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A Comprehensive Review on Effect of Linalool on Cancer

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Abstract: Cancer is the disease that is widely spread rapidly globally. Natural products, such as essential oils and their components, have been utilized for their biological activities.Many anticancer drugs in clinical use today have been derived from or inspired by substances found in plant species. Linalool is one of them. Linalool, a naturally occurring monoterpene alcohol is widely recognized for its anticancer properties, and also aromatic properties, particularly its presence in essential oils like lavender. Linalool (2,6-dimethyl-2,7-octadien-6-ol) is a fragrant monoterpene alcohol frequently present in essential oils and extensively used in perfumes, cosmetics, household cleaners, and food additives. Recent research has revealed its potential as an anticancer agent. It inhibited cell proliferation by inducing G_0/G1 and/or G2/M cell cycle arrest without affecting cell viability of normal lung WI-38 cells. This review provides an overview of the current understanding of linalool's effects on various cancer types, exploring its mechanisms of action, including the induction of apoptosis, inhibition of cell proliferation, anti-metastatic properties, and anti-inflammatory effects. Additionally, the challenges and future directions for linalool in cancer therapy are discussed. Linalool is used as anticancer on Breast cancer, Liver Cancer, Lung Cancer, and Skin Cancer. Linalool shows effect on depression also. It has an antidepressant agent.

Keywords: Linalool, Cancer, Monoterpene, Natural products

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Introduction

Nowadays pharmaceutical science is growing forward on the use of natural compounds for its innovative activity and therapeutic effects. Essential oils have been used for therapeutic purposes in traditional medicine for thousands of years. Cancer remains a leading cause of morbidity and mortality worldwide. Despite advancements in treatment, there is an ongoing need for novel therapeutic agents with improved efficacy and safety profiles. Natural compounds, including essential oils and their constituents, have garnered attention for their potential anticancer properties. Linalool, a major component of many essential oils, has been extensively studied for its wide range of biological activities, including its role in cancer

inhibition (Hassen *et al.*, 2015).

Linalool refers to two enantiomers of a naturally occurring terpene alcohol found in many flowers and spice plants. Linalool has multiple commercial applications, the majority of which are based on its pleasant scent. A colorless oil, linalool is classified as an acyclic monoterpenoid. Formula of linalool is $C_{10}H_{18}O$, molar mass is 154.25 g/mol, density is 858 kg/m^3 and boiling point is 198 to 199 °C (388 to 390 °F; 471 to 472 K). Linalool shows anti-inflammatory, anticancer, antihyperlipidemic, antimicrobial, antinoceptive, analgesic, anxiolytic, antidepressant and neuroprotective properties (Lapczynski *et al.*, 2008).

Linalool (Fig. 1) is a small molecule with low molecular weight, a hydroxyl group that imparts polarity and makes it chemically reactive. Although the compound has polar characteristics, its hydrocarbon structure causes it to have poor water solubility. On the other hand, linalool is highly soluble in organic solvents like alcohol, chloroform, and ether, as well as in fixed oils and propylene glycol. At room temperature, linalool is a colorless to slightly yellow aromatic liquid.

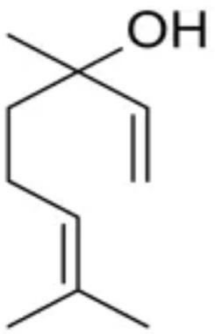

Fig. 1: Structure of linalool.

Linalool has demonstrated potential anti-cancer effects in several studies. It can slow down the growth of cancer cells by triggering their death (apoptosis) and stopping tumors from spreading (metastasis). Additionally, linalool may improve the effectiveness of some chemotherapy drugs and help reduce the side effects of cancer treatments. However, further research is required to fully understand its potential in cancer therapy (Rodenak-Kladniew *et al.*, 2014; Iwasaki *et al.*, 2016).

