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Role of Herbal Essential Oil in Cervical Cancer: A Systematic Review

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ABSTRACT

Cancer of the cervix is a disease that is ubiquitous and frequently severe, and it affects women all over the world. Conventional treatment methods, which include surgical procedures, chemotherapy, and radiation therapy, have been shown to dramatically enhance survival rates; nevertheless, these methods are frequently accompanied with adverse effects and difficulties that might have an influence on the quality of life of a patient. In recent years, there has been a growing interest in the utilisation of essential oils in the cancer treatment and management of cervical cancer. This review offers a comprehensive investigation into the function that various essential oils play in the development of cervical cancer. It also includes insights into the possible advantages of these oils as well as the body of research that has been conducted on them. Additionally, the analysis dives into the future directions and issues that will be faced in this developing industry, with a particular focus on advancements in delivery methods and interesting research areas. For the purpose of enhancing the anticancer qualities of essential oils, the encapsulation of essential oils with solid lipid nanoparticles, the nanoemulsification of essential oils, or the combining of essential oils with conventional treatments have all demonstrated promising results. This review attempts to provide a comprehensive viewpoint, balancing the potential of these natural therapies with the obstacles and issues that need to be addressed. As the employment of essential oils in the treatment or management of cervical cancer continues to develop, this study will attempt to provide a comprehensive perspective. The study will attempt to strike a balance between the potential of these natural treatments and the obstacles and issues that need to be addressed.

Keywords- essential oil, natural product, phytomedicine, cancer, drug delivery, nanoparticle.

I. INTRODUCTION

Pain encompasses physical, psychological, and quality of life domains, and it frequently occurs in conjunction with the so-called cancer symptoms cluster, which includes anxiety, depression, and sleep problems [1,2]. The term "cancer pain" is the most accurate way to describe the multidimensional and multifaceted nature of pain. The problem that is caused by cancer pain, which is caused by surgery and chemotherapy treatment in addition to the characteristics that are special to the tumor, is a matter of urgency because of its close connection with a decrease in the overall quality of life and the growing number of patients who are impacted by cancer. There is a constant increase in the number of cancer survivors, with an anticipated 18 million people in the United States having a history of cancer up until the beginning of 2022 [3]. This is due to the combination of the advancement of early detection methods and the aging of the global population.It is possible that all of the cancer symptom clusters share common biologic bases. This is most likely owing to the participation of severe

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and smoldering inflammatory and immunological responses that are evoked by the environment in which cancer is induced, but also by treatment [4] Over seventy to eighty percent of patients who are affected by tumors are reported to suffer from cancer pain in meta-analyses that were concerned with the prevalence of cancer pain over a period of forty years [5,6]. This pain is known to be intolerable in as many as thirty-three percent of patients [7], and it reaches ninety-five percent in patients who are affected by advanced disease [8]. As a result, cancer pain is a significant challenge in the management of oncologic patients. Furthermore, the most recent systematic analysis that deals with the prevalence of pain in cancer survivors was conducted in 2022 [9]. This review highlights the fact that the prevalence of pain in solid tumor survivors who had completed treatment at least three months previously is 47%, with a heterogeneity of 98.99% among studies. These findings lend credence to the significance of cancer pain treatment in terms of both the management of cancer patients and the enhancement of their quality of life. The most common form of gynecologic cancer is cervical cancer, which also happens to be the fourth most common type of cancer among women worldwide. As a result, cervical cancer is currently one of the leading causes of death [10]. [11] It was anticipated that there were 604,000 new cases of this cancer among women in the year 2020, and that there were also 342,000 deaths caused by this malignancy. The fatality rates associated with cervical cancer vary from country to country, and research indicates that around 90 percent of these deaths occur in low- and middle-income nations due to restricted access to preventative interventions [12]. In addition, cervical cancer never exhibits any symptoms until it has reached a more advanced stage during its progression. It has been reported by the World Health Organization [13] that these nations are experiencing an increase in the mortality rate from cervical cancer due to a lack of access to therapies for malignant lesions. These treatments include chemotherapy, radiation therapy, and surgical procedures. In addition to any abnormal discharge from the vagina (increased monthly bleeding, bleeding between the two menstrual cycles, and post-menopausal hemorrhage), the most common symptoms of cervical cancer are severe pelvic discomfort, significant weight loss, and anorexia. Other symptoms include anorexia and considerable weight loss. The term "cancer pain" is the most accurate way to describe the multidimensional and multifarious nature of pain. This is because pain encompasses the physical, psychosocial, and quality of life domains, and it frequently occurs in conjunction with the so-called cancer symptoms cluster, which includes anxiety, depression, and sleep problems [1,2]. The problem that is caused by cancer pain, which is caused by surgery and chemotherapy treatment in addition to the characteristics that are special to the tumor, is a matter of urgency because of its close connection with a decrease in the overall quality of life and the growing number of patients who are impacted by cancer. There are an anticipated 18 million persons in the United States who have a history of cancer up until the beginning of 2022 [3]. This means that the advancement of early detection systems and the aging of the world population are both contributing factors to the continual increase in cancer survivors. There is a possibility that all of the cancer symptom clusters share common biologic bases. This is most likely because of the participation of severe and smoldering inflammatory and immunological responses that are provoked by the nature of the environment in which cancer is induced, as well as by treatment [4]. Over seventy to eighty percent of patients who are affected by tumors are reported to suffer from cancer pain in meta-analyses that pertain to the prevalence of cancer pain over a period of forty years [5,6]. This pain is considered intolerable in as many as thirty-three percent of patients [7], and it reaches ninety-five percent in patients who are affected by advanced disease (see [8]). As a result, cancer pain is a significant challenge in the management of oncologic patients. Furthermore, the most recent systematic analysis that deals with the prevalence of pain in cancer survivors was conducted in 2022 [9]. This review highlights the fact that the prevalence of pain in solid tumor survivors who had completed treatment at least three months previously is 47%, with a heterogeneity of 98.99% among studies. These findings lend credence to the significance of cancer pain treatment in terms of both the management of cancer patients and the enhancement of their quality of life. Among women around the world, cervical cancer is the fourth most common type of cancer, making it one of the leading causes of death [10]. It is also the most common form of gynecologic cancer. It is anticipated that there were 604,000 new cases of this disease among women in the year 2020, and that there were 342,000 deaths caused by this malignancy [11]. The fatality rates associated with cervical cancer vary from country to country, and research indicates that around 90 percent of these deaths occur in low- and middle-income nations due to restricted access to preventative interventions [12]. In addition, cervical cancer never exhibits any symptoms until it has reached a more advanced stage during its progression. In these nations, there is a lack of access to treatments for malignant lesions, such as chemotherapy, radiation, and surgery, which leads to an increase in the mortality rate from cervical cancer. This is according to the World Health Organization [13], which states that this lack of access affects the mortality rate. In addition to any abnormal discharge from the vagina (increased monthly bleeding, bleeding between the two menstrual cycles, and post-menopausal hemorrhage), the most common symptoms of cervical cancer are severe pelvic discomfort, significant weight loss, and anorexia. Other symptoms include anorexia and considerable weight loss.

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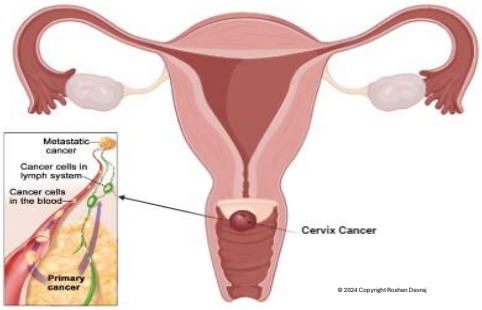

Fig: 1 Last stage of cervical cancer. Cancer has spread to other parts of the body, such as the lymph nodes, lungs, liver, or bone

II. LITERATURE RESEARCH METHODOLOGY

We are searching from different sources like Pub Med, Publon, Web of Science, Scopus, UGC care , study timing August 2023 to August 2024

Human Papillomavirus as Risk Factors of Cervical Cancer

The human papillomavirus, sometimes known as HPV, is considered to be the most prevalent sexually transmitted viral disease in the United States. It is also one of the most common causes of sexually transmitted diseases in both men and women around the world. Due to the fact that genital HPV infection is not a disease that is required to be reported, the actual incidence and prevalence figures are unknown. Nevertheless, it is estimated that the incidence of new infections in the United States ranges from 1 million to 5.5 million per year, and the prevalence is estimated to be as high as 20 million (14). Due to the fact that the rates of infection appear to be constantly growing, the topic of human papillomavirus (HPV) continues to be an important one. Papillomaviruses are found in a wide number of species, including humans, and have been found to be particular to their respective hosts. They are prevalent and have been found in a wide variety of animals. On the basis of DNA sequence data demonstrating genetic variations, more than two hundred different varieties of human papillomavirus (HPV) have been identified. There are 85 HPV genotypes that have been thoroughly described. There are an additional 120 isolates that have potentially novel genotypes that have been partially described (15). Basal epithelial cells of the skin or the inner lining of tissues are susceptible to infection by human papillomaviruses (HPVs), which can be classified as either cutaneous or mucosal kinds. The epidermitrophic cutaneous forms of human papillomavirus (HPV) are the ones that target the skin of the hands and feet. Anogenital epithelium, the lining of the mouth, the throat, and the respiratory tract are all susceptible to infection by mucosal types. There are two categories of human papillomavirus (HPV): high-risk and low-risk. These categories are determined by the HPVs' connection with cervical cancer and precursor lesions. Among the kinds of HPV that pose a low risk are types 6, 11, 42, 43, and 44. Types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70 are examples of kinds of HPV that are considered to be high-risk.

