Section A-Research Paper
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Essential Oils: A Natural Therapy for the Treatment of Cancer

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ABSTRACT

Nature has always played a significant role in the treatment of various diseases including cancer, one of the most significant health challenges in the world nowadays. Among the available natural products used in therapy natural essential oil constituents play a key role in the prevention and treatment of cancer. Natural essence in the form of essential oil has been explored comprehensively by various groups of researchers in the field of cancer treatment. It works via several mechanisms such as antioxidant, anti-mutagenic, anti-proliferative, etc. for their chemo preventive action. Even aromatherapy with the use of essential oils has been widely employed to reduce the complications occurring during cancer/chemotherapy treatment like nausea, vomiting, etc. This review focuses on the various constituents of essential oils with their potential therapeutic efficacy against cancer along with their potent mechanism of action.

Keywords: Cancer, essential oil, anti-proliferative, aromatherapy, chemotherapy, treatment

INTRODUCTION

Cancer is a worldwide health issue with highest morbidity and mortality and having both psychological and economic challenges. [1] Terrifyingly, by 2030, cancer deaths will be elevated to about 13.1 million. Therefore, the entire healing for cancer is still a challenge for human beings. [2] As reported by some authors, in New Zealand, North America, Australia and Western Europe the incidence of cancer and mortality are higher than the remaining worldwide. In the United States, about one in four deaths is ascribed to cancer according to reports in some studies. [3] Mostly, cancer has been identified in the older adults, but due to unavoidable exposure to radiation and chemicals, and changes in lifestyle leads to progression of carcinogenesis in early phases of human life also. [4] Basically, cancer is an abnormal growth of cells in the body that results to death. It is characterized through the multiplication of the abnormal cells that fails to respond properly to normal regulatory mechanism. Generally, the cells of cancer attacks and ruin the normal cells. Imbalance in the body results cancerous cells to grow which results more imbalance in the body. Mutations in the DNA are one of important factor which results in progression of cancer by the rapid division and multiplication of cells. However, normal cells have the capability to repair the

majority of mutations in their DNA, but when the normal cells lost the capability to repair the mutation then the cells grow rapidly and become cancerous as shown in Fig.1.

