, EOs containing compounds like thujone, 1,8-cineole and camphor can trigger negative effects such as convulsions and epileptic seizures (Bahr et al., 2019). These conflicting effects emphasize the imperative of thorough neurological safety profiling of EOs before considering them as potential anticancer agents. Additionally, compounds like cinnamaldehyde, citral, and β-pulegone in EOs can easily cross the placental membrane, posing risks in pregnant women (Dosoky & Setzer, 2021). Addressing these constraints of EOs necessitates a deep comprehension of their pharmacokinetics, mechanisms of action, and delivery. Research must prioritize refining delivery, improving selectivity, and overcoming hurdles to fully exploit the therapeutic capabilities of EOs and EO compounds in cancer therapy.

3 | ANTICANCER ACTIVITIES OF EOs IN IN VITRO BC MODELS

Over the last two decades, a large number of studies have claimed that EOs show multimodal chemopreventive effects against several preclinical cancer models. Interestingly, we found that there are at least 30 EOs that showed IC_{50} value <30 μg/mL against different BC cell lines. The effects of EOs in BC in in vitro models and the mechanisms of their action are summarized in Table 1. Interestingly, some studies have found that BC cells display higher sensitivity to EO treatments compared to other cancer cells. For instance, compared to C6 (rat glioma) and A549 (human lung adenocarcima) cells, MCF-7 (human breast carcinoma cells) were found to be more sensitive to *Vitex agnus castus* EO treatment, also demonstrating inhibition of DNA synthesis and apoptosis (Duymuş et al., 2014). Similarly, *Dictamnus dasycarpus* EO displayed significantly stronger cytotoxicity against human BC cell lines ZR-75-30 and MCF-7 than other four cancer cell lines (Lei et al., 2008). Furthermore, a recent study has shown that *Artemisia sieberi* EO (ASEO) displayed highest cytotoxicity against MCF-7 cells compared to other cancer cells including HepG2, A549, and HCT116. Additionally, the authors report that ASEO suppressed migration, induced S-phase arrest and apoptosis in MCF-7 cells by downregulating the ERK signaling pathway (Bin Break et al., 2023). Interestingly, selective cytotoxicity of *Decatropis bicolor* EO has been reported against MDA-MB-231 cells, with an IC_{50} approximately four times higher compared to normal MCF-10A breast cells. Additionally, this EO induced intrinsic apoptosis pathway by activating caspases-9 and -3, as well as the Bax protein (Estanislao Gómez et al., 2016). Similarly, *Juniperus oxycedrus* EO also induced the intrinsic pathway of apoptosis in MCF-7 cells through activation of caspases 9 and 7 along with significant loss of mitochondrial membrane potential in the cell and cycle arrest in phase S (El-Abid et al., 2019). Interestingly, *Ocimum sanctum* EO exerted antiproliferative effect and induced apoptosis by increasing the expression of pro-apoptotic genes p53, Bid, and Bax/Bcl2 ratio in MCF-7 cells (Manaharan et al., 2016). Whereas,

TABLE 1 Essential oils (EOs) against breast cancer (BC) on in in vitro models.

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Aloysia polystachya • Verbenaceae • Leaves • Hydrodistillation	R-carvone, R-limonene, dihydrocarvone	MCF-7 9.53 ± 0.45 (24 h)	• Anti-proliferative activity	Moller et al. (2021)
Artemisia judaica • Asteraceae • Leaves • Hydrodistillation	β-Thujone, L-camphor, Chrysanthenone, α-thujone, 1,8-cineole	MCF-7 28.51 ± 1.1 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)
Artemisia monosperma • Asteraceae • Leaves • Hydrodistillation	Capillene, γ-terpinene, β-pinene, terpinen-4-ol	MCF-7 15.15 ± 1.1 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)
Artemisia sieberi • Asteraceae • Aerial parts • Hydrodistillation	*Cis*-crysanthenyl acetate, davanone, 1,8-cineole, caryophyllene diepoxide	MCF-7 38.7 (72 h)	• ↓ ERK expression • Suppression of cell migration • S-phase cell cycle arrest and apoptosis.	Bin Break et al. (2023)
Blepharocalyx salicifolius • Myrtaceae • Leaves • Steam distillation	Bicyclogermacrene, globulol, viridiflorol, α-eudesmol, γ-eudesmol	MDA-MB-231 46.60 ± 8.22 (48 h)	• Cytotoxicity with the reduction of the cellular metabolic capacity	Furtado et al. (2018)
Boswellia sacra • Burseraceae • Gum resins • Hydrodistillation	α-Thujene, β-pinene, and myrcene	T47D, MCF-7, MDA-MB-231 IC_{50} not reported	• Induced apoptosis • Prevented the cellular network formation (MDA-MB-231) on Matrigel and caused the breakdown of multicellular tumor spheroids	Suhail et al. (2011)
Callistemon viminalis • Myrtaceae • Leaves • Hydrodistillation	1,8-Cineole, α-pinene, terpinen-4-ol, octadecanoic acid	MCF-7 25.15 ± 0.3 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)
Chrysopogon zizanioides • Poaceae • Rhizome • Steam distillation	β-Caryophyllene, biphenylene, β-cedrene, 2-carene, cuminone	4T1 (60) T47D (112) (48 h)	• ↑ ROS • Cell cycle arrest • Interaction with cannabinoid receptors	Hanifa et al. (2022)
Cinnamomum burmanii • Lauraceae • Cinnamon bark • Steam distillation	Cinnamaldehyde, propenol, Benzylpropanal, eucalyptol	4T1 IC_{50} not reported	• ↑ ROS • Inhibited MMP-9 expression • ↑ cytotoxicity in combination with doxorubicin	Aliyah et al. (2022)
Cinnamomum glanduliferum • Lauraceae • Cinnamon bark • Hydrodistillation	Eucalyptol, terpinen-4-ol, α-terpineol	MCF-7 57.3 (48 h)	• Anti-proliferative activity	Taha and Eldahshan (2017)
Cinnamomum zeylanicum l. • Lauraceae • Cinnamon bark	Cinnamaldehyde, cinnamyl acetate, eugenol, linalool, eucalyptol, limonene	MCF-7, MDA-MB-231 IC_{50} not reported	• Induced apoptosis • Impaired mitochondrial membrane potential	Kubatka et al. (2020)
Citrus aurantifolia • Rutaceae • Fruits peel • Hydrodistillation	Limonene, β-pinene, α-citral, γ-terpinene, α-terpineol	MCF-7 11.11 ± 0.3 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)
Citrus limon • Rutaceae • Fruits peel • Hydrodistillation	Limonene, β-pinene, γ-terpinene, α-citral, β-citral, α-terpineol	MCF-7 9.52 ± 1.6 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)

TABLE 1 (Continued)

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Citrus microcarpa • Rutaceae • Fruit pericarp waster after juice production • Steam distillation	D-limonene, α-pinene, β-pinene, 2-carene	MCF-7 7.98 ± 1.77 (72 h)	• Anti-proliferative activity • Twice higher cytotoxicity on cancer cells than normal AA8 cells	Palma et al. (2019)
Citrus paradisi • Rutaceae • Fruits peel • Hydrodistillation	Limonene, linalool, linalool oxide, β-citral, α-fenchol	MCF-7 8.1 ± 1.5 (48 h)	• Anti-proliferative activity	Elansary et al. (2018)
Cordia africana • Boraginaceae • Leaves • Hydrodistillation	b-Caryophyllene, germacrene D, d-cadinene, phytol	MCF-7 12.90 (24 h)	• Induced apoptosis by ↑ caspase 8 expression and ↓ Ki67 expression	Ashmawy et al. (2021)
Cunila angustifolia • Lamiaceae • Leaves • Hydrodistillation	Pulegone, isomenthol, menthone, neomenthol	MCF-7 34.3 (24 h)	• Anti-proliferative/cytotoxic activity	de Sousa et al. (2020)
Cupressus macrocarpa • Cupressaceae • Leaves • Hydrodistillation	Terpinen-4-ol, sabinene, β-citronellol, γ-terpinene	MCF-7 25.4 ± 2.6 (48 h)	• Anti-proliferative/cytotoxic activity	Elansary et al. (2018)
Cyperus longus • Cyperaceae • Dried whole plant • Hydrodistillation	β-Himachalene, β-caryophyllene oxide, aristolone, longiverbenone	MCF-7 21.17 ± 2.01 (24 h)	• Anti-proliferative/cytotoxic activity	Memariani et al. (2016)
Cyphostemma juttae • Vitaceae • Leaves • Hydrodistillation	Phytol, neophytadiene, hexadecanoic acid, isophytol	MDA-MB-231 (46) SUM 149 (64) (48 h)	• Suppressed NF-κB activation and cytotoxic activity	Zito et al. (2019)
Decatropis bicolor • Rutaceae • Leaves • Hydrodistillation	1,5 Cyclooctadiene,3-(methyl-2) propenyl, β-terpineol, 1-(3-methyl-cyclopent-2-enyl)-cyclohexene	MDA-MB-231 53.81 ± 1.691 (48 h)	• Cytotoxic effect • Induced of apoptosis • Activation of Bax, caspases 9 and 3	Estanislao Gómez et al. (2016)
Dictamnus angustifolius • Rutaceae • Air-dried and ground roots • Hydrodistillation	Fraxinellone, salsoline, machilol, α-elemol	MCF-7 15 ± 1.40 (72 h)	• Anti-proliferative activity	Sun et al. (2015)
Eryngium amethystinum *Eryngium campestre* • Apiaceae • Flowering aerial parts • Hydrodistillation	Germacrene D, allo-aromadendrene, β-elemene, Spathulenol	MDA-MB-231 *E. amethystinum* 5.32 (48 h) *E. campestre* 2.99 (48 h)	• Anti-proliferative/cytotoxic activity	Cianfaglione et al. (2017)
Erythrina Corallodendron • Fabaceae • Leaves • Hydrodistillation	Linalool, 1,4-cineole, menthone	MDA-MB-231 3.44 ± 0.18 MCF-7 4.91 ± 0.26 (48 h)	• Inhibited proliferation, migration and invasion	Xing et al. (2019)
Eucalyptus salmonophloia • Myrtaceae • Trunk bark • Hydrodistillation	Decanoic acid, nonanoic acid, *trans*-myrtanol, α-terpineol	MDA-MB-231 50.04 ± 2.36 (48 h)	• Anti-proliferative/cytotoxic activity	Lahmadi et al. (2021)

(Continues)

TABLE 1 (Continued)

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Eucalyptus torquata • Myrtaceae • Trunk bark • Hydrodistillation	Trans-myrtanol, myrtenol, (E)-β-ionone, nonanoic acid	MDA-MB-231 40.66 ± 1.87 (48 h)	• Anti-proliferative/cytotoxic activity	Lahmadi et al. (2021)
Foeniculum vulgare • Apiaceae • Aerial parts • Hydrodistillation	*Trans*-anethole, p-anisaldehyde, carvone	MCF-7 59 ± 5 (24 h)	• Induced apoptosis • ↑ Bax ↓ Bcl2	Sharopov et al. (2017)
Garcinia atroviridis • Clusiaceae • Leaves • Hydrodistillation	(E)-β-Farnesene, β-caryophyllene	MCF-7 71 (48 h)	• Induced cytotoxicity • Synergistic effect with tamoxifen	Tan et al. (2018)
Glandora rosmarinifolia • Boraginaceae • Branches with leaves • Hydrodistillation	m-Camphorene, heptacosane, nonacosane	SUM 149 (65.0 ± 4.2) MDA-MB-231 (46.5 ± 2.1)	• Anti-proliferative/cytotoxic activity	Poma et al. (2018)
Guatteria friesiana • Annonaceae • Leaves • Hydrodistillation	β-eudesmol, γ-eudesmol, α-eudesmol, spathulenol, elemol	MDA-MB-435 9.4 (72 h)	• Anti-proliferative/cytotoxic activity	Britto et al. (2012)
Hedyosmum sprucei • Chloranthaceae • Aerial parts • Hydrodistillation	Germacrene D, *β*-caryophyllene, *δ*-cadinene, α-copaene	MCF-7 32.76 ± 4.92 (48 h)	• Anti-proliferative/cytotoxic activity	Guerrini et al. (2016)
Helichrysum gymnocephalum • Asteraceae • Leaves • Hydrodistillation	1,8-cineole, p-cymene, (E)-β-ocimene, 2,3-dihydro-1,8-cineole	MCF-7 16 ± 2 (48 h)	• Anti-proliferative/cytotoxic activity	Afoulous et al. (2011)
Iryanthera polyneura • Myristicaceae • Leaves • Hydrodistillation	Spathulenol, α-cadinol, τ-muurolol	MCF-7 22.28 ± 3.83 (48 h)	• Anti-proliferative/cytotoxic activity	Martins et al. (2019)
Juniperus oxycedrus • Cupressaceae • Air-dried leaves and fruits • Hydrodistillation	α-Pinene and β-myrcene 3-carene, β-pinene, D-limonene	MCF-7aro IC_{50} not reported	• Induced intrinsic pathway of apoptosis • S-phase cell cycle arrest • Loss of mitochondrial membrane potential	El-Abid et al. (2019)
Laurus nobilis • Lauraceae • Air-dried leaves and fruits • Hydrodistillation	1,8-Cineole, terpinyl acetate, β-elemene, terpinene-4-ol	MCF-7 41.9 ± 3.3 (24 h)	• Anti-proliferative/cytotoxic activity	Abu-Dahab et al. (2014)
Lippia citriodora • Verbenaceae • Leaves • Hydrodistillation	Geranial, neral, nerol, geraniol, spathulenol, I,8-cineol	DA3 96.4 ± 8.9 70.7 ± 5.5 (24 h-72 h)	• Inhibited migration • Induced apoptosis	Spyridopoulou et al. (2021)
Matricaria recutita • Asteraceae	Caryophyllene, D-cadinene, caryophylle neoxide, α-muurolene	MDA-MB-231 IC_{50} not reported	• Inhibited the phosphorylation of PI3K, Akt, and mTOR and suppressed the growth, migration, and invasion.	An et al. (2023)
Morinda citrifolia • Rubiaceae • Fresh fruits • Hydrodistillation	Caprylic acid, hexanoic acid, octanoic acid	MCF-7 78.15 (48 h)	• Anti-proliferative/cytotoxic activity	Piaru et al. (2012)