Conventional Treatment of Cervical Cancer

The cervix, which is the tiny aperture into the uterus and is related to the vagina through the endocervical canal (figure A), is the location where cervical cancer first begins [16]. The cervix is composed of two distinct layers: the ectocervix and the endocervix. The ectocervix is covered with stratified squamous epithelial cells, whilst the endocervix is made up of simple columnar epithelial cells. To produce the squamocolumnar junction in the endocervical canal, stratified squamous and columnar epithelium are the components that come together. The area where both regions meet is referred to as the "transformation zone," and it is made up of metaplastic epithelium that replaces the columnar lined epithelium that is found in the endocervix. Because it is a prominent site of premalignant transformation that occurs as a result of persistent HPV infection (figure A), this zone is the most likely location for the development of cervical cancer [17].

Squamous cell carcinoma (SCC) and adenocarcinoma are the two primary histological subtypes of cervical cancer. Squamous cell carcinoma is the more common version. Adenocarcinoma is a kind of cervical carcinoma that arises from glandular cells that create mucus in the endocervix, in contrast to squamous cell carcinoma (SCC), which develops from squamous cells in the ectocervix and affects around 75% of cervical carcinoma cases [18]. Given that SCC is the most prevalent subtype, the primary focus of this review will be on characterizing its evolution.

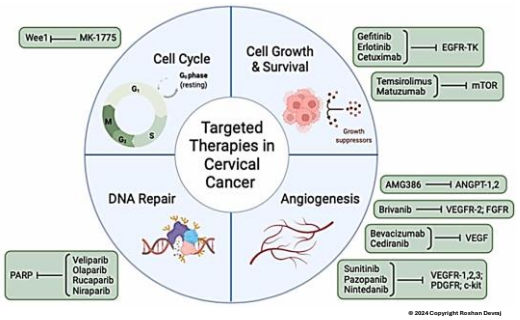

Fig: 2 Therapeutic agents targeting biological pathways and their main molecular targets in various stages of cervical cancer.

Essential Oils: Composition and Their Potential Benefits

The majority of essential oils comprise between 20 and 60 molecules, although they can contain as many as 300 distinct compounds. Essential oils can contain hundreds of different molecules. The majority of these molecules are composed of terpene compounds;

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however, there are also phenylpropanoids and other compounds, such as nitric and sulfuric compounds, but the frequency of these compounds is lower and their fraction is comparable. In addition, there is a possibility that certain essential oils involve the presence of nitrogen and sulfur molecules [19,20,21,22].

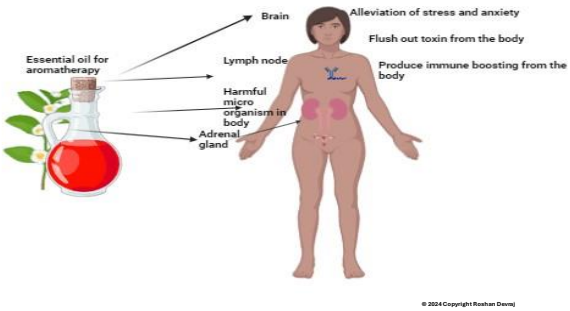

Fig: 3 The role of essential-oil based aromatherapy in strengthening immunity and producing anti-stress effects

The Essential Groups of Essential Oils

In the literature, there are about three thousand different terpenes that have been described [23]. Terpenes and terpenoids are the major categories. This group consists of monoterpenes, which have ten carbon atoms in their molecule, sesquiterpenes, which have fifteen carbon atoms, and diterpenes, which have twenty carbon atoms [24]. In general, terpenes have the formula $(C_5H_8)_n$, which indicates that they are organic molecules that are composed of a multiple of five carbon atoms. Isoprene is the chemical making up the base [25]. Isoprene, when in its reactive state, takes the form of isoprenoylpyrophosphate (IPP), which undergoes a partial conversion to dimethylallylpyrophosphate (DMAPP). Geranylpyrophosphate (GPP), a precursor of C10 monoterpenes, is produced when the molecules IPP and DMAPP combine with one another on a molecular level. Farnesylpyrophosphate (FPP), a precursor of C15 sesquiterpenes, is produced when a second molecule of PPI reacts with GPP with the intention of producing it [26]. Because of the reaction between a third PPI molecule and FPP, geranylgeranylpyrophosphate (GGPP) is produced. This compound is a precursor to C20 diterpenes. C25 sesterpenes, C30 triterpenes, and C40 carotenes are all formed as a result of this process, which continues [27]. According to [28], the boiling point of terpenes rises in proportion to the number of carbon atoms present in the molecule. This indicates that molecules with a higher mass are less volatile. Essential oils are normally obtained using steam distillation or hydro-distillation, which results in a high concentration of monoterpenes. It is vital to highlight that essential oils are obtained through these traditional processes. Nevertheless, they have significantly lower concentrations of diterpenes and even fewer triterpenes than other plants.

Table 1: A list of important essential oils and their therapeutic applications during cancer suppressive aromatherapy

Essential Oil	Major Constituent	Study Model, Treatment Regimen	Important Findings
Achillea millefolium (Yarrow)	1,8-Cineole (27.3%) Camphor (24.3%) β-Eudesmol (18.7%)	HeLa human cervical epithelioid carcinoma cells	Reduced cell viability (IC_{50} ND). Blocked cells in G0/G1 phase
Acorus calamus (Sweet flag)	β-Asarone (31.56–91.27%) α-Asarone (1.05–52.96%)	SiHa human cervical cancer cell	Reduced cell viability (IC_{50} 55.5%) at 300 µg/mL.
Aegle marmelos (L.) Correa (Bael tree)	p-Mentha-1,4(8)-diene (33.2%) Limonene (13.1%) p-Cymen-α-ol (9.5%) γ-Gurjunene- (7.9%) β-Phellandrene (4.3%)	HeLa cells	Reduced cell viability (IC_{50} 85.6 µg/mL). Effective in suppressing ROS.
Aloysia citriodora (Lemon verbena)	α-Citral (43.46–47.62%) α-Curcumene (11.35–14.39%) trans-1,2-Bis-(1-methylethenyl)cyclobutane (10.08–15.07%)	HeLa cells	Reduced cell viability (IC_{50} 84.5 and 33.31 µg/mL, vs. IC_{50} 22.01 µg/mL (Doxorubicin)). Inhibited COX-1 and COX-2 enzymes.
Alpinia nigra (Gaertn.) Burtt (Black Galangal	Leaves: β-pinene (56.27%) α-Farnesene (7.92%) Caryophyllene (6.46%) Rhizomes: β-pinene (38.03%) myrtenol (9.35%) α-Humulene (7.82%) Humulene epoxide II (6.00%)	HeLa cells	Inhibited 60% (leaves EO) and 79% (rhizomes EO) proliferations at 20 µg/mL.
Artemisia arborescens (Vaill.) L. (Silver wormwood)	β-Thujone (79.16–89.64%) Camphor (5.34–6.58%) β-Pinene (2.01%) Sabinene (3.44%)	HeLa cells	Reduced cell viability (IC_{50} 326 and 467 µg/mL). Inhibit COX-1 and COX-2.