Linalool helps reduce inflammation by blocking the production of substances that cause it. It can also lower oxidative stress and support the immune system, making it useful for treating inflammation-related conditions (Ku *et al.*, 2013)

Sources of Linalool

Linalool ($C_{10}H_{18}O$) is a monoterpene alcohol found in over 200 plant species, including lavender (*Lavandula angustifolia*), basil (*Ocimum basilicum*), coriander (*Coriandrum sativum*), and some citrus fruits. It is characterized by a pleasant, floral aroma, making it a popular ingredient in the perfume and flavor industries. The chemical structure of linalool consists of two isomers: (R)-linalool and (S)-linalool, both of which are present in various plants but differ slightly in their biological activities (Herman *et al.*, 2016; dos Santos *et al.*, 2018).

1. Lavender (*Lavandula angustifolia*): A rich source of linalool, particularly in lavender essential oil.
2. Coriander (*Coriandrum sativum*): Linalool is abundant in coriander seeds and their essential oil.
3. Basil (*Ocimum basilicum*): Linalool is found in both the leaves and essential oil of basil.
4. Rosewood (*Aniba rosaeodora*): The essential oil from rosewood is a significant source of linalool.
5. Citrus Fruits: Linalool is present in the peel of fruits like oranges, lemons, and limes.
6. Mint (*Mentha* species): Certain mint varieties also contain linalool.
7. Frankincense (*Boswellia carterii*): Linalool is a major component of frankincense oil (Lapczynski *et al.*, 2008; dos Santos *et al.*, 2018).

Properties of Linalool

- *Antioxidant*: DPPH inhibition was significantly

higher in experimental groups as compared to their controls. Inhalation of linalool lowered systolic and diastolic blood pressure, as well as pulse rate, in the CTS group, and reduced pulse rate in the non-CTS group. However, there were no significant differences in nitrite levels, blood pressure, or pulse rate among the study groups. Overall, linalool inhalation enhances antioxidative activity and reduces blood pressure and pulse rate in CTS patients (Hassen *et al*., 2015; Filip *et al.*, 2016).

- *Anti- inflammatory*: Inflammation is the body's response to harmful stimuli. Frankincense oil from *Boswellia carterii* has been widely used in Chinese medicine to treat inflammation and pain, including menstrual cramps, muscle pain, stomach pain, and rheumatic pain. Linalool, a major component of frankincense oil, helps reduce inflammation and pain (Ku *et al*., 2013). Recent studies have shown that linalool reduces pulmonary inflammation induced by cigarette smoke (CS) (Kim *et al.*, 2019).
- *Anti-bacterial*: Linalool is an effective antibacterial agent and also exhibits antifungal properties. Linalool can significantly boost the antimicrobial power of essential oils. The essential oils is commercially available from Thyme, Juniper, Geranium, Bergamot, Grapefruit, Lavender, Cinnamon, Tea tree (Bajpai *et al*., 2013).
- *Antidepressant*: In many developed countries mental illness takes a wide range of space. In Brazilian Amazon traditional medicine, the essential oils of *Aniba rosaeodora*, *Aniba parviflora*, and *Aeollanthus suaveolens* are highly regarded for their sedative and antidepressant properties. These oils are especially recognized for their high linalool content (dos Santos *et al.*, 2022).
- *Anti-cancer*: Linalool, a monoterpenoid alcohol widely used as a flavoring agent, has demonstrated anticancer potential. It is present in red wine, lavender essential oil, and coriander fruits. Research shows that linalool can effectively target solid tumors, including those in gastric, lung, skin, and liver cancers (HepG2), as well as various leukemia cell lines. Additionally, linalool has been found to induce apoptosis, increase oxidative stress, and modulate immune responses (Iwasaki *et al*., 2016; Rodenak-Kladniew *et al*., 2020).
- *Antifungal effect*: Linalool shows promise as an antifungal treatment that targets resistant strains of *Candida albicans* while minimizing side effects. Kordali *et al*. (2016) investigated the effects of linalool on fluconazole-resistant vulvovaginal *Candida albicans* isolates and explored its mechanism of action through *in vitro* tests and molecular docking.
- *Aromatic*: linalool has good aromatic property, used in popular ingredient in perfumes,and fragrances.(Api *et al.*, 2015) detergent and cleaning agent are prepared as non-cosmetics product by linalool (Gonçalves *et al*., 2020). Aromatic plants have been important for a long time, with their use going back to ancient times in the Middle East (Lapczynski *et al.*, 2008). Linalool is also used in food product for flavor .(de Cássia Silveira *et al.*, 2017).
- *Analgesic:* Linalool relieves pain by blocking pain signals and calming the nervous system. It can help with muscle aches, headaches, and inflammation-related pain.(Pereira *et al.*, 2018).Various animal studies shows that, components of various oil such as linalool have been reported to exert analgesic effect (Liu *et al*., 2013).