TABLE 1 (Continued)

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Myrcia splendens • Myrtaceae • Leaves • Hydrodistillation	*Trans*-carvone, α-bisabolol β-caryophyllene	MCF-7 5.59 ± 0.13 (48 h)	• Anti-proliferative/cytotoxic activity	Scalvenzi et al. (2017)
Myristica fragrans • Myrtaceae • Fresh fruits • Hydrodistillation	γ-terpinene, α-pinene, terpineol-4, myristicin	MCF-7 66.45 (48 h)	• Anti-proliferative/cytotoxic activity	Piaru et al. (2012)
Ocimum sanctum • Lamiaceae • Leaves • Hydrodistillation	Not specified	MCF-7 170 (48 h)	• Inhibited proliferation • Induced apoptosis • ↑ genes p53 and Bid • ↑ Bax/Bcl-2 ratio	Manaharan et al. (2016)
Oliveria decumbens • Apiaceae • Aerial parts • Hydrodistillation	Thymol, carvacrol, p-cymene, γ-terpinene	2D cells MDA-MB-231 (31.2) MCF-7 (27) 3D Spheroids MDA-MB-231 (128.5) MCF-7 (117.5)	• ↑ ROS • Loss of mitochondrial membrane potential • Cell cycle arrest, and apoptosis	Jamali et al. (2018)
Origanum vulgare • Lamiaceae • Leaves • Hydrodistillation	Pulegone, menthone, *cis*-isopulegone, piperitenone	MCF-7 (8.11 ± 1.0) (48 h)	• Anti-proliferative/cytotoxic activity	Elansary et al. (2018)
Otanthus maritimus • Asteraceae • Aerial parts • Hydrodistillation	α-Pinene, β-pinene	MCF-7 (2D cells) MCF-7 spheroids IC_{50} not reported	• Anti-proliferative activity • ↑p21 and G2/M cell cycle arrest • Apoptosis induction	Beeby et al. (2020)
Pallenis spinosa • Asteraceae • Flowers and leaves • Hydrodistillation & Solid phase microextraction	Acorenone, α-muurolol, α-cadinol, δ-cadinene, germacrene-D-4-ol	MCF-7 0.25 ± 0.03 (24 h) MDA-MB-231 0.21 ± 0.03 (24 h)	• Induced cytotoxicity • Cell cycle arrest • Induced caspase-dependent and independent apoptosis	Saleh et al. (2017)
Phoebe bournei • Lauraceae • Leaves • Hydrodistillation	α-Copaene, α-muurolene, d-cadinene, 1 s-calamenene	MCF-7 40.5 (24 h)	• Anti-proliferative/cytotoxic activity	Ding et al. (2020)
Pinus sylvestris • Pinaceae • Pine needles • Hydrodistillation	α-pinene, camphene, δ-3-carene, bornyl acetate	MDA-MB-231 (29.23) MCF-7 (28.67) (48 h)	• Anti-proliferative/cytotoxic activity	Mag et al. (2015)
Piper boehmeriifolium • Piperaceae • Fresh leaves, stems and whole plant • Hydrodistillation	β-Caryophyllene, caryophyllene oxide, β-elemene	MCF-7 14.33 ± 0.26 (72 h)	• Anti-proliferative/cytotoxic activity	Wang, Gao, et al. (2020)
Prangos pabularia • Apiaceae • Shoot parts • Hydrodistillation	Durylaldehyde, bicyclo [3.1.1] hept-2-en-4-ol, chrysanthenyl acetate, (−)-spathulenol	MCF-7 18 (24 h)	• Anti-proliferative/cytotoxic activity	Banday et al. (2022)
Ridolfia segetum • Apiaceae • Whole plant • Hydrodistillation	α-Phellandrene, terpinolene, β-phellandrene, dillapiol	MCF-7 2D and 3D spheres IC_{50} not reported	• Antiproliferative effects in 2D models • Reduced growth of spheroids • ↑p21, Cleaved PARP • Cell cycle arrest and induction of apoptosis	Beeby et al. (2021)

(Continues)

TABLE 1 (Continued)

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Rosmarinus officinalis • Lamiaceae • Leaves • Hydrodistillation	1,8-Cineole, camphor, α-pinene, verbenone, borneol, linalool	MCF-7 36.5 ± 2.1 (48 h)	• Anti-proliferative/cytotoxic activity	Elansary et al. (2018)
Ruta chalepensis • Rutaceae • Aerial parts • Hydrodistillation	2-Cyclohexen-1-one, 2-nonanone, methyl hexadecanoate, 4,5-dimethoxy-6-prop-2-enyl-1,3-benzodioxole	MCF-7 80.03 ± 0.04 (48 h)	• Inhibited proliferation • Morphological changes, and membrane blebbing • Induced caspase-8 dependent apoptosis	Althaher et al. (2022)
Schefflera heptaphylla • Araliaceae • Leaves • Hydrodistillation	β-Pinene, limonene, β-myrcene, 3-carene	MCF-7 7.3 (72 h)	• Anti-proliferative/cytotoxic activity	Li et al. (2009)
Schinus molle • Anacardiaceae • Leaves • Hydrodistillation	α-Phellandrene, β-phellandrene, elemol, τ-muurolol, γ-eudesmol	MCF-7 41.33 ± 2.1 (48 h)	• Anti-proliferative/cytotoxic activity	Elansary et al. (2018)
Schinus terebinthifolius • Anacardiaceae • Leaves • Hydrodistillation	β-Longipinene, germacrene D, biclyclogermacrene	MCF-7 45.3 ± 0.2 (24 h)	• Anti-proliferative/cytotoxic activity	Santana et al. (2012)
Seseli tortuosum • Apiaceae • Aerial parts • Hydrodistillation	Chrysanthenone, verbenyl acetate	MCF-7 MCF-7 spheroids IC_{50} not reported	• Anti-proliferative activity • ↑p21 and G2/M cell cycle arrest • Apoptosis induction	Beeby et al. (2020)
Tamarix aphylla • Tamaricaceae • Aerial parts • Hydrodistillation	Trimethyl-2-pentadecanone, *β*-ionone, dodecanoic acid, tetradecanoic acid	MCF-7 26.65 ± 3.09 (72 h)	• Anti-proliferative/cytotoxic activity	Alhourani et al. (2018)
Thuja occidentalis • Cupressaceae • Leaves • Hydrodistillation	α-Pinene, δ-3-carene, α-cedrol, α-terpinolene	MCF-7 57.35 ± 2.3 (48 h)	• Anti-proliferative/cytotoxic activity	Elansary et al. (2018)
Thymus alternans • Lamiaceae • Dried aerial parts • Hydrodistillation	(E)-Nerolidol, neryl acetate, germacrene D, neral, geraniol	MDA-MB-231 5.96 ± 0.46 (72 h)	• Anti-proliferative/cytotoxic activity	Dall'Acqua et al. (2017)
Thymus vulgaris • Lamiaceae • Dried aerial parts • Hydrodistillation	p-cymene, γ-terpinene, thymol, carvacrol	MCF-7 52.65 (24 h)	• Anti-proliferative/cytotoxic activity	Niksic et al. (2021)
Trachyspermum ammi • Apiaceae • Dried seeds • Hydrodistillation	Thymol, γ- terpinene, para-cymene	MDA-MB-231 35 (48 h)	• Induced cytotoxicity • Low-level laser irradiation	Karimi et al. (2022)
Vitex agnus castus • Lamiaceae • Aerial parts • Hydrodistillation	Sabinene, 1,8-cineole, (Z)-β-farnesene, α-pinene	MCF-7 70.0 ± 10.0 (24 h)	• Inhibition of DNA synthesis • Induced apoptosis	Duymuş et al. (2014)
Zataria multiflora • Lamiaceae • Leaves and flowers • Hydrodistillation	carvacrol, g-terpinene, p-cymene, thymol	T47D > MCF-7 > MDA-MB-231 > MDA-MB-231 spheroids 20.09 > 25.06 > 29.89 > 118.4, respectively	• Selective cytotoxicity • ↑ ROS • Loss of mitochondrial membrane potential • Caspase 3 activation leading to apoptosis • Binds with DNA • Cell cycle arrest	Salehi et al. (2017)

TABLE 1 (Continued)

EO source plant, family name, and part of the plant used	Major components	BC cell line IC_{50} (μg/mL)	Effect/mechanism of action	Reference
Zingiber officinale • Zingiberaceae • fresh rhizome • Hydrodistillation	Not specified	MCF-7 IC_{50} not reported	• Inhibited cell proliferation • ↓ Expression of SDHB, SDHC, and SOD2 and affected TCA cycle • ↑ Oxidative stress and apoptosis	Lei et al. (2020)

Cyphostemma juttae EO has been shown to inhibit NF-κB activation and reducing the expression of target genes such as XIAP, survivin, Bcl2, and P-gp leading to the growth arrest of MDA-MB-231 and SUM149 cells (Zito et al., 2019).

EOs have been also shown to suppress the invasive and metastatic properties of BC cells. For instance, frankincense, pine needle, and geranium EOs reduced the viability, migration, invasiveness, and induced apoptosis in MCF-7 cells. All these EOs increased pAMPK, decreased p-mTOR, and its downstream effector p4E-BP1 (Ren et al., 2017). Furthermore, a recent study showed that chamomile EO derived from *Matricaria recutita* L. effectively inhibited the growth, migration, and invasion of MDA-MB-231 cells, even at concentrations as low as 1–2 μg/mL. Notably, this EO inhibited the phosphorylation of PI3K, Akt, and mTOR, and blocked the activation of the PI3K/Akt/mTOR signaling axis to exert these anticancer effects (An et al., 2023). It has been recently shown that *Zingiber officinale* EO (GEO) inhibited the proliferation of BC MCF-7 cells induced by bisphenol A (BPA), compound that promotes growth and metastasis of BC. Interestingly, a quantitative proteomics analysis of the cells treated with the combination of GEO and BPA demonstrated that changes caused in the oxidative phosphorylation pathway affected the tricarboxylic acid cycle and decreased the expression of SOD2 leading to oxidative stress and cell death (Lei et al., 2020). *Erythrina corallodendron* EO (ECEO) also suppressed the proliferation, migration, and invasion of MCF-7 and MDA-MB-231 cells. Notably, ECEO treatment changed the morphology of the cells from a loose and spindle-shaped form to a tight and round form, indicating the reversal of epithelial-to-mesenchymal transition (EMT). Expression of EMT markers such as N-cadherin, vimentin, snail, and slug were also reduced at mRNA and protein levels, while E-cadherin expression was up-regulated after ECEO treatment (Xing et al., 2019).

Interestingly, recent studies have shown that EOs can also exert antitumor effects in 3D cultures or spheroid models of BC. For examples EOs from *Zataria multiflora* (ZEO) and *Oliveria decumbens* (OEO) has been shown to induce cytotoxicity in 2D monolayer and 3D spheroids of MDA-MB-231 cells. Interestingly, ZEO and OEO bind with DNA via intercalation, increase ROS generation that results in DNA fragmentation, loss of mitochondrial membrane potential and caspase-3 activation. As a result, MDA-MB-231 cells treated with ZEO and OEO showed cycle arrest and apoptosis induction (Jamali et al., 2018; Salehi et al., 2017). Molecular mechanisms mediated by EOs to suppress the growth of BC cells are summarized in Figure 1.

4 | ANTICANCER ACTIVITIES OF EOs IN IN VIVO BC MODELS

Numerous studies have reported the efficacy of EOs and their constituents in various in in vivo BC models. For instance, oral administration of *Lippia citriodora* EO (LCEO) in BALB/c mice bearing DA3 murine BC cells xenograft. Treatment with LCEO also reduced the expression of survivin and increased the expression of cleaved caspase-3 in tumor tissues (Spyridopoulou et al., 2021). High level of serum malondialdehyde (MDA) is correlated to the advanced BC stages. Whereas reduced glutathione, plays crucial roles as an antioxidant by free radical scavenging (Rojas-Armas et al., 2022). Interestingly, EO of *Annona muricata* (AMEO) had an ameliorative effect in murine BC model through an antioxidant mechanism. Compared to the control group of Female Holtzman rats who received only DMBA injections, rats that received oral administration of the AMEO showed significantly lower levels of MDA and higher levels of reduced glutathione. As a result, AMEO treatment substantially decreased the tumor incidence frequency and tumor volume (Rojas-Armas et al., 2022).