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Cephalotaxus griffithii Hook. f. (Griffith's plum yew)	ND	HeLa cells	Reduced cell viability (IC_{50} ND). Induced apoptosis (up-regulated caspase-3 expression, reduced cell volume, increased cytoplasmic membrane blebbing, nuclear contraction, nuclear fragmentation, and formation of apoptotic bodies). Inhibit cell migration.
Chenopodium botrys L. (Jerusalem-oak)	α-Eudesmol (16.81%) Elemol acetate (13.2%) Elemol (9.0%) α-Chenopodiol-6-acetate (7.9%)	HeLa cells	Reduced cell viability (IC_{50} 79.62 µg/mL). Increased numbers of apoptotic cells. Induced cell cycle arrest in G1 phase. Increased *p21*, *p53*, *Bax*, and *caspase-3* expressions.
Cinnamomum zeylanicum Blume (Cinnamon)	Cinnamaldehyde (77.34%) *trans*-Cinnamyl acetate (4.98%) Benzene dicarboxylic acid (3.55%) α-Pinene (2.6%)	HeLa cells	Reduced cell viability (IC_{50} 0.13 µg/mL).
Crassocephalum crepidioides (Thickhead weed)	β-Myrcene (65.9%) β-Phellandrene (8.8%) α-Pinene (3.1%) α-Copaene (1.5%)	SiHa cells	Reduced cell viability (IC_{50} 45.9 µg/mL)
Curcuma aromatica (Wild turmeric	ar-Tumerone (ND)	HeLa cells	Reduced cell viability (IC_{50} 72.02 µg/mL).
C. longa L. (Turmeric)	ar-Tumerone (ND)	HeLa cells	Reduced cell viability (IC_{50} 24.82 µg/mL)
	ar-Turmerone (33.2%) α-Turmerone (23.5%) β-Turmerone (22.7%)	HeLa cells	Reduced cell viability (IC_{50} 36.6 µg/mL). HeLa cell morphology showed condensation of chromatin, loss of cell membrane integrity with protrusions, and cell content leakage.
C. zedoaria (Christm.) Roscoe (White turmeric)	Zerumbone (17.2%) Camphor (17.56%) Curzerenone (10.2%) Isovelleral (6.6%)	HeLa and SiHa cells	Reduced HeLa cell viability (IC_{50} 6.4 µg/mL vs. IC_{50} 6.5 µg/mL (doxorubicin)). Reduced SiHa cell viability (IC_{50} 9.8 µg/mL vs. IC_{50} 7.8 µg/mL (doxorubicin))
Cymbopogon nardus (Citronella grass)	Citronellal (33.06%) Geraniol (28.40%) Nerol (10.94%) Elemol (5.25%)	HeLa cells	Reduced cell viability (IC_{50} 142 µg/mL).
Dittrichia viscosa (L.) Greuter (Yellow fleabane)	1,8-Cineole (16.41%) Caryophyllene oxide (15.14%) α-Terpinyl acetate (13.92) α-Muurolol (13.75%)	HeLa cells	Reduced cell viability (IC_{50} 660 µg/mL).
Ephedra intermedia Schrenk and Mey	2-Ethyl-pyrazine (67.37%) γ-Elemene (9.21%) Benzyl acetate (9.10%) 2-Methyl-butyl acetate (5.28%)	HeLa cells	Reduced cell viability (IC_{50} 423.22 µg/mL).
Erigeron canadensis L. (Canadian horseweed)	Limonene (65.68%) (Z)-β-ocimene (6.87%) β-Pinene (6.29%) Germacrene (4.03%)	HeLa cells	Reduced cell viability (IC_{50} 6780 µg/mL vs IC_{50} 1120 µg/mL (Limonene alone)). Cells showed nuclear pyknosis and abnormal chromatin condensation after EO treatment. Decreased G1 phase cells and increased G2/M phase cells. Increased expression of Caspase-3, -9, and -12 proteins. Inhibited mitochondrial membrane potential.
Ferula tingitana (L.) Apiaceae (Giant Tangier fennel)	Leaves: δ-Cadinol (13.8%) γ-Eudesmol (9.7%) 7-α-Eudesma-3,5-diene (9.0%) Elemol (8.3%)	HeLa cells	Reduced cell viability (IC_{50} 10.9 µg/mL (leaves EO), IC_{50} 8.6 µg/mL (fruits EO) vs. IC_{50} 4.7 µg/mL (doxorubicin)).

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	Fruit[s]: 3-Carene (13.9%) α-Thujene (13.5%) Elemol (8.9%) Myrcene (8.1%)		
Foeniculum vulgare (Fennel)	*trans*-Anethole (36.8%) p-Anisaldehyde (7.7%) α-Ehyl-p-methoxybenzyl alcohol (9.1%)	HeLa cells	Reduced cell viability (IC_{50} 207 mg/L).
	trans-Anethole (80.63%) L-Fenchone (11.57%) Estragole (3.67%) Limonene (2.68%)	HeLa cells	Reduced cell viability (IC_{50} 1.26 µg/mL).
	trans-Anethole (88.28%) Estragole (4.25%) D-Limonene (2.04%) Fenchone (2.03%)	HeLa cells	Reduced cell viability (IC_{50} 56.43 µg/mL vs. 17.95 µg/mL (Paclitaxel)).
Ganoderma applanatum	γ-Terpinene (30.3%) d-Limonene (23.6%) Cis-2-methyl-4-pentylthiane-s,s-dioxide (15.3%) Cymene (12.7%	HEp-2 cervical cancer cells	Reduced cell viability (IC_{50} 43.2 µg/mL).
Hedychium coronarium (White ginger lily)	1,8-Cineole (ND)	HeLa cells	Reduced cell viability (IC_{50} 87.98 µg/mL).
Helichrysum italicum (Roth) G. Don (Curry plant)	α-pinene (21.6%) γ-curcumene (21.6%) Neryl acetate (7.9%)	HeLa cells	Reduced cell viability (IC_{50} 7.5 µg/mL). No effect on cell cycle. Induced apoptosis.
Hyptis suaveolens (L.) Poit. (Pignut)	Sabinene (14.03%) Eucalyptol (12.78%) β-Caryophyllene (11.27%) Bicyclogermacrene (8.08%)	HeLa cells	Reduced cell viability (IC_{50} 181.37 µg/mL vs. IC_{50} 4.32 (cisplatin)). Induced G0/G1 cell cycle arrest and a decreased G2/M phase.
Inula graveolens (Linnaeus) Desf (Stinkwort)	Bornyl acetate (69.15%) Camphene (11.11%)	HeLa cells	Reduced cell viability (IC_{50} 64.1 µg/mL, IC_{50} 72.0 µg/mL (bornyl acetate) vs. IC_{50} 126.75 µg/mL (cisplatin)).
Juniperus communis (Common Juniper)	α-Pinene, limonene, and sabinene (49.1–82.8%) 4-Terpineol	SiHa cells	Reduced cell viability (IC_{50} 150.6 µg/mL).
Kaempferia galanga (Sand ginger)	Ethyl p-methoxycinnamate (ND)	HeLa cells	Reduced cell viability (IC_{50} 44.18 µg/mL).
Lantana camara Linn. (Common Lantana)	Sabinene (20.38%) β-Caryophyllene (17.88%) Eucalyptol (10.56%) α-Humulene (6.68%)	HeLa cells	Reduced cell viability (IC_{50} 229.27 µg/mL).
Lavandula pubescens Decne. (Downy Lavender)	Carvacrol (72.7%) Carvacrol methyl ether (7.0%) Caryophyllene oxide (5.9%)	HeLa cells	Reduced cell viability (IC_{50} < 10 µg/mL).
Litsea cubeba (Mountain pepper)	Geranial (37.67%) Neral (32.75%) Limonene (10.55%)	HeLa cells	Reduced cell viability (IC_{50} 67.7 µg/mL).
Melaleuca alternifolia (Maiden and Betche) Cheel (Tea tree)	Terpinen-4-ol (41.9%) γ-Terpinene (17.8%) α-Terpinene (8%) p-Cymene (4.6%)	HeLa cells	Reduced cell viability (IC_{50} ND).
Mentha piperita L. (Peppermint	Menthol (43.9%) Menthone (23.1%) 1,8-Cineole (6.6%) Menthyl acetate (4.9%)	HeLa cells	Reduced cell viability (IC_{50} ND).
Mikania micrantha Kunth (Bittervine)	Isoledene (16%) δ-Cadinene (11.2%) Debromofiliformin (9.4%) trans-Caryophyllene (9.1%)	HeLa cells	Reduced cell viability (IC_{50} 422.8 µg/mL).
Moringa oleifera Lam. (Horseradish tree)	ND	HeLa cells	Reduced cell viability (IC_{50} 422.8 µg/mL).

