

The Therapeutic Potential of Essential Oils in Cancer Management: An In Vitro and In Vivo Review

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Abstract: Cancer remains one of the major causes of global morbidity and mortality. Despite significant advances, conventional cancer treatments, such as chemotherapy and radiotherapy, frequently encounter challenges, including metastasis, relapse, multi-drug resistance, and severe side effects. Consequently, the search for novel, less toxic, and more efficacious therapeutic strategies, often derived from natural products, is crucial. Essential oils (EOs), which are volatile secondary metabolites of plants, possess a wide array of pharmacological properties, including significant anti-cancer effects. This systematic review aimed to consolidate current evidence on the antineoplastic efficacy of various EOs, such as those derived from *Boswellia* sp. (Frankincense), *Eucalyptus globulus*, *Zingiber officinale*, and *Lantana camara*, across different cancer models. Chemical analysis typically identifies α -pinene as a major constituent (e.g., 35.81% in *B. carterii* EO and up to 67.9% in *B. sacra* EO). Results consistently demonstrate that EOs are capable of reducing cell viability, inducing apoptosis (via caspase activation and PARP cleavage), and modulating crucial cell proliferation and survival signaling pathways (such as Wnt/ β -catenin, PI3K/AKT, and MAPK/ERK1/2). Notably, several EOs exhibit selective cytotoxicity toward tumor cells (e.g., A549, Colo-320, MCF-7, HeLa) while preserving normal cells (e.g., human fibroblasts, WI-38). The incorporation of EOs into nanocarriers (e.g., FEO-CSNPs, nanoemulsions) significantly enhances therapeutic efficacy, leading to the downregulation of oncogenes (PIK3CA, HER2, WNT1) and the upregulation of tumor suppressor genes (TP53, CDH1, PTEN) in vivo. In conclusion, EOs and their optimized nano-formulations represent promising candidates for developing innovative adjuvant or primary treatment strategies against cancer.

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1. Introduction

Colorectal cancer (CRC) is ranked among the most common lethal cancers globally. High mortality rates are largely attributable to metastasis, relapse, and treatment resistance [12]. Colorectal cancer stem cells (CSCs), characterized by surface markers like CD133, play important biological functions in tumor progression and resistance [3]. While traditional treatments, such as radiotherapy and chemotherapy, can effectively eliminate differentiated cancer cells, CD133⁺ CSCs often escape treatment, survive quiescence, and continue to proliferate [1]. Therefore, effective and accurate targeted therapies for CSCs are critically needed.

It has been established that natural products are promising leads for developing sensitive, safe, and multi-targeted novel chemotherapeutic drugs. Historically, approximately 25% of chemotherapy agents are derived directly from plants, and another 25% are chemically modified versions of phytoproducts. Essential oils (EOs), volatile, complex compounds extracted from aromatic plants, have been traditionally utilized in medicine and aromatherapy. EOs are composed primarily of terpenoids (monoterpenes, sesquiterpenes) and have shown efficacy in cancer treatment by interacting directly with tumor cells and modulating the tumor microenvironment [14]. Research into the anti-cancer therapeutic potential of EOs is rapidly expanding.

This review aims to systematically evaluate recent findings regarding the cytotoxic, anti-proliferative, and pro-apoptotic activities of various EOs and their formulated drug delivery systems against human cancer cell lines, focusing on breast, colorectal, cervical, and lung cancers.

2. Materials and Methods

The information presented herein is a synthesis of findings from diverse preclinical studies that utilized in vitro (cell culture) and in vivo (mouse xenograft) models.

2.1. Chemical Analysis

The chemical composition of EOs, such as *Boswellia* sp. [1,2,8] and *Lantana camara* [4] EOs, was routinely determined using Gas Chromatography–Mass Spectrometry (GC-MS). The identification of volatile compounds was achieved by comparing their mass spectra and linear retention indices (LRI) with commercially available databases (e.g., Wiley GC/MS Library, NIST Library) and in-house libraries. The relative percentage amounts of the separated components were typically calculated from FID chromatograms.

2.2. Evaluation of Biological Activity and Cytotoxicity

Cell viability and growth inhibition were assessed primarily using the MTT assay or the XTT assay. Cell lines investigated include:

- Breast Cancer: MCF-7, MDA-MB-231, T47D, and the murine 4T1.
- Colorectal Cancer (CRC): Colo-320 (including CD133+ CSCs), SW48, SW742, DLD-1, HCT116, LoVo, and SW480.
- Cervical Cancer: HeLa.
- Lung Cancer: A549.
- Normal Cells (Safety Control): Human fibroblasts, WI-38 lung cells, C-166 mouse endothelial cells, and MCF10-2A normal breast epithelial cells.

2.3. Investigation of Molecular Mechanisms

To confirm cell death mechanisms, apoptosis was detected using flow cytometry (Annexin V/PI staining) and morphological staining (Acridine Orange/Ethidium Bromide).

Molecular pathway analysis involved several techniques:

1. Western Blotting: Used to monitor the expression or activation (phosphorylation) of proteins related to apoptosis (Caspase-3, Caspase-9, PARP) and survival (pAkt, pERK1/2, cdk4, cyclin D1).
2. Immunocytochemistry (ICC): Employed for the semi-quantitative grading (HSCORE) of proteins such as FasL, Caspase-3, β -catenin, and Ki-67.

