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Review Article

LUNG CANCER THERAPY USING NATURALLY OCCURRING PRODUCTS AND NANOTECHNOLOGY

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ABSTRACT

Lung cancer is a severe type of cancer with highest mortality rate among all cancers. Natural products such as theaflavins, quercetin, arctigenin, EGCG, curcumin, and cinnamaldehyde are quite capable anti-inflammatory and anti-cancerous agents which are able to suppress ERK-MAPK, JAK-STAT, p38, AMPK, PI3K/Akt, MAPK, mTOR, STAT3, and Wnt/β-catenin signal transduction pathways. These APIs inhibit the inflammatory and proliferator enzymes such as COX-2, caspase-3, MMP-9, MMP-2, NF-κB, p53, Bcl-xL, Bcl-2,Mcl-1, miR-210, cyclin D1, iNOS, IL-1β, TNF-α, IFN-γ, IL-6, and IL-1α. All the above properties clearly show the anti-cancerous potential, but the problems arise because of their instability at gastrointestinal tract pH. All the compounds either degrade at gastric pH or loss their cancerous potential. New generation nanoparticles such as transferosomes are quite stable at 7.4 pH and its efficacy and drug entrapment potential are better than other conventional nanoparticle systems. If these APIs are added inside the nanovesicular structure of transferosomes and then loaded in pMDI canisters such as fluorocarbon polymerization (FCP), plasma-coated canisters with a better propellant such as HFA-134a and delivered with the help of spacers can cure lungs cancer economically, efficiently with minimal side effects and it also ensures that the cancer will not reoccur.

Keywords: Theaflavins, Quercetin, Arctigenin, EGCG, Curcumin, Cinnamaldehyde, Lung Cancer, Nanotechnology.

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INTRODUCTION

Among all malignancies, lung cancer has the greatest fatality rate. According to 2020 research, lung cancer has the greatest incidence rate of 2.21 million new cases and the highest mortality rate of 1.80 million fatalities [1]; the death rate is twice that of breast cancer in women and 3 times that of prostate cancer. Smokers are 20 times more vulnerable than non-smokers [2], with the 50–69 age range being the most vulnerable. Lung cancer has a 2.5-fold increased hereditary risk [3]. It is responsible for 32% of male fatalities and 20% of female fatalities. For many years, it has been observed that Blacks had a higher incidence rate than Caucasians [4]. Lung cancer comes in a variety of forms. The most common varieties of lung carcinoma are adenocarcinoma (ADC), squamous cell carcinoma (SQCC), small cell carcinoma (SCC), and large cell carcinoma (LCC), however, there are also some unusual variants.

Traditional lung cancer treatment procedures and chemotherapy are exceedingly expensive, have terrible side effects, and the recurrence rate of lung cancer is very high after these arduous stages. Because of their less adverse effects, cost efficiency, and simplicity, non-invasive technique which comprises natural components is becoming more popular.

Different types of lung cancer

Adenocarcinoma (ADC), also known as bronchoalveolar carcinoma, is an invasive malignant epithelial tumor with glandular cells that differentiate or produce mucin. These tend to be smaller begins in the glands that border the lining of one of your organs and are more peripherally placed. It is responsible for 40% of all lung cancers [4,5].

Squamous cell carcinoma (SQCC), smoking is highly linked to SQCC. It spreads exophytically into the bronchial lumen, accumulating bulk intraluminal, and causing bronchus blockage and atelectasis. Before changing into cancer, SQCC normally goes through metaplasia or dysplasia. It accounts 25% of all cases [6].

Small cell carcinoma (SCC) is a cancer that is induced by cigarette smoking and is extremely aggressive, making it extremely deadly. They primarily develop in the lung's periphery or major bronchi, with no pre-invasive phase. It is made up of tiny cells of various shapes and sizes. It accounts for 5–10% of the total [7].

Large cell carcinoma (LCC) is a type of lung cancer that grows in the outer layer of the lungs. The cell size is larger than a normal cell, and it has a high proclivity for spreading to lymph nodes and distant places; it is the most aggressive of all lung cancers. Pleural effusion develops as a result (fluids accumulate in the pleural cavity). It accounts for 10–15% of all lung cancer cases (Fig. 1)[8].

