Review Paper

Investigating Anti-cancer, Anti-oxidant and Immunomodulatory Effects of Essential Oils: Focusing on *Oliveria Decumbens* and *Zataria Multiflora* Essential Oils

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ABSTRACT

Background: Cancer therapy necessitates innovative approaches with enhanced efficacy and reduced side effects. Essential oils have gained attention because of their diverse biological properties and relatively low toxicity. *Zataria multiflora* essential oil (ZEO) and *Oliveria decumbens* essential oil (OEO) exhibit promising anti-cancer effects, particularly in modifying oxidative stress and inflammation. Both oils boast complex compositions rich in bioactive compounds, including oxygenated monoterpenes and phenolic compounds like carvacrol and thymol. Hence, this study investigates essential oils' anti-cancer, anti-oxidant and immunomodulatory effects, focusing on ZEO and OEO.

Materials and Methods: This review briefly considers the intricate mechanisms of several essential oils, encompassing anti-oxidant, anti-inflammatory and anti-cancer properties. Then the review delves into the multifaceted mechanisms underlying the anti-cancer properties of ZEO and OEO.

Results: Studies showcase the ability of ZEO and OEO to induce apoptosis in cancer cells through various pathways, such as mitochondrial dysfunction, reactive oxygen species (ROS) generation and DNA damage while sparing normal cells. Our studies further validated the immunomodulatory effects of OEO and ZEO in tumor-bearing mice, resulting in reduced tumor volume. Additionally, this review confirmed the synergistic effect of ZEO when combined with doxorubicin to inhibit cancer cells.

Conclusion: Some essential oils, such as ZEO and OEO, present promising natural compounds in cancer therapy, offering diverse mechanisms of action targeting various aspects of tumor biology.

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Introduction

Cancer remains a formidable challenge in healthcare, urging clinicians and researchers to seek more effective treatments with fewer side effects than conventional therapies like chemotherapy and radiation. This has led to a growing interest in exploring alternative therapeutic options for better outcomes [1, 2].

In the search for innovative cancer treatments, natural compounds, particularly essential oils, have gained attraction because of their potent biological properties and low toxicity. These oils, derived from aromatic plants through distillation or extraction, contain diverse bioactive molecules with varied physiological effects. Phytochemicals, found in plants, are key determinants of essential oil properties and therapeutic effects, influenced by various factors, like plant species, growing conditions, and extraction methods [3-6]. Terpenes, the largest and most diverse group of phytochemicals in essential oils, contribute to their characteristic aroma and have different biological activities, including antimicrobial, anti-inflammatory and antioxidant properties. Phenolic compounds, such as phenols, flavonoids, and tannins, found in essential oils also exhibit antimicrobial and anti-inflammatory effects. Aldehydes, like citral and cinnamaldehyde, contribute to essential oils' antimicrobial properties and may have sedative and analgesic effects. Ketones, such as camphor and menthone, offer therapeutic benefits like analgesia and mucolysis but can be toxic in high concentrations. Ethers, including eugenol and anethole, display antimicrobial, analgesic, and anti-inflammatory properties, with some showing antispasmodic effects. The combination and concentration of these phytochemicals determine essential oils' overall properties and therapeutic effects. Understanding their composition is crucial for optimizing their use in aromatherapy, herbal medicine and cosmetics while ensuring safety and efficacy [7-9].

Essential oils have demonstrated the ability to modulate oxidative stress, a key factor in cancer initiation and progression. Oxidative stress results from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanisms, contributing to DNA damage, inflammation and unchecked cell growth, which are the hallmarks of cancer. By acting as antioxidants, essential oils scavenge free radicals, restoring ROS balance and mitigating oxidative damage, thus potentially preventing cancer development and progression. However, some studies suggest that essential oils may act as pro-oxidants, inducing oxidative stress in certain situations. The effects of essential oils on oxidative stress likely vary depending on the specific oil and its application context [6, 10, 11].

Moreover, essential oils possess potent anti-inflammatory properties, augmenting their effectiveness as anticancer agents. Chronic inflammation plays a crucial role in cancer development and progression, promoting tumor growth, angiogenesis, and metastasis. Essential oils contain bioactive compounds that target inflammatory pathways, decreasing the generation of pro-inflammatory molecules and increasing the synthesis of anti-inflammatory markers. By modulating the tumor microenvironment, essential oils create a less favorable setting for cancer cells, hindering their growth and spread.

In addition to their anti-oxidative and anti-inflammatory properties, certain components of essential oils possess immunomodulatory abilities, enhancing the body's immune response against cancer. Specific natural compounds found in essential oils can promote a shift from a Th2 to a Th1 cytokine profile, which enhances antitumor immunity. By boosting the activity of cytotoxic T cells, natural killer cells, and macrophages, essential oils strengthen the immune system's ability to eliminate cancer cells, complementing traditional anticancer treatments [12, 13]. Cancer cells vary in their sensitivity to ROS and immune responses, highlighting differences in their ability to sense and respond to oxidative stress. In short, essential oils represent forefront contenders in cancer therapy, with diverse bioactive compounds targeting various aspects of tumor biology. As research progresses, their potential as invaluable assets in cancer treatment continues to grow. *Zataria multiflora* essential oil (ZEO) and *Oliveria decumbens*e essential oil (OEO) have garnered considerable attention for their multifaceted properties. ZEO and OEO have been studied for their potential therapeutic effects, including antimicrobial, anti-inflammatory and antifungal properties [14, 15].

Z. multiflora, also known as "Shirazi thyme" or "Avishan-e-Shirazi," is a flowering plant native to the Middle East, particularly Iran. It belongs to the Lamiaceae family and is renowned for its aromatic leaves and flowers. The essential oil obtained from *Z. multiflora* is rich in bioactive compounds, including oxygenated monoterpenes, monoterpene and sesquiterpene hydrocarbons, along with other phytochemicals, such as carvacrol, γ-terpinene, carvacrol methyl ether, p-cymene and thymol.

O. decumbens, commonly known as "Shavasara" or "Moshk Choopan," is a plant species belonging to the Apiaceae family [16, 17]. It is native to the Mediterra-

nean region, particularly Southwest Iran. OEO analysis showed a high concentration of phenolic compounds, with thymol, carvacrol, p-cymene, and γ-terpinene as predominant components [18]. The exact amounts of these components may vary depending on various factors, such as collection time, geographical variation, etc.