4.1 | Immunomodulatory effects of EOs in in vivo BC models

Immunomodulatory drugs can improve the effectiveness of cancer therapy by boosting the antitumor immunity and thereby facilitate the immune cells to eliminate cancer cells. Azadi et al. reported that ZEO decreased tumor growth potentially through immunomodulatory effect. Specifically, in mice bearing 4T1 xenograft tumors, treatment with ZEO shifted the balance of cytokines in favor of Th1 expansion, leading to increased secretion of TNF-α (Azadi et al., 2020). Similarly, EO also promoted Th1 expansion and antitumor immune response in mice bearing 4T1 xenograft tumors by lowering the levels of IL-10, IL-6, TGF-β, and IL-1 and increasing the levels of IL-2, IFN-γ, and TNF-α (Jamali et al., 2020). Furthermore, a study reported that *Cinnamomum zeylanicum* EO (CZEO) possessed immunomodulatory effect in Ehrlich ascites carcinoma (EAC)-bearing mice. CZEO increased the

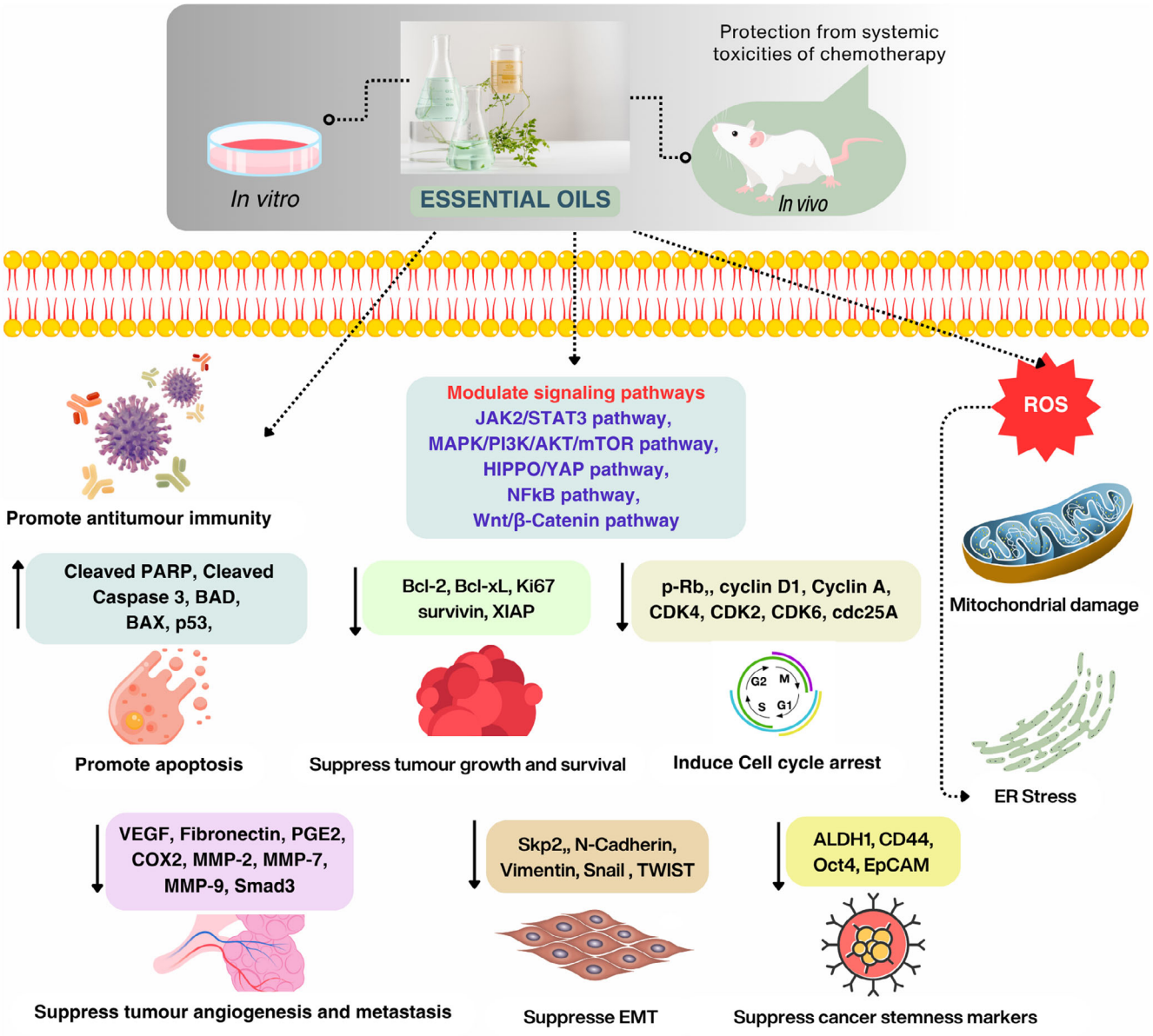

FIGURE 1 Schematic representation of mechanism of anti-breast cancer effect of essential oils and constituents. They induce ROS and inhibit oncogenic signaling pathways, resulting in inhibition of epithelial-to-mesenchymal transition and inducing ER stress and apoptosis.

proportion of splenic T helper ($CD3^+$, $CD4^+$) and T cytotoxic ($CD3^+$, $CD8^+$) cells, resulting in cycle arrest at the G0/G1 phase and inhibition of tumor growth in in vivo (Morsi et al., 2022). Interestingly, no significant body weight loss was found in the EOs treated mice groups during these studies. Moreover, evaluation of the plasma activities of liver-related enzymes (AST and ALT) proved that the EOs did not compromise the healthy function of the liver, reassuring the safety profile, and minimal toxicity of these EOs in rodent models (Azadi et al., 2020; Jamali et al., 2020; Morsi et al., 2022).

Taken together, these works illustrate that EOs can be administered in in vivo to treat highly metastatic breast tumors without systemic toxicity. In in vivo anticancer activities of EOs against BC are summarized in Table 2.

5 | CHEMICAL CLASSIFICATION OF EO COMPOUNDS

The chemical composition of EOs can vary according to various factors such as plant species, plant parts used, geographical origin, and climatic conditions (Sadgrove et al., 2022). EO components are primarily classified based on their biosynthetic origin, number of carbon atoms present, type of parent backbone, and the nature of side groups. Accordingly, the compounds can be clustered mainly into two major groups: terpenes and phenylpropanoids (Sadgrove et al., 2022). Terpenes constitute a diverse group of natural hydrocarbons, with their fundamental structure being the interlinked isoprene units (2-methyl-1,3-butadiene). This structure is represented by the general

TABLE 2 Essential Oils (EOs) against breast cancer (BC) on in in vivo models.

EO/EO compounds	In in vivo BC model	Effects/mechanism of action	Reference
Annona muricata	• DMBA induced mammary tumor in female Holtzman rats, aged between 6 and 8 weeks • Oral administration OF EO daily in doses of 50, 100 and 200 mg/kg/day of body weight for 13 weeks	• Decreased tumor incidence frequency and tumor volume • Decreased serum levels of MDA and increased glutathione levels	Rojas-Armas et al. (2022)
Boswellia sacra	• MCF-7 xenograft in 4–5-week-old female nude mice • Subcutaneous injection of the EO at every 4 days for 12 days.	• Suppressed tumor growth and reduced tumor volume by increasing apoptosis	Ren et al. (2017)
Cymbopogon citratus	• DMBA induced mammary tumor in female Holtzman rats, aged between 6 and 8 weeks • Oral administration of EO daily in doses of 50, 100 and 200 mg/kg/day of body weight for 14 weeks	• Reduced tumor volume • Reduced mitosis and tumor necrosis	Rojas-Armas et al. (2020)
Lippia citriodora	• DA3 xenograft in female BALB/c aged between 6 and 8 weeks • Oral administration of the EO at a daily dose of 0.552 g/kg of animal body weight for 14 days	• Reduced tumor growth • ↑cleaved caspase-3 • ↓ Survivin	Spyridopoulou et al. (2021)
Oliveria decumbens	• 4T1 xenograft in 5–6 weeks old female BALB/c mice • Intraperitoneal injection of the EO, every 2 days for 2 weeks	• Reduced tumor growth • Immunomodulatory effect by promoting Th1 expansion/↑ IL-2, INF-γ, and TNF-α & ↓ IL-6, IL-10, IL-1β, and TGF-β	Jamali et al. (2020)
Zataria multiflora	• 4T1 xenograft in 5–6 weeks old female BALB/c mice • Intraperitoneal injection of half LD_{50} dose (500 mg/kg) for eight days in every other day.	• Reduced tumor growth • Immunomodulatory effect, ↑ TNF-α and promoted Th1 expansion	Azadi et al. (2020)

formula $(C_5H_8)_n$, where "*n*" signifies the number of linked isoprene units. Monoterpenes, consists of two isoprene units and have a molecular formula of $(C_{10}H_{16})$. α-pinene, myrcene, and limonene are examples of monoterpenes contained in EOs (El Asbahani et al., 2015). Several EO compounds are oxygenated derivatives of monoterpenes called as monoterpenoids. They are modified terpenes containing different functional groups such as alcohols (linalool, thymol, geraniol), ketones (carvone, camphor), and aldehydes (citronellal). Sesquiterpenes, contain three isoprene units with the molecular formula of $(C_{15}H_{24})$. Elemene, β-bisabolene, and caryophyllene are major sesquiterpenes found in EOs. Sesquiterpenoids are derivatives of sesquiterpenes with modified functional groups such as lactones (costunolide [CS], alantolactone [ATL]), alcohols (α-santalol, carvacrol, curcumol), and ketones (germacrone, zerumbone [ZER]) (El Asbahani et al., 2015). Diterpenes are composed of four isoprene units, and are larger and less common in distilled EOs due to their lower volatility. The distillation process heats plant material to extract volatile compounds, but higher boiling points and lower volatility of diterpenes hinder their effective vaporization and transfer into distillates. Examples of EO diterpenes include cembrene and sclareol, found in small quantities (Sadgrove et al., 2022). Phenylpropanoids are the second major class of compound present in EOs. They are organic compounds derived from the amino acid phenylalanine. These compounds are also characterized by a phenylpropane backbone and have various functional groups such as hydroxyl, methoxy, and/or glycosyl groups attached to them. Eugenol, *trans*-anethole, and cinnamaldehyde are few examples of phenylpropanoids found in EOs (Bunse et al., 2022). In the following sections, we will discuss the anticancer activities of these EO compounds against BC.

5.1 | Anticancer activities of monoterpenes against BC

Monoterpenes constitute the major group of EO compounds and are characterised by pleasant, fruity, and floral fragrances. They have various medicinal properties, including anti-inflammatory, antimicrobial, and antioxidant activities (Koziol et al., 2015). Recently, accumulating evidence has shown that monoterpenes have anticancer activities against various cancers, including BC (Machado et al., 2022). This section summarises the anticancer activities of monoterpenes in BC models. Structures of monoterpenes with anti-BC activities are illustrated in Figure S1.

5.1.1 | Carvone

Carvone is the major monoterpene present in spear mint EO (*Mentha spicata*) that gives its rich minty odour and sweet flavour. Carvone

specifically inhibited the growth of BC cells MDA-MB-231 and MCF-7 (sparing healthy breast epithelial cells MCF-10A) via ROS-mediated downregulation of antiapoptotic proteins phospho-p53 and phospho-Bid. Significant increase in apoptotic proteins such as Bad, cleaved caspase-3, and cleaved PARP was also observed (Patel & Thakkar, 2014).

5.1.2 | Citral

Citral is the major component of the widely used traditional medicine herbs such as lemon grass (*Cymbopogon citratus*) and lemon balm (*Melissa officinalis*). The acyclic monoterpene has shown anticancer activities in various cancer models, including BC. A study found that citral displays effective targeting of BC stem cells both in in vitro and in in vivo. Notably, it exhibits significant growth suppression of MDA-MB-231 spheroids at a lower IC_{50} value when compared to monolayer culture. Additionally, citral demonstrates inhibition of secondary sphere formation and the self-renewal ability of $ALDH1^+$ drug resistant MDA-MB-231 spheroids. This effect is attributed to the suppression of the Wnt/β-catenin pathway (Nigjeh et al., 2018). Moreover, citral fed orally has been shown to be effective in reducing the number of $ALDH^+$ cells and the size of tumors in 4T1 xenografts that carry BALB/c mice in in vivo. Additionally, tumorigenicity was delayed in citral-fed mice after reimplantation of primary tumor cells in normal mice, supporting its potential to target BC stem cells and reduce the risk of tumor recurrence in BC (Nigjeh et al., 2019).

5.1.3 | Geraniol

Geraniol is an acyclic monoterpene found in the EOs of lemon cypress (*Cupressus macrocarpa*), lemon verbena (*L. citriodora*), and rose geranium (*Pelargonium graveolens*). Geraniol selectively suppressed the growth of MCF-7 cells by inducing G1 phase cycle arrest through inhibition of cyclin D1, E, and A as well as cyclin-dependent kinases CDK2 and CDK4 in a dose-dependent manner (Duncan et al., 2004).

5.1.4 | D-Limonene and perillyl alcohol

D-Limonene and its hydroxylated analogue perillyl alcohol (POH) are monoterpenes that are found most frequently in EOs from citrus plants. In a clinical trial investigation, Miller et al. identified that early stage patients who received 2 g of limonene orally every day for 2–6 weeks had preferentially concentrated levels of limonene in their breast tissues, which led to a reduction in cyclin D1 expression and an increase in insulin-like growth factor I levels (Miller et al., 2013). They then performed metabolic profiling of plasma samples from patients that revealed alterations in 72 of 397 identified metabolites, of which 47 metabolites were linked to the reduction of cyclin-D1 (Miller et al., 2015). On the other hand, POH suppressed the growth and metastasis of ER positive human BC cells (KPL-1 and MCF-7) and ER negative human BC cells (MKL-F and MDA-MB-231) human BC cells proliferation by reducing the expression of cyclin D1, cyclin E and an increase in p21Cip1/Waf. Additionally, in in vivo experiments demonstrated that the intraperitoneal administration of POH, at a dosage of 75 mg/kg, three times a week for 6 weeks, effectively suppressed the growth of orthotopically transplanted KPL-1 tumor cells and prevented regional lymph node metastasis in nude mice (Yuri et al., 2004).

5.1.5 | Linalool

Linalool is a monoterpene alcohol found in the EOs of several aromatic plants including *Citrus paradisi*, *Pelargonium graveolens*, *Rosmarinus officinalis*, and *Thymus vulgaris*. In T47D cells, linalool exerted cytotoxic effects by activating antitumor immunity by inducing the Th1 cellular immune response (Chang & Shen, 2014). Furthermore, a recently published report demonstrated that linalool induced apoptosis in MDA-MB-231 and MCF-7 cells (Elbe et al., 2022).

5.1.6 | β-myrcene

β-myrcene is a monoterpene component in the EO of *Pinus koraiensis* cones. It has been reported that β-myrcene suppressed TNFα-induced NF-κB signaling pathway and reduce the expression of MMP-9 that contributes to chemopreventive activity against highly invasive and metastatic BC spheroids of MDA-MB-231 (Lee et al., 2015).

5.1.7 | α-pinene

We have recently reported that one of the main compounds of *Pinus mugo* EO with anticancer activity is α-pinene (Thalappil et al., 2022). It has been shown that α-pinene reduced TNF-α-induced MMP-9 gene expression and invasive capability of MDA-MB-231 spheroid cells by inhibiting the NF-κB activity (Kang et al., 2016).

5.1.8 | Thymoquinone

Thymoquinone (TQ) is a monoterpene found mainly in EO extracted from the seeds of *Nigella sativa*. The anticancer mechanisms of TQ against BC have been extensively investigated and have already been reviewed by several researchers (Adinew et al., 2021). Recently, using chromatin immunoprecipitation sequence (ChIP-Seq) analysis, Khan et al. demonstrated that epigenetically upregulated interleukin-17 receptor type D expression of TQ and effectively reduced cell growth and metastasis of BT-549 and MDA-MB-231 (Khan et al., 2022).