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Moringa peregrina (Ben tree)	ND	HeLa cells	Reduced cell viability (IC_{50} 366.3 µg/mL).
Nectandra leucantha Nees and Mart	Bicyclogermacrene (28.44%) Germacrene A (7.34%) Spathulenol (5.82%) Globulol (5.25%)	HeLa & SiHa cells	Reduced cell viability (IC_{50} 60 µg/mL, 12.4 µg/mL (Bicyclogermacrene), vs. 20 µg/mL (cisplatin)).
Nepeta curviflora Boiss (Syrian catmint)	1,6-Dimethyl spiro [4.5] decane (27.5%) Caryophyllene oxide (20.1%) β-caryophyllene (18.3%)	HeLa cells	Reduced cell viability (IC_{50} 746.9 and 453.1 µg/mL). Inhibit cell migration.
Nepeta rtanjensis Diklić and Milojević (Rtanj catmint)	*trans,cis*-Nepetalactone (71.66%) *cis,trans*-Nepetalactone (17.21%) α-Pinene (3.28%)	HeLa cells	Reduced cell viability (IC_{50} 0.050 µL/mL). Cells demonstrated cytoplasmic shrinkage and nuclear condensation and fragmentation, cell membrane blebbing, and occurrence of apoptotic bodies. Induced cell cycle perturbations. Increased number of cells with fragmented DNA. Up-regulated *Bax* and *p53* expressions. Down-regulated *Bcl-2* and *Skp2* expressions.
Nepeta sintenisii Bornm.	4aα,7α,7aβ-Nepetalactone (51.74%) β-Farnesene (12.26%) 4aα,7α,7aα-Nepetalactone (8.01%) Germacrene-D (5.01%)		Reduced cell viability (IC_{50} 20.37 µg/mL).
Origanum acutidens (Hand-Mazz.) Ietswaart	Carvacrol (61.69%) p-Cymene (17.32%) γ-Terpinene (4.05%) Borneol (3.96%)	HeLa cells	Reduced cell viability (IC_{50} < 10 µg/mL).
Perilla frutescens (L.) Britt.	Perilla ketone (80.88%) Apiol (1.77%) β-Caryophyllene (1.59%)	HeLa cells	Reduced cell viability (IC_{50} 34.58 µg/mL).
Peucedanum dhana A. Ham	trans-Piperitol (51.2%) o-Cymene (11.1%) γ-Terpinene (9.2%)	HeLa cells	Reduced cell viability (IC_{50} 56.63 µg/mL vs 7.07 µg/mL (trans-piperitol)).
Pinus eldarica (Eldar pine)	β-Caryophyllene (14.8%) Germacrene D (12.9%) α-Terpinenyl acetate (8.15%) α-Pinene (5.7%)	HeLa cells	Reduced cell viability (IC_{50} ND).
lentiscus var. *chia* (Mastic tree)	α-Pinene (56.2%, 51.9%) Myrcene (20.1%, 18.6%) β-Pinene (2.7%, 3.1%) Cultivated plant: α-Pinene (70.8%) β-Pinene (5.7%) Myrcene (2.5%)	HeLa cells	Reduced cell viability (IC_{50} 20.11–18.81 µg/mL, IC_{50} 7.62 µg/mL vs. IC_{50} 2.14 µg/mL (Doxorubicin)).
Piper cernuum Vell. (Pariparoba)	β-Elemene (30.0%) Bicyclogermacrene (19.9%) (E)-Caryophyllene (16.3%) Germacrene D (12.7%)	HeLa cells	Reduced cell viability (IC_{50} 7 µg/mL (germacrene D), 11 µg/mL (α-chamigrene), 32 µg/mL (β-caryophyllene) vs. 20 µg/mL (cisplatin)).
Piper regnellii (Miq) C. DC. var. *regnellii* (C. DC.) Yunck	Germacrene D (45.6–51.4%) α-Chamigrene (8.9–11.3%) β-Caryophyllene (8.2–9.5%)	HeLa cells	Reduced cell viability (IC_{50} 0.011 µg/mL).
Rosmarinus officinalis L. (Rosemary	1,8-Cineole (23.56%) Camphene (12.78%) Camphor (12.55%) β-pinene (12.3%)	HeLa cells	Reduced cell viability (IC_{50} 0.011 µg/mL).
Salvia officinalis L. (Garden sage)	α-Thujone (ND) 1,8-Cineole (ND) Camphor (ND)	HeLa cells	Reduced cell viability (IC_{50} ND).
Salvia sclarea L. (Clary sage)	ND	HeLa cells	Reduced cell viability (IC_{50} 80.69 µg/mL). Cells demonstrated apoptotic bodies, e.g., blebbing, cell breakage, and chromatin

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			condensation.
Satureja boissieri Hausskn. Ex Boiss. (Catri/Kekik	p-Cymene (23.15%) γ-Terpinene (22.84%) Carvacrol (21.25%) Thymol (18.96%)	HeLa cells	p-Cymene (23.15%) γ-Terpinene (22.84%) Carvacrol (21.25%) Thymol (18.96%)
Siegesbeckia pubescens	Caryophyllene oxide (21.89%) trans-longipinocarveol (5.87%) dehydrosaussurea lactone (4.85%)	HeLa cells	Reduced cell viability (IC_{50} 37.72 µg/mL).
Syzygium aromaticum (L.) Merr. and L.M. Perry (Clove]	Eugenol (85.2%) (E)-β-Caryophyllene (9.9%)	HeLa cells	Reduced cell viability (IC_{50} ND).

Role of Essential Oils in Cervical Cancer : Evidence from LaboratoryWutigri Nimlamool et,al

After the acquisition of the Zingiber ottensii (ZO) essential oil, the cytotoxic effects of the oil on HeLa cervical cancer cells were identified by the utilization of an MTT assay. Through the use of a two-fold dilution procedure, HeLa cells were subjected to a treatment with ZO essential oil at a range of dilutions ranging from 1:50,000 to 1:48 for a period of twenty-four hours. After increasing the concentration of ZO essential oil, the findings of the MTT assay made it abundantly evident that the essential oil had a significant impact on the vitality of HeLa cells. More specifically, ZO essential oil at dilutions of 1:12,500, 1:25,000, and 1:50,000 was not hazardous to the cell. This is evidenced by the fact that the viability of HeLa cells was maintained at about 100% as compared to the group that was not treated with the oil. However, when ZO essential oil was diluted to a ratio of 1:6250, it began to lower the viability of HeLa cells to around 80 percent. Furthermore, it was observed that the concentration of ZO essential oil at approximately 1:3000 was the one that caused a 50% reduction in the viability of HeLa cells. Furthermore, it was observed that ZO essential oil at greater concentrations (via dilutions ranging from 1:1562 to 1:48) caused the greatest reduction in cell viability. Additionally, we examined the cytotoxic effects of ZO essential oil on the viability of normal cells, which were human primary fibroblast cells. These cells were used in our study. As demonstrated in, we discovered that the IC50 of ZO essential oil for human primary fibroblast cells was approximately 1:390. Furthermore, we discovered that the dilutions of ZO essential oil at 1:3000 and 1:6000 did not have any harmful effects on human primary fibroblast cells. In every instance, when we examined the morphology of human primary fibroblast cells that had been treated with 1:3000 and 1:6000 of ZO essential oil, we found that there were no significant differences between the groups that had not been treated with ZO and those that had been treated with ZO. To be more specific, HeLa cervical cells that were treated with ZO essential oil at 1:3000 and 1:6000 did not display any apoptotic characteristics, but they did keep the shape of healthy fibroblast cells. According to the findings presented here, the treatment with ZO essential oil is more effective in treating HeLa cervical cancer cells than it is in treating human primary fibroblast cells. In light of the fact that our primary objective was to investigate the effects of ZO essential oil on inducing The ability of ZO essential oil to trigger HeLa cervical cancer cell death was evaluated by selecting the concentration of the oil at dilutions of 1:6000 and 1:3000 (IC50) in order to determine its effectiveness in this regard.