Accordingly, this review thoroughly investigates the biological activities of diverse essential oils, covering antioxidant properties, anti-cancer effects, antitumor activity, immunomodulatory effects, and combination cancer therapy. Special focus is placed on the biological activity of ZEO and OEO after each section, enhancing our comprehension of their impact. This study allows for a deeper understanding of the therapeutic potential of these oils and encourages further research into their mechanisms of action and clinical applications.

Anti-oxidant activity of essential oils

Essential oils are renowned for their potent anti-oxidant properties, contributing to their therapeutic effects and health benefits. These natural compounds can neutralize harmful free radicals, thus reducing oxidative stress and inflammation. Anti-oxidant activity in essential oils is attributed to the presence of bioactive molecules, such as phenolic compounds, terpenes, and flavonoids. Studies have shown that regular use of essential oils rich in antioxidants can help mitigate the risk of chronic diseases, improve total well-being, and promote longevity [11]. Additionally, the antioxidant activity of essential oils makes them valuable ingredients in skin care products, as they can protect the skin from environmental damage and premature aging.

Evidence from a study confirmed the potent anti-oxidant capabilities of clove bud oil, highlighting its efficacy in scavenging free radicals and inhibiting lipid peroxidation [19]. Additionally, another investigation unveiled significant anti-oxidant activity in thyme oil, suggesting its potential therapeutic utility against free radicals and lipid peroxidation [20]. Furthermore, a separate review emphasized the substantial anti-oxidant properties inherent in cinnamon bark oil, attributing this to its rich cinnamaldehyde content and proposing its application in both food preservation and health contexts [21, 22].

Comparative analysis across several essential oils revealed differences in anti-oxidant potential, with rosemary exhibiting relatively weak activity compared to counterparts like clove and oregano [23]. Peppermint essential oil administration in mice led to reduced anxiety-related behaviors and oxidative stress markers, suggesting its potential for anxiety management [24]. Moreover, treatment with frankincense essential oil was found to enhance cognitive function and diminish oxidative stress in aged rats, indicating potential neuroprotective effects [25]. The observations from a different study showcased the ability of eucalyptus oil supplementation to reduce oxidative stress markers and bolster liver function in rats subjected to induced liver damage [26]. Similarly, administering cumin oil was shown to decrease oxidative stress markers and enhance cognitive function in aged mice, implying potential neuroprotective effects [27]. Oregano essential oil was found to effectively diminish oxidative stress and lemon balm essential oil demonstrated notable anti-oxidant activity and potential for scavenging free radicals [28]. Similarly, ginger essential oil exhibited significant anti-oxidant and anti-inflammatory properties, suggesting potential health benefits across various conditions [29].

Several investigations on the antioxidant activity of the essential oil of ZEO showed this essential oil's ability to scavenge free radicals and prevent lipid oxidation, indicating its potential as a natural food preservative [30, 31]. These findings suggested that ZEO could be utilized as a natural anti-oxidant agent to mitigate oxidative damage and related health conditions. The pretreatment of lipopolysaccharide-stimulated macrophages with ZEO leads to a significant reduction in the production of hydrogen peroxide (H_2O_2) and nitric oxide (NO). Additionally, the anti-oxidant effect of *Z. multiflora* was assessed in human monocytes in the presence of glucose. The study found that treatment with ZEO reduced NO and H_2O_2 production, as well as the activity of nicotinamide adenine dinucleotide phosphate oxidase (NOX), an enzyme responsible for superoxide production, and inducible nitric oxide synthase (iNOS), an enzyme responsible for NO production, preventing nitrosative stress and lipid peroxidation [32]. Additionally, a study showed the ZEO's anti-oxidant effect in vitro and rats, observing a significant reduction in oxidative stress through scavenging 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and decreasing malondialdehyde (MDA) as lipid peroxidation markers [33]. Another study compared the antioxidant activity of six different chemotypes of the essential oil, highlighting the significant variation in potency based on the plant's geographical origin and chemical composition [15]. Furthermore, the results of the anti-oxidant assay showed that both the essential oil and methanolic extract inhibit DPPH radicals and exhibited an anticholinesterase effect [34]. In a study on rats, the findings suggested that ZEO may be a proper source of natural therapeutic components for the treatment of Alzheimer disease through anti-oxidant and anti-inflammatory effects [35]. Meanwhile,

another study showed that Persian gum-ZEO dispersion increased the activity and expression of NO synthase, NOX, catalase, superoxide dismutase, glutathione peroxidase, nitrite reductase, nitrate reductase and polyamine oxidase at 50 µg/mL as well as NO and H_2O_2 production [36]. Another study showed that dendrosomal-ZEO exhibited noble anti-lipid peroxidation, anti-protein oxidation, anti-glucose oxidation, and anti-protein glycation activity. Meanwhile, dendrosomal ZEO strongly reduced NOX expression peroxide and activity and intracellular hydrogen in hyperglycemia-treated macrophages while increasing catalase and superoxide dismutase expression and activity synergistically. Hyperglycemia-treated murine macrophages displayed a high level of NF-kB expression while a decreased level of NRF2 expression compared to controls. The action mechanism of ZEO in managing diabetes and oxidative stress involves sequestering H_2O_2 and reducing NOX activity, making it a recommended approach for anti-diabetic activity [37].

Our previous study evaluated the extracellular antioxidant capacity of OEO and its main components compared to gallic acid, a standard anti-oxidant. In-vitro analysis demonstrated that OEO displayed concentration-dependent scavenging activities against 2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), DPPH, superoxide anion, and NO radicals, with half-maximal inhibitory concentration (IC50) values comparable to gallic acid. Thymol and carvacrol, as the main components of OEO, also exhibited radical scavenging activities similar to apocynin (as the control), while p-cymene and γ-terpinene showed no significant scavenging activity. The potency of radical removal ranked as OEO>apocynin>thymol>carvacrol>cymene=terpinene>L-name (as the control). The high antioxidant capacity of OEO may be attributed to the synergism between phenolic monoterpenes and oxygenated monoterpenes in the essential oil cocktail. Phenolic compounds are known for their strong hydrogen donation, radical oxygen quenching, and metal-chelating abilities, which protect tissues and cells against oxidative damage by scavenging reactive oxygen and nitrogen species and inhibiting lipid oxidation [38].