5.1.9 | Carvacrol

Carvacrol, a phenolic monoterpene found in the EOs of several plants such as *Origanum vulgare*, *Thymus vulgaris*, and *Lepidium flavum*. Carvacrol has been reported to suppress proliferation and cell cycle arrest in MDA-MB-231 cells by inhibiting TRPM7 ion channels (Li et al., 2021). Similarly, inhibition of the PI3K/AKT signaling pathway mediated by carvacrol treatment reduced the expression of cell cycle regulatory proteins p-Rb, cyclin D1, CDK4, and CDK6 that causes apoptosis and G0/ G1 phase cell cycle arrest in MCF-7 cells (Mari et al., 2021). Moreover, a recent study has reported the anti-BC activity of carvacrol in in vivo. The results showed that Carvacrol can induce mitosis and necrosis, leading to regression of tumor growth in rats with DMBA-induced BC (Rojas-Armas et al., 2020).

5.2 | Anticancer activities of sesquiterpenes against BC

Sesquiterpenes are made up of three isoprene units. They have been shown to exhibit a broad spectrum of biological activities, ranging from anti-inflammatory, antibacterial, antifungal, and anticancer effects. Their anticancer activities have been studied extensively in numerous BC cell lines and in in vivo BC models, which are summarized in this section. Sesquiterpene structures that have demonstrated anti-BC activities are illustrated in Figure S2.

5.2.1 | Alantolactone and isoalantolactone

ATL and isoalantolactone (IATL) are sesquiterpene lactones found in the EOs of plant species such as *Inula helenium* and *Inula japonica*. ATL has shown significant anticancer activities mediated by a diverse set of mechanisms against multiple BC models in in vitro and in in vivo (Babaei et al., 2021). Notably, ATL has been found to regulate multiple signaling pathways including p38 MAPK, NF-κB, and Nrf2 pathways and lead to induction of apoptosis through Bax/Bcl2 regulation and suppression of migration and colony formation by downregulation of MMP2, MMP7, and MMP9 in MCF-7 cells (Zhang et al., 2012). Recently, we reported that several EOs inhibit STAT3 signaling activation and induce apoptosis in cancer cells (Thalappil et al., 2022). Chun et al. showed that ATL inhibited constitutive and inducible STAT3 activation and prevented nuclear translocation of STAT3 and NF-κB, leading to inhibition of migration, invasion, adhesion, growth, and colony formation of MDA-MB-231 cells. ATL administration also significantly decreased in p-STAT3, Ki-67, and cyclin D1 expression in tumor tissues of MDA-MB-231 xenograft mice (Chun et al., 2015). Phosphorylation of VEGFR2 is one of the key mechanisms driving tumor angiogenesis. Recently, Liu et al. reported that ATL downregulated VEGFR2 phosphorylation and its downstream targets, including PLCγ1, FAK, Src and Akt, resulting in antiangiogenic activity and delayed tumor growth in mice with MDA-MB-231 xenograft tumor (Liu et al., 2018). Furthermore, ATL has been shown to suppress TrxR1 activity, a key antioxidant system present in high levels in TNBCs often exhibit high levels of TrxR1. Consequently, suppression of TrxR1 activity leads to increased ROS formation and apoptosis in both MDA-MB-231 cells and xenografts. Lastly, ATL treatment has been found to cause ER-stress by increasing phosphorylated eIF2α, ATF4, and CHOP protein levels via ROS-mediated mechanisms (Yin et al., 2019).

On the other hand, IATL has been found to induce cytotoxicity in MDA-MB-231 and MCF-7 cells without affecting non-transformed breast epithelial cells MCF-10A. The mechanism of action involves inhibiting SIRT1, which leads to p53 activation through acetylation. Moreover, IATL also activate the p38 and JNK pathways in a ROS-dependent manner, increases the Bax/Bcl-2 ratio, promotes mitochondrial membrane potential depolarization, and releases cytochrome C from mitochondria to the cytoplasm, ultimately resulting in G2/M cell cycle arrest and apoptosis via the caspase cascade and PARP cleavage (Li et al., 2016).

5.2.2 | β-caryophyllene and β-caryophyllene oxide

β-caryophyllene (BCP) is a bicyclic sesquiterpene and is one of major components of EOs of a variety of plants. Researchers have shown that BCP has promising antiproliferative effects on various types of cancer cells, including BC cells (Di Sotto et al., 2020; Fidyt et al., 2016). For example, BCP induced cytotoxicity against MDA-MB-468 cells and enhanced the anticancer activities of two terpene-rich organic extracts from inflorescences of *Felina* hemp (Di Giacomo et al., 2021). β-caryophyllene oxide (BCO) is an oxidation product of BCP. BCO inhibited the constitutively active PI3K/AKT/mTOR/S6K1 signaling cascade and activated MAPK signaling in a ROS-dependent manner culminating in the inhibition of proliferation and apoptosis induction in MCF-7 cells. Subsequently, BCO decreased the expression of several downstream gene products that govern cell proliferation, survival, metastasis, and angiogenesis, while the expression of tumor suppressors p53 and p21 was elevated. Furthermore, pretreatment of cells with *N*-acetylcysteine prevented BCO-induced apoptosis (Park et al., 2011).

5.2.3 | β-Bisabolene and α-bisabolol

β-bisabolene and its alcoholic analogue, α-bisabolol are the major components of the EOs of *Commiphora* species. The findings of Yeo et al. suggest that β-bisabolene could be a promising drug candidate against BC. They have shown that β-bisabolene selectively induced cytotoxicity and apoptosis in in vitro in both human (MCF-7, MDA-MB-231, SKBR3 and BT474) and murine (MG1361 and 4T1) BC cell lines (Yeo et al., 2016). On the other hand, α-bisabolol show antitumor activities in in vivo against the induction and growth of spontaneous mammary tumors in HER-2/neu transgenic mice. The analysis of the gene expression matrix showed that following α-bisabolol treatment, several genes involved in angiogenesis (EGFR, FGF1), suppression of

apoptosis (Birc5), and carcinogenesis pathways (NF-kB, Map2k, Mapk14, and HER2/neu) were differentially regulated. α-bisabolol also increased antitumor immunity by elevating the percentage of NK cells, NK cell cytotoxicity, and the percentage of T cell subsets (CD4 and CD8) (Costarelli et al., 2009).

5.2.4 | Costunolide and dehydrocostuslactone

Dehydrocostuslactone (DCE) and CS are sesquiterpene lactones found in several plant species such as *Laurus nobilis* L., *Magnolia sieboldii* L., and *Sassurea custus* L. These compounds demonstrate various biological and immunological activities, including anti-inflammatory and antifungal effects. Additionally, studies have shown that these compounds induced a proapoptotic effect in various human cancer cells (Butturini et al., 2011). Furthermore, different studies have shown that DCE and CS improved tumor cell chemosensitivity to standard chemotherapy drugs (Butturini et al., 2019). In MDA-MB-231 and MCF-7 cells, CS induced cell cycle arrest in the G2/M phase by downregulating Cyclin D1, Cyclin D3, CDK4, CDK6 and upregulating p18 INK4c, $p21^{CIP1/Waf-1}$ and $p27^{KIP1}$ (Roy & Manikkam, 2015). CS also induced ROS-dependent extrinsic apoptosis pathway in MDA-MB-231 cells by activating the Fas death receptor and caspases-8 and -3 (Choi et al., 2012). On the other hand, DCE induced G0/G1 phase cell cycle arrest in MCF-7 cells by downregulating the expression of cyclin D, cyclin A, CDK2, and cdc25A and upregulating p53 and p21 (Kuo et al., 2009). Whereas, in MDA-MB-231 cells, DCE caused G2/M phase cell cycle arrest by upregulating p21 expression, activating chk1, and suppressing the expression of cyclin A, cyclin B, cdc25A, and cdc25C (Kuo et al., 2009). In both cell lines, DCE induced apoptosis by increasing BAX/Bcl2 ratio and the nuclear translocation of mitochondrial factors AIF and endonuclease G (Kuo et al., 2009). Furthermore, DCE modulates JAK/STAT3 survival signaling through upregulation of SOCS-1 and SOCS-3 and inhibition of STAT3 signaling in MDA-MB-231 xenografts in nude BALB/c mice (Kuo et al., 2009).

5.2.5 | Curcumol

Curcumol is another sesquiterpene lactone and the major component of the EOs of *Rhizoma curcumae*. Research suggests that Curcumol can be a potential drug candidate against BC, particularly TNBC. Huang et al. showed that in MDA-MB-231 cells, curcumol promoted G1 phase cell cycle arrest and apoptosis by downregulating mutant p53 and upregulating the expression of apoptotic proteins p73, PUMA, and Bak. Curcumol-induced tumor growth inhibition has been also observed in in vivo in an MDA-MB-231 mouse xenograft model (Huang et al., 2017). Furthermore, Ning et al. demonstrated the anti-metastatic activity of curcumol in MDA-MB-231 and 4T1 cells. At noncytotoxic concentrations, curcumol effectively blocked metastatic signaling events such as expression of MMP-9, activation of JNK1/2 and Akt, nuclear translocation of NF-kB p65 and suppressed the migration, invasion, and adhesion (Ning et al., 2016). Curcumol also suppressed AKT phosphorylation and inhibited the viability of IV2-1 cells, an aggressive TNBC model that has acquired anoikis (a form of programmed cell death) resistance by phosphorylating YAP1 and suppressing its expression. It also suppressed the production of Skp2, an EMT protein that is overexpressed in IV2-1 cells and mediates anoikis resistance (Li et al., 2020).

5.2.6 | Germacrone

Germacrone is a sesquiterpene compound found in different curcuma plants such as *Rhizoma curcumae*, *Curcuma leucorhiza*, and *Curcuma wenyujin*. In MDA-MB-231 and MCF-7 cells, Germacrone induced cell cycle arrest, impaired mitochondrial membrane potential and induced apoptosis through increasing Bak expression and cytochrome C release (Lim et al., 2016). Germacrone also induced apoptosis in MCF-7 cells by blocking the recruitment of Erα to estrogen receptor elements and consequently downregulating the expression of Erα target genes and BC prognostic markers such as trefoil factor 1, growth regulating estrogen receptor binding 1, cyclin D1, and c-Myc (Zhong et al., 2011).

5.2.7 | Furanodiene

The EO of *Curcuma wenyujin* contains the sesquiterpenoid called furanodiene. It has been reported that furanodiene inhibited the proliferation of MDA-MB-231 and MCF-7 cells in a dose-dependent manner. This compound also induced LDH release, mitochondrial membrane potential depolarization, chromatin condensation, and DNA fragmentation. Furthermore, furanodiene also arrested the cell cycle at the G0/G1 phase, inhibited the expression of several proteins related to cell cycle progression and anti-apoptosis, and increased the proteolytic cleavage of caspase-9, caspase-7, and PARP. Furanodiene also significantly suppressed tumor growth in in vivo in a nude mouse MCF7 tumor xenograft model (Zhong et al., 2012). Furthermore, Zhong et al. reported that furanodiene inhibited the adhesion, migration, and invasion of BC cells MDA-MB-231 and 4T1 at low doses without inducing cytotoxicity, apoptosis, or cell cycle arrest. These effects were mediated by downregulating MMP-9, FAK, and its interaction with Integrin V with the consequent inhibition of activation of Akt, PI3K, and p85 activation (Zhong et al., 2014).

5.2.8 | Xanthorrhizol

Xanthorrhizol is a bioactive sesquiterpene contained in the EOs of *Curcuma longa* and *Curcuma zanthorrhiza*. Xanthorrhizol has been reported to induce mitochondrial mediated apoptosis in MDA-MB-231 cells (Cheah et al., 2008). Furthermore, combination of xanthorrhizol with curcumin synergistically enhances growth inhibitory activity and induction of apoptosis in MDA-MB-231 cells (Cheah et al., 2009).

5.2.9 | β-Elemene

β-elemene is a sesquiterpene contained in EO extracted from several plants. In fact, eight species of plants described in Table 1 contain β-elemene as one of the main components. β-Elemene has demonstrated remarkable anticancer properties against several tumor models in in vitro and in in vivo and has already received approval from the China Food and Drug Administration for clinical use (Zhai et al., 2018). In 4T1 murine cells, β-elemene inhibited the migration and invasion by inhibiting the expression of heparanase and downregulating the phosphorylation of ERK and AKT (Zhang et al., 2017). Furthermore, in MCF-7 cells, β-elemene blocked TGF-β1-induced EMT, migration, and invasion by inhibiting the expression of nuclear transcription factors SNAI1, SNAI2, TWIST, and SIP1 through the suppression of Smad3 (Zhang et al., 2013). Pan et al. demonstrated that β-elemene exerts anti-BC activity by blocking aerobic glycolysis. Specifically, β-elemene inhibits the tetrameric transformation and nuclear translocation of pyruvate kinase M2 (PKM2), which are crucial events for cancer metastasis. This inhibition leads to a reduction in glucose utilization and the production of pyruvate and lactate. Additionally, β-elemene suppresses the EGFR-importin α5-mediated nuclear translocation mediated by EGFR-importin 5 of PKM2, as well as the expression of GLUT1, MCT1, MCT4, and LDHA (Pan et al., 2019).

5.2.10 | Zerumbone

ZER is a sesquiterpene commonly found in EO extracted from subtropical *ginger*. According to a growing body of research, ZER mediates several mechanisms to exert anti-breast effects. MCF-7 and MDA-MB-231 cells treated with ZER displayed arrest and apoptosis of the G2/M cell cycle through robust activation of Bax and Bak. Furthermore, ZER suppressed the growth of the MDA-MB-231 xenograft in in vivo (Sehrawat et al., 2012). In HER2 overexpressing MCF-7 cells, ZER treatment suppressed the constitutive activation of NF-κB signaling, concurrently downregulated the expression of CXCR4 and attenuated CXCL12-induced BC cell invasion (Sung et al., 2008). Kim et al. (2014) have shown that ZER inhibited CD44 activation by EGF through suppression of the STAT3 signaling pathway in SKBR3 human BC cells. ZER also suppressed migration of HCC1806 TNBC cells by suppressing TGF-β1 induced Smad3 phosphorylation and expression of fibronectin, MMP-2, and MMP-9 (Kim et al., 2016).