Essential Oils with High Monoterpenes Acyclic Monoterpene Derivatives Geraniol

Additionally known as trans-3,7-dimethyl-2,6-oktadien-1-ol, geraniol is a primary terpene alcohol that is acyclic, doubly unsaturated, and possesses a distinctive aroma that is floral and reminiscent of roses. This particular monoterpene is obtained by extracting the essential oils of a number of fragrant plants, such as Cinnamomum tenuipilum Kosterm., Valeriana officinalis subsp. collina (Wallr.) Nyman, and Phyla scaberrima (Juss. ex Pers.) Moldenke, amongst others [29]. A significant demand from the taste, fragrance, and other industries cannot be satisfied by the limited production of geraniol by plant extraction. This demand can only be satisfied through the manufacture of geraniol through the utilization of innovative biotechnological techniques. There are a number of favorable medical qualities that geraniol possesses, such as antioxidant, anti-inflammatory, antibacterial, anticancer, hepatoprotective, cardioprotective, and neuroprotective capabilities [30,31].

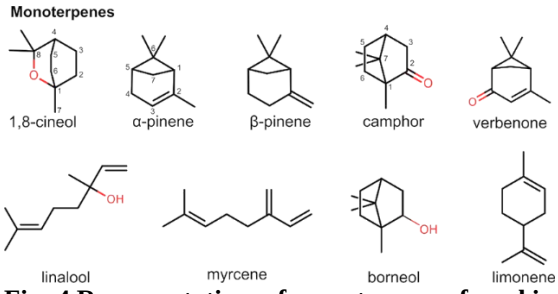

Fig: 4 Representatives of monoterpenes found in essential oils for treatment of cancer

In order to meet the demand for carboxylesterase (CES) inhibitors that are both effective and selective, a series of

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3-oxo-2-tolylhydrazinylidene-4,4,4-trifluorobutanoates that have higher or natural alcohol moieties in their structures were devised and synthesized under the direction of [32]. One of them is the ester derivative of naturally occurring geraniol, which has been demonstrated to be an extremely effective and specific inhibitor of human CES2 (hCES2), preventing the enzyme from functioning within the nanomolar range (IC50 to approximately 5 nM). There is a compound known as geranyl (2Z)-4,4,4-trifluoro-2-[2-(4-methylphenyl) hydrazinylidene. According to Figure 4, 3-oxobutanoate 1 possesses the ability to scavenge radicals and exhibits low acute toxicity. This is the reason why the ester derivative of geraniol 1 that was evaluated has a significant potential for use as a biomedicinal inhibitor.

Ester derivatives of naturally occurring geraniol.

Geranyl cinnamate ester 2 (Figure 5) shown remarkable antibacterial action against Gram-positive and Gram-negative bacteria when it was tested on Staphylococcus aureus and Escherichia coli. Furthermore, this compound has the potential to be utilized in the field of biotechnology. Geraniol and cinnamic acid were the two natural substrates that were coupled to provide synergistic effects, which were proved by the inhibitory zone for 2. There were some intriguing findings on physiologically active geraniol derivatives that were presented by Chavez et al. [33]. For the purpose of determining whether or not they are effective as inhibitors of mycelial growth of Phytophthora cinnamomic, a vast series of geranylated phenol/methoxyphenol compounds were produced and tested in vitro.

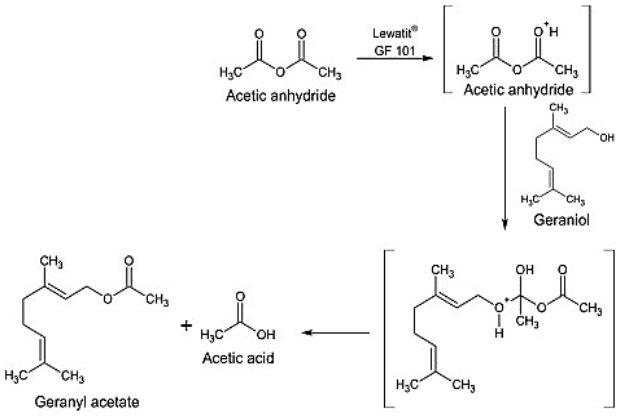

Fig: 5 Synthesis of geranyl acetate by esterification of geraniol with acetic anhydride through heterogeneous catalysis using ion exchange resin

The isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid derivatives of geraniol.

The biofouling that takes place on the surface of submerged objects is a source of technical and economic challenges, primarily in the marine industry, but also in many biotechnological processes. This phenomenon serves as a catalyst for the development and synthesis of antifouling compounds that are not only effective but also safe and environmentally friendly. Takamura's research group was inspired by these obstacles, and as a result, they created and synthesised a hybrid of molecules that had butanolide and geraniol moieties [34]. A collection of geraniol derivatives that have been developed is made up of eight different compounds. Figure 6 includes a few examples of the elements that are indicative of this series (14–17). According to the findings of the biological assessment conducted on the geraniol-butanolide hybrid compounds 13, it was demonstrated that these molecules possess antifouling activity against the cypris larvae of the barnacle Balanus amphitrite (Darwin, 1854). The EC50 values associated with these compounds were found to fall within the range of 0.30–1.31 μM. Geraniol derivatives have the potential to be used effectively as antifouling agents due to the fact that the majority of these compounds, thirteen of them, exhibit low or no toxicity. The biofouling that takes place on the surface of submerged objects, which is a source of technical and economic issues primarily in the marine industry but also in many biotechnological processes, serves as a catalyst for the development and synthesis of antifouling compounds that are not only effective but also safe and environmentally friendly. A hybrid of molecules that had geraniol and butanolide moieties was created and synthesised by Takamura's research group [34]. This was motivated by the hurdles that were presented to them. A collection of geraniol derivatives that have been developed is made up of eight different compounds. Figure 6 includes a few examples of the elements that are indicative of this series (14–17). The biological examination of the geraniol-butanolide hybrid compounds 13 demonstrated that these molecules possess antifouling activity against the cypris larvae of the barnacle Balanus amphitrite (Darwin, 1854). The EC50 values of these molecules were found to fall within the range of 0.30–1.31 μM. It is possible that geraniol derivatives could be successfully employed as antifouling agents due to the fact that the majority of these compounds, thirteen, exhibit low or no toxicity

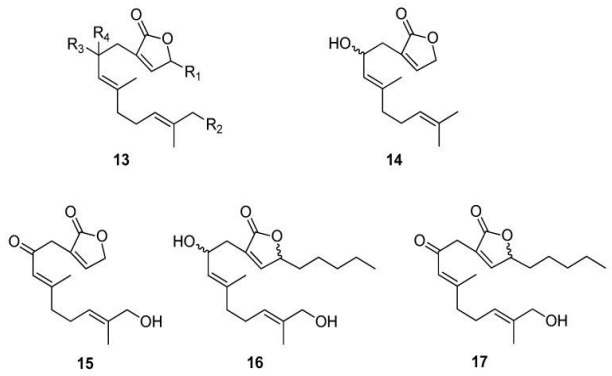

Fig: 6 The isomers of 6,7-dihydroxy-3,7-dimethyloct-2-enoic acid derivatives of geraniol.

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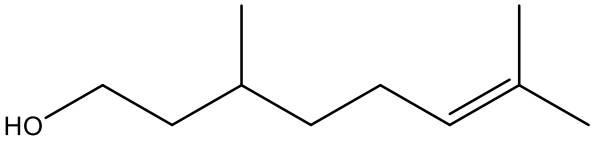
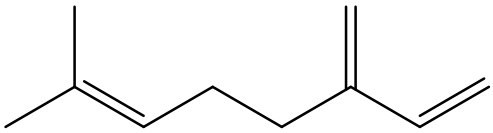


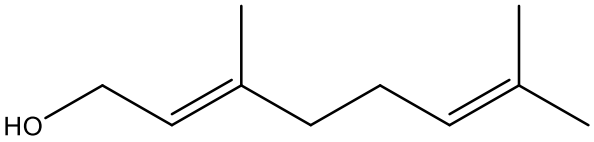
3,7-dimethyl-6-octen-1-ol

Citronellol



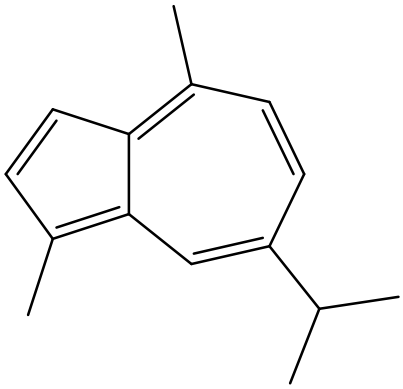
7-methyl-3-methylideneocta-1,6-diene

Myrcene



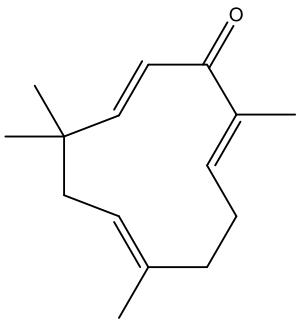
(2E)-3,7-dimethylocta-2,6-dien-1-ol

Geraniol



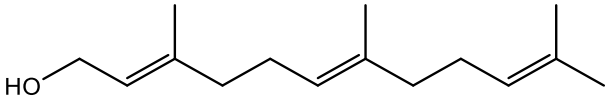
1,4-dimethyl-7-(propan-2-yl)azulene

Guaizulene



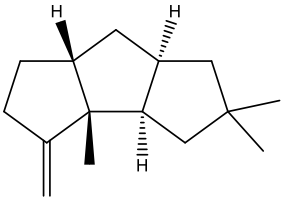
(2E,6E,10E)-2,6,9,9-tetramethylcycloundeca-2,6,10-trien-1-one