Based on our studies, in lipopolysaccharides-stimulated macrophages, treatment with OEO, carvacrol and thymol in low concentrations (1, 5 and 10 M) significantly reduces ROS levels while also decreasing the expression and activity of NOX. OEO exhibits comparable ROS scavenging activity and NOX (NOX subunits) down-regulation compared to its main components, with carvacrol and thymol showing slightly greater inhibitory effects on NOX activity. The multi-component nature of OEO, including phenolic monoterpenoid components, monoterpenoids, and monoterpenes, likely contributes to its superior performance. These findings suggest that OEO in low concentrations can effectively decrease superoxide production by suppressing NOX expression and activity in macrophages, highlighting its anti-oxidative properties and potential therapeutic applications in reducing inflammation and oxidative stress [38]. In addition, treatment of macrophages with OEO, carvacrol, and thymol significantly reduces NO production in lipopolysaccharides-stimulated cells, indicating their inhibitory effects on NO generation. OEO in low concentrations [1, 5 and 10 mM) exhibits strong antioxidant properties, potentially more potent than its main components, with carvacrol and thymol showing slightly greater inhibitory effects on iNOS activity. The multi-component nature of OEO likely contributes to its superior activity, suggesting synergistic effects among its components. These findings suggest that OEO effectively reduces oxidative stress by suppressing iNOS expression and activity, highlighting its potential therapeutic applications in combating inflammation and oxidative stress [38].

Furthermore, we employed molecular modeling techniques to investigate the interaction between ligands and key enzymes involved in oxidative stress and inflammation. Docking simulations revealed that thymol and carvacrol, the main components of OEO, interacted with a subsection of NOX and iNOS active sites, indicating potential inhibitory effects. Thymol and carvacrol exhibited binding energies comparable to the natural substrate of iNOS, suggesting their ability to inhibit enzyme activity competitively. Molecular dynamics simulations further supported these findings, indicating structural changes in the enzymes upon ligand binding. Overall, the in-silico results suggest that the inhibitory effects of OEO on the activity of iNOS may be attributed to the blocking of enzyme active sites (the binding site of arginine as the substrate) by its major components, thymol, and carvacrol [38]. Further research into the impact of essential oils on anti-oxidant markers in humans remains limited; however, ongoing clinical trials are exploring their potential across a range of conditions.

Anti-cancer effects and mechanisms of essential oils

The potential anti-cancer effects of essential oils have garnered significant interest in recent years, with numerous studies exploring their therapeutic properties.

Many essential oils have been found to possess antioxidant, anti-inflammatory, and antimicrobial properties, which contribute to their potential anti-cancer ef-

fects (Table 1). One of the primary mechanisms through which essential oils may exert anti-cancer effects is by inducing apoptosis, or programmed cell death, in cancer cells. Studies have shown that certain essential oils can trigger apoptosis pathways in cancer cells, leading to their destruction. Additionally, essential oils have been found to inhibit cancer cell proliferation by interfering with cell cycle progression. By disrupting the cell cycle, essential oils can prevent cancer cells from dividing and multiplying, thereby slowing down tumor growth. Additionally, research has explored the potential of essential oils to inhibit angiogenesis, a process crucial for tumor growth, as it enables the development of new blood vessels to supply nutrients to the growing cancer cells. By inhibiting angiogenesis, essential oils can deprive tumors of oxygen and nutrients, ultimately leading to their regression. Moreover, some essential oils have demonstrated anti-inflammatory effects, which may be beneficial in cancer prevention and treatment. Chronic inflammation is closely linked to the development and progression of cancer, and essential oils with anti-inflammatory properties can help mitigate this risk.

While there is growing evidence supporting the anticancer potential of certain essential oils, more research is needed to fully understand their actions, optimal concentration, and safety profile.

Some oils like lavender, frankincense, and clove have shown the ability to induce apoptosis (programmed cell death) in cancer cell lines in vitro. However, these studies exist in controlled lab environments and do not guarantee translation to human systems [39-44]. Oils like geranium and thyme have displayed in vitro capacity to inhibit cancer cell growth [45, 46]. A study found that clove oil inhibited the growth of colon cancer cells by triggering cell cycle arrest mechanisms [42]. Furthermore, research demonstrated thyme oil's capacity to reduce breast cancer cell proliferation and induce apoptosis [47]. Another study highlighted curcumin's potential to modulate various cancer cell signaling pathways, thereby impeding growth [48]. Similarly, observations indicated frankincense oil's ability to suppress inflammatory pathways in prostate cancer cells [49]. Ginger oil exhibited anti-inflammatory and anti-proliferative effects in lung cancer cells, as reported in a study [50]. Additionally, eugenol showed promise in interfering with cancer cell survival pathways in leukemia cells [51].

Thymol and carvacrol have also been studied for their potential anti-cancer effects [52]. Research has shown that these components exert anti-cancer effects by suppressing cell growth and inducing apoptosis in various cancer cell lines, including gastric, lung, breast, prostate, colorectal, and cervical cancer cells. The action mechanism of thymol involves various processes, such as the intrinsic mitochondrial pathway, induction of oxidative stress, and modulation of signaling pathways like PI3K/Akt and MAPK/ERK [53]. Carvacrol induces the inhibition of cell invasion, migration and the induction of apoptosis via the mitochondria-mediated pathway and the regulation of various signaling pathways, such as p-ERK1/2, p-AKT and p-STAT3. Carvacrol has also been found to suppress the growth of different cancer cell lines, including hypopharyngeal carcinoma cells, by targeting key biomarkers and signaling pathways involved in cancer progression [54]. In a study, carvacrol was shown to interact with signaling pathways associated with cancer cell growth and survival in pancreatic cancer cells [55]. Furthermore, a study confirmed that carvacrol effectively suppressed the proliferation of MCF-7 breast cancer cells and triggered apoptosis by inhibiting the PI3/AKT signaling pathway [56]. Some results suggested that thymol decreases oxidative stress in hepatocellular carcinoma HepG2 cell line and triggers apoptosis and genotoxicity [57]. Meanwhile, a study showed that thymol leads to cellular damage, including lipid degeneration, mitochondrial impairment, nucleolar disruption, and apoptosis at varying concentrations in intestinal Caco-2 cells [58]. At low micromolar ranges in HL-60 acute promyelocytic leukemia cells, thymol-induced caspase-dependent apoptosis. Thymol also caused mitochondrial dysfunction and apoptosis in oral squamous carcinoma and cervical cancer cells derived from mouse xenografts [59]. Finally, thymol elicits apoptotic cell death via an intrinsic mitochondrial pathway in AGS cells [52, 60].