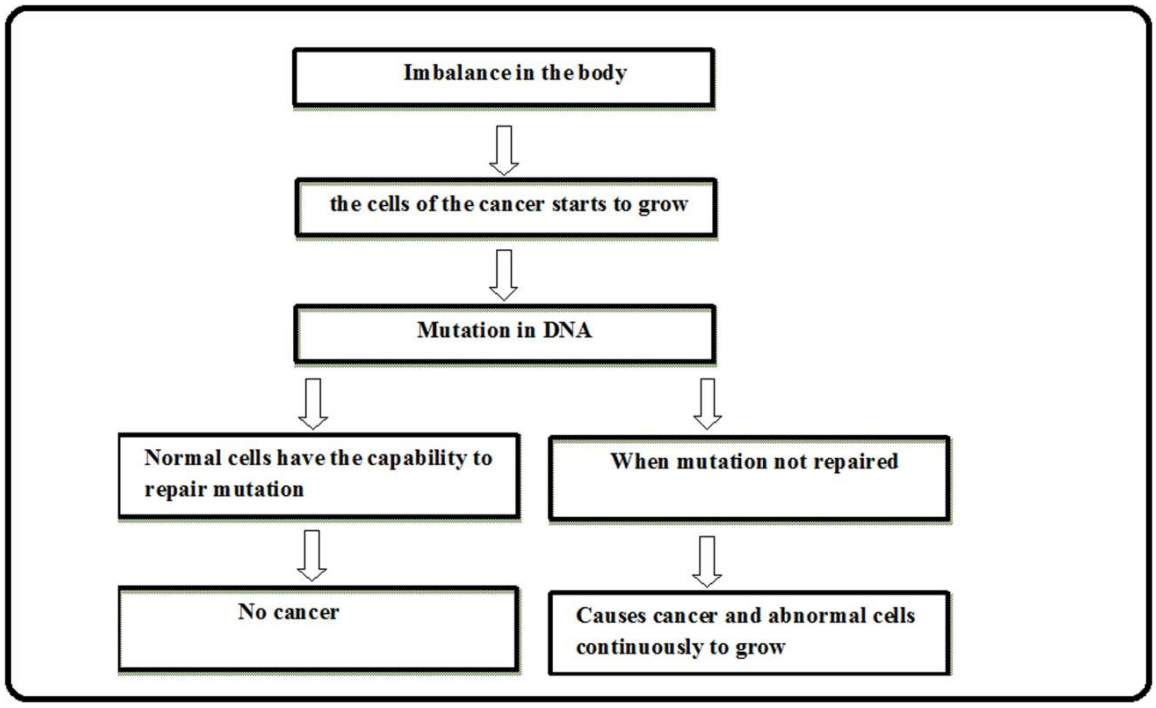

Fig. 1 Mutagenic factors in DNA for cancerous development

Term "carcinogenesis" is used to explain expansion of cancer, which is a multiple-step process comprising of initiation, promotion and progression of uncontrolled cells. The initiation step includes damage in DNA. At the promotion step, cells starts to multiply and extend into abnormal cells. During the final step i.e. progression step, changes in the abnormal cells takes place which results in formation of malignant cells as shown in Fig.2 [5, 6].

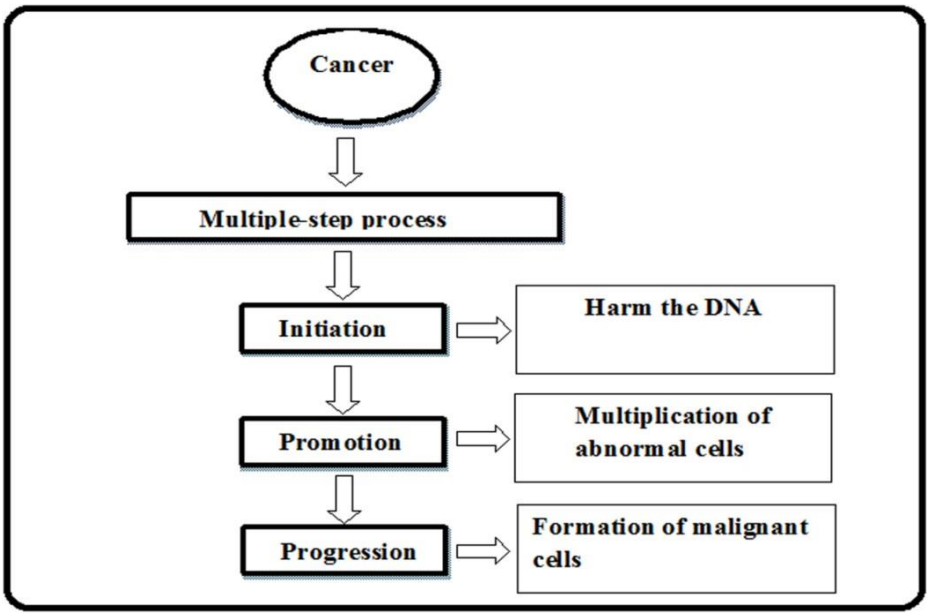

Fig. 2 Carcinogenesis: A multistep process

Allopathic treatment of cancer with chemotherapeutic drugs leads to many toxicity problems such as myelotoxicity, cardiotoxicity, renal toxicity, bladder toxicity, etc. [3] Natural source based drugs could be a better alternative to avoid such toxicological problems. Now days, plants are reservoirs of new chemical entities which gives an encouraging line for research on cancer. Due to pleiotropic actions of phytochemicals on the target sites through several ways, these are examined as appropriate aspirates for anticancer drug development. [7] During the past few years, invention of natural-product-based drug is expanding on the basis of novel technologies like combinatorial synthesis and high-throughput screening, and their related approximates. [8] Many natural herbs as well as fruits and vegetables such as carrots [9], gallicacid extracted from grape seed [10], ginkgo biloba [11], have been recommended for the treatment of cancer in traditional medicine. Also several flavonoids found in fruits, vegetables and medicinal herbs such as celery, onion leaves, parsely etc. having capability to serve as anticancer agent against several forms of human malignancies like breast, glioblastoma, lung, colon, prostate, and pancreatic cancers. [12] Various types of essential oils like sandalwood oil, turmeric oil, peppermint oil, etc. has been utilized for the treatment of skin papilloma. [13] The wide range of plants, vegetables and fruits, like onion, broccoli and buckwheat [14], natural compounds like vincristine, etoposide, irinotecan and paclitaxel have been employed for the prevention and treatment of cancer. [8]

Nutrition intervention also helps to the patient in the prevention of ordinary types of cancer. [15] About 40% of growing cancer danger can be cured by dietary alterations which is one of the major encouraging lifestyle changes. [16] A broad range of studies over decades has determined the existence of several potent chemopreventive agents in generally consumed beverages like tea, coffee, and wine as well as in fruits, nuts, raisins and herbal extracts. [1]