Zerumbone



(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol

Trans,trans-farnesol



(3aR,3bR,6aS,7aR)-3a,5,5-trimethyl-3-methylidene-1,2,3b,4,6,6a,7,7a-octahydrocyclopenta[a]pentalene

Hirsutenol

Fig: 7 Selected examples of some mixed hybrid compounds from plant derivatives essential oil

III. INNOVATION IN THE DELIVERY OF ESSENTIAL OILS

Drug delivery systems based on nanomedicine are tailored to achieve specific site- targeting cancer cells rather than normal cells. In the last few years, researchers have sought to tailor various promising delivery designs with EOs established for cancers. Here, we highlight several systems that show efficient anticancer effects compared with free EOs. The improvements include enhanced anticancer effects, improved anticancer mechanisms of action, and reduced side effects of anticancer drugs in cases involving combination treatments (Figure 10). As indicated by the literature describedin Figure 8 the research reflects possible future strategies for investigating nanoformulation delivery systems based on EOs.

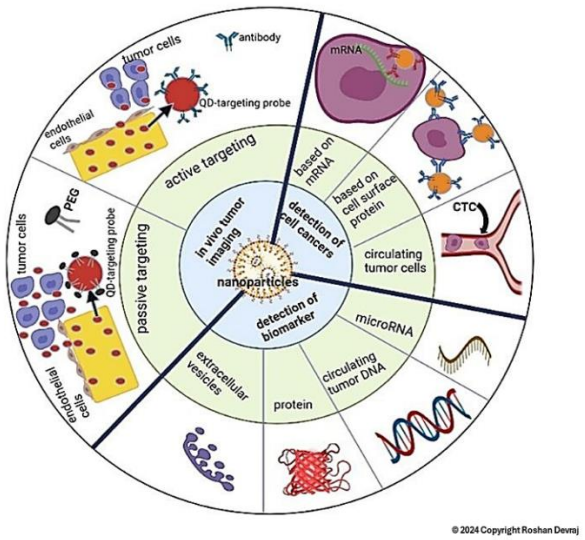


Fig: 8 Schematic illustration of the impacts of nanoformulations with EOs as compared withfree EOs in cancer applications.

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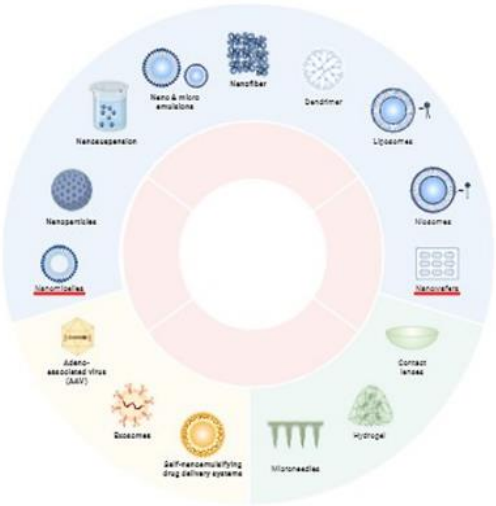

Fig: 9 Schematic representation of the current and potential future research strategies for nanoformulation delivery systems using EOs.

In comparison to other diagnostic modalities, various nanoparticle-based measurements in nanotechnology have demonstrated improved selectivity and sensitivity, as well as provided support for obtaining information that traditional measurements cannot. By leveraging the exceptional optical and electrical properties of nanomaterials, such as gold nanoparticles, along with their significantly larger surface area, they can be integrated with various types of sensors, including electrochemical sensors and DNA biosensors, to effectively detect biomarkers. This approach successfully addresses the limitations of traditional sensors, such as low conductivity, low sensitivity, and high cost (56). This enables early detection of tumoronset and timely intervention, ultimately aiming to enhance patient survival. Nanoparticles can also be utilized to monitor disease progression in patients, facilitating the formulation of more precise treatment strategies (57). Depending on the characteristics of the tumor microenvironment, such as hypoxia and acidity, nanoparticles can be designed to respond effectively in various environments, thereby enhancing treatment outcomes. By modifying the properties of nanoparticles, they can facilitate the uptake of drugs into the tumor tissue of the uterine cervix, increase their concentration in tumor tissue, and improve treatment efficacy. In addition, nanoparticles can be used as efficient carriers for drug delivery due to their good biocompatibility, permeability, and retention. Utilizing nanoparticles as delivery systems for anticancer agents can enhance drug efficacy, reduce dosing and treatment frequency, and potentially minimize the toxicity of antitumor drugs to the human body (58). With the deepening of research on nanotechnology, researchers have also designed some progressively stimuli-responsive drug delivery systems based on this foundation, which can enhance drug delivery more effectively (59). Furthermore, certain nanoparticles can be employed as specific markers targeting cancer cells (60).For example, using exosomes isolated from the tumors of cervical cancer patients as nanocarriers to transport drugs can robustly target the target cells (61). The development of nanotechnology has significantly enhanced various aspects of medicine, particularly in the field of cancer diagnosis and treatment, where improved diagnostic methods and novel drug delivery systems hold great promise (62). The combination of nanotechnology and cervical cancer research may yield unexpected advancements in the future.

Currently, there is no research analyzing the application of nanotechnology in cervicalcancer using the bibliometrics approach. Bibliometrics involves analyzing published information, such as books, journal articles, and data sets, along with their associatedmetadata like abstracts, keywords, and citations. It also includes using statistical information to describe the relationship between published works. Tools like VOSviewer and CiteSpace can be used to visualize and analyze academic literature inthis research field (63). By employing bibliometrics, we can gain a better understanding of existing research, identify current areas of interest, and predict future trends in nanotechnology for cervical cancer.

IV. CHALLENGES OF USING ESSENTIAL OILSN IN CERVICAL CANCER TREATMENT

Anti-Cancer Properties of Essential Oils

According to the International Agency for Research on Cancer (IARC), in 2012, the numberof new cases of cancer worldwide was 14.1 million, resulting in 8.2 million deaths [64]. Currently, cancer is the leading cause of death, and it is expected to increase by 70% over the next two decades, cancers of the lung, liver, stomach, colorectal, breast, prostate and esophagus being responsible for the majority of deaths [65,66]. These statistics emphasize the increasing demand for the development of novel and innovative chemotherapeutic drugs in the coming years.

Cancer can be broadly divided into three distinct stages. First, there is the initiation stage, in which exposure to carcinogens and impaired DNA repair mechanisms leads to damage and mutations in cells. Subsequently, the promotion stage ensues, characterized by excessive cell proliferation, alterations in tissue structure, and inflammation resulting fromthe expansion of the initially affected cells. Finally, there is the progression stage, in which preneoplastic cells form tumors through clonal expansion, promoted by increased genomic instability and alterations in gene expression [67].

Due to the progressive nature of cancer and changes in susceptibility to treatment, each stage of carcinogenesis requires specific chemotherapeutic approaches. More specifically, tumor progression is

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associated with genomic instability resulting from the accumulation of mutations affecting factors involved in cell proliferation, apoptosis and DNA repair, among other processes [68,69]. Chemotherapy drugs act mainly during the promotion stage, by inhibiting cell proliferation, increasing the rate of cell death, and inducing tumorcell differentiation [70].

Although research into the use of essential oils (EOs) as cancer therapeutic agents is relatively recent, it is interesting to note that nearly half of conventional chemotherapy agents are of plant origin, of which approximately 25% are directly derived from plants and 25% are chemically modified versions of plant products [71]. An example of such molecules is paclitaxel, also known by the trade name Taxol, which was originally extracted from the bark of the *Taxus brevifolia* tree [72]. The mechanism of action of this substance relies on disrupting the process of cell division, known as mitosis, by specifically targeting tubulin, a protein component of the cellular cytoskeleton. This action triggers the activation of the mitosis checkpoint and subsequently induces apoptosis, or programmed cell death, in cancer cells. [73]. Paclitaxel is used as a therapeutic agent, alone or in combination with other drugs, to treat different types of cancer, including ovarian, breast, and pancreatic cancers [74]. Due to the depletion of natural sources, the laboratory synthesis of this drug was necessary, mainly by a synthetic route involving patchoulol, a component of essentialoils, to produce patchoulol oxide [75].