The investigation into the cytotoxic effects of ZEO and OEO presents compelling evidence of their potential as therapeutic agents against breast cancer.

Based on previous studies, ZEO induces apoptosis in human colon cancer cell lines, HCT116 and SW48 and inhibits cell proliferation, colony formation, and tumor growth in vivo [61]. Additionally, solid lipid nanoparticles containing ZEO demonstrated high anti-cancer efficacy against breast cancer and melanoma cell lines [62, 63]. Moreover, the study on the HepG2 cell line showed that nanoliposomes containing ZEO have anti-cancer properties, trigger cell apoptosis, and inhibit cell growth in the G2 phase [64].

The comprehensive analysis conducted in our study encompassed various aspects, from evaluating the viability of cancer cells in different monolayer cell cultures (2D) and more complex multicellular spheroids (3D) to elucidating the mechanisms underlying their cytotoxic and apoptotic effects.

One of the significant findings of our study was the dose-dependent decline in the viability of breast cancer monolayer cells treated with ZEO and OEO, including MCF-7, T47D, 4T1 and MDA-MB 231 cells [65-67]. Importantly, ZEO demonstrated selective cytotoxicity toward cancer cells while sparing normal fibroblast cells, suggesting a favorable therapeutic window (ZEO treatment [for 48 h]: IC50=25.06 mg/mL for MCF-7, 20.09 mg/mL for T47D, 30 mg/mL for 4T1, 29.89 mg/mL for MDA-MB 231 and >200 mg/mL for normal L929). The observation of morphological changes indicative of cytotoxicity, such as cell rounding, detachment, and cytoplasmic vacuolation, further corroborates the cytotoxic effects of ZEO on breast cancer cells.

Moreover, the induction of apoptosis by ZEO in MDA-MB-231 cells was supported by various apoptosis assays, including fluorescent microscopy with acridine orange/ethidium bromide staining, flow cytometry of annexin V-FITC/PI staining and terminal deoxynucleotidyl transferase dUTP nick end labeling assay, DNA fragmentation analysis, and cell cycle analysis. These assays revealed distinct morphological changes related to apoptosis, such as nuclear fragmentation, DNA fragmentation, and chromatin condensation, providing mechanistic insights into the apoptotic effect of ZEO on breast cancer cells. The results showed that ZEO can arrest cell proliferation in the G1/G2 phase and induce apoptosis. Furthermore, the different types of spectroscopic methods confirmed that ZEO can non-covalently interact with the minor groove of DNA and might help cell death in this way [65].

In addition, our in-vitro findings demonstrated that the use of ZEO results in notable suppression of cell growth and induction of apoptosis in TC1 cervical cancer cells (IC50=25 mg/mL) [68].

Similarly, based on our findings, OEO exhibited cytotoxic effects on breast cancer cells in 2D (OEO treatment [for 24 h]: IC50=31.2 mg/mL for MDA-MB231, 27 mg/mL for MCF-7, 47.3 mg/mL for 4T1, and >250 mg/mL for normal L929). The observation of apoptosis induction characterized by chromatin condensation and loss of membrane integrity in OEO-treated cancer cells further strengthens its potential as an anti-cancer agent. The concentration-dependent induction of early apoptosis by OEO, as evidenced by annexin V/PI flow cytometry and DNA laddering assay, highlights its ability to trigger apoptotic pathways in cancer cells.

Furthermore, the study delved into the molecular mechanisms underlying the apoptotic effects of OEO, revealing a significant increase in caspase-3 activity in treated cells compared to controls. This finding suggested that OEO induces apoptosis through a caspase-3-dependent pathway, further elucidating its mode of action against cancer cells.

Western blot analysis revealed a decrease in the expression levels of procaspase-9, procaspase-8, and procaspase-3 in OEO-treated cells compared to control cells. Additionally, the Bax/Bcl-2 ratio, which is associated with mitochondrial membrane potential ($\Delta\Psi m$) reduction and apoptosis induction, was altered by OEO treatment. Specifically, the expression of Bax, a proapoptotic protein, increased, while the expression of Bcl-2, an antiapoptotic protein, decreased in treated cells. This modulation of apoptotic proteins suggested that OEO induces apoptosis through intrinsic and possibly extrinsic pathways, ultimately promoting cell death by activating downstream signaling pathways. The findings also highlighted the potential of OEO to induce S-phase arrest in breast cancer, deserving further study [66].

Some assays demonstrated that OEO triggers cytotoxicity specifically in A549 lung cancer cells while having minimal impact on L929 fibroblast normal cells (OEO: IC50 of 22.14 mg/mL for A549, >100 mg/mL for L929 cell lines) [38]. Furthermore, various analyses, including colorimetric assay, western blot analysis, flow cytometry, and fluorescence microscopy confirmed that OEO-induced cell death in A549 cells is apoptotic, relying on caspase-3 activity and alterations in the Bax/Bcl2 ratio. Additionally, in-vitro experiments with different methods of spectroscopy, indicated that OEO interacts with DNA minor grooves established by the docking method.

Examination of spheroids obtained from 3D cultures, a stage between 2D culture and in-vivo studies, showed that ZEO and OEO can induce apoptotic death as well. However, the IC50 of ZEO and OEO in 3D cultures was much more than in 2D cultures in all cancer cell lines considered [65, 67].

Overall, ZEO and OEO were 5 to 10 times more effective on cancer cells than normal cells in these studies. In-depth investigations into the mechanisms of action of ZEO and OEO have unveiled their ability to induce apoptosis, trigger mitochondrial dysfunction, and elevate levels of ROS in cancer cells. This oxidative stress-mediated apoptosis, coupled with cell cycle arrest and DNA interaction, underscores their antiproliferative effects and potential as apoptosis-inducing agents in cancer therapy.