5.3 | Anticancer activities of phenylpropanoids against BC

In this section, we provide an overview of the activity of phenylpropanoids against BC. The structures of phenylpropanoids are illustrated in Figure S3.

5.3.1 | Cinnamaldehyde

The anticancer activities of cinnamon EOs and their active constituents, including cinnamaldehyde (CA) and eugenol, have been reported against different cancer models (Hong et al., 2016). Liu et al. (2020) predicted the major components of cinnamon and integrated them specifically with potential therapeutic targets against BC using network pharmacology. From various databases, they screened out 12 promising compounds of which linoleic acid, oleic acid, diisobutyl phthalate, and CA were the first four compounds. Through the integration of data obtained from popular databases GeneCards and OMIM, 61 BC-related targets that match cinnamon targets were identified as prospective targets for cinnamon's anti-BC activities (Liu et al., 2020). Consistent with these theoretical results, in in vitro assays on MDA-MB-231 have shown that CA treatment inhibited migration and invasion, induced morphological and cytoplasmic changes, and resulted in apoptosis. It is also predicted that CA can modulate several signaling pathways, including the PI3K-Akt, PPAR, cAMP, NF-κB, and HIF-1 pathways, to exert these anti-BC activities (Liu et al., 2020).

5.3.2 | Eugenol

Eugenol is a phenylpropanoid rich in *Syzygium aromaticum* EOs. Several studies have reported anticancer activities of eugenol (Begum et al., 2022; Zari et al., 2021). In HER2 positive SK-BR-3 and triple negative MDA-MB-231 cells, eugenol has been found to reduce the expression of MMP2 and MMP9, which in turn impaired the viability, proliferation, and migration of cancer cells. Interestingly, in transformed normal-like HER2 cell line (MCF-10AT), eugenol could effectively hinder the development of precancerous breast lesions by blocking the HER2/PIEK-AKT signaling network (Ma et al., 2017). It has also been reported that eugenol suppress BC growth in in vitro and in in vivo by downregulating E2F1, NF-κB, and survivin (Al-Sharif et al., 2013). Another study has shown that by inhibiting the PI3K/AKT/FOXO3a pathway, eugenol induced autophagy and potentiated apoptosis induction in BC cells MDA-MB-231 and SK-BR-3 (Abdullah et al., 2021). A recent study by Al-Kharashi et al. demonstrated that eugenol can effectively deactivate BC-associated fibroblasts (CAFs) in in vitro and in mice orthotopic tumor xenografts. This effect is mediated through an epigenetic mechanism, in which eugenol negatively regulates the expression of DNMT1 and DNMT3A, leading to the inactivation of E2F1 through hypomethylation. Consequently, the expression of myofibroblast biomarkers, including SMA, SDF1, TGF1, and IL6, is significantly downregulated, resulting in the suppression of stemness and EMT markers in BC cells. These markers include CD24 low/CD44 high/ALDH high, N-cadherin, Vimentin, ZEB1, and Twist-1 (Al-Kharashi et al., 2021).

5.3.3 | Anethole

Anethole is a phenylpropanoid found in *Foeniculum vulgare* EO (de Oliveira et al., 2015). Chen et al. have recently shown that anethole suppressed survival of BC cell lines MCF-7 and MDA-MB-231 irrespective of their estrogen status. Mechanically, it was identified that the transcriptional activity of NF-κB was suppressed by anethole, which has resulted in upregulation of p53 and c-Flip and cleavage of caspase-9 and PARP1 (Chen & DeGraffenried, 2012).

6 | COMBINATION OF EOs AND CONSTITUENTS WITH CHEMOTHERAPY DRUGS FOR BC

Accumulating evidence have shown the synergistic activity of EOs and EO constituents with chemotherapy agents and certain other therapies in BC models. EOs from *Inula japonica* and *Angelicae dahuricae* and the main component IATL has been shown to enhance the sensitivity of MCF-7 cells resistant to doxorubicin (MCF-7/ADR) by 2–3-folds and mediating multiple mechanisms like suppressing ABCB1 expression and disturbing lipid raft stability (Wu et al., 2016). Furthermore, another study found that combination of *Cinnamomum burmanii* EO with doxorubicin synergistically enhanced ROS generation and potentiated the cytotoxic and antimetastatic effects of doxorubicin in 4T1 cells (Aliyah et al., 2022).

Combinations of monoterpenes with standard chemotherapy drugs has been shown to be effective in mitigating BC chemoresistance and reducing the toxicities of standard chemotherapy drugs. For instance, subtoxic concentrations of linalool has been reported to show significant synergism with doxorubicin and reverse doxorubicin resistance in multidrug resistant MCF-7 cells (MCF7 AdrR). The IC_{50} (μM) values of doxorubicin were lowered from 16.16 ± 0.94 to 3.0 ± 0.25 when combined with 10 μM linalool and to 1.24 ± 0.26 when combined with 50 μM linalool, with an excellent combination index of 0.3–0.5. Moreover, the combination also potentiated doxorubicin-induced cytotoxicity and pro-apoptotic effects (Ravizza et al., 2008). Furthermore, a study reported that R-(−)-carvone is highly synergistic with doxorubicin in MCF-7 cells, and combined injection of 75 or 150 mg/kg of R-(−)-carvone with 20 mg/kg doxorubicin ameliorated doxorubicin induced cardiotoxicity in BALB/c mice by elevating catalase activity and lowering serum levels of creatinine kinase and lactate dehydrogenase (Abbas et al., 2020).

Combinations of EO sesquiterpenes with standard chemotherapy drugs have also been reported to enhance anti-BC effects through various mechanisms. According to Wang et al., sesquiterpene compound curcumol alone had no significant effect on TNBC cells, whereas combination of curcumol with chemotherapy drug metformin, enhanced apoptosis, anti-metastatic and anti-EMT activities of metformin in in vitro and suppressed tumor growth in in vivo. Specifically, combination of 50 μM curcumol with 10 μM metformin reversed proliferation, migration, invasion, and EMT induced by rucaparib, and enhanced the effect of metformin in MDA-MB-231 TNBC cells. Moreover, injecting 60 mg/kg curcumol in combination with 100 mg/kg metformin in mice bearing MDA-MB-231 xenografts inhibited tumor growth when compared to metformin alone by promoting the inhibition of the Wnt2/β-Catenin signaling pathway and the expression of EMT markers (Wang, Dong, et al., 2020). Curcumol also enhanced the chemosensitivity of BC cells to doxorubicin in a doxorubicin-resistant MDA-MB-231 cell line with high expression of ABCC3 protein and low levels of miR-181b-2-3p. Interestingly, combined treatment of curcumol (40 μg/mL) and doxorubicin (1 μM) increased the expression of miR-181b-2-3p and decreased the expression of ABCC3, promoting the chemotherapeutic effects of doxorubicin both in in vitro in MDA-MB-231 cells and in in vivo in a patient derived xenograft model (Zeng et al., 2020). Lastly, combination of curcumol and paclitaxel (250 μM + 2.5 μM) also synergistically enhanced the antiproliferative and proapoptotic effects on the MDA-MB-231 cells in in vitro and in in vivo (curcumol 100 mg/kg plus paclitaxel 10 mg/kg), by suppressing ZBTB7A expression through the inhibition of NF-κB signaling pathway (Mao et al., 2022).

At a non-toxic concentration, doxorubicin has been shown to induce cell migration and invasion in highly metastatic MDA-MB-231 cells. Zhong et al. (2017) found that co-treatments with furanodiene (5–20 μM) and doxorubicin (0.1 μM) synergistically suppressed the metastatic potential and induced apoptosis in BC cells by suppressing the expression of MMP-9, FAK, Integrin αV, and the downstream phosphorylation of Src, Paxillin, AKT, and p85. Furthermore, combination of furanodiene (0, 50, and 100 μM) with doxorubicin (2 μM) has been shown to re-sensitize doxorubicin resistant MCF-7 cells (MCF-7/DOX cells) and induce apoptosis by altering mitochondrial function and reducing cellular ATP levels through the regulation of AMPK signaling pathway (Zhong et al., 2016).

Several studies have reported the potential of β-elemene to counteract chemoresistance and sensitize BC to various chemotherapy drugs. For instance, Zhang et al. reported that treatment with 10 μg/mL β-elemene induces re-expression of ERα through the MAPK pathway and effectively reversed tamoxifen resistance in MCF-7 cells (Zhang et al., 2012). β-elemene (30 μM) had a strong potency to increase the cytotoxicity of doxorubicin to chemoresistant MCF-7/DOX cells, with a reversal fold of 6.38 by inhibiting P-glycoprotein, leading to increased intracellular accumulation of doxorubicin (Bin Xu et al., 2012). β-elemene has been shown to reverse drug resistance and increase the apoptosis rate in of two chemoresistant BC cell lines (MCF-7/Adr and MCF-7/Doc) by targeting exosomes. Interestingly, β-elemene treatment (50 μM, 30 h) resulted in the differential expression of miRNAs related to multidrug resistance in the exosomes. Treatment with β-elemene also significantly increased the expression of PTEN and decreased the expression of P-gp, both in the cells and their exosomes (Zhang et al., 2015). Finally, combination of β-elemene (50 μM) and 5-fluorouracil (10 μM) significantly suppressed the invasiveness, migration and increased apoptosis of TNBC cell lines, MDA-MB-231 and BT-549by targeting multiple pathways, including MAPK, NF-κB, COX2, and PI3K/AKT. The combined effect also decreased expression of stemness markers including CD44, OCT4, and Nanog and led to the inhibition of sphere formation (Su et al., 2020). Lastly,

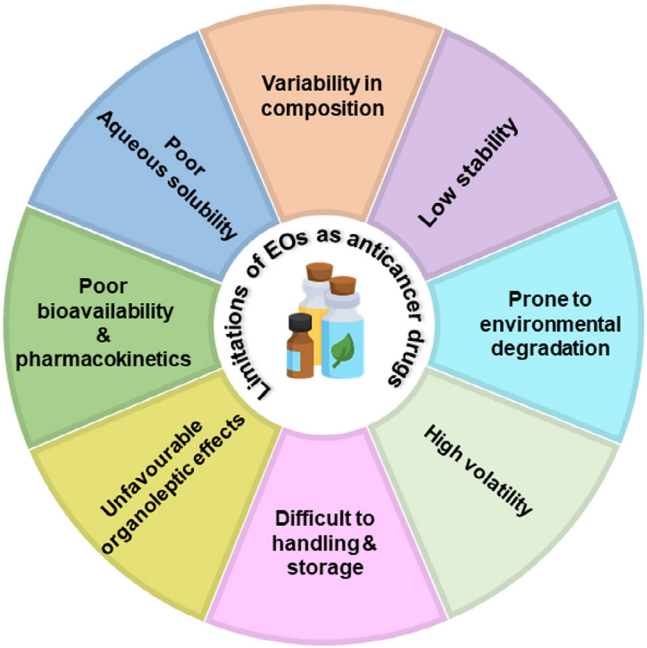

FIGURE 2 Schematic illustration of clinical translation restriction of essential oils.

germacrone also has been shown to enhance the sensitivity of MCF-7 cells to chemotherapy drugs methotrexate and 5-fluorouracil by inhibiting ERα signaling (Lim et al., 2016).

Some studies have showed the combinatorial effects of EO phenylpropanoids with chemotherapy drugs. For instance, combination of doxorubicin with anethole (0.5 + 50 mM and 0.5 + 100 mM) synergistically increased ROS production and ER stress, decreased colony formation, reduced mitochondrial membrane potential, and triggered apoptosis in MDA-MB-231 cells (Arumugam et al., 2021). Interestingly, combination of eugenol (1 mM) and doxorubicin (0.0625–1 μM), potentiated the effects of doxorubicin by increasing the expression of histone acetyl transferase and global histone acetylation in MCF-7 cells. Furthermore, the combination also elicited immunomodulatory effect by increasing the levels of IFN-γ and a lowering TNFα levels. The combination also caused cell cycle shift from G2/M to S and G0/G1 phases and induced apoptosis by increasing the BAX/Bcl-2 ratio (Fouad et al., 2021).

Taken together, these studies point out that EO compounds can be used in combination with chemotherapy drugs to overcome drug resistance and enhance chemosensitivity of BC, and with detailed mechanistic studies and safety profiles, these compounds could be used clinically as adjuvant chemotherapy agents.

7 | CHALLENGES TO THERAPEUTIC UTILIZATION OF FREE EOs AND EO COMPOUNDS

Multitude of anti-tumor effects of EOs and EO compounds against BC have been supported by in in vitro and in in vivo experimental data. Additionally, in-silico analysis conducted by Adam Feyaerts et al. evaluated 175 chemically well-defined commercial EOs for drug discovery and development using standard drug discovery filters. The analysis indicated that the majority of EO and EO components meet modern medicinal chemistry standards and are potentially suitable for use as drug candidates (Feyaerts et al., 2020). Despite increasing preclinical data, EOs and constituents are not yet reached the clinical stage due certain limitations that are depicted in the Figure 2.

Poor aqueous solubility and poor pharmacokinetic profile of EOs components also hinders their rational therapeutic use. EOs and components are known for their aroma. But in some cases, the aroma of EOs can have undesirable organoleptic effects on the patients (Liao et al., 2021). High volatility and hydrophobicity of EOs are other major roadblocks from drug development perspective. The volatile nature also makes these compounds less stable and prone to damage by environmental factors such as light and temperature (Lammari et al., 2020). Reducing the volatility of EOs has been a longstanding challenge in various applications. Researchers have explored several methods to address this issue in the past. One of the simplest methods was to dilute EOs with carrier oils or solvents. This approach reduces volatility but also lowers the concentration of the active compounds in the final product, which is not good for therapeutic purposes. Simple emulsification was another strategy by which EOs were often incorporated into water-in-oil (W/O) emulsions to reduce volatility. However, emulsions can become unstable over time, and the EO could still evaporate from the emulsion. EOs were also adsorbed onto solid carriers like starch or silica to reduce volatility. This method improved stability but may not be suitable for all applications, especially when a liquid form is required (Weisany et al., 2022). By interacting with xenobiotic metabolizing enzymes, EO compounds frequently undergo metabolism to form hydrophilic derivatives (Bunse et al., 2022). For instance, thymol is metabolized to thymohydroquinone and t-anethole is converted to 4-methoxybenzoic acid in human studies (Kohlert et al., 2000). As a result, they are eliminated from the body through renal excretion. This poses a major challenge to the bioavailability of the active EO compounds in the bloodstream and target sites (Horky et al., 2019; Kohlert et al., 2000). There are cases where EO compounds or their metabolic derivatives interact with other drugs in the system, affecting the activity and metabolism of the latter (Zehetner et al., 2019). For example, carveol, which is a product of carvone and limonene metabolism, reportedly decreased the metabolism rate of short-acting anesthetic drug propofol (Zehetner et al., 2019).