More recently, researchers including Altshuler and his team have found that the enantiomer (+)-citronellal, a major component of the essential oils of *Corymbia citriodora* and *Cymbopogon nardus*, is also an effective compound in disrupting microtubule formation, similarly to well-known microtubule-disrupting agents such as colchicine and vinblastine [76]. This discovery highlights the potential of essential oils as anti-cancer therapeutic agents and opens new perspectives for their use in the treatment of cancer. However, it should be emphasized that more research is needed to assess their effectiveness and safety, as well as to determine the best application and dosage approaches.

EOs have demonstrated anticancer properties through various mechanisms. These include cancer prevention mechanisms, direct effects on established tumor cells, and interactions with the tumor microenvironment (fig 10) [77,78].

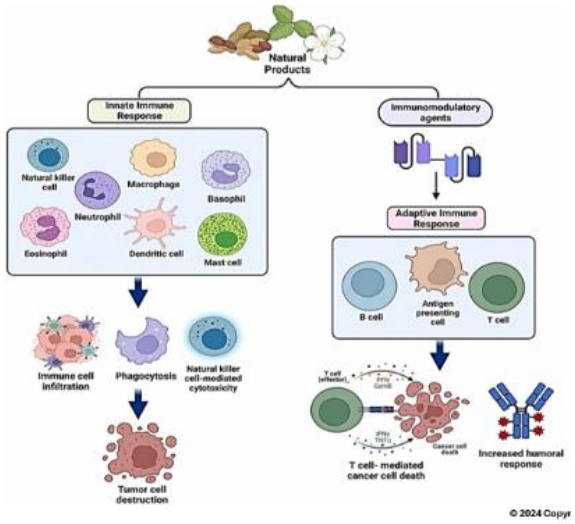

Fig: 10 Role of natural products in innate and adaptive immune responses. Natural products stimulate non-specific innate responses that leads to the elimination of tumor cells by various mechanisms such as immune cell infiltration, phagocytosis and NK-cell mediated cytotoxicity. Natural products also possess immunomodulatory properties that can cause the activation of the adaptive immune system leading to T-cell mediated tumor cell death and enhanced humoral responses. (NK: natural killer).

Antitumor Properties of Essential Oils

Although significant progress has been made in comprehending the mechanisms of cell transformation, cancer continues to pose a significant global health challenge, primarily due to the emergence of multidrug resistance (MDR) in transformed cells. Cellular plasticity and flexibility, as well as high exposure to anticancer drugs, make tumors resistant [79,80,81,82]. EOs whose antitumor properties have been known since antiquity through empirical studies, have been the subject of numerous publications confirmed by in vitro studies, showing their cytotoxic action against different tumor cell lines (Table 1). Several molecules present in essential oils; in particular, phenols (such as carvacrol, thymol and eugenol), alcohols (such as linalool), and aldehydes (such as cinnamaldehyde) possess antitumor properties [83]. EOs containing high levels of these compounds typically demonstrate the most effective anti-tumor properties when tested against human cancer cell lines [84]. Certain plant essential oils, such as eucalyptus, chamomile, mugwort, and verbena officinalis, possess the ability to induce apoptosis in tumor cells. Additionally, other essential oils have the capacity to disrupt the mitochondrial membrane potential [85].

Resistance to cell death, sustained proliferative signaling, and evasion of growth suppressants are key hallmarks of cancer [86]. Consequently, it is vital to devise therapeutic approaches that target apoptosis

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(programmed cell death) induction and cell proliferation arrest. Research has shown that EOs can trigger both intrinsic (mitochondria-dependent) and extrinsic (death receptor-dependent) pathways of apoptosis.

Girola et al. (2015) examined the antitumor properties of a compound called camphene, isolated from the essential oil of *Piper cernuum*, on melanoma cells. Their results showedthat this compound was able to induce apoptosis by activating the caspase-3 pathway, while also triggering endoplasmic reticulum (ER) stress signaling [87]. Another study investigated the mechanism of action of carvacrol, a monoterpenoid phenolic compound abundant in the essential oils of oregano and thyme [88]. In a metastatic breast cancer cell line called MDA-MB-231, carvacrol induced apoptosis by causing permeabilization of the mitochondrial membrane, resulting in release of cytochrome C, activation of caspases (indicated by cleavage of poly ADP ribose polymerase (PARP)), and DNA fragmentation [89]. Frankincense extracts derived from *Boswellia sacra* have also been studied and shown an ability to induce apoptosis with PARP cleavage in MDA-MB-231 cells, with increased specificity towards cancer cells [90]. Studies have also revealed that citral, present in several essential oils, induces caspase activation and, consequently, apoptosis indifferent types of cancer cells, including colorectal cancer and glioblastoma [91,92,93]. Inaddition, citral treatment was associated with reduced expression of factors promoting cancer cell growth and survival, such as aldehyde dehydrogenase 1A3 (ALDH1A3) and microtubule affinity regulatory kinase 4 (MARK4) [94,95].

Protein kinase B (PKB) is a key molecule involved in cell metabolism, transcription, cell cycle progression, and survival [96]. A study showed that *Litsea cubeba* seed oil vapor induced cell cycle arrest and apoptosis in non-small cell lung carcinoma cells, a type of cancer with a high mortality rate [97]. These effects were attributed to a significant decrease in the expression of the protein mTOR (mechanistic target of rapamycin) and phosphorylation capacity of PPDK1 (protein pyruvate dehydrogenase kinase 1), which led to the dephosphorylation of PKB and activation of the caspase-dependent apoptosis pathway [98]. In addition, PKB dephosphorylation inactivated the mdm2 (murine double minute 2) protein, leading to increased p21 expression and subsequent caspase initiation after G1 phase arrest/S of the cell cycle [99]. The dual mechanism of action of essential oils provides them with antiproliferative and antioxidant properties. Direct vapor inhalation of essential oils may offer advantages for localized delivery to the site of lung cancer [100].

In another study, Wu et al. (2013) demonstrated that administration of organosulfur compounds from garlic significantly reduced cell viability in a dose- and time-dependent manner, with diallyl trisulfide being the most effective [101]. These effects were observed in a hepatic tumor cell line called J5, where they induced G2/M phase cell cycle arrest and cell death through decreased expression of cyclin-dependent kinase (CDK) 7, resulting in inhibition of the CDK1/cyclin complex [102].

Abnormally elevated expression of nuclear factor κB (NFκB) is associated with cancer initiation and progression [103,104,105]. *α*-Terpineol, a monoterpenoid alcohol, has been shown to downregulate NFκB transcription in different tumor cell lines, with a particularly pronounced inhibitory effect on the small-cell lung carcinoma cell line NCI-H69 [106]. Additionally, *α*-terpineol has been found to have synergistic properties with linalyl acetate, another monoterpene, in colon cancer cells. This combination inhibited NFκB expression and led to apoptosis [107].

Cancer Cell Specificity of Essential Oils

Conventional chemotherapy drugs are more cytotoxic to cancer cells due to their higher rate of cell division. However, this cytotoxic action presents problems of cell specificity and associated toxicity for healthy cells [108]. The resulting side effects can impede healing and pose a danger to the patient's life. Current therapeutic approaches, such as surgery followed by chemotherapy, radiotherapy, and immunotherapy offer better chances of cancer treatment and remission [109]. However, they do not fully address the need for cancer cell- specific therapy or a larger therapeutic window between normal and cancer cells. Although the new targeted strategies represent a significant improvement, they still face cell- specificity issues and high attrition when moving from preclinical studies to clinical application [110]. The use of monoclonal antibodies shows high selectivity, but limited cytotoxic activity [111]. Thus, the combined administration of monoclonal antibodies and conventional chemotherapy drugs represents a potential route to address this issue, delivering the highly cytotoxic agent specifically to cancer cells [112].