According to our previous studies, thymol triggered apoptosis in MDA-MB231 cancer cells after 24 h (IC50=56 mg/mL) through several mechanisms, such as DNA fragmentation, the induction of oxidative stress and mitochondrial dysfunction, and activation of the intrinsic apoptotic pathway. Furthermore, thymol reduced cell viability and inhibited cell division in cancer cell lines by arresting MDA-MB231 cancer cells in the S-phase of the cell cycle. We also indicated that thymol retains its anti-cancer properties when applied to 3D cell cultures [66].

These findings primarily stem from in-vitro and animal studies, underscoring the need for extensive human research before definitive conclusions can be drawn.

Antitumor activity of essential oils

Several essential oils (Table 2) have demonstrated the ability to inhibit the growth of tumors in mice. The oral administration of *Lippia citriodora* essential oil for 14 days in mice decreased the size of tumors in the DA3 murine breast tumor model. Notably, the tumor tissue of the *L. citriodora* essential oil-treated mice showed elevated levels of the apoptotic marker-cleaved caspase-3 and reduced protein expression of survivin [69]. *Cymbopogon citratus* essential oil and carvacrol had an antitumor effect on 7, 12-dimethylbenz (a) anthracene-induced breast cancer in female rats [70] A result of an anti-tumor experiment showed that the *Pinus koraiensis* pinecones nanoemulsion can effectively inhibit the growth of the MGC-803 tumor and promote apoptosis. Furthermore, immunohistochemical analysis revealed that this essential oil can prevent the proliferation of MGC-803 cells by downregulating the expression of YAP1/TEAD and its target proteins GLI2, AREG and CTGF. This mechanism suggests that the oil modulates the HIPPO/YAP signaling pathway and its associated downstream signaling cascades [71]. Another study exhibited that cinnamon essential oil has potent antitumor and immunostimulatory properties against Ehrlich ascites carcinoma in vivo [72].

Both OEO and ZEO demonstrated significant inhibition of tumor growth in experimental mouse models of cancer. ZEO inhibited the in-vivo growth of breast 4T1 and cervical TC1 tumor cells in BALB/c and C57BL/6 mice models, respectively. Tumor volume and weight were significantly reduced in the ZEO-treated groups compared to the control group. Additionally, no significant body weight loss was observed in the ZEO-treated groups during the study, indicating the absence of toxicity. Furthermore, ZEO treatment did not show any toxicity in the liver, as indicated by the evaluation of plasma activities of liver-related enzymes aspartate aminotransferase and alanine aminotransferase [68].

Similarly, mice injected with OEO showed lower tumor volume and weight compared to other 4T1 tumor-bearing control groups, despite having higher body weight. This suggests a significant decrease in tumor growth rate due to OEO administration. OEO treatment also did not show any toxicity in the liver. However, in a group exposed to both the 4T1 cell line and OEO simultaneously to evaluate OEO's preventive role in tumorigenesis, no effect of OEO on preventing tumor development or reducing tumor growth was observed [67].

Role of oxidative stress in anti-cancer activities of *Z. Multiflora* essential oil and *O. Decumbens* essential oil

Our previous study demonstrated that ZEO treatment with IC50 of 29.89 µg/mL induces apoptosis in MDA-MB-231 monolayer cell lines through an increase in ROS levels, as evidenced by flow cytometry. This rise in ROS production was associated with mitochondrial dysfunction, as indicated by a significant reduction in $\Delta\Psi m$ following ZEO treatment. The observed decrease in $\Delta\Psi m$ suggested the involvement of the mitochondrial apoptotic pathway in ZEO-induced apoptosis [65].

Additionally, ZEO induced DNA damage in MDA-MB-231 cells, as evidenced by increased levels of 8-oxo, a marker of oxidative DNA lesions. Furthermore, comet assay analysis revealed a significant increase in DNA fragmentation, confirming the occurrence of DNA oxidation and strand breaks upon ZEO treatment [65].

The induction of intracellular ROS generation by OEO in higher concentrations (IC50 of 47.3 mg/mL for 4T1, 31.2 mg/mL for MDA-MB231, and 22.14 mg/mL for A549) highlighted the role of oxidative stress in their cytotoxic effects in cancer cell lines [38, 66, 67]. ROS, including hydroxyl radicals, superoxide anions, and H_2O_2, were known to induce cellular damage and trigger apoptotic pathways. The significant elevation of ROS levels in treated MDA-MB231, 4T1 and A549 cancer cells suggested that OEO-mediated cytotoxicity may be partially attributed to oxidative stress-induced cellular damage, leading to apoptosis. ROS levels were evaluated by Dichloro-dihydro-fluorescein flow cytometry or colorimetric assay [38].

Table 1. A review of some anti-cancer activities of essential oils

Essential Oil	Cell	Outcome	Reference
Lavender	Prostate cancer cell lines (PC-3 cell line)	Inducing apoptosis	[41]
Frankincense	Melanoma cancer cell lines (mouse [B16-F10] and human melanoma [FM94])	Suppressing the growth through down-regulation of Bcl-2/Bax cascade signaling	[43]
Frankincense	Pancreatic cancer cell lines (MIA PaCa-2, Panc-28, BxPC-3 and DANG cells)	Inducing death in cultures	[44]
Clove	Colon cancer cell lines (Caco-2 cells)	Inducing apoptosis, Triggers cell cycle arrest	[39]
Geranium	Breast Cancer Cells (MCF-7 cell)	Inhibiting cancer cell growth	[45, 46]
Thyme	Breast cancer cell lines (MDA-MB-231)	Inhibiting cancer cell growth, inducing apoptosis	[47]
Curcumin	Different cancer cell lines	Modulating cancer cell signaling pathways	[48]
Ginger	Different cancer cell lines	Exhibiting anti-inflammatory and anti-proliferative effects	[50]
Eugenol	Leukemia cells (HL-60 cells)	Interfering with cancer cell survival pathways	[51]
Zataria multiflora	Colon cancer cells (HCT116 and SW48 cells)	Inducing apoptosis in-vitro and inhibiting tumor growth in-vivo	[61]
Zataria multiflora	Breast cancer and melanoma cancer cell lines (MDA-MB-468 and A-375 cells)	High anti-cancer efficacy with solid lipid nanoparticles	[62, 63]
Zataria multiflora	liver cancer cell line (HepG2 cell line)	Inducing apoptosis and Stopping cell growth in G2	[64]
Zataria multiflora	Human breast cancer cell lines (MDA-MB231, MCF-7 cell lines)	Cytotoxic effects, inducing apoptosis, DNA interaction, cell cycle arrest	[65, 66]
Zataria multiflora	Murine breast cancer cell lines (4T1 cell lines)	Cytotoxic effects, inducing apoptosis	[68]
Zataria multiflora	Murine cervical cancer cell lines (TC1 cell lines)	Cytotoxic effects, inducing apoptosis	[68]
Oliveria decumbens	Human breast cancer cell lines (MDA-MB231 and MCF-7, cell lines)	Cytotoxic effects, inducing apoptosis, DNA interaction, cell cycle arrest	[66]
Oliveria decumbens	Murine breast cancer cell lines (4T1cell lines)	Cytotoxic effects, inducing apoptosis	[67]
Oliveria decumbens	Lung cancer cell line (A549 cells)	Triggers cytotoxicity, induces apoptosis	[38]
Thymol	Various cancer cell lines	Suppressing cell growth, inducing apoptosis	[58-60, 57, 53, 54]
Carvacrol	Various cancer cell lines	Suppressing cell growth, inducing apoptosis	[53-56, 58]