3. Quantitative Real-Time PCR (qPCR): Used to quantify relative fold changes in gene expression, including tumor suppressors (TP53, CDH1, PTEN, DR5, FADD, Bax) and oncogenes (PIK3CA, HER2, WNT1, Bcl-2, NF-kappa B, STAT-3).

2.4. In Vivo Studies and Nano-formulations

Studies utilized in vivo murine models (Balb/c mice inoculated with 4T1 mammary carcinoma cells) to evaluate anti-tumor efficacy. Delivery optimization strategies involved formulating EOs into chitosan nanoparticles (FEO-CSNPs) and nanoemulsions (F1, F2). Parameters monitored in vivo included tumor volume, body weight changes (for systemic toxicity assessment), and histopathological analysis.

3. Statistical Analysis

The statistical methods employed across the reviewed studies were standardized to ensure robustness. Data were generally presented as the mean $\pm$ standard deviation (SD) or mean $\pm$ standard error of mean (SEM). Comparative analyses between groups were often conducted using one-way Analysis of Variance (ANOVA), followed by appropriate post hoc tests (such as Tukey's or Dunnett's test). For comparing gene expression changes, the student's t-test was utilized. A statistical significance threshold was consistently set at p-value < 0.05 .

4. Results and Discussion

4.1. Chemical Constituents and Selectivity Profile

The anti-cancer activity of EOs is closely linked to their complex chemical profiles, predominantly consisting of monoterpenes and sesquiterpenes. The major compound in *Boswellia sacra* (BS) essential oil, obtained via hydrodistillation, was α -pinene (up to 67.9%). Similarly, the analysis of *Boswellia carterii* (Frankincense) essential oil identified 48 compounds, with α -pinene (35.81%) as the main constituent.

Tumor Cell Specificity: EOs demonstrated crucial selective cytotoxicity, often sparing non-cancerous cells.

- *B. sacra* EO: Induced apoptosis in T47D, MCF7, and MDA-MB-231 breast cancer cells, while immortalized normal breast epithelial MCF10-2A cells were resistant. The EO distilled at 100°C showed superior cytotoxic potency compared to that distilled at 78°C.
- *Zingiber officinale* EO (ZO EO): Exhibited cytotoxicity against HeLa cells (IC50 \1:3000 dilution) but was significantly less toxic to human primary fibroblast cells (IC50/1:390 dilution).
- *Eucalyptus globulus* EO (EGEO): Was effective against SW48 colon cancer cells (IC50= 0.2%) at concentrations (e.g., 0.05%) that did not cause toxicity in normal fibroblast cells. However, EGEO exhibited high toxicity on human fat cells at all concentrations tested, and doses greater than 0.5% were highly cytotoxic to normal cells.
- *Rosa Damascena* EO: Showed a complex, biphasic effect on SW742 colon cancer cells and normal fibroblasts. The evaporated phase inhibited cell proliferation in both lines, but the water-soluble phase demonstrated potent cell growth-inducing properties, particularly on fibroblasts at low volumes (e.g., 2 or 3 \muL).

4.2. Mechanisms of Anti-Cancer Activity

4.2.1. Colorectal and Cervical Cancer

EOs actively suppressed cancer proliferation by modulating key oncogenic pathways and inducing programmed cell death:

- *B. sacra* EO and Wnt/ β -catenin: Treatment with BS essential oil significantly decreased β -catenin immunoreactivity in both CD133+ and CD133- Colo-320 cells. Since β -catenin regulates oncogenes and is key to proliferation in colorectal carcinogenesis, its suppression suggests a therapeutic strategy against colorectal CSCs.

- *T. fallax* EO and Antioxidant Effects: Thyme essential oil (IC₅₀ of 0.347 mg/mL for DLD-1 cells) demonstrated a strong antioxidant effect (IC₅₀ of 0.382 mg/mL in DPPH assay). The anti-proliferative activity may be linked to this antioxidant capacity.

Z. ottensii EO and Apoptosis: ZO EO induced HeLa cell death through the caspase-dependent pathway, as verified by the cleavage of pro-caspase-9, pro-caspase-3, and full-length PARP, while increasing active caspase levels. The total percentage of apoptotic HeLa cells increased in a dilution-dependent manner. ZO EO also suppressed cell survival signaling by inhibiting the phosphorylation of ERK1/2 and Akt.

Lantana camara EO: Showed cytotoxicity against the HeLa cervical cancer cell line, with an IC₅₀ value of 44.86 μ g/mL $\pm$ 0.07. The main constituents were Caryophyllene (27.65%) and Germacrene D (23.01%).

The enhancement of EO efficacy through nanocarriers was particularly pronounced in breast and lung cancer models:

4. Conclusion

Aromatherapy presents a valuable adjunctive therapy in pediatric healthcare, offering non-invasive solutions for anxiety management, pain relief, and improved well-being. The documented benefits of essential oils, particularly in managing procedural distress and enhancing patient comfort, underscore their potential as a holistic alternative or complement to traditional treatments. However, the broader implementation of aromatherapy faces challenges, including the need for standardized protocols, enhanced caregiver education, and institutional support. Future research should prioritize these areas while exploring the therapeutic synergy of essential oils to validate their efficacy further. By addressing these challenges, aromatherapy could become an integral component of patient-centered care, fostering improved outcomes and developmental trajectories for children.

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