Some rare type of lung cancers

- Adenosquamous carcinoma (a hybrid of ADC and SQCC).
- Large cell neuroendocrine carcinoma (an aggressive subtype of non-small cell lung cancer).
- Salivary gland-type lung carcinoma.
- Lung carcinoids
- Mesothelioma (develops in mesothelium)
- Mediastinal tumors.

EGCG

Green tea is made from the *Camellia sinensis* L. plant, which belongs to the Theaceae family. Green tea's main component, EGCG, is a good chemopreventive drug that has a stronger antiproliferative impact than 5-flurouracil. Neuroprotective, antidiabetic, antibacterial, anti-atherosclerotic, cardioprotective, anti-viral, antioxidant, anti-inflammatory, antiproliferative, and antiobesity are some of the features it possesses. EGCG has a higher antioxidant activity than Vitamin C and Vitamin E [9-12].

Working of EGCG against cancer

- EGCG suppresses lung cancer proliferation and anchorage-independent growth by upregulating the expression of miR-210 (a major cancer preventative) by binding HIF-1α [13].

- HGF-induced c-Met phosphorylation is inhibited by EGCG, which increases the antiproliferative efficacy of EGFR inhibitors, causing additional regulation of growth factor receptor signaling in adenocarcinoma [14].
- EGCG inhibits cyclin D1 and boosts p21 production, which inhibits cell growth or promotes cell arrest, reducing cancer cells [15].
- EGCG produces a breakdown in cancer cells DNA, triggering apoptosis, by causing intracellular ROS (reactive oxygen species) and oxygen distress.
- EGCG suppresses lung cancer cell proliferation, colony formation, migration, and invasion through activating the AMPK signaling pathway [16].
- EGCG downregulates the expression of NF-κB and NF-κB target genes are induce cancer by proliferation (MYC and cyclin D1), metastasis (MMP2 and TWIST1) inflammation (COX-2 and TNF-α), and survival (Bcl-xL and Bcl-2) (Fig. 2) [17].

Theaflavins

Black tea has a lot of theaflavins. Antiviral, antibacterial, anti-osteoporotic, anticancer, anti-atherosclerotic, anti-inflammatory, anti-obesity, and anti-dental caries capabilities are all properties of this polyphenolic molecule [18,19].

Theaflavin working against cancer

- Theaflavin exhibited substantial cell arrest at the G2/M phase which inhibits proliferation and cell division of cancer cells [20].
- Theaflavins inhibit ERK-MAPK, JAK-STAT, and p38 signal transduction pathways in cancer cells which further stops overexpression of COX-2 thus stopping the production of prostaglandins from arachidonic acid [21].
- Theaflavin inhibits or delays hyperplasia and dysplasia.
- Theaflavins operate through both the intrinsic and extrinsic pathways of apoptosis hence producing oxidative distress in cancer cells.
- Theaflavin increases both expression and activation of pro-enzyme caspase-3 which catalyzes the specific cleavage of many important cellular proteins which plays an important role in apoptosis [22].
- Theaflavin also downregulates invasion-related proteins (MMP-9 and MMP-2). Theaflavins suppresses inducible signal transducer and activator of STAT3 (transcription 3) phosphorylation which further downstream antiapoptotic proteins (Bcl-2 and survivin) (Fig. 3) [23].

Curcumin

Turmeric (*Curcuma longa* Linn.) produces curcumin. It has anti-inflammatory, antioxidant, hypotensive, anti-mutagenic, anticoagulant, antiprotozoal, antifertility, anti-aging, hepatoprotective, anti-venom, antidiabetic, antibacterial, anti-fibrotic, antifungal, antiviral, antiulcer, and hypocholesterolemic properties. Even at high doses, it has little or no negative effects [24,25].