IMMUNOREGULATION

The observed reduction in Δψm following treatment of MDA-MB231 cancer cells with OEO in the IC50 suggested their involvement in mitochondrial-dependent apoptosis related to oxidative stress. Moreover, the detection of increased levels of 8-oxo-dG, in cells treated with OEO provided further evidence of their ability to induce cellular injury. Oxidative DNA damage can lead to activation of DNA damage response pathways and genomic instability, finally culminating in apoptosis. The dose-dependent increase in 8-oxo-dG levels suggested a direct correlation between OEO exposure and oxidative DNA damage, reinforcing their apoptotic effects through this mechanism [66].

Furthermore, thymol and carvacrol have been shown to induce the generation of ROS in cancer cells, contributing to their anti-cancer effects. Research has demonstrated that thymol and carvacrol increase ROS production in various cancer cell lines, including colorectal, gastric, lung and prostate cancer cells. This elevation of ROS was associated with the induction of apoptosis and the inhibition of cell migration, highlighting the potential of ROS-mediated toxicity as a principal mechanism for the anti-cancer effects of thymol and carvacrol. The generation of ROS by thymol and carvacrol was linked to the activation of the intrinsic mitochondrial pathway, depolarization of the mitochondrial membrane, and the activation of proapoptotic proteins in cancer cells. These findings suggested that the induction of ROS by thymol and carvacrol plays a significant role in its anti-cancer activity [66].

Table 2. A review of some anti-tumor activities of essential oils

Essential Oil	Model	Outcome	Reference
Lippia citriodora (LCO)	Murine breast tumor model	Decreased tumor size, elevated cleaved caspase-3, reduced survivin expression in tumor tissue	[69]
Cymbopogon citratus	DMBA-induced breast cancer in female rats	Antitumor effect	[70]
Pinus koraiensis	MGC-803 tumor model (mice)	Inhibited tumor growth, promoted apoptosis, down-regulated YAP1/TEAD and its target proteins	[71]
Cinnamon oil	Ehrlich ascites carcinoma bearing mice	Anti-proliferative and immunomodulatory potencies	[72]
Frankincense	C57BL/6 mice melanoma model	Reducing the tumor burden ,Ameliorating hepatotoxicity via phase I and II drug metabolizing enzymes	[43]
Frankincense	Heterotopic xenograft mouse model with pancreatic tumors	Anti-proliferative and pro-apoptotic activities against pancreatic tumors in the heterotopic xenograft mouse model.	[44]
Zataria multiflora	Cervical TC1 tumor model (C57BL/6 mice)	Significant inhibition of tumor growth, no toxicity observed	[68]
Zataria multiflora	Breast 4T1 tumor model (BALB/c mice)	Significant inhibition of tumor growth, no toxicity observed	[68]
Oliveria decumbens	Breast 4T1 tumor model (BALB/c mice)	Significant inhibition of tumor growth, no liver toxicity observed	[67]

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Overall, this review underscores the multifaceted nature of OEO, ZEO and thymol-induced cytotoxicity in cancer cell lines, involving mitochondrial dysfunction, ROS generation, and oxidative DNA damage. Understanding these mechanisms provides valuable insights into the potential therapeutic applications of OEO and thymol in cancer treatment.

Immunomodulatory effect of essential oils

A study has demonstrated that pretreatment with ZEO can effectively protect rats from liver damage caused by CCl4 exposure by modulating TGF-β1, hyaluronan and hydroxyproline levels, indicating its potential as a therapeutic agent in mitigating liver injury [73]. Thymol has been observed to regulate T cell function in Jurkat leukemia cells by reducing IL-2 and IFN-γ secretion, potentially mediated through the downregulation of NFAT-2 and AP-1 transcription factors [74]. Furthermore, thyme extract (from Thymus vulgaris) has been reported to influence the expression of IL-1β, IL-8 and NF-κB subunits p65 and p52 in human lung cancer (H460) cells [75].

Essential oils have been found to possess immunomodulatory activities, influencing the immune response in various ways. Research has indicated that certain essential oils, such as clove, eucalyptus, tea tree and lavender, exhibit immunomodulatory effects, which can include immunostimulation and immunosuppression. These effects have been observed in in-vitro and in-vivo studies, suggesting the potential of essential oils to modulate the immune system. Additionally, the immunomodulatory properties of essential oils from various plants, including clove, lemongrass, rosemary and thyme, have been studied in both cell and animal models. The findings highlight the potential of essential oils as immunomodulators, which could have implications for various health applications.

Research has indicated that essential oils can modulate the production of pro- and anti-inflammatory cytokines, possess antiproliferative and chemotactic properties, and exert antiparasitic effects. These effects are attributed to the ability of essential oils to influence the immune system, either as immunosuppressors (e.g. in allergies and cancer) or as immunopotentiators (e.g. in immunodeficiencies to prevent infections)

ZEO and OEO have been found to possess immunomodulatory properties, influencing the activity of the immune system. Studies have shown that ZEO and OEO can impact the production and secretion of various cytokines, which are key signaling molecules involved in immune response regulation.