As per reported by Avni G. Desai et.al, (2008), the National Cancer Institute (NCI) has screened about 35,000 plant species for potent anticancer activity, from which nearly 3,000 plant species have displayed the reproducible anticancer activity. [3]

ROUTES OF EXPOSURE TO CARCINOGENS

Carcinogens can enter into the body via ingestion, inhalation and dermal contact. The ordinary routes through which carcinogens can be ingested are via contaminated water, food and breast milk. These are generally the major route of exposure to Persistent Organic Pollutants (POPs) and heavy metals. Inhalation is the primary pathway of exposure to carcinogens present in the air involving Polycyclic aromatic hydrocarbons (PAHs), detected in the tobacco smoke and in the form of particles in air pollutants. As skin is the major organ in the body so transdermal is also a common pathway for exposure to coal tars which causes cancer. [4]

VARIOUS RESPOSIBLE FACTORS OF CANCER

There are various factors which leads to cancer such as changes in life style which includes incorrect diet, smoking, tobacco habits and intake of alcohol which causes elevating the activation of pro-carcinogens as well acting as a solvent for introduction of destructive carcinogens into the body cells [17], and biological factors which is based upon age, hormonal changes, changes in immunity in body and genetic mutations. [18] Exposure to chemicals and ionizing radiations has been found to be the prime factor in occupational type of cancerous diseases. [7] Other factors likelack of physical activity [5] and infectious microbesetcalso shows considerable influence on disease expression and progression as discussed in Fig.3 [19].

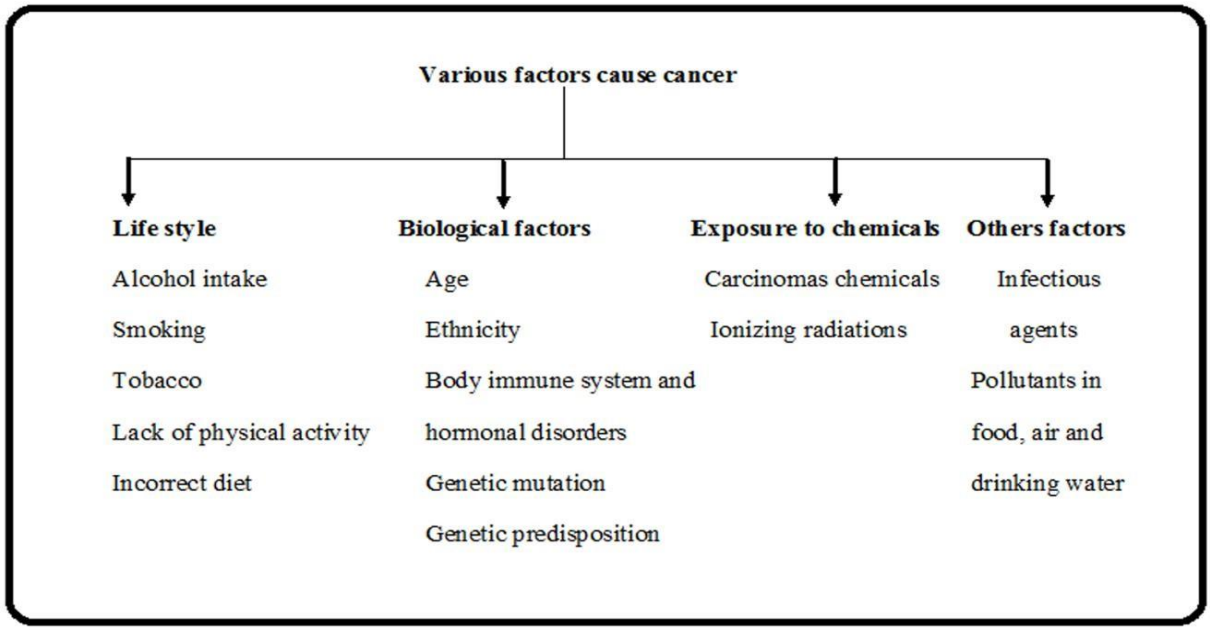

Fig. 3 Responsible factors of cancer

ESSENTIAL OILS IN THE TREATMENT OF VARIOUS TYPE OF CANCER

Essential oils are also known as volatile oils. They are complex, natural, volatile and odorous molecules synthesized via secretory cells of the aromatic plants. Natural essential oil plays a significant role in the prevention and treatment of cancer. [21] Essential oils exhibits several properties like virucidal, bactericidal, insecticidal, antiparasitic, fungicidal, etc. and are broadly utilized in cosmetic, sanitary, agriculture, food and pharmaceutical industries. Anticancer activity of the essential oil has been reported by various researchers. They are richly present in the leaves, bark, fruit and rhizomes of plant. Several mechanisms such as improvement of immune functions and surveillance, antimutagenic, antioxidant, enzyme induction, enhancing detoxification, anti-proliferative, variation of multi-drug resistance and synergistic mechanism of volatile constituents are accountable for their chemo preventive properties. Essential oil increases the activity of white blood cells, making it more effective for eliminate foreign particles and microbes from the body. [20-21] Some of the constituents of essential oil which has been reported for their anticancer activity are summarized in the Table 1and Fig.4.