Nanoencapsulation of EOs and components is an emerging strategy being explored to mitigate these challenges which include reducing the volatility of EOs, offering improved stability, controlled release, and enhanced performance compared to traditional methods like dilution, emulsification, and solid carriers. These advancements have opened up new possibilities for incorporating EOs into a wide range of nanocarriers for therapeutic utilization (Lammari et al., 2020; Swain et al., 2023; Weisany et al., 2022).

8 | NANOENCAPSULATION OF EOs AND THEIR CONSTITUENTS

Nanomedicine is a highly sought and rapidly growing area wherein various innovative nanotechnology tools are harnessed for medical application (Wei et al., 2021). Accumulating evidence efficiently proves that nanodelivery systems have edge over the conventional free drug delivery as they protect the drugs from environmental damages, improve pharmacokinetics, solubility, biodistribution, and aid in selective tumor targeting either through passive or active targeting (Mohapatra et al., 2020). In addition to this, nanodelivery allows for loading of more than one therapeutic, diagnostic, or theragnostic agent and also helps in controlled and sustained release of the entrapped drug (Wei et al., 2021). These advantages help to reduce the therapeutic dose required to elicit the desirable effect, minimize systemic toxicity and unfavorable side effects (Wei et al., 2021) as illustrated in the Figure 3. Researchers have developed several nanostructured systems for encapsulating Eos. Nanoencapsulation of EOs offers a great deal of advantages to their therapeutic use such as controlled drug release, improved physical stability, reduced volatility, increased bioactivity, and lowered toxicity (Weisany et al., 2022).

According to de Matos et al. (2019), EOs encapsulated nanosystems can be categorized into two main groups: polymer-based nanostructured systems using natural and synthetic polymers, and lipid-based nanostructured systems. Polysaccharides (including chitosan, alginate, pectin, cellulose, arabic gum, carrageenan, and zein) and proteins (albumin, gelatin, soy proteins, and casein) are the two primary categories of natural polymers. Natural polymers have advantages such as biocompatibility, biodegradability and environmental friendly production prospects which makes them suitable for the fabrication of nanocarriers. But compared to synthetic polymers they have certain limitations such as source-based variability and limited mechanical strength that would compromise the shelf life and physical integrity of the nanocarriers (Begines et al., 2020). On the other hand, building blocks for synthetic polymer include polylactic acid, polyglycolic acid, polylactic co-glycolic acid, and polyvinyl alcohol (de Matos et al., 2019). Synthetic polymers can be engineered with precise properties, including mechanical strength, size, and release kinetics. This allows for more precise control over the encapsulation and release of bioactive compounds. However, compared to natural polymers synthetic polymers often lack biodegradability and may raise concerns about toxicity and biocompatibility. Moreover, the production of synthetic polymers typically involves petrochemical-based processes, which can have a higher environmental impact compared to natural polymers (Begines et al., 2020).

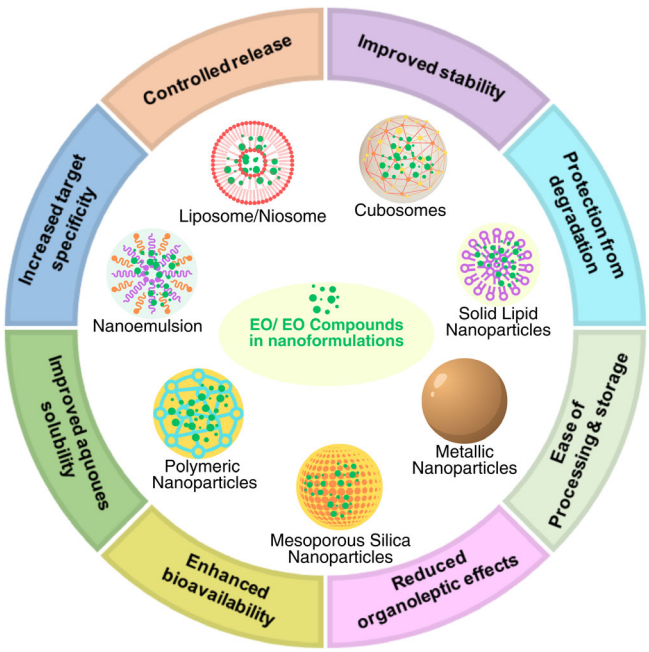

FIGURE 3 Schematic representation of different types of nanocarrier systems and their effect on enhancing the properties of essential oils and constituents.

Lipid-based nanostructured systems consist of self-nanoemulsifying drug delivery systems, solid lipid nanoparticles (NPs), liposomes, and nanoemulsions (Jampilek & Kralova, 2022). In this section, we are attempting to provide a descriptive account of the in in vitro and in in vivo studies regarding the application of nanotechnology for delivery of EO and EO components specifically, against BC. Table 3 summarizes various nanoformulations of EOs and constituents proposed for BC treatment.

8.1 | Polymer-based nanostructures against BC

Researchers have successfully fabricated submicron-sized (1–1000 nm) colloidal nanosystems such as NPs, nanogels and nanofibers from a wide range of biodegradable natural and synthetic polymers (Begines et al., 2020). The ease of encapsulating EOs and specific EO components in various polymeric nanosystems and their advantages in treating preclinical cancer models, particularly BC have gained enormous attention in the last decade (Granata et al., 2018).

8.1.1 | EOs in chitosan-based nanoparticles

Chitosan (CS) is a natural-product-based semi-synthetic mucoadhesive biocompatible polysaccharide which is known to possess several bioactivities such as antimicrobial and anticancer activities. Moreover, CS is also an FDA-approved polymer for tissue engineering and drug delivery (Sharifi-Rad et al., 2021). Interestingly, CS is intrinsically positively charged and shows high affinity for negatively charged cancer cells and effectively it releases the drug into the acidic tumor microenvironment. This property renders chitosan nanosystems suitable for tumor targeted drug delivery (Sharifi-Rad et al., 2021). Researchers have used chitosan NPs to enhance the stability and bioavailability of *Cynometra cauliflora* EO. The encapsulation process improved the EO's stability, protected its bioactive constituents from degradation, and sustained biphasic EO release. Moreover, EO-containing NPs exhibited more cytotoxicity than the free EOs and reduced cytoxicity

TABLE 3 Nanoformulations of essential oils (EOs) and constituents proposed for breast cancer (BC) therapy.

EO/EO compounds	Nanodelivery system	BC model	Advantages/mechanisms of action	Reference
Achillea millefolium	Niosome	MCF-7	• Sustained EO release, and effectively caused higher anticancer cytotoxicity	Emtiazi et al. (2022)
α-Santalol	Chitosan nanoparticles	MDA-MB-231, MDA-MB-231 xenograft in mice	• Suppressed the proliferation and induced apoptosis • Efficient drug release • Reduced tumor weight and volume than the free EO • Minimized systemic toxicity	Zhang et al. (2020)
Borago officinalis	Nanoemulsion	MCF-7, MDA-MB-231	• Synergistically enhanced chemotherapeutic potential of docetaxel and thymoquinone	Alkhatib et al. (2020)
Camellia sinensis	Chitosan nanoparticles	MCF-7 Ehrlich ascites carcinoma (EAC) tumor-bearing mice	• Enhanced cytotoxicity • Excellent biodistribution	Farrag et al. (2021)
Caryocar brasilense	Nanoemulsion	4T1	• Improved oil bioavailability • Compared to free EO, nanoemulsion exhibited enhanced anticancer effects	Ombredane et al. (2022)
Cinnamaldehyde	Chitosan nanoparticles	MCF-7/ADR	• Cinnamaldehyde in the nanoformulation synergized with doxorubicin	Chen et al. (2022)
	Fe_3O_4 magnetic nanoparticles	MCF-7, MDA-MB-231	• Improved bioavailability	Kumar et al. (2020)
	Hyaluronic acid conjugated cationized gold nanocluster	4T1, 4T1 xenograft in mice	• Improved ROS responsiveness • Potentiated photodynamic therapy and anti-tumor immunity • Suppressed tumor growth	Yu et al. (2019)
	HA coated mesoporous silica nanoparticles	MCF-7	• Preserved from oxidation and boosted bioavailability of cinnamaldehyde • Synergistically promoted ROS-mediated intrinsic apoptosis with doxorubicin	Dong et al. (2020)
	Mesoporous silica nanoparticles functionalized with PBA and PAA	MCF-7 cells, 4T1 xenograft in mice	• Enhanced mitochondrial damage, cell cycle arrest and apoptosis • Reduced tumor growth	Ghosh et al. (2022)
Citral	Nanostructured Lipid carrier	MDA-MB-231, 4T1 cells xenograft in mice	• Induced apoptosis, cell cycle arrest, impaired mitochondrial membrane potential, and suppressed the invasiveness • Suppressed tumor growth	Nordin et al. (2019)
	Nanostructured Lipid carrier	4T1 cells xenograft in mice	• Increased EO solubility • Suitable for oral administration • Increased apoptosis • Reduction of NFkB and downstream MMP-9, iNOS and COX2	Nordin et al. (2020)

(Continues)

TABLE 3 (Continued)

EO/EO compounds	Nanodelivery system	BC model	Advantages/mechanisms of action	Reference
Citrus sinensis, *Citrus limon* and Limonene	Chitosan nanoparticles	MDA-MB-468	• Enhanced cytotoxicity	Alipanah et al. (2021)
Coriandrum sativum	Nanoemulsion/ nanoemulgel	MCF-7	• Improved tissue penetration • Enhanced cytotoxicity with respect to free EO	Eid et al. (2021)
Curcuma longa	Chitosan/alginate nanoparticles	MDA-MB-231, MCF-7	• Sustained EO release • Enhanced cytotoxicity compared to the unencapsulated EO	San et al. (2022)
Curcumol	Metal organic framework nanocarrier- porphyrin and Cu^{2+}	4T1 xenograft in mice	• High loading capacity and acidic pH responsive release • Facilitated synergistic action of photodynamic therapy and CUR-mediated chemotherapy • Enhanced antitumor immunity	Zhang et al. (2022)
Cymbopogon citrus EO	PEGylated liposomes	MCF-7, MDA-MB-231, SKBR3	• Higher rate of apoptosis	Zehetner et al. (2019)
Cynometra cauliflora	Chitosan nanoparticles	MDA-MB-231, MCF-7, MCF-10A	• Improved stability and protected the bioactive constituents of EO • Sustained biphasic EO release • More cytotoxicity than the free EO • Reduced the cytoxicity against normal breast epithelial cells	Samling et al. (2022)
Cyperus articulatus	Chitosan nanoparticles	MDA-MB-231	• Increased antioxidant activity • Enhanced anticancer effects than free EO	Kavaz et al. (2019)
D-Limonene	Niosome	MCF-7	• Enhanced cytotoxicity	Hajizadeh et al. (2019)
Elemene	Nanoemulsion	4T1 xenograft in mice	• Targeted the tumor microenvironment • ROS scavenging and antioxidant effect • ↓ HIF 1α and CD31 • ↓ IL-1β, NLRP3 and caspase-1 • Inhibited tumor metastasis	Han et al. (2021)
Eucalyptol	Nanostructured lipid carrier	4T1, MDA-MB-231	• Enhanced cytotoxicity and induced apoptosis with respect to the free eucalyptol	Izham et al. (2021)
Eugenol	BSA-CaFe2O4-Folic acid-magnetic nanoparticles	MCF-7	• Super paramagnetic nanohybrid carrier presented higher release of Eugenol and good stability at physiological pH • Selective interaction with the folate receptors and ↓ the IC_{50} by 20–30 folds compared to free eugenol	Uma Maheswari et al. (2021)

TABLE 3 (Continued)

EO/EO compounds	Nanodelivery system	BC model	Advantages/mechanisms of action	Reference
Ferula assa-foetida	Nanoemulsion	MCF-7, TUBO cells transplanted in mice	• Improved the solubility, stability, and efficacy of the free EO • Suppressed tumor growth	Azani et al. (2022)
Ferula assa-foetida	PLGA Nanoparticles	TUBO xenograft in mice	• Antioxidant effects • Suppressed tumor growth	Mokhtareeizadeh & Homayouni Tabrizi, (2022)
Ginger and *Frankincense*	Nanoemulsion	MCF-7	• Improved the anticancer effects of mitomycin-c	Al-Otaibi et al. (2018)
Heracleum persicum	Nanoemulsion	MDA-MB-231	• Inhibited the proliferation and migration	Bashlouei et al. (2022)
Isofuranodiene	GMO-nanoparticles (cubosomes)	MDA-MB-231	• Potentiated the cytotoxicity	Pisani et al. (2020)
Jasminum grandiflorum	Pectin/chitosan nanoparticles	MCF-7	• Improved EO's thermal stability • Enhanced cytotoxicity compared to free EO	Attallah et al. (2020)
Jasminum humile and *grandiflorum*	Nanoemulsion	MCF-7	• Enhanced cytotoxicity of the free EOs	Mansour et al. (2022)
Linalool	Glutathione conjugated gold-nanoparticles	MCF-7	• Increased anticancer activity compared to free linalool • Functionalization with CALNN peptide improved BC targeting	Jabir et al. (2019)
Mentha piperita	Nanoemulsion	MDA-MB-231, MDA-MB-468, MCF-7	• Enhanced EO bioavailability and cytotoxicity	Kelidari et al. (2022)
Nigella Sativa	Nanoemulsion	MCF-7	• Improved the stability of the free EO • Reduced cell viability and altered nuclear morphology	Periasamy et al. (2016)
Origanum vulgare	Liposomes	MCF-7	• Increased cytotoxic activity	Kryeziu et al. (2022)
Pistacia atlantica	Solid lipid nanoparticles	MDA-MB-231	• Induced apoptosis	Dousti et al. (2022)
Salvia officinalis	Nanoemulsion	MCF-7	• Synergistically improved chemotherapeutic potential of ifosfamide	Alkhatib et al. (2019)
Santalum album	Liposomes	MCF-7	• Improved stability and bioavailability • Enhanced cytotoxicity and genotoxicity	Ortiz et al. (2016)
Satureja hortensis	Iron nanoparticles	MCF-7	• Potential antioxidant activity and cytotoxicity	Ahmadi et al. (2021)
Satureja khuzestanica	Nanoemulsion	MDA-MB-231	• EO in the nanoemulsion synergized with paclitaxel	Attari et al. (2021)
	Solid lipid nanoparticles	MCF-7	• Enhanced cytotoxicity • Induced apoptosis • Induced cell cycle arrest	Tabatabaeain et al. (2022)
Syzygium aromaticum	Chitosan nanoparticles	MDA-MB-468	• Significantly improved the cytotoxic potency compared to the free EO	Valizadeh, Khaleghi, Alipanah, et al. (2021)