In a study conducted on C57BL/6 mice, the untreated turmeric group exhibited reduced levels of IFN-γ. Interestingly, the administration of ZEO significantly increased the IFN-γ levels, although the increase did not reach the baseline levels observed in the control group. Similarly, TNF-α levels were significantly increased in mice injected with ZEO compared to the control group. IL-2 levels were significantly increased in ZEO-injected C57BL/6 mice, both in tumor-bearing and tumor-lacking groups. Conversely, IL-4 secretion was significantly diminished in ZEO-injected C57BL/6 mice with tumors, regardless of whether ZEO was administered simultaneously with cancer cells or after tumor develop-

Table 3. A review of combination cancer therapy of some essential oils and their components

Combination Therapy	Mechanism of Action	Reference
Cymbopogon citratus essential oil and citral with doxorubicin	Regulation of doxorubicin metabolism, toxicity and multidrug transporters	[78]
Inula japonica and *Angelicae dahuricae* essential oils with doxorubicin	Increased sensitivity of doxorubicin-resistant MCF-7 cells (MCF-7/ADR) through ABCB1 suppression and disruption of lipid raft stability	[79]
Cinnamomum burmanii essential oil with doxorubicin	Synergistic increase in ROS generation and intensified cytotoxic and antimetastatic effects of doxorubicin in 4T1 cells	[80]
Anethole with doxorubicin	Synergistic increase in ROS production and ER stress, decreased colony formation, reduced mitochondrial membrane potential, and induced apoptosis in MDA-MB-231 cells	[81]
Curcumol and paclitaxel	Synergistically amplified antiproliferative and proapoptotic effects on MDA-MB-231 cells through ZBTB7A downregulation via NF-κB pathway inhibition	[82]
Limonene with docetaxel	Sensitization of DU-145 prostate cancer cells to docetaxel in a dose-dependent manner	[83]
β-Caryophyllene with paclitaxel	Enhancement of paclitaxel activity by altering cell membrane permeability, facilitating paclitaxel uptake	[84]
Geraniol with 5-fluorouracil	Heightened sensitivity of cancer cells to 5-FU, facilitation of drug absorption, and chemoprotective properties against DNA damage	[85]
Thyme oil with chemotherapy	Enhanced treatment efficacy in breast cancer models	[49]
Thymol with TMZ	Synergistic increase in cytotoxicity in human U-87 malignant glioblastoma cells	[57]
Fructus bruceae oil with radiotherapy	Potential improvement of radiotherapy efficacy in esophageal cancer	[50]
ZEO with doxorubicin	Reduction in doxorubicin dosage, inhibition of PC3 cancer cell proliferation, promotion of apoptosis, increased expression of pro-apoptotic genes, decreased expression of anti-apoptotic genes	[86]
ZEO with doxorubicin	Increased cytotoxic effect of Nalm-6, increased expression of pro-apoptotic genes (Bax, P53, P21), decreased expression of anti-apoptotic gene (Bcl-2), potential interactions with Bcl-2 proteins	[87]

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ment. No significant differences in IL-4 and IL-2 secretion were observed among different groups of BALB/c mice bearing 4T1 breast cancer [68].

Untreated and vehicle-treated tumeric mice showed elevated levels of inflammatory mediator IL-6, proinflammatory cytokines IL-1β, multifunctional cytokine TGF-β and immunosuppressive cytokine IL-10, with low levels of pro-inflammatory cytokines IFN-γ, TNF-α and IL-2 compared to control groups. Treatment with OEO in 4T1 inoculated mice led to reduced levels of IL-10, TGF-β, IL-1β, and IL-6 while IFN-γ, TNF-α and IL-2 increased in this group compared to other tumor-bearing groups. However, IL-4 levels did not change significantly across all groups. Based on these consequences and the ratio of IFN-γ/IL10, it suggests that the Th1 type of immune response is more likely involved in OEO-treated tumor-bearing mice than in other mice. The observed shift in cytokine levels towards a more pro-inflammatory and anti-tumor immune profile suggests that OEO treatment may help bolster the immune system's ability to distinguish and remove cancer cells. By modulating the cytokine balance in favor of anti-tumor immunity and reducing immunosuppression, OEO and ZEO hold promise as a potential immunotherapy agent for cancer treatment [67].

Combination cancer therapy of essential oils

The synergistic effect of essential oils and their components with chemotherapy or other cancer therapies refers to the enhancement of treatment efficacy when they are used in combination with conventional cancer treatments. This synergy can result in improved therapeutic outcomes, reduced side effects, and even the potential for overcoming drug resistance. By modulating cellular pathways and signaling mechanisms, essential oils can make cancer cells more susceptible to the cytotoxic effects of conventional treatments. When used in combination with chemotherapy, which also induces apoptosis, essential oils can augment the apoptotic response, leading to more effective elimination of cancer cells. Chemotherapy resistance is a significant challenge in cancer treatment. Essential oils have been shown to overcome or reduce resistance mechanisms employed by cancer cells, thereby restoring their sensitivity to chemotherapy drugs. This can improve the efficacy of chemotherapy and overcome treatment resistance. Essential oils can inhibit tumor angiogenesis (the formation of new blood vessels) and metastasis (the spread of cancer cells to distant sites). When combined with chemotherapy, which primarily targets rapidly dividing cancer cells, essential oils can complement treatment by inhibiting tumor growth, metastatic spread, and the development

of secondary tumors. Chemotherapy often causes side effects, such as nausea, vomiting, fatigue, and immune suppression. Essential oils possess anti-inflammatory, anti-oxidant, and antiemetic properties that can mitigate these side effects and improve the overall well-being of cancer patients undergoing chemotherapy. When used alongside chemotherapy or immunotherapy, essential oils may boost the activity of immune cells, such as T cells and natural killer cells, leading to a more robust anti-cancer immune response.

Essential oils can complement the effects of other cancer therapies, such as radiation therapy and targeted therapy. They may help alleviate radiation-induced skin toxicity, enhance the effectiveness of targeted therapies by sensitizing cancer cells, or improve the overall response to combined treatment modalities [5, 40, 76, 77].