Table 1 Constituents of some essential oil and their mechanism of action against cancer

Name of the constituents	**Source and family**	**Mechanism of action reported**	**Cell line used / Model used**	**References**
Zerumbone	Ginger (Zingiberaceae)	Reduce platelet aggregation	Healthy Saudi people between ages 18 to 60 years, both males and females	KimMihye *et al.*, (2009), AlAskarAhmed *et al.*, (2019), [22-23]
Perillyl alcohol	Mint (Lamiaceae), Cherries (Rosaceae), Celery seeds (Umbelliferae) Lemongrass (Poaceae), and Caraway (Apaiaceae) etc.	Inhibit cell proliferation, In cell cycle increase the G0/G1 fraction and simultaneous decline the cell population in the S phase (G1/S arrest)	HCT 116 human colon carcinoma cells	BardonSylvie *et al.*, (2002), BoachonBenoît *et al.*, (2018), M. mccuneLetita *et al.*, (2011), Kooti1 Wesam *et al.*,(2014), [24-27]
		Inhibits UVB-induced murine skin	Squamous cell tumor models,	PavithraP.S. *et al.*, (2018), Wifek1 Mahouachi *et al.*,

		Carcinogenesis, 7,12-dimethylbenz[a]anthracene(DMBA)-induced murine melanoma, inhibited photocarcinogenesis, inhibited UVB-induced activator protein (AP)-1 transactivation.	nonmelanoma model of mouse skin carcinogenesis and human keratinocytes	(2016), Johri R. K., (2010) [13,28, 29]
Geraniol	Rose (Rosaceae), Palmarosa (Poaceae), and Lemongrass (Poaceae)	Increase sensitivity to 5-fluorouracil treatment	Human colon cancer cell line Caco-2	Pavithra P.S. *et al.*, (2018), Wifek1 Mahouachi *et al.*, (2016), Carnesecchi S. et.al, (2002), Smitha G.R. *et al.*, (2018), [13,28,30, 31]
		Inhibit Mevalonate Biosynthesis	C57BL female Mice	Yu Suzahne G. *et al.*, (1995), [32]
Citral	Lemongrass (Poaceae)	Caused the externalization of phoshpotidylserine and decreased the potential of mitochondrial membrane in HCT116 and HT29 cells	HCT116 and HT29 cells	Wifek1 Mahouachi *et al.*, (2016), SheikhaBassem Y. *et.al.*, (2017), [28,33]
		Antiproliferative effect through the induction of apoptosis	NB4 cells	Xia Hailong *et al.*, (2012), [34]
		Modulation of cellular oxidative status and intracellular signaling	B16F10	Sanches1 Larissa Juliani *et al.*, (2017), [35]
		Inhibition of cell growth via cycle arrest in G2/M phase and apoptosis induction	Human breast cancer cell line MCF-7.	Chaouki Wahid *et al.*, (2009), [36]

Eugenol	Leaf and stem of clove (Myrtaceae), Cinnamon leaves (Lauraceae), and Leaves of basil (Lamiaceae)	Decrease intracellular non-protein thiols and enhance lipid layer break	HT-29 and HCT-15	Lesgards Jean-François *et al.*, (2014), JaganathanSaravana Kumar *et al.*, (2011), [37, 38]
		Arrests cells in the S phase of the cell cycle, Inhibition of E2F1 Transcriptional Activity	WM1205Lu	Ghosh Rita *et al.*, (2005), [39]
		Inhibits cell proliferation throughs NF-κB suppression in a rat model	N-methyl-N′-nitro-N-nitrosoguanidine (MNNG)	Manikandan P. *et al.*, (2011), [40]
		suppressed the COX-2 (cyclooxygenase-2) gene expression, Inhibited cell proliferation	HT-29 cells	Kim Sun Suk *et al.*, (2005), [41]
		Apoptosis and S Phase Cell Cycle Arrest	G361 Human Melanoma Cells	Choi Byul-Bo Ra *et al.*, (2011), [42]
Carvacrol	Thyme and Oregano (Lamiaceae)	Reduce potential of mitochondrial membrane of the cells, Caspase activations	MDA-MB231 cells (Human metastatic breast cancer cell line)	Memar Mohammad Y. *et al.*, (2017), Arunasree K.M., (2010), [43-44]
		Cell cycle arrest in the G2/M phase,	HCT116	