Curcumin working against cancer

- Curcumin is a very good inhibitor of COX-2 and 5-LOX and inhibits the productions of interleukins [26,27].
- Curcumin inhibits iNOS which stops the production of NO.
- Curcumin is also involved in PPARγ activation which suppresses airway hyper-responsiveness, which reduces inflammation and epithelial hyperplasia in the airway.
- Inhibits the production of interleukins: IL-1, IL-2, IL-6, IL-8, and IL-12 [28]. It also decreases inflammatory mediator (IL-4, IL-5, and IL-13) synthesis and release which reduces mucus hypersecretion and inhibits collagen deposition.
- Regulates chemokine monocyte chemoattractant protein (MCP).
- Curcumin inhibits the TLR4 (toll-like receptor 4) which stops the activation of transcription of inflammatory molecules through stimulation by MyD88 pathway hence directly regulates the release of pro-inflammatory cytokines [29].
- Curcumin also degrades the production of IκB-α, which further stops the activation of NF-κB (nuclear factor kappa B), a pro-inflammatory transcription factor.
- Curcumin inhibits TNF-α, which is mediator of inflammation [30].
- It shows inhibitory action on Janus kinase (JAK)-STAT signaling which contributes to its anti-inflammatory activity (Fig. 4).

Cinnamaldehyde

Cinnamaldehyde is an active compound in cinnamon that has anti-inflammatory, antimicrobial, antifungal, antioxidant, antidiabetic, anti-termites, nematicidal, mosquito larvicidal, insecticidal, anti-mycotic, and anticancer properties. It also helps with dental issues (halitosis, toothaches, and oral microbiota) and improves uterine blood circulation [31].

Cinnamaldehyde working against cancer

- Cinnamaldehyde has the potential to stop the production of NO by inhibiting the iNOS [32].
- Cinnamaldehyde inhibits activation of transcription factor nuclear factor-kappa B (NF-κB).
- It inhibits the secretion of cytokine interleukin-1β (IL-1β) which is a key mediator of the inflammatory response [33].
- It also obstructs the production of tumor necrosis factor-alpha (TNF alpha) [34].
- Cinnamaldehyde suppresses interferon-gamma (IFN-γ), interleukin (IL-6), and interleukin-1 alpha (IL-1α) which is produced by lipopolysaccharide (LPS) or lipoteichoic acid (LTA) [35].
- Cinnamaldehyde also suppresses COX-2, ERK, JNK, p38, and MPAKs phosphorylation in the cells (Fig. 5).

Quercetin

Quercetin is a flavonoid found in onions, berries, apples, Ginkgo biloba, St. John's wort, American elder, and Buckwheat tea, among other plants and foods. Quercetin has anti-inflammatory, anticancer, anti-protozoal, anti-viral, ocular protective, antimicrobial, cardioprotective, antiarthritis, and anti-inflammatory characteristics, as well as increasing metabolic properties [36]. Platelet aggregation, lipid peroxidation, and capillary permeability are all inhibited by quercetin, whereas mitochondrial biogenesis is stimulated [37].

Quercetin working against cancer

- Quercetin can inhibit lipopolysaccharide (LPS)-induced TNF-α production in macrophages and LPS-induced IL-8 production [38].
- Quercetin possesses mast cell stabilizing properties. It also has an immunosuppressive effect on dendritic cells function.
- In glial cells, quercetin can inhibit LPS-induced mRNA levels of TNF-α and interleukin (IL)-1α, this effect of quercetin results in a diminishing apoptotic neuronal cell death which is induced by microglial activation.
- Quercetin also inhibits the production of COX-2 and LOX [39].
- Quercetin inhibits Src- and Syk-mediated phosphatidylinositol-3-Kinase (PI3K)-(p85) tyrosine phosphorylation which further limits LPS-induced inflammation and also forms a complex with toll-like receptor 4 (TLR4)/MyD88/PI3K which stops the activation of downstream signaling pathways [40].
- It inhibits pro-inflammatory cytokines mediated by FcεRI which are tryptase and histamine; this inhibition is due to inhibition of Ca^{2+} influx, as well as inhibition in phospho-protein kinase C (PKC).
- Quercetin also acts against H_2O_2-induced inflammation by downregulating the CD80 expression and vascular cell adhesion molecule 1 (VCAM-1) [41].
- Quercetin induces the production of Th-1 derived which is derived from interferon-γ (IFN-γ) and downregulates Th-2 derived which is derived from interleukin 4 (IL-4).
- Quercetin treatment with activated T cells shows blocking of IL-12-induced tyrosine phosphorylation of TYK2, JAK2, STAT3, and STAT4, resulting in a decrease in IL-12-induced T-cell proliferation and Th1 differentiation (Fig. 6) [42].