(Continues)

TABLE 3 (Continued)

EO/EO compounds	Nanodelivery system	BC model	Advantages/mechanisms of action	Reference
Thymoquinone	PLGA nanoparticles	MDA-MB-231	• Enhanced antioxidant and growth inhibitory effect compared to free thymoquinone	Mokhtareeizadeh & Homayouni Tabrizi, (2022)
	PEG_{400} nanoparticles	MCF-7, EAC tumor- bearing mice	• Reduced cell migration and induced apoptosis • ↓ Systemic toxicity • ↓ LDH, alkaline phosphatase, aspartate transaminase and alanine transaminase	Bhattacharya et al. (2015)
	PEGylated liposomes	MCF-7	• Co-loading of Thymoquinone with docetaxel into PEGylated liposomes enhanced the drug encapsulation efficiency and chemosensitivity	Odeh et al. (2019)
	mPEG-DSPE-TPGS-lipid nanocapsules	MCF-7, MDA-MB-231, EAC tumor- bearing mice	• Enhanced anticancer effect • Increased antimetastatic activity and reduced tumor volume	Zafar et al. (2020)
	GMO-nanoparticles (cubosomes)	MCF-7 MDA-MB-231	• Improved endocytosis and internalization • Exerted higher antitumor activities than the free thymoquinone	Mehanna et al. (2020)
	Niosome	MCF-7	• Displayed enhanced cytotoxicity, inhibited migration, induced apoptosis more potently than the free thymoquinone	Barani et al. (2019)
	PVPylated Fe_3O_4 magnetic nanoparticles	MDA-MB-231	• Due to positive charge interacts better with negatively charged cancer cells • ↑ ROS generation, loss of mitochondrial membrane potential and apoptosis	Kumar et al. (2020)
	Zinc oxide nanoparticles	MDA-MB-231	• Enhanced anticancer activity • Induced cell cycle arrest, DNA damage and apoptosis	Sjs et al. (2021)
	Mesoporous silica nanoparticles	MCF-7	• Increased solubility and photostability • ↑ ROS generation	Goel & Mishra, 2019)
Trans-anethole	PEGylated liposomes	MCF-7, T47D	• Higher stability and sustained release • Enhanced cytotoxicity	Shahbazian et al. (2015)
Zataria multiflora	Nanoemulsion	MDA-MB-231, T47D, MCF-7	• ↑ Stability of the EO • ↑ DNA damage • ↑ ROS and apoptosis • ↓ Mitochondrial membrane potential	Salehi et al. (2022)
	Chitosan nanoparticles	MCF-7, MDA-MB-231, T47D	• Protects volatile EO components • Enhanced DNA damage, mitochondrial membrane permeabilization, ROS production, and apoptosis • Reduced toxicity in normal cells	Salehi et al. (2020)

TABLE 3 (Continued)

EO/EO compounds	Nanodelivery system	BC model	Advantages/mechanisms of action	Reference
	Solid lipid nanoparticles	MDA-MB-468	• Showed higher anticancer activity than the free EO	Valizadeh, Khaleghi, Roozitalab, et al. (2021)
Zingiber ottensii	Nanoemulsion	MCF-7	• Enhanced anticancer effects of the free EO • Specific cytotoxicity	Panyajai et al. (2022)

against normal breast epithelial cells (Samling et al., 2022). Furthermore, a recent study showed that compared to unencapsulated EO, *C. longa* EO encapsulated in a blend of chitosan and alginate nanocluster demonstrated enhanced cytotoxicity against two BC cells, MDA-MB-231 and MCF-7 (San et al., 2022). Similarly loading of *Jasminum grandiflorum* EO in chitosan and pectin blend NPs improved EO's thermal stability, consistency of its total phenolic content and as a result showed enhanced cytotoxicity compared to free EO (Attallah et al., 2020). It has been shown that green tea EO loaded CS NPs complexed with technetium-99m (99mTc) radionuclide can be simultaneously used to precisely radiolabel the solid tumor (in a mouse model of EAC) and selectively induce cytotoxicity against the cancer cells (Farrag et al., 2021). Recently, Zhang et al. showed that α-santalol-encapsulated chitosan NPs exhibited promising potential for targeted cancer therapy. Nanoformulation selectively inhibited tumor cell proliferation by suppressing the expression of Polo like kinase-1 and induced apoptosis in MDA-MB-231 cells. In in vivo treatments reduced tumor weight and volume more effectively than the unencapsulated α-santalol in MDA-MB-231 xenograft bearing mice. Additionally, NPs efficiently released the drug selectively in the acidic pH which minimized the toxicity to healthy cells (Zhang et al., 2020).

8.1.2 | EOs in synthetic polymer-based nanoparticles

Technology has enabled the use of high purity and safe synthetic polymers such as poly lactic-co-glycolic acid (PLGA) for the preparation of nanosystems for drug delivery applications (Begines et al., 2020). PLGA is an amorphous copolymer made up of lactic acid and glycolic acid and in the physiological environment or in tumor sites, PLGA can slowly decompose into the original monomers (Mirakabad et al., 2014). This biodegradable nature of PLGA makes an excellent biosafety polymer for drug delivery applications. Efficient methods such as emulsification-solvent evaporation and nanoprecipitation have been developed to incorporate hydrophobic drugs including EOs into PLGA NPs (Mirakabad et al., 2014; Singh & Sahoo, 2022). According to Ercin et al. (2022), *Laurus nobilis* L. EO encapsulated in PLGA NPs demonstrated good stability and controlled release, making the nanoformulation a possible therapy option for cancer. Moreover, *Ferula assa-foetida* EO (FAEO)-loaded PLGA NPs suppressed tumor growth in a mice xenograft model of BC (Mokhtareeizadeh & Homayouni Tabrizi, 2022). A recently published study shows that *Boswellia sacra* EO (BEO) loaded into a blended PLGA and poly (ε-caprolactone, PCL) PLGA-PCL NPs resulted in a lower IC_{50} value and increased apoptotic effect compared to free BO in MCF-7 cells. Interestingly, encapsulation of BEO in PLGA-PCL NPs doubled the percentage of apoptotic and necrotic cells exerted by free BEO, demonstrating the potential use of BEO/PLGA-PCL NPs in BC treatment (Azzazy et al., 2022). Noor et al. demonstrated the effective induction of cytotoxicity in chemoresistant BC cells, including paclitaxel-resistant MDA-MB-231 cells and tamoxifen-resistant MCF-7 and UACC732 (inflammatory breast carcinoma cells) using thymoquinone-loaded PLGA NPs. These findings suggest the potential of utilizing nanoencapsulation of EO components to overcome chemoresistance (Noor et al., 2021). Polyethylene glycol (PEG) is another synthetic biodegradable polymers highly utilized in nanomedicine. It has been shown that PEG_{400}-TQ NPs were more effective in reducing the MCF-7 cells migration and inducing cell death than the free TQ. Moreover, PEG_{400}-TQ NPs also protected the EAC tumor bearing mice from tumor-induced systemic toxicity by downregulating the lactate dehydrogenase, alkaline phosphatase, aspartate transaminase and alanine transaminase (Bhattacharya et al., 2015). Thomas et al. have identified citral as a potent inhibitor of ALDH1A3 activity among a panel of compounds. They also demonstrated that encapsulating citral in polyethylene glycol-block-polycaprolactone (PEG-b-PCL) polymeric NPs (citral-NPs) induced apoptosis, inhibited colony formation, and reduced tumor growth of MDA-MB-231 cells (Thomas et al., 2016).

8.2 | Lipid-based nanostructures against BC

Lipid-based drug carriers, generally contain a non-polar core structure that makes them a convenient choice for researchers to utilize them to encapsulate lipophilic EOs and EO components (Cimino et al., 2021; Jampilek & Kralova, 2022). EOs and their components have been successfully loaded into different lipid-based nanocarriers such nanoemulsions, liposomes, niosomes, solid lipid NPs and nanostructured lipid carriers (NLC) for anticancer applications (Jampilek & Kralova, 2022).

8.2.1 | EOs in nanoemulsion

Nanoemulsions are colloidal dispersions that are composed of two immiscible liquids, the organic phase and the aqueous phase that are dispersed and stabilized by appropriate surfactants (Barradas & de Holanda e Silva, 2021). Size of nanoemulsion droplets vary between 20 and 500 nm, a range that escapes rapid renal clearance which in turn improves tissue accumulation. Large surface area of the nanoemulsion droplets helps to encapsulate lipophilic EOs to protect their physicochemical attributes and ensure controlled release. There has been a considerable increase in the number of reports regarding EO loaded in nanoemulsions for drug delivery applications (Barradas & de Holanda e Silva, 2021). It has been reported that nanoemulsions containing the EOs of *Jasminum humile* and *grandiflorum* enhanced the cytotoxicity of the EOs by several folds and exhibited lower IC_{50} values compared to the standard drug doxorubicin (Mansour et al., 2022). Interestingly, nanoemulsion of *Zingiber ottensii* EO has been found to exhibit stronger anticancer properties against MCF-7 cells compared to free EO (Panyajai et al., 2022). Similarly, nanoemulsion containing EO from the Brazilian plant *Caryocar brasiliense* demonstrated enhanced cytotoxicity in 4T1 cells than EO alone (Ombredane et al., 2022). Han et al. showed that β-elemene administered in nanoemulsion inhibited tumor metastasis to lung and liver and prolonged the survival of mice carrying 4T1 mouse TNBC tumor xenograft (Han et al., 2021). Moreover, by effectively scavenging the ROS both in in vitro and in in vivo, elemene nanoemulsion was found to reduce the stabilization of hypoxia-inducible factor-1α (HIF-1α) and decrease angiogenesis within the tumor microenvironment. The nanoemulsion was also found to decrease the level of NLRP3 inflammasomes and the production of IL-1β, highlighting its potential as a therapeutic option for BC (Han et al., 2021).

8.2.2 | EOs in liposomes

Liposomes are spherical lipid vesicles composed of amphiphilic phospholipid bilayer (unilamellar or multilamellar) and an aqueous core (Olusanya et al., 2018). In 1995, PEGylated liposomal doxorubicin became the first FDA approved nanomedicine (Fulton & Najahi-Missaoui, 2023). Various techniques like thin film hydration, microfluidic channel method and the supercritical fluidic method have been used to prepare liposomes. Phospholipids like phosphatidylserines, phosphatidylethanolamines, phosphatidylcholines, and phosphatidylglycerols are typically derived from sources like soybean and egg yolk, making them favored choices for liposome formulations. However, synthetic options such as 1,2-distearoyl-sn-glycero-3-phosphocholine among others, are also employed (Zehetner et al., 2019). These phospholipids with amphiphilic properties tend to self-assemble in aquoues phase, creating bilayer structures that encapsulate the bioactive, such as EOs (Zehetner et al., 2019).

Studies show that liposomes hold promise as effective carriers of EOs and EO compounds to enhance anticancer therapeutic efficiency (Sherry et al., 2013). For instance, a recent study found that liposomes containing *C. citratus* EO, prepared using soybean phosphatidylcholine and modified with PEG, exhibited increased apoptosis in three BC cell lines (MCF-7, MDA-MB-231, and SKBR3) compared to the free EO (Rahimi et al., 2023). Likewise, *O. vulgare* EO-loaded in phospholipon 90H liposomes demonstrated significantly higher cytotoxic activity against MCF-7 cells than the free EO (Kryeziu et al., 2022). Interestingly, liposomal formulation of sandal wood EO has been reported to selectively induce cytotoxicity and genotoxicity in MCF-7 cells while sparing the normal breast epithelial MCF-10A cells unharmed (Ortiz et al., 2016). Furthermore, PEGylated liposomal formulation of *trans*-anethole increased the cytotoxicity against MCF-7 and T47D cells by approximately nine- and eight-fold than the free anethole (Shahbazian et al., 2015).

8.2.3 | EOs in niosomes

Niosomes are spherical, closed-bilayer structures formed by self-clustering of cholesterol and non-ionic surfactants in aqueous fluids. Researchers developed niosomes as an alternative to liposomes due to their limitations, such as difficulty in scaling up manufacturing and low stability. Niosomes exhibit physicochemical features akin to liposomes, yet they surpass them in terms of stability, simplicity of fabrication, and lower production expenses (Karim et al., 2010). Various EOs have been successfully incorporated into niosomes for different applications such as cosmetics, food packaging and pharmaceuticals (Purohit et al., 2022). In a recently published work, liposomal and niosomal nanoformulations of *Achillea millefolium* EO were synthesized and evaluated for their cytotoxicity against MCF-7 cells. Both nanoformulations demonstrated improved selectivity compared to free EO but the niosomes presented a sustained EO release resulting in greater anticancer cytotoxicity (Emtiazi et al., 2022). Similarly, niosomes loaded with D-limonene also exerted enhanced cytotoxicity against cancer cell lines including MCF-7 (Hajizadeh et al., 2019). Additionally, niosomes loaded with TQ using an herbal lipid called ergosterol inhibited migration, and induced G2/M cell cycle arrest and apoptosis in MCF-7 cells more potently compared to free EO (Hajizadeh et al., 2019).