For instance (Table 3), a study showed that *C. citratus* essential oil and citral effectively counter doxorubicin resistance in cancer cells by regulating the drug's metabolism, toxicity, and multidrug transporters [78]. Essential oils extracted from Inula japonica and *Angelicae dahuricae*, along with their primary component IATL, have demonstrated the ability to increase the sensitivity of doxorubicin-resistant MCF-7 cells (MCF-7/ADR) by two to threefold. These effects are mediated through various mechanisms, including the suppression of ABCB1 expression and disruption of lipid raft stability [79]. Furthermore, a study found that combining *Cinnamomum burmanii* essential oil with doxorubicin synergistically enhanced ROS generation, intensifying the cytotoxic and antimetastatic effects of doxorubicin in 4T1 cells [80]. Similarly, the combination of doxorubicin with anethole (0.5+50 mM plus 0.5+100 mM) resulted in a synergistic increase in ROS production and endoplasmic reticulum stress. This combination also led to decreased colony formation, reduced mitochondrial membrane potential, and induced apoptosis in MDA-MB-231 cells [81]. Additionally, the combination of curcumol and paclitaxel (250 μM plus 2.5 μM) synergistically amplified the antiproliferative and proapoptotic effects on MDA-MB-231 cells both in-vitro and in-vivo (curcumol 100 mg/kg plus paclitaxel 10 mg/kg), achieved by downregulating ZBTB7A expression through the inhibition of the NF-κB signaling pathway [82]. A study revealed that limonene, a specific compound, possesses cytotoxic activity against the DU-145 prostate cancer cell line when administered independently. Moreover, when combined with docetaxel, limonene sensitized the cells to this drug in a dose-dependent manner. This synergistic effect enabled the use of significantly lower doses of docetaxel, achieving the IC50 at concentrations ranging from 2.8 nM to 1.9 mM [83]. β-Caryophyllene, despite lacking cytotoxicity as a standalone agent, exhibited a notable ability to enhance the cytotoxic activity of paclitaxel across various cancer cell lines. Particularly striking was its impact on DLD-1 cells when combined with paclitaxel, with the most significant effect observed at a concentration of 10 μg/mL−1 β-caryophyllene, augmenting paclitaxel activity by approximately tenfold. This enhancement was attributed to β-caryophyllene's capacity to increase cell membrane permeability, facilitating the uptake of paclitaxel. Accumulation of β-caryophyllene within the lipid bilayer altered membrane permeability, thereby enhancing the intracellular delivery and efficacy of paclitaxel, offering a promising strategy to potentiate the effectiveness of chemotherapy in cancer treatment [84]. Studies have demonstrated that geraniol can heighten the sensitivity of cancer cells to 5-fluorouracil, a commonly used chemotherapeutic agent, and facilitate drug absorption. Additionally, in animal models, geraniol has shown chemoprotective properties against DNA damage induced by the potent carcinogen dimethylhydrazine, particularly in normal colonic cells. This protective effect was attributed to a reduction in DNA damage compared to control groups not receiving essential oil extract [85]. Combining thyme oil with chemotherapy in breast cancer models yielded promising results, suggesting enhanced treatment efficacy [49]. Furthermore, *Fructus bruceae* oil was suggested to potentially improve the efficacy of radiotherapy in esophageal cancer [50]. Moreover, another study based on a combination therapy displayed that the cytotoxic effects of thymol synergized with TMZ to increase cytotoxicity in human U-87 malignant glioblastoma (GB) cells [57].

Moreover, we reported a synergistic effect of ZEO when combined with doxorubicin, a chemotherapeutic agent, resulting in a reduction in the necessary dosage of doxorubicin and a concurrent inhibition of PC3 cancer cell proliferation, accompanied by the promotion of apoptosis. This combined treatment strategy demonstrated the potential for enhancing the therapeutic efficacy of doxorubicin while minimizing its dosage-related adverse effects [86].

In addition, a study aimed to assess the effects of ZEO, DOX, and their combinations on Nalm-6 cells, a type of lymphocyte precursor cell. Apoptosis was confirmed in this study. Gene expression analysis via real-time polymerase chain reaction revealed increased expression of pro-apoptotic genes (*Bax*, *P53* and *P21*) and decreased expression of the anti-apoptotic gene *Bcl-2* upon treatment with ZEO/DOX combination. Molecular docking studies indicated potential interactions of ZEO com-

ponents (carvacrol and thymol) with the active sites of Bcl-2 and Bcl-xl proteins. Consequently, the results suggested that ZEO exhibited a dose-dependent effect on Nalm-6 cells and synergistically enhanced the cytotoxic effect of DOX [87].

Based on these studies, ZEO has the potential to be used as a combinatorial therapy to reduce the doses of chemotherapy drugs and improve outcomes for cancer patients undergoing treatment with Dox [87].

To the best of our knowledge, there is currently no available information regarding the concurrent impact of OEO alongside anti-cancer medications. Exploring this aspect appears to hold potential value and could offer valuable insights into cancer therapy.

Conclusion

Preclinical studies using 2D and 3D cell culture models, along with tumor-bearing mice models, have revealed ZEO and OEO's efficacy in inhibiting cancer cell proliferation and tumor growth. They prompt cancer cell apoptosis through various mechanisms, including mitochondrial dysfunction, ROS generation, cell cycle arrest, and DNA damage, while sparing normal cells, indicating a promising therapeutic window. Additionally, both oils demonstrate selective cytotoxicity towards cancer cells and exhibit immunomodulatory effects, promoting a pro-inflammatory cytokine profile conducive to antitumor immunity.

OEO's dual effects, depending on concentration and cellular context, are intriguing. At low concentrations, it demonstrates antioxidant properties, protecting normal cells against oxidative stress. However, at higher concentrations, it induces ROS generation in cancer cells, leading to cytotoxicity or apoptosis. Understanding the shift from antioxidant to pro-oxidant activity at higher concentrations requires further investigation, highlighting the importance of dosage optimization and context-dependent effects in considering OEO as a therapeutic agent.

Moreover, combining ZEO with doxorubicin shows synergistic effects in suppressing cancer cells, suggesting OEO's potential as an adjuvant drug. The effectiveness of OEO and ZEO as antioxidants and anticancer agents may surpass that of their primary components, thymol, and carvacrol, due to complex interactions between multiple compounds, resulting in synergy and unique actions against cancer cells and oxidative stress.

Further research is necessary to elucidate their precise mechanisms, optimize treatment doses, evaluate clinical efficacy, and address the limitations identified in our review, such as the absence of clinical trial investigation and the insufficiency of animal studies.

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Compliance with ethical guidelines

All ethical principles were considered in this article.

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All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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