Arctigenin

Arctigenin is a lignan found in certain plants of the Asteraceae, including the greater burdock and *Saussurea heteromalla*. It possesses anti-inflammatory, antitumor, hepatoprotective effect, cardioprotective effect, antioxidant, and antiviral activities [43].

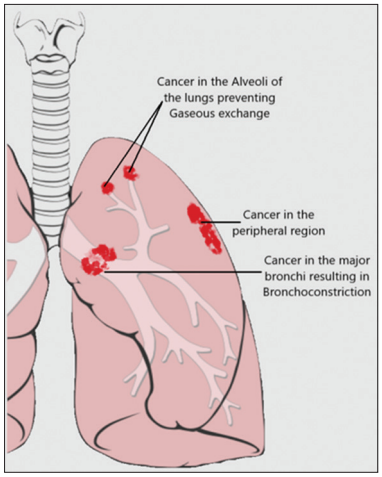

Fig. 1: Sites of lung cancer

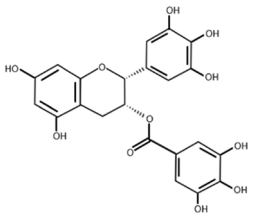

Fig. 2: EGCG

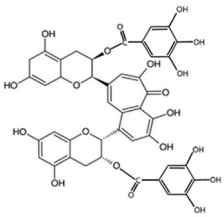

Fig. 3: Theaflavins

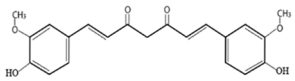

Fig. 4: Curcumin

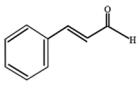

Fig. 5: Cinnamaldehyde

Arctigenin working against cancer

- Arctigenin suppresses the metastasis of cancer cells by downregulation of MMP-2, MMP-9, and heparanase [44].
- Shows an inhibitory effect on phosphoinositide 3 kinase/Akt (PI3K/Akt) signaling pathways [45].
- Arctigenin promotes apoptosis in breast cancer pathogenesis through the p38 MAPK pathway.
- NF-κB and p53 are also involved in arctigenin-induced cell apoptosis [46].
- Downregulation of Bcl-xL and Mcl-1 which promotes cell apoptosis.
- Arctigenin activates chondriosome-dependent pathway and extrinsic apoptosis pathways.

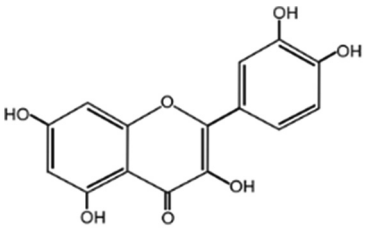

Fig. 6: Quercetin

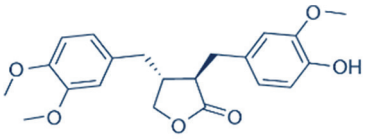

Fig. 7: Arctigenin

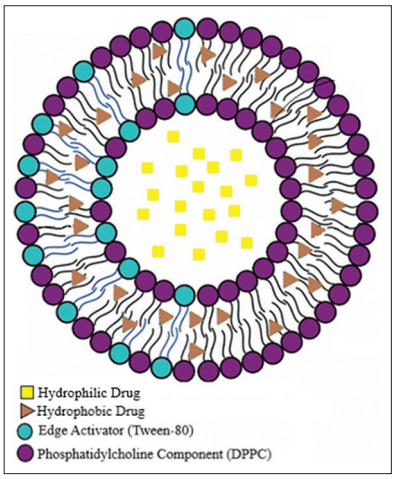

Fig. 8: Transferosomes

- Arctigenin also triggers mTOR, STAT3, and Wnt/β-catenin pathways (Fig. 7) [47].

Delivery methods

All the compounds theaflavins, cinnamaldehyde, quercetin, arctigenin, curcumin, and EGCG were quite unstable and degrade quickly at 7.4 pH hence cannot be delivered through conventional methods. Nanoparticles such as transferosomes are new generation novel drug delivery system which is quite stable at 7.4 pH and its efficacy and drug entrapment potential are better than other conventional nanoparticle systems. These natural products loaded in nanoparticles then loaded in pMDI canisters such as fluorocarbon polymerization (FCP) plasma-coated canisters with a better propellant such as HFA-134a and delivered with the help of spacers can cure lungs cancer economically, efficiently with minimal side effects and it also ensures that the cancer will not reoccur [48].