8.2.4 | EOs in solid lipid nanoparticles

Solid Lipid Nanoparticles (SLNs) are particulate systems prepared by utilizing lipids that remain solid at room temperature, which include palmitic acid, oleic acid and stearic acid. Surfactants (such as polysorbate 80, poloxamer 188) and stabilizers like PVA are often utilized to optimize SLN synthesis (Scioli Montoto et al., 2020). Compared to other nanocarriers including nanoemulsions, liposomes and polymeric NPs, SLNs are more stable and effective in controlled release of the encapsulated pharmaceuticals. SLNs have been extensively utilized as carriers of hydrophobic drugs including EOs to enhance the bioactivity and safety for therapeutic applications (Scioli Montoto et al., 2020). For instance, encapsulation of ZEO in SLNs enhanced the anticancer efficacy of the EO against MDA-MB-468 cells (Valizadeh, Khaleghi, Roozitalab, et al., 2021). Another study

demonstrated that *Satureja khuzistanica* EO loaded into SLN-modified with chitosan-folate, induced a selective cytotoxicity against MCF-7 cells compared to normal cells (Tabatabaeain et al., 2022).

8.2.5 | EOs in nanostructured lipid carrier

One of the main limitations of SLNs was the crystallization of the solid lipids which reduced the drug loading capacity and the controlled release. To overcome this, the next generation of lipid-based nanocarriers termed NLC was introduced (Elmowafy & Al-Sanea, 2021). NLCs are fabricated by using a mixture of solid and liquid lipids that aid the formation of formless but more stable non-ideal crystalline matrix (Elmowafy & Al-Sanea, 2021). Accumulating evidence suggests that the lipophilicity of EOs is suitable for the encapsulation in NLCs which can enhance their therapeutic efficiency by improving stability, bioavailability, and controlled release (Katopodi & Detsi, 2021). Izham et al. (2021) loaded eucalyptol into a NLC (NLC-Eu) and observed that NLC-Eu showed enhanced cytotoxicity by multiple folds on 4T1 and MDA-MB-231 cells compared to free eucalyptol in the same cell lines. According to Nordin et al., encapsulation in NLC facilitated easy oral administration of citral and the antitumor effects of citral against BC was also shown to be enhanced by encapsulating in NLC (NLC-citral). Specifically, NLC-citral enhanced apoptosis, induced G2/M cell cycle arrest, impaired mitochondrial membrane potential, and suppressed the invasiveness in MDA-MB-231 cells. Additionally, NLC-citral also suppressed tumor growth in mice model implanted with 4T1 cells xenograft (Nordin et al., 2019). In a subsequent study, the same group further revealed the mechanisms of NLC-citral in a 4T1 mice BC model. The results showed that the NLC-citral group had a greater reduction in the expression of metastasis related genes such as NF-κB, MMP-9, iNOS, and COX2 compared to the group that received free citral. Additionally, proteome profiler analysis showed that NLC-citral was more effective than free citral in reducing pro-angiogenesis proteins, serum levels of cytokines (IL-10 and IL-1β), and levels of nitric oxide and MDA (Nordin et al., 2020).

8.3 | Inorganic nanocarriers against BC

Inorganic materials, such as gold, iron, and silica, are commonly utilized in the synthesis of nanostructured materials for drug delivery and imaging purposes. These NPs can be precisely engineered to have various sizes, structures, and geometries (Mitchell et al., 2021). Researchers have successfully fabricated a variety of inorganic nanostructures as drug carriers of EOs and EO components for cosmetic and therapeutic applications. Here, we discuss advantageous utilization of inorganic nanostructures to deliver EO/EO components to BC models.

8.3.1 | EOs in metallic nanoparticles

EOs are being used as natural alternatives to synthetic reducing agents in the bioreduction of metal ions for the fabrication of metallic NPs. The use of EOs can have additional therapeutic values (Pathania et al., 2021). For example, magnetic iron NPs prepared using *Satureja hortensis* EO and a homogenous suspension of ferrous sulfate and ferric chloride demonstrated significant antioxidant activity and proved to be cytotoxic to multiple cancer cells, including MCF-7 (Ahmadi et al., 2021). Uma Maheswari et al. incorporated eugenol in a folic acid functionalized BSA-$CaFe_2O_4$ nanohybrid system. This super paramagnetic nanocarrier demonstrated higher release of eugenol at acidic pH and good stability at physiological pH indicating the potential for specific drug delivery into tumor sites. Moreover, due to the selective interaction with the folate receptors on MCF-7 cells, this nanohybrid system reduced the IC_{50} by 20–30 folds compared to free eugenol (Uma Maheswari et al., 2021). TQ incorporated zinc oxide NPs exhibited enhanced anticancer activity against MDA-MB-231 cells by inducing G2/M phase cell cycle arrest, DNA damage and apoptosis (Sjs et al., 2021). Zhang et al. demonstrated that loading of curcumol into a pH responsive, metal–organic frameworks using porphyrin and Cu^{2+} (CUR-CuTPyP/F68) facilitated efficient accumulation and internalization in tumor cells. Additionally, tumor tissues of CUR@CuTPyP/F68 treated mice showed increased infiltration of $CD4^+$ and $CD8^+$ T cells, as well as elevated levels of IFN-γ, IL-12, and TNF-α in their blood. Altogether, photodynamic therapy potential of the metal–organic frameworks and the immunomodulatory effect of curcumol synergistically suppressed the growth of breast tumor in 4T1 cells and in 4T1 xenograft in mice (Zhang et al., 2022).

8.3.2 | EOs in mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) are one of the most widely studied inorganic nanocarriers due to their advantages such as good biocompatibility, high stability, and tuneable pore size. A recent study has shown that TQ-loaded monodispersed MSN could overcome the limitations of free TQ, including hydrophobicity, low water stability and improved its anticancer activity in MCF-7 cells by enhancing ROS (Goel & Mishra, 2019). Ghosh et al. developed a new nanoconjugate by functionalizing MSNs with 3-carboxy-phenyl boronic acid (PBA) and polyacrylic acid (PAA) for specifically targeting breast tumors. They incorporated cuminaldehyde to the nanoconjugate and demonstrated that it enhanced mitochondrial damage, cell cycle arrest and apoptosis in MCF-7 cells. Furthermore, intravenous injection of the nanoconjugate facilitated cuminaldehyde accumulation without any systemic toxicity to 4T1 tumor bearing mice and efficiently reduced tumor growth in in vivo (Ghosh et al., 2022).

9 | CO-LOADING OF EOs AND CONSTITUENTS WITH CHEMOTHERAPEUTIC DRUGS IN NANOCARRIERS

Using nanotechnology to co-administer standard chemotherapy drugs with anticancer phytochemicals, such as EOs or their constituents, has emerged as a promising approach in BC therapy research. This

strategy enables the combination of multiple therapeutic agents in a single delivery system, which can potentially increase the efficacy of treatment (Chen et al., 2023). For instance, nanoemulsion co-loaded with the EO of the *Satureja khuzestanica* and chemotherapeutic drug paclitaxel and showed that the EO in the nanoemulsion synergized the effect of paclitaxel, re-sensitized the paclitaxel-resistant MDA-MB-231 cells and induced apoptosis (Attari et al., 2021). Furthermore, a recent study reported that pH-responsive niosomes co-loaded with *Cananga odorata* EO (Ylang Ylang Oil) and another platinum-based chemotherapy drug, oxaliplatin, exhibited the lowest IC_{50} values and induced higher rates of apoptosis in MDA-MB-231 cells compared to their unloaded counterparts (Sedky et al., 2023).Co-loading of Ifosfamide, another broad-spectrum chemotherapeutic drug into EO-based nanoemulsions from clove, lemon and salvia EOs significantly lowered the IC_{50} compared to free Ifosfamide and demonstrated enhanced apoptosis in MCF-7 cells (Alkhatib et al., 2019; AlMotwaa, 2021).

Chen et al. developed dual pH-responsive, chitosan NPs in which they co-loaded cinnamaldehyde along with doxorubicin. Interestingly, cinnamaldehyde in the NPs overcame multidrug resistance in human BC cells (MCF-7/ADR) and reduced tumor growth in MCF-7/ADR tumors in mice (Chen et al., 2022). In another work, a combination of cinnamaldehyde and doxorubicin was co-loaded into MSNs that were modified with hyaluronic acid and graphene oxide. This approach not only preserved the efficacy of cinnamaldehyde by protecting it from oxidation but also increased its bioavailability and enhanced its ability to synergistically induce ROS-mediated intrinsic apoptosis in MCF-7 cells. Furthermore, this nanoformulation demonstrated a promising ability to mitigate the cardiotoxicity typically associated with doxorubicin (Dong et al., 2020).

A recent study demonstrated the potential of co-loading docetaxel and TQ in mPEG-DSPE-Vitamin E TPGS-lipid nanocapsules, resulting in increased cytotoxicity in in vitro and reduced tumor volume and metastatic activity in in vivo. The safe profile of the nanocapsules was also demonstrated, as there were no blood biochemical or histological changes during treatment in in vivo, suggesting potential for hepato- and nephro-protection. These findings suggest that co-loading EO constituents in lipid nanocapsules could be a safe and effective adjuvant therapy to mitigate chemotherapy drug toxicity (Zafar et al., 2020). Lastly, a combination of docetaxel and TQ co-loaded into a borage EO-based nanoemulsion synergistically induced apoptotic effects in MCF-7 and MDA-MB-231 cells (Alkhatib et al., 2020).

Altogether, the approach of co-loading EOs and EO compounds with standard chemotherapy drugs present a potential strategy to reduce the effective doses and thereby mitigate the side effects and enhance the therapeutic effects.

10 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

BC is a complex disease in terms of molecular heterogeneity and symptom manifestations. Existing treatment modalities for BC often fail clinically due to chemoresistance, metastasis, and relapse. Novel drug candidates sourced from natural products have emerged as an alternative to mitigate these limitations to a large extent as they demonstrate selective, safe, and effective anticancer effects with least complications to normal cells. In the last couple of decades, accumulating reports have highlighted the broad-spectrum therapeutic values of EO and constituents which includes excellent anticancer activities against various cancer models. A particularly higher proportion of research has been focused on the anticancer activities of EO and constituents against preclinical BC models. Interestingly, researchers have also demonstrated that EOs or EO constituents co-loaded with existing chemotherapy drugs enhance the anticancer effects and often reduce the toxicities of chemotherapy drugs. In this review, we have provided a comprehensive account of in vitro and in in vivo results highlighting the multimodal mechanisms mediated by EOs and constituents in BC models. EOs and constituents are not advanced to the clinical phase due to limitations such as high volatility and poor aqueous solubility. To counteract these limitations and rationalize their therapeutic utilization, as novel drug candidates, researchers have resorted to nanotechnology which has been extensively used in oncology to enhance the inherent characteristics of conventional therapeutics. Literature we discussed in this review suggests that nanomedicine approach could be the solution to facilitate the use of EOs or their constituents clinically against BC. Increasing number of studies report the therapeutic advantages of nanoencapsulated EOs and constituents against cancer, although several studies are limited by inadequate analytical methods to quantify the EOs or constituents incorporated in the nanostructures. This limitation can be curated by employing innovative analytical methods such as coupling solid phase microextraction technique along with GC or high-performance liquid chromatography, to have more reliable quantification of EO compounds (El Asbahani et al., 2015).

Although research in the field of EOs and EO compounds for BC therapy has shown promise, there are several potential future directions and areas of research that could be explored. First of all, establishing standardized protocols for EO extraction, formulation, and testing is essential for ensuring consistency and reproducibility across different studies. Comprehensive pharmacokinetic studies on animal models are needed to understand how EO compounds are metabolized and eliminated from the body. Additionally, thorough toxicity studies are crucial to assess potential adverse effects and establish safe dosing regimens (Izzo et al., 2016). When studying the bioactivity of EOs, potential synergistic or antagonistic effects of EO compounds arising from the interactions between the compounds is highly overlooked. However, there are a few studies that looked into this interesting aspect. A very recent paper authored by Glumac et al. assessed the synergistic and antagonistic effects of *Helichrysum italicum* EOs individual components by testing pure compounds and their synthetic mixture for cytotoxic activity on MDA-MB-231 BC cells. The results revealed that EO's biological activity is much greater than the sum of the effects of its components. Contrarily, the synthetic mixture containing five major compounds in the EO

(linalool, α-terpineol, terpinene-4-ol, nerol, and nerolidol) demonstrated an IC_{50} value higher than that of the individual compounds, implying antagonistic interaction between the compounds. This also suggest that in the natural EO there would be synergistic interactions between the other individual components (Glumac et al., 2023). The interplay of synergistic and antagonistic interactions among bioactive compounds of EOs holds significant importance in cancer therapy as it has the potential to either enhance therapeutic effect or make the treatment ineffective. Studies directly comparing the effects of multiple EOs or EO compounds that mediate multifarious anticancer mechanisms would be needed, so that clinical translation of lead candidates with most promising potential can be accomplished.

Additionally, personalized treatment strategies could be developed by identifying biomarkers that predict individual responses to EO therapies. We discussed synergistic effects when EOs or EO compounds when combined with standard chemotherapy drugs. Similarly, exploring the combinatorial effects with other treatment modalities like immunotherapy, or radiation therapy can be considered. With regard to the use of nanotechnology platforms for EO delivery, substantial progress can be achieved through fine-tuning formulation variables to enhance the encapsulation efficiency and long-term stability of bioactive EO compounds. Additionally, the possibility of developing EO-loaded nanocarriers with ligands tailored to BC biomarkers presents an avenue for exploring enhanced targeted delivery.

AUTHOR CONTRIBUTIONS

Muhammed Ashiq Thalappil: Conceptualization; resources; writing – original draft. **Priya Singh:** Conceptualization; visualization; writing – original draft. **Alessandra Carcereri de Prati:** Supervision; validation; writing – review and editing. **Sanjeeb Kumar Sahoo:** Conceptualization; supervision; writing – review and editing. **Sofia Mariotto:** Funding acquisition; supervision; writing – review and editing. **Elena Butturini:** Conceptualization; validation; writing – review and editing.

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All authors gave their consent for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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