		Reduced cyclin B1 expression, cell invasion, Inhibits proliferation and induces apoptosis		Fan Kai *et al.*, (2015), [45]
		DNA fragmentation and induces apoptosis	HeLa and SiHa cells	Mehdi Syed Jafar *et al.*, (2011), [46-47]
D-limonene	Orange, Lemon, Grapefruit, Mandarin, and Lime (Rutaceae)	Modifies oxidative stress, inflammation, and Ras-ERK pathway. Decreased the TPA induced edema and hyperplasia, orinithine decarboxylase activity, thymidine inclusion into DNA and expression of cyclooxygenase-2.	Female Swiss albino mice (6–8 weeks old; 20–25 g)ss	Rafiq Shafiya *et al.*, (2016), Chaudhary SC *et al.*, (2012), [48- 49]
		Circulating metabolites selectively suppressed the isoprenylation of cellualar protein	NMU-induced rat mammary tumours	Chanderl S.K. *et al.*, (1994), [50]
		Induce apoptosis through the mitochondrial death pathway and inhibition of the PI3K/Akt pathway	LS174T human colon cancer cell line	JiaShu-sheng *et al.*, (2013), [51]
		Improve latency	Female Sprague-Dawley rats	ElegbedeJ.A. *et al.*, (1984), [52]
		Minimize tumor multiplication and reduce the size of tumor, Suppress the breaat tumor growth	Hras128 rats	Asamoto Makoto *et al.*, (2002), [53]
		Suppressed the development of human prostate cancer cells and induced apoptotic cell death,	Human prostate cancer cells PC-3 and LNCaP	Bommareddy Ajay *et al.*, (2012), SubasingheUpul, (2013), [54, 55]

Alpha-Santalol	Sandalwood oil (Santalaceae)	Induced apoptosis via activation of caspase-3		
		Induced G2/M phase cell cycle arrest, Modified expressions of cell cycle protein, Resulting in depolymerization of microtubules in UACC-62 cells	p53-mutated human epidermoid carcinoma, A431 cells and p53 wild-type human melanoma UACC-62 cells	Zhang Xiaoying *et al.*, (2010), [56]
		Suppress cell viability, Suppress cell proliferation, Induced DNA fragmentation in Breast Cancer Cells, Induced G2/M phase cell cycle arrest, Initiation of apoptosis, Modify protein levels	Human Breast cancer cells (MCF-7 cells and MDA-MB-231 cells)	Santha Sreevidya *et al.*, (2013), [57]
		Decreased in entire survivin level and protein expression in cultured cancer cells	Breast Cancer Cells (Cell lines MDA-MB-231 and MCF-7)	Bommareddy Ajay *et al.*, (2015), [58]
Camphene	Piper cernuum oil (Piperaceae)	Induce apoptosis via intrinsic pathway, Modify endoplasmic reticulum and mitochondria, Damage potential of mitochondrial membrane and improved caspase-3 activity, Evoke ER-stress proteins and caspase-3,	Melanoma cells	Girola Natalia *et al.*, (2015), [59]

		In-vivo suppress subcutaneous tumor development		
Menthol	Lemongrass (Poaceae), Palmrosa (Poaceae), Eucalyptus (Myrtaceae), and Peppermint (Lamiaceae)	Suppress topoisomerase I, IIα and IIβ, Enhance the levels of NF-IB gene expression, Impair DNA	Human Gastric Cancer SNU-5 Cells	Wifek1 Mahouachi *et al.*, (2016), Smitha G.R. et.al, (2018), Jing-Pin Lin et.al, (2005), Shah Gagan *et al.*, (2016), Salehi Bahare *et al.*, (2018), [28, 31, 60-62]
		Influx of extracellular Ca^{2+}, Inhibits cellular viability via TRPM8 activation	Human Melanoma Cells	Slominski Andrzej, (2008), [63]
		Suppress the cell development, Induced cell cycle during G0/G1 phase, Down-regulation of focal-adhesion kinase	Prostate Cancer DU145 Cells	WangYongzhi *et al.*, (2012), [64]
		Induce cytotoxicity against WEHI-3 cells, Suppress the distinguish of the precursor of macrophage and granulocyte.	WEHI-3 Leukemia Cells	Lu Hsu-Fung *et al.*, (2007), [65]
	Sweet basil (Lamiaceae), Mentha citrate			Lesgards Jean-François *et al.*, (2014), Salehi Bahare *et al.*, (2018), Sahib

