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REVIEW ARTICLE

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ROLE OF PHYTOCONSTITUENTS BASED NANOTECHNOLOGY IN THE MANAGEMENT OF LUNG CANCER

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ABSTRACT: Lung cancer (LC) is the largest cause of cancer mortality, accounting for around 18.4% of all cancer deaths in both sexes combined. One of the key treatments for LC is the use of systemic medicines. However, the therapeutic efficacy of these medications is restricted because to the significant side effects, systemic toxicity, and poor selectivity associated with them. In contrast, pulmonary anticancer medication administration has several advantages over traditional routes. The inhalation method allows for the direct delivery of chemotherapeutic drugs to the target LC cells, which may boost antitumor effectiveness and lead to reduced dose and fewer systemic effects. Nonetheless, this method has numerous physiological and technological obstacles that may have a major impact on lung deposition, retention, and efficacy. Phytochemicals, or naturally occurring plant molecules, are important sources for new medications and are also used to treat cancer. Taxol analogues, vinca alkaloids like vincristine and vinblastine, and analogues of podophyllotoxin are a few typical examples. These phytochemicals frequently work by controlling molecular pathways that are connected to the development and spread of cancer. The precise processes include boosting antioxidant status, neutralizing carcinogens, reducing proliferation, inducing cell cycle arrest and apoptosis, and immune system control.

Keywords: Lung cancer, Nanotechnology, Phyto-constituents, Chemotherapeutic drugs

INTRODUCTION

Lung cancer is a malignant disease comprising two primary histological subtypes of lung cancer, small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), are both malignant diseases. The three most common subtypes of NSCLC are adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC) [1]. Lung cancer-related deaths, which account for 18.4% of all cancer deaths today, are still a significant contributor to cancer mortality (mostly NSCLC). By 2025, nearly 1 in 5 persons in nations with limited access to healthcare may pass away from cancer because effective preventive measures are not being implemented. Eliminating alcohol and tobacco use, reducing pollution, getting enough exercise, and eating a balanced diet are some of the cancer prevention strategies that are advised [2].

Targeted therapies have become standard therapies for patients with non-small cell lung cancer (NSCLC). A phase III trial of carboplatin and paclitaxel with and without bevacizumab in patients with advanced NSCLC with non-squamous histology demonstrated a statistically significant improvement in efficacy [3]. Non-small cell lung cancer is the most common variety accounting for 84% of the cases. For a subset of patients with actionable mutations, targeted therapy continues to provide durable responses. Advances in molecular and immunohistochemical techniques have made it possible to usher lung cancer into the era of personalized medicine, with the patient getting individualized treatment based on these markers [4]. Lung cancer can now be treated with advanced techniques, although this is still insufficient for the disease. For the treatment, there are a number of synthetic chemotherapeutic drugs available. The survival rate is still 15-18%, nonetheless, because of their harmful effects. Additionally, there is a great variety of naturally occurring compounds from medicinal plants that can prevent lung cancer [5]. Compared to chemotherapy medicines; phytochemicals have a wider therapeutic index. Therefore, using phytochemicals alone or in combination with authorized chemotherapies may be beneficial for NSCLC patients [6]. Numerous medicinal plants have been suggested to have an anticancer effect based on traditional practices and experimental research. Several phytochemicals have also been proven in *in vitro* research or animal studies to have antiproliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic properties [7].

2. ROLE OF NANOTECHNOLOGY IN LUNG CANCER

Conventional treatment strategies for lung cancer lack specificity and are limited by undesirable toxicities in normal cells, as well as a high rate of recurrence. By overcoming the current limitations in conventional medicines, the application of nanotechnology has significantly altered the treatment of lung cancer. Lung cancer therapy may be more advanced and effective as a result of pulmonary administration of nano-based medication formulations [8].

The discovery and use of nanotechnology in the treatment of cancer has made huge advancements in recent years. Because they work more selectively than conventional agents, nanostructured methods are preferable. As a result of these developments, nanomedicine, a brand-new area of cancer treatment, was created [9].

Researchers have shown that treatments based on nanotechnology have fewer adverse effects and are more effective than traditional chemotherapy or radiotherapy. Liposomes, dendrimers, polymers, micelles, inorganic nanoparticles including carbon nanotubes and gold nanoparticles, as well as siRNA delivery systems, are just a few of the nanoparticles, nanomaterials, and nanosystems that have been researched. Given that these nanosystems have a remarkable potential for many biomedical applications, such as anti-tumor activity or gene therapy, their cytotoxicity is a questionable concern, and nanotechnology-based delivery systems must be improved to increase the bioavailability, biocompatibility, and safety profiles [10].

With less toxicity and more therapeutic efficacy, nanotechnology offers a viable approach that boosts the bioavailability of anticancer medications at the tumor site. The detection and treatment of lung cancer have both been enhanced by nanotechnology. Numerous nanocarriers, including liposomes, polymeric nanoparticles, magnetic nanoparticles, and various theranostic techniques, have already received medical approval for usage, while others are still in the preclinical and clinical stages of development.therapy [11].