Transferosomes

Transferosomes are a special type of liposomes, consisting of phosphatidylcholine and an edge activator. They're soft, pliable vesicles designed to distribute active substances more effectively. They can actively transport both hydrophilic and lipophilic molecules in a single entity particle and also protect the active pharmaceutical ingredients from distortion while transportation through the body.

Preparation method of transferosomes (thin-film hydration technique/rotary evaporation-sonication method)

A volatile organic solvent mixture (for example, chloroform and methanol in an appropriate (v/v) ratio) is used to dissolve the phospholipids and

edge activator (vesicle-forming components) in a round-bottom flask. This is where the lipophilic medication can be added. A rotary vacuum evaporator is used to evaporate the organic solvent above the lipid transition temperature under reduced pressure to generate a thin layer. To eliminate the last residues of the solvent, keep it under vacuum. The thin film is then hydrated by rotating it for a specific amount of time at a specific temperature while using a buffer solution with the proper pH. This is the time to include the hydrophilic medication. To obtain tiny vesicles, the resultant vesicles are inflated at room temperature and sonicated in a bath or probe sonicator. Extrusion across a sandwich of 200 nm to 100 nm polycarbonate membranes homogenizes the sonicated vesicles (Fig. 8) [49].

RESULTS

Theaflavins suppress ERK-MAPK, JAK-STAT, and p38 signal transduction pathways and inhibit COX-2, caspase-3, MMP-9, and MMP-2.

Quercetin inhibits TNF-α, IL-4, IL-8, IL-12, COX-2, LOX, TLR4, PKC, and VCAM-1 and downregulates Src- and Syk-mediated phosphatidylinositol-3-kinase (PI3K)-(p85), TYK2, JAK2, STAT3, and STAT4.

Arctigenin suppresses the metastasis of cancer cells by downregulation of MMP-2, MMP-9, and heparanase, shows an inhibitory effect on PI3K/Akt, MAPK, mTOR, STAT3, and Wnt/β-catenin signaling pathways, and downregulates NF-κB, p53,Bcl-xL and Mcl-1.

EGCG inhibits lungs cancer by suppressing miR-210, cyclin D1, AMPK signaling, NF-κB, MMP2, TWIST1, COX-2, TNF-α, Bcl-xL, and Bcl-2 and it also promotes p21 signaling, these all EGCG effects contribute to apoptosis and inhibit cell proliferation.

Curcumin inhibits COX-2,5-LOX, iNOS, IL-1, IL-2, IL-6, IL-8, IL-12, TLR4, and NF-κB and regulates (JAK)-STAT signaling pathway.

Cinnamaldehyde inhibits iNOS, NF-κB, IL-1β, TNF-α, IFN-γ, IL-6, IL-1α, and COX-2, it also downregulates ERK, JNK, p38, and MPAKs signaling pathways.

However, all these natural products are quite unstable at gastric pH.

CONCLUSION

Nanoparticles are used in novel drug delivery systems because of their high permeability and resistance against different body conditions. Transferosome is one of the finest nanoparticles because of its drug entrapping efficiency and cell-penetrating ability; it can also contain both lipophilic and hydrophilic chemical entities inside its vesicular structure.

Although theaflavins, quercetin, arctigenin, EGCG, curcumin, and cinnamaldehyde have potent anticancer properties, they are unable to produce these effects in the body due to their instability at pH 7.4. However, when loaded in nanoparticles such as transferosomes, they can use their potential against cancer cells and even exceed it.

Traditional cancer therapy's negative effects will not occur here, and the treatment will be safe, affordable, and shorter in duration. Because the approach is non-invasive, patient compliance will improve. The accumulation of medications will not be visible, and patients' psychological difficulties will be lessened.

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AUTHORS' CONTRIBUTION

Syed Saif Imam proposed the idea and all the other authors have contributed data to the paper.

CONFLICTS OF INTEREST

The authors confirm that the content of the article has no conflicts of interest.

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DATA AVAILABILITY

The original data that support the findings of this study are included in the article.

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