Linalool	(Lamiaceae), And Coriander seeds (Apiceae)	Chemosensitizing agent	Human Breast Adenocarcinoma Cells	Najla Gooda et.al, (2012), Ravizza Raffaellaet.al, (2008), [37, 62, 66, 67]
Linalool		Induce apoptosis through p53 up-regulation and cyclin-dependent kinase inhibitors,	Leukemia cells	Gu Ying *et al.*, (2009), [68]
		Suppress mitochondrial complexes I and II, Enhance reactive oxygen species, Reduced ATP and GSH levels	HepG2	Usta Julnar *et al.*, (2009), [69]
1,8-Cineole	Eucalyptus globules (Myrtaceae)	Upregulate p53 pathway Induce apoptosis and G2/M arrest, Alteration mitochondrial memberane	A431 cells (Skin carcinoma cells)	Shah Gagan *et al.*, (2016), Sampath Sowndarya *et al.*, (2018), [61,70]
		Induce apoptosis, Inhibits human colorectal cancer proliferation, Inactivate survivin and Akt and activate p38,	RKO cells and Human Colon Cancer Cell Lines HCT116	Murta Soichiro *et al.*, (2013), [71]
1,6-dimethyl spiro[4.5]decane, caryophyllene oxide, and β-caryophyllene	Nepetacurviflora (Lamiaceae)	Inhibitory effect against HeLa cancer cell, an inhibitory role in cervical cancer cell migration and proliferation	HeLa cells, cervical cancer cells culture	Jaradat *et al.*, (2020), [72]
Alpha-pinene, Beta-pinene, and Sabinene	Cedrusatlantica (Pinaceae)	mitochondrial dehydrogenase enzymes of active cells reduce the MTT to blue formazan reflecting cell viability	MCF-7 breast cancer cell line	Belkacem *et al.*, (2021), [73]

catechins, Epigallocatechin3gallate	Green tea (Theaceae)	EPR effect	Human liver (HepG-2), Breast (MCF-7) and Colon (HCT-116) cancer cell-lines	Farrag *et al.*, (2021), [74]

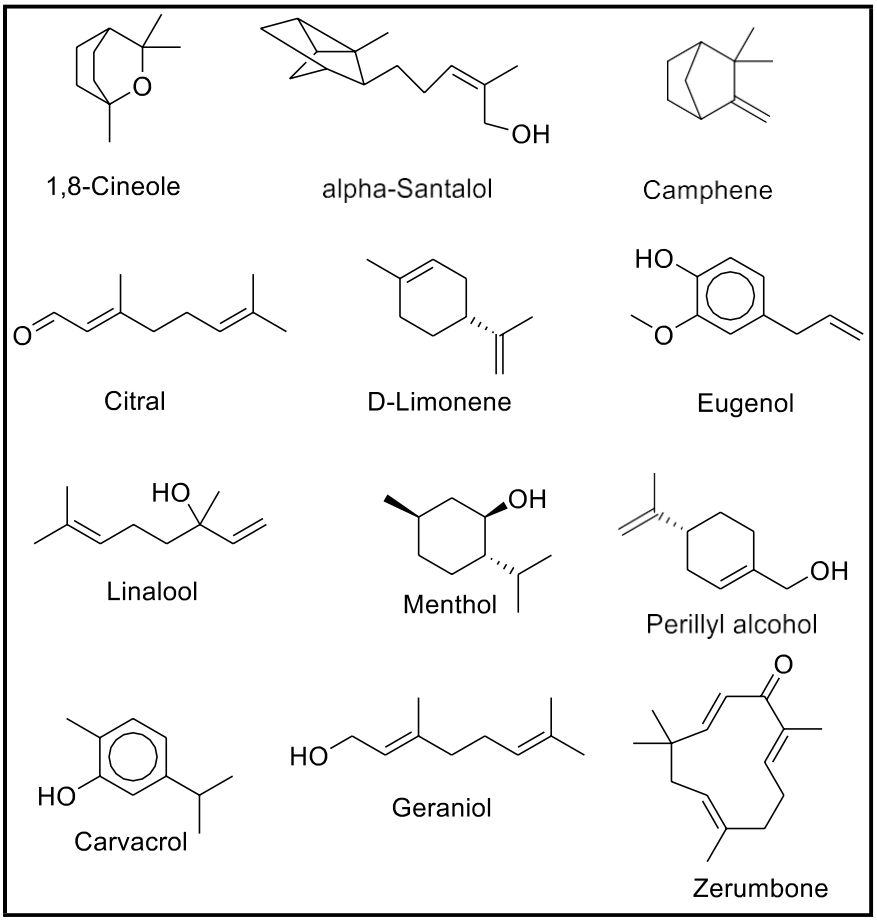

Fig.4 Structure of various constituents of essential oil

MECHANISM OF ACTION OF CANCER INHIBITION

ANTI-MUTAGENIC METHOD

Antimutagenic activity of essential oil is contributed to certain anticancer mechanisms of action represented in Fig.5 involving inhibit penetration of mutagens into cells, activate cell antioxidant

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enzymes, inactivate mutagens via scavenging activity, and inhibit metabolic conversion of mutagens by P450.