3.1 Nanotechnology-based drug delivery systems

The use of nanotechnology in medicine has the potential to have a significant positive impact on human health, from disease prevention to disease diagnosis and treatment [12]. Through the targeted and site-specific administration of precise medications, nanotechnology has many advantages in the treatment of chronic human diseases. There have recently been several notable uses of nanomedicine (including chemotherapeutic medicines, biological agents, immunotherapeutic agents, etc.) in the management of various disorders [13]. Nanoparticles (NPs) are the newly discovered means of drug delivery into tumour cells with the least amount of drug leaking into healthy cells. A powerful therapeutic strategy to effectively treat cancer is the conjugation of NPs with ligands of cancer-specific tumour biomarkers [14].

3.1.1 Vesicular drug delivery system

The Vesicular medication Delivery System has vesicles as its preferred medication delivery method. The highly organised vesicular system is made up of a lipid bilayer that forms when particular amphiphillic building blocks come into contact with water. The genesis of these biological vesicles was initially discovered by Bingham in 1965 [15]. There are various VDDSs available that can entrap both hydrophilic and lipophilic medicines. There are numerous types of VDDSs, such as aquasomes, ethosomes, liposomes, transferosomes, ufasomes, colloidosomes, and niosomes [16].

TABLE 1: PHYTOCONSTITUENTS LOADED IN VESICULAR DRUG DELIVERY SYSTEM FOR THE MANAGEMENT OF LUNG CANCER

S. no.	*Phytoconstituents*	*Source*	*VDDS*	*Findings*
1	Curcumin	Curcuma longa(Turmeric)	Liposomes	Curcumin efficiently abolished lung CSC traits, as evidenced by reduced tumorsphere formation, as well as proliferation inhibition and apoptosis induction [17,18]
2	Resveratrol	Grapes, berries, peanuts, and pines	Liposome	Resveratrol liposomes induced the apoptosis of both non-resistant and resistant cancer cells by dissipating mitochondria membrane potential [19]
3	Berberine	*Phellodendronamurense*, *Coptischinesis*, and *Hydrastis canadensis*	Niosomes	Berberine is able to disrupt the B-cell Lymphoma-2/Bcl-2 associated protein X (Bcl-2/Bax) ratio, which in turn decreases the mitochondrial membrane potential of tumor cells [20]
4	Genistein	Genistein are soy-based foods, such as soy cheese or soy drinks	liposomes	Genistein induced G2/M arrest has been found to be associated with upregulated p21 expression in breast, prostate and lung cancer [21]

3.1.2 Nanoparticles

Nanoparticles are extremely small materials, ranging in size from 1 to 100 nm. Based on their characteristics, shapes, or sizes, they can be divided into many classifications [22]. Nanoparticles can be classified in various types based on their structures, sizes or physical and chemical properties. Organic Nanoparticles, inorganic Nanoparticles, Metal-Based Nanoparticles, Metals such as aluminum, copper, gold, iron, silver, Metal Oxide-Based Nanoparticles etc [23]. They also have a very high surface area and they permit many functional groups to be adhered to them which in turn, can bind to tumor cells. They have proven to be an excellent replacement for radiation and chemotherapy as they can easily assemble in the micro environment of the tumor [24].

3.1.2.1 Lipidic and polymeric nanoparticles

Polymeric nanoparticles (NPs) are tiny particles with a size between 1 and 1000 nm with the ability to contain or have active substances surface-adsorbed onto the polymeric core. Polymeric NPs are advantageous as drug carriers because they can be used for controlled release, have the ability to shield drugs and other molecules from the environment, increase their bioavailability, and have a higher therapeutic index [25]. Due to the biocompatibility of the lipid matrix, lipid nanoparticles (LNPs) are frequently used in drug delivery [26]. One of the most effective nano-delivery methods for cytotoxic chemotherapeutic drugs, antibiotics, and nucleic acid therapies is the use of lipid nanoparticles (LNPs) [27].

TABLE 2: PHYTOCHEMICAL LOADED LIPIDIC AND POLYMERIC NANOPARTICLE FOR MANAGEMENT OF LUNG CANCER

S. no.	*Phytoconstituents*	*Source*	*Findings*
1.	Geraniol	Present in rose oil, citronella, lemongrass, lavender, and other aromatic plants	The A549 cell viability loss was increased (1.8–3.2 fold) after Geraniol encapsulation into NLC, which resulted non-toxic to normal lung fibroblasts WI-38 cells [28].
2.	Quercetin	Mostly in onions, grapes, berries, cherries, broccoli, and citrus fruits.	Quercetin could significantly reverse Paclitaxel resistance by inhibiting Akt and ERK phosphorylation and MMP depolarization [29].
3.	Resveratrol	Grapes, berries, peanuts, and pines	A549 cells of lung cancer, upon treatment with resveratrol was found to arrest the cell cycle in G_0/G_1 phase by down regulating the expression levels of cyclin-dependent kinase-4 (CDK4) and CDK6 [30].
4.	Thymoquinone(TQ)	Nigella sativa	The differential effect of TQ- in cell cycle analysis was observed, where cancer cells were accumulated on G2-M and pre-G1 phases [31].
5.	Curcumin	Curcuma longa(turmeric)	The curcumin loaded SLNs were found to be effective against lung cancer as compare to plain SLNs [32].