Mechanisms of Anticancer Action

Several studies have demonstrated linalool's potential to inhibit cancer through various mechanisms:

Induction of Apoptosis

Apoptosis, or programmed cell death, is a crucial mechanism by which the body eliminates damaged or unwanted cells. Many cancer therapies aim to induce apoptosis in cancer cells. Linalool has been shown to activate apoptosis in

multiple cancer types, like in breast cancer cells, linalool triggers the mitochondrial pathway, leading to cytochrome c release and activation of caspases, which ultimately results in cell death (Zhao *et al*., 2021).

Inhibition of Cell Proliferation

Linalool's ability to halt the proliferation of cancer cells has been observed in various studies. It interferes with the cell cycle, particularly by inducing cell cycle arrest in the G1 phase, thereby preventing the replication of cancer cells. This effect has been noted in cancers such as liver and lung cancer (Iwasaki *et al*., 2016).

Anti-metastatic Properties

Metastasis, the spread of cancer from its primary site to other parts of the body, is a significant challenge in cancer treatment. Linalool has demonstrated anti-metastatic properties by downregulating proteins like matrix metallo-proteinases (MMPs), which play a key role in cancer cell invasion and metastasis. In animal models of lung cancer, linalool has been shown to reduce tumor metastasis effectively (Komata *et al*., 2003; Iwasaki *et al*., 2016).

Anti-inflammatory Effects

Chronic inflammation is closely linked to cancer progression. Linalool possesses notable anti-inflammatory properties, which may contribute to its anticancer effects. By reducing the production of pro-inflammatory cytokines and inhibiting key inflammatory pathways, linalool creates a less favorable environment for cancer growth (Ku *et al*., 2013).

Oxidative Stress Reduction

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidants, can lead to DNA damage and cancer development. Linalool's antioxidant properties help to mitigate oxidative stress, thereby protecting cells from genetic mutations and other cancer-promoting changes (Guzmán-Gutiérrez *et al.*, 2012; dos Santos *et al*., 2022).

Linalool in Specific Cancer Types

Breast cancer

Breast cancer is the most common cancer in women and a major cause of death. It can be treated with surgery, radiation, and drugs like chemotherapy. Chemotherapy is still the main treatment, but it can lower white blood cells, making it easier to get infections. That is why scientists are looking for new treatments (Zhao *et al*., 2021). Linalool has been widely studied in breast cancer models, where it has been shown to induce apoptosis and inhibit cell proliferation. Its effects are particularly significant in estrogen receptor-positive (ER+) breast cancer cells, suggesting potential for targeted therapy. Linalool showed greater effectiveness on MCF-7 human breast cancer cells when used in smaller concentrations (Elbe *et al.*, 2022).

Liver Cancer

Liver cancer is notoriously difficult to treat due to its aggressive nature and resistance to conventional therapies. Linalool has exhibited promising effects in inhibiting liver cancer cell growth, particularly through mechanisms involving apoptosis and cell cycle arrest.

Cervical cancer

According to a World Health Organization statistical report, cervical cancer ranks as the second most common cancer among women, with over 250,000 deaths estimated annually. Cervical cancer and leukemia are common types of secondary cancers, highlighting the need for more effective treatments. In Taiwan, nearly 70% of cervical cancer cases are caused by two types of human papillomavirus (HPV), strains 16 and 18. Acute myeloid leukemia (AML) is the most common type of leukemia in adults, so the AML cell line U937 was used for research. The study investigates how a compound called linalool affects cancer cells, specifically U937 leukemia cells and HeLa cervical cancer cells. Previous research showed that linalool helps normal immune cells fight cancer. In this study, linalool was found to be effective at killing both types of

cancer cells in lab tests (Ryzhakova *et al*., 2013; Chang *et al*., 2014).