V. CONCLUSION

Due to the fact that pain is experienced by more than eighty percent of cancer patients, it is considered to be one of the most terrifying outcomes of cancer [113]. For the purpose of managing pain associated with cancer, the present systematic review and meta-analysis draws attention to the limited number of clinical trials that have been conducted in the field of aromatherapy and the use of essential oils. All of the studies that are suitable for inclusion in this analysis involve patients who are older than 18 years old, with the exception of the trials that were carried out by Ndao and collaborators [114] and Triana and coworkers [115] that focused on a paediatric population population. Nevertheless, there are numerous types of cancer that allow for longer survival than in the recent past; hence, the probability of age-related comorbidities needs to be taken into consideration. The capability of self-reporting pain and

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of responding to the assessment of pain intensity through the VAS/NRS/VRS is one of the most common inclusion criteria of the studies that were retrieved by this systematic search. In particular, the study that was conducted by Triana and colleagues, in which pain is inferred and rated by the nurse [116], is the only one that does not meet this requirement. The significance of this element lies in the fact that it highlights the necessity of doing more accurate pain assessments during cancer treatment. In example, cancer-related pain is characterised by a multidimensional nature comprising of diverse physiopathology and aetiology and including substantial sensory, affective, cognitive, and behavioural components, and research still lacks the identification of these key elements [117]. As a result, the usage of unidimensional scales for the assessment of pain should be abandoned and replaced with the utilisation of multidimensional scales such as the Brief Pain Inventory (BPI) [118]. This is because unidimensional measures are suitable for acute situations and for the evaluation of the solitary intensity domain. In point of fact, the BPI is able to quantify not only the sensory dimension of pain intensity but also the reactive dimension of the interference that pain has in the life of the patient [119]. In the field of integrative oncology, this is becoming an increasingly crucial factor in determining whether or not essential oils are effective and safe in treating pain. There is a primary effect that essential oils have on both general well-being and sleep, as demonstrated by the studies that were discovered via the current search of databases and the inspection of references across the literature. However, it is possible that the processing of pain is connected to these symptoms and the benefits that they bring. [120], despite the fact that it is not always recognised by an appropriate measurement method, particularly in patients who are older and in cases of depression [121]. A meta-analysis that confirms the efficiency of essential oils used as aromatherapy in the reduction of the intensity of cancer-related pain, as measured by unidimensional pain measures ($p = 0.002$), lends the aforementioned assertion credibility. The high heterogeneity among the studies ($I2 = 96\%$) and the publication bias that occurs in the field of essential oils, as well as oral supplements and nutraceuticals [122,123] are two other factors that demonstrate that only six out of the twelve studies that were included in the synthesis are eligible for meta-analysis. This is in agreement with the fact that there was a lack of use of homogeneous and appropriate devices. In particular, the studies that were included highlight extremely various study designs, as well as certain issues regarding the possibility of bias. These concerns mostly stem from the insufficient baseline assessment and outcome data, as well as the small sample size. One example is the research carried out by Triana and her colleagues [124], which, due to the limited number of participants in the study, is given a lower weight in the meta-analysis presented here. The issue of pain assessment is even more important for elderly populations that are experiencing cognitive decline. These populations require appropriate observational tools [125,126,127], as well as valid and reliable methods that have good psychometric and clinimetric properties in this context. Furthermore, it is important to take into consideration additional sources of pain and the treatment of those sources [128,129,130,131,132]. The fact that various forms of cancer might have varying degrees of discomfort is another factor that makes the comparison more challenging. The essential oil of lavender is one of the most often used essential oils; nevertheless, due to the fact that it primarily affects the cholinergic system, it does not possess a robust preclinical explanation for analgesic activity [133,134]. This is the case with BEO, which is the most commonly used essential oil. Given that the latter did not prove to be effective in the research conducted by Ndao and his colleagues The fact that the sample size was very small and consisted of patients with varying diagnoses and treatment histories may, at the very least, partially explain the findings of [135]. In addition, the fact that essential oils did not reduce the severity of pain in some studies may be related to the fact that the treatment was started too late. Essential oils can only be used as a palliative treatment when chronic pain has already been established, particularly for chronic intermittent pain; however, this should be avoided by beginning treatment earlier [136,137].

For this reason, it is vital to establish for natural products a step-by-step preclinical-to-clinical pathway in order to provide a justification for effective and safe usage. This is necessary in order to provide good certainty of the body of evidence for the therapy of cancer-related pain using essential oils.Due to the fact that pain is experienced by more than eighty percent of cancer patients, it is considered to be one of the most terrifying outcomes of cancer [113]. For the purpose of managing pain associated with cancer, the present systematic review and meta-analysis draws attention to the limited number of clinical trials that have been conducted in the field of aromatherapy and the use of essential oils. With the exception of the trials that were carried out by Ndao and collaborators [114] and Triana and coworkers [115] that focused on a paediatric population, all of the studies that are suitable for inclusion in this analysis contain patients who are over the age of 18. Nevertheless, there are numerous types of cancer that allow for longer survival than in the recent past; hence, the probability of age-related comorbidities needs to be taken into consideration. One of the most common inclusion criteria of the studies that were retrieved by this systematic search is the capability of self-reporting pain and of responding to the assessment of pain intensity through the VAS/NRS/VRS. This is in particular the case with the exception of the study that was carried out by Triana and colleagues, in which the nurse infers and rates the level of pain [116]. The

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significance of this element lies in the fact that it highlights the necessity of doing more accurate pain assessments during cancer treatment. In instance, cancer-related pain is characterised by a multifaceted nature comprising of diverse physiopathology and aetiology and including substantial sensory, affective, cognitive, and behavioural components, and research still lacks the identification of these key elements [117]. Therefore, the usage of unidimensional measures for the assessment of pain should be complemented and replaced by the utilisation of multidimensional scales such as the Brief Pain Inventory (BPI) [118].

This is because unidimensional scales are suitable for acute situations and for the evaluation of the solitary intensity domain. In point of fact, the BPI is able to quantify not only the sensory dimension of pain intensity but also the reactive dimension of the interference that pain causes in the life of the patient [119]. In the field of integrative oncology, this is becoming an increasingly crucial factor in determining whether or not essential oils are effective and safe in treating pain. There is a primary effect that essential oils have on both general well-being and sleep, as demonstrated by the studies that were discovered via the current search of databases and the inspection of references across the literature. However, it is possible that the processing of pain is connected to both these symptoms and the advantages they provide [120], despite the fact that it is not always recognised by an appropriate measurement method, particularly in patients who are older and in cases of depression [121]. A meta-analysis that confirms the effectiveness of essential oils used as aromatherapy in the reduction of the intensity of cancer-related pain, as measured by unidimensional pain measures ($p = 0.002$), contributes to the support of this assertion. However, in accordance with the absence of homogeneous and appropriate devices, only six out of the twelve studies that were included in the synthesis are suitable for meta-analysis. This is demonstrated by the high heterogeneity that exists among the studies ($I2 = 96\%$) and by the publication bias that is present in the field of essential oils, as well as in the field of oral supplements and nutraceuticals [122,123]. In particular, the studies that were included highlight extremely various study designs, as well as certain issues regarding the possibility of bias. These concerns mostly stem from the insufficient baseline assessment and outcome data, as well as the small sample size. For example, the research carried out by Triana and her colleagues [124] has a smaller sample size, which results in it having a lower weight in the meta-analysis. Additionally, the issue of pain assessment is of even greater significance for elderly populations that are experiencing cognitive decline. These populations require appropriate observational tools [125,126,127], as well as valid and reliable methods that have good psychometric and clinimetric properties in this context. Furthermore, it is important to take into consideration additional sources of pain and the treatment of these sources [128,129,130,131,132]. In addition, the fact that different forms of cancer might result in varied levels of discomfort makes the comparison more challenging. Lavender essential oil is one of the most often used essential oils; yet, due to the fact that it primarily affects the cholinergic system, it does not possess a robust preclinical explanation for analgesic efficacy [133,134]. This is the case with BEO, which is the most commonly recommended essential oil. There is a possibility that the ineffectiveness of the latter un the research conducted by Ndao and colleagues [135] could be explained, at least in part, by the small sample size that consisted of patients who had diverse diagnoses and treatment histories. Furthermore, the failure of essential oils to reduce the intensity of pain in some trials may be attributable to a delayed initiation of treatment, which can only serve as a palliative measure when chronic pain has already been established, particularly in the case of chronic intermittent pain and nausea (CIPN), whereas it should be prevented through early therapy [136,137]. For this reason, it is vital to establish for natural products a step-by-step preclinical-to-clinical pathway in order to provide a justification for effective and safe usage. This is necessary in order to provide good certainty of the body of evidence for the therapy of cancer-related pain using essential oils.

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