3.1.2.2 Metallic nanoparticles

Metallic nanoparticles have captivated scientists for more than a century, and they are now widely used in engineering and biological sciences. They are the subject of attention due to their enormous potential in nanotechnology. In order to use them in these imaging modalities, numerous nanoparticulated contrast agents were developed, including magnetic nanoparticles (Fe_3O_4), gold, and silver nanoparticles. Additionally, more recent multifunctional nanoshells and nanocages have been created in order to utilise different imaging techniques in combination [33].

TABLE 3: PHYTOCONSTITUENTS LOADED METALLIC NANOPARTICLE FOR THE MANAGEMENT OF LUNG CANCER

S. no.	*Phytoconstituents*	*Source*	*Metallic Nanoparticles*	*Findings*
1	*Andrographis macrobotrys*	Leaf extract	Silver nanoparticles	The anticancer activity of AgNPs exhibited 68.15 % at 100 µg/mL concentration against A549 lung cancer cells [34].
2	Nigella sativa	Essential oil	Gold nanoparticles	The IC50 value showed that Nigella sativa essential oil-gold nanoparticles was highly effective in inhibiting the A549 lung cancer cells compared [35]
3	Musa *paradisiaca*	Aqueous peel extract	Gold nanoparticles	Musa *paradisiacal* gold nanoparticles effectively controlled the viability of human (A549) lung cancer cells altering morphology [36].
4	*Euphorbia nivulia*	Latex	Silver Nanoparticles	These NPs are found to be cytotoxic against human lung carcinoma cells (A549) in a dose-dependent manner [37]
5	*Moringa oleifera*	Leaf, flower, fruit	Gold nanoparticles	*Moringa oleifera* flower-mediated gold nano-particles exhibited cytotoxic effects on the A549 human lung cancer cell line and normal healthy human peripheral lymphocytes [38].

3.1.2.3 Liquid crystalline nano-particles

Liquid-crystalline nanoparticles are a fascinating new class of materials with numerous possible uses [39]. LCNs offer a unique biocompatible drug delivery method and have honeycombed (cavernous) structures with diameters ranging from 10-500 nm by fusing supramolecular ordering with the fluid properties of the liquid-crystalline state. They resemble dots, but they're actually probably spherical structures. In the lipid water system, each dot denotes the presence of a pore that contains an aqueous cubic phase [40].

TABLE 4: PHYTOCONSTITUENT LOADED LIQUID CRYSTALLINE NANOPARTICLE FOR THE MANAGEMENT OF LUNG CANCER

S. no.	*Phytoconstituents*	*Source*	*Findings*
1	Zerumbone	Roots of *Zingiber zerumbet*	Zerumbone-LCNs, prepared in the study, inhibited the proliferation and migration of A549 cells. These inhibitory effects were superior to the effects of ZER alone at a concentration 10 times lower than that of free ZER, demonstrating a potent anti-cancer activity of ZER-LCNs [41].
2	Naringenin	It is widely distributed in several Citrus fruits, bergamot, tomatoes and other fruits	Naringenin-loaded LCNs posses anticancer activity by the inhibition of proliferation and migration of cells. They also attenuated colony formation and induced apoptosis in the A549 cells [42].
3	resveratrol	grapes, berries, peanuts, and pines	pemetrexed -resveratrol LCNPs manifested superior concentration and time dependent cytotoxicity profile against A549 lung cancer cells with IC_{50} 4.0628 µg/mL [43].
4	Rutin	Buckwheat, Japanese pagoda tree, and Eucalyptus are sources of rutin	Rutin-LCNs showed promising anti-proliferative and anti-migratory activities. Rutin-LCNs also induced apoptosis in the A549 cells and inhibited colony formation [44]
5	Berberine		Berberine-loaded LCNs were significant in suppression of proliferation, inhibition of colony formation and proliferation related proteins associated with cancer progression [45].

4. CONCLUSION

The majority of cancer deaths-18.4% of all cancer deaths in both sexes combined are caused by lung cancer (LC), which is the most common type of cancer. The use of systemic medications is one of the main LC therapies. However, these drugs' substantial adverse effects, systemic toxicity, and poor selectivity limit their ability to be therapeutically effective. As opposed to conventional ways, pulmonary anticancer drug administration has a number of benefits. Direct delivery of chemotherapeutic medications to the target LC cells is made possible by the inhalation approach, which may increase antitumor effectiveness and result in a lower dose and less systemic side effects. In addition to being used to treat cancer,

phytochemicals, or naturally occurring plant compounds, are significant sources for novel drugs. Typical examples include analogues of taxol, vinca alkaloids like vincristine and vinblastine, and analogues of podophyllotoxin. These phytochemicals frequently function by regulating molecular pathways linked to the growth and metastasis of cancer. The precise mechanisms including enhancing antioxidant status, lowering proliferation, neutralizing carcinogens, causing cell cycle arrest and apoptosis, and immune system regulation. The further studies may include the identification and development of new drug delivery systems with plant based potent drugs.

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