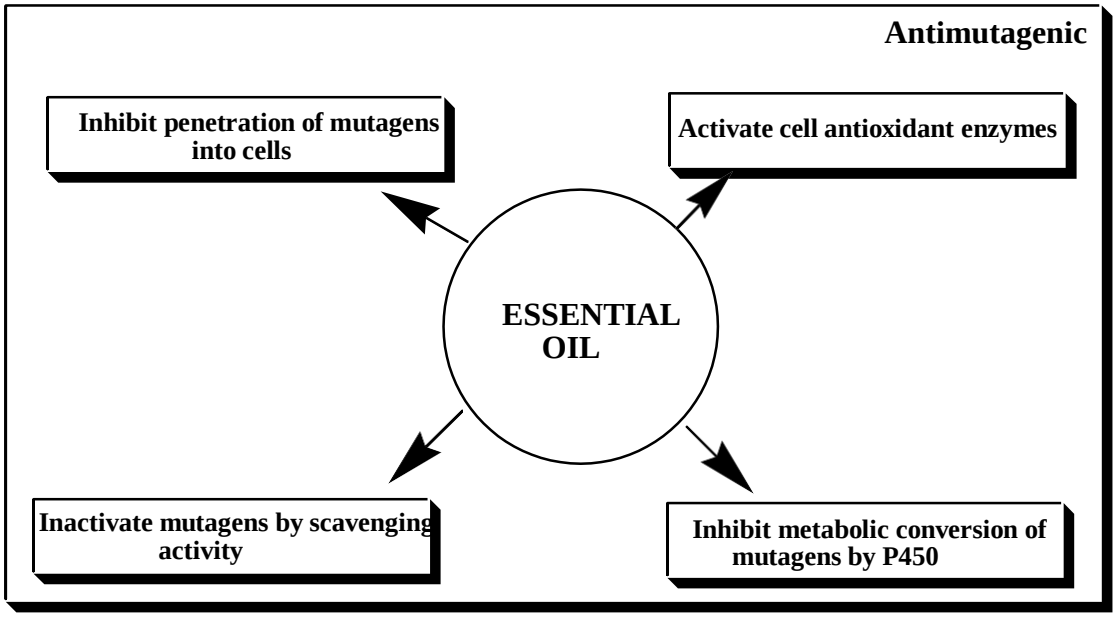

Fig.5 Anti-mutagenic action of essential oil in cancer inhibition

Antiproliferative method

The antiproliferativemechanism of action of essential oil has been shown in Fig.6 which showed DNA fragmentation and initiation of caspase-3 that might be due to contribution of apoptosis. Anti-proliferative effects of essential oil also relying on activation of apoptosis response which includes lower the potential of mitochondrial membrane and enhance the release of cytochrome c from mitochondria membrane decrease in ratio of Bc1-2/BaX, increase caspase activity.

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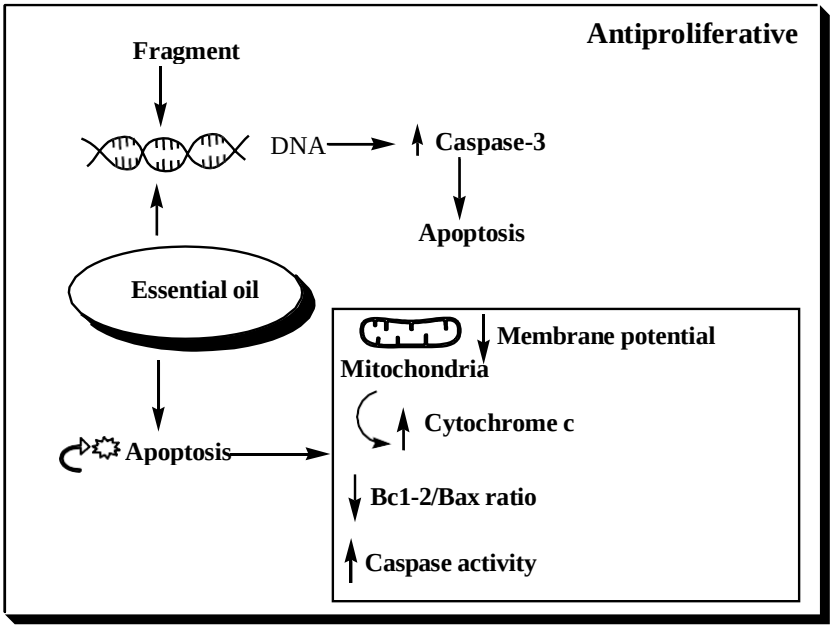