Lung Cancer

Lung cancer is one of the most common and deadly cancers worldwide. Studies have indicated that linalool can reduce tumor size and prevent metastasis in lung cancer models, making it a potential candidate for further investigation as an adjunct therapy. Linalool and 1,8-cineole, found in various plants, have medical benefits, including potential anticancer effects. Previous research showed they can slow lung cancer cell growth, especially when combined with simvastatin. This study aims to explore how they work against lung cancer cells (Rodenak-Kladniew *et al*., 2020).

Ovarian Carcinoma

Linalool is a natural terpenoid alcohol produced by various plants, including herbs, spices, and fruits. It has potential to be cytotoxic and can boost immune responses.(Chang *et al.*, 2014). Linalool can induce apoptosis, or programmed cell death, in cancer cells by targeting the proteins that control cell survival. It also affects key signaling pathways that are important for cancer cell growth and survival, helping to reduce the viability and spread of ovarian cancer cells (Han *et al*., 2016).

Colon cancer

Colorectal cancer ranks as the fourth most common cause of cancer-related deaths globally, with the annual death toll now reaching approximately 700,000 (Braun *et al.*, 2011). Chemotherapy is the most common treatment for cancer, but it has some side effect such as hair loss, low blood counts, hand-foot syndrome, and neuropathy, may depress the patient's quality of life (Braun *et al.*, 2011; Teker *et al.*, 2015). So natural compound which show anticancer effect on colon cancer line linalool are used for cancer treatment. Linalool causes apoptosis in human colon cancer cells. Using phase contrast microscopy, changes in the HCT 116 cell line, and cell toxicity after linalool treatment have been reported. While cancer cells grow quickly under normal conditions, they stopped growing after linalool treatment and showed signs of apoptosis, such as chromatin fragmentation, surface blebbing, and cell shrinkage (Iwasaki *et al.*, 2016; Hou *et al*., 2022).

Skin Cancer

The potential of linalool in skin cancer prevention and treatment is linked to its ability to reduce UV-induced oxidative stress and inflammation. Animal studies have shown that linalool can protect against the development of skin tumors, highlighting its potential as a topical preventive agent (Komata *et al*., 2003; Iwasaki *et al*., 2016). A single exposure to UVB light increased p53 levels in skin cells, which led to higher Bax expression and lower Bcl-2 expression. Linalool treatment helps protect against UVB-triggered cell death, likely by preventing DNA damage and stopping the activation of apoptosis. Similarly, melatonin and its byproducts reduce UVB-induced damage in skin cells by neutralizing harmful molecules (ROS/RNS) and promoting anti-growth and cell differentiation effects (Fischer *et al.*, 2004; Janjetovic *et al*., 2014).

Challenges and Future Directions

While linalool's anticancer effects are promising, several challenges remain. The majority of current research is based on *in vitro* studies and animal models. There is a need for more clinical trials to assess the efficacy and safety of linalool in humans. Additionally, optimal dosing, delivery methods, and potential side effects require thorough investigation. Moreover, the variability in linalool's effects depending on its source and isomer composition must be addressed to ensure consistency in therapeutic applications. The combination of linalool with other anticancer agents also holds potential for synergistic effects, warranting further exploration.

Conclusion

Linalool, a naturally occurring terpene, shows significant anticancer potential across various cancer types through mechanisms such as apoptosis induction, cell cycle arrest, and anti-

metastatic effects. While the current research is promising, further studies, particularly clinical trials, are essential to fully understand and harness linalool's therapeutic potential in cancer treatment. As research progresses, linalool may emerge as a valuable component of integrative cancer therapies, offering a natural, less toxic alternative or adjunct to conventional treatments.

Conflict of Interest

The authors declare no conflicts of interest.

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