Fig. 6 Anti-proliferative action of essential oil in cancer inhibition

ANTIOXIDANT METHOD

Antioxidant mechanism of action of essential oil which showed that damaged mitochondria DNA prevents the inclusion of electron transport protein which gives rise to formation of reactive oxygen species (ROS) as shown in Fig.7. Essential oil then combines with these free radicals, results to form reactive phenoxy radicals which furthermore combine with ROS and prevent any more destruction.

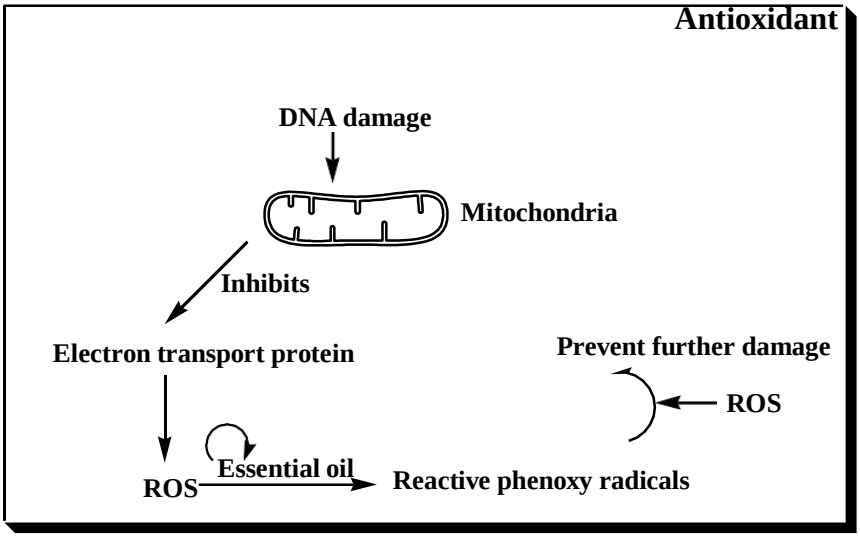

Fig. 7 Antioxidant action of essential oil in cancer inhibition

ROLE OF ESSENTIAL OILS IN AROMATHERAPY DURING CANCER TREATMENT

Aromatherapy is the utilization of essential oils obtained from the plants parts such as flowers, barks, seeds, etc. to boost mind, body and spirit. There are various essential oils employed in the aromatherapy, involving basically from lemon, ginger,cedarwood, tea tree, etc.(https://www.cancer.gov/about-cancer/treatment/cam/hp/aromatherapy-pdq). [75]
Aromatherapyis being used in the form of inhalation, bathing and massage via essential oils gained from aromatic herbs. Farahani *et al.*, 2019, reported that aromatherapy improves the ordinary difficulties of cancer patients. [76] Keyhanmehr *et al.*, 2018, reported that aromatherapy has prominent effects on eradicating the difficulties of cancer patients, involving nausea, vomiting, pain, sleep disorders, anxiety, fatigue, and depression and also helps in boosting the immune system of patient.In other terms, aromatherapy upgrades the quality of life. [77] Along with chemotherapeutic factors essential oils were found to relief against side effects of cancer during the treatment by aromatherapy means.

CONCLUSION

Essential oil constituents have an excellent potential to prevent and treat cancer. Various studies have been shown *in-vivo* and *in-vitro* antitumor activity of the many essential oil constituents. Essential oil constituents act by different mechanisms to inhibit the growth of cancer such as anti-proliferative, anti-mutagenic and antioxidant etc. During chemotherapy severaladverse effects occurs in the patients of cancer. Natural therapies like utilization of plant derived products in the treatment of cancer might be reducedtheir side effects. Aromatherapy with essential oils obtained from the aromatic herbs and reduces the difficulties of cancer patients. Therefore, it could be explored for future applications in therapeutics and continue to study for moreover pharmaceutical applications.

DISCLOSEURE STATEMENT

The authors declare that there is no conflict of interests.

AUTHORS CONTRIBUTION

All authors contributed equally to this work.

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