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Potent Cytotoxic Potential of Carboplatin and Phytosomes against Lung Cancer Cells: A Review

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ABSTRACT

According to World Health Organization, cancer is a vast category of diseases that can begin in practically any organ or tissue of the body and spread to other organs when abnormal cells proliferate uncontrollably, invade adjacent regions of the body, and/or move to other organs. Cancer is the second biggest cause of death worldwide, accounting for 9.6 million fatalities in 2018, or one in every six deaths. This review was focused on the elaboration of scientific facts in terms of Phytosomes and Carboplatin in the cure of lung cancer. The review consists of an extensive survey of literature from Scopus, PubMed, Springer Nature, and other international reputed sources. Lung cancer is the most often diagnosed cancer in the world, accounting for 12.4 percent of all cancer diagnoses and the main cause of cancer-related fatalities. In the treatment of metastatic bladder transitional cell carcinoma (TCC), the platinum/gemcitabine combination and MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) are two first-line regimens with similar anti-tumor activity. The ability of the rosiglitazone/carboplatin combination regimen to reduce tumor growth in multiple genetically modified animal models of lung carcinogenesis in a synergistic manner suggests the possibility of a broadly successful anticancer therapy. Carboplatin is a cisplatin analog that lacks much of the parent compound's renal toxicity, neurotoxicity, and ototoxicity. Anti-tumor, anti-inflammatory, etc. The considerable drop in the IC50 value of TQ-phytosomes (4.31 2.21 M) against the A549 cell line revealed a noteworthy increase in dose-dependent cytotoxicity. TQ-phytosomes had a different effect in cell cycle analyses, with cancer cells accumulating in the G2-M and pre-G1 stages. In conclusion, it was possible to obtain a sustained release profile with much improved anticancer potential using TQ by this phytosomal nanocarrier platform. This review suggests developing phytosomes and carboplatin in a novel drug delivery system to achieve optimum drug action.

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INTRODUCTION

According to World Health Organization, cancer is a vast category of diseases that can begin in practically any organ or tissue of the body and spread to other organs when abnormal cells proliferate uncontrollably, invade adjacent regions of the body, and/or move to other organs. The latter is known as metastasizing, and it is a leading cause of cancer-related death. Cancer is sometimes referred to as a neoplasm or a malignant tumor. Cancer is the second biggest cause of death worldwide, accounting for 9.6 million fatalities in 2018, or one in every six deaths. Men's cancers include lung, prostate, colorectal, stomach, and liver cancer, whereas women's cancers include breast, colorectal, lung, cervical, and thyroid cancer (Cancer, WHO, 2021). Since 1987, lung cancer has claimed the lives of more women than breast cancer. In the United States, it is estimated that 225,000 new cases of lung cancer are diagnosed each year, with 160,000 individuals dying from the disease. It's worth noting that lung cancer was a relatively uncommon disease at the turn of the century. Its remarkable rise in recent decades is mostly due to an increase in both male and female smoking. Lung cancer, also known as bronchogenic carcinoma, is a type of cancer that starts in the lung parenchyma or the bronchi. In the United States, it is one of the top causes of cancer-related deaths. (Miller et al. 2016; Kocher et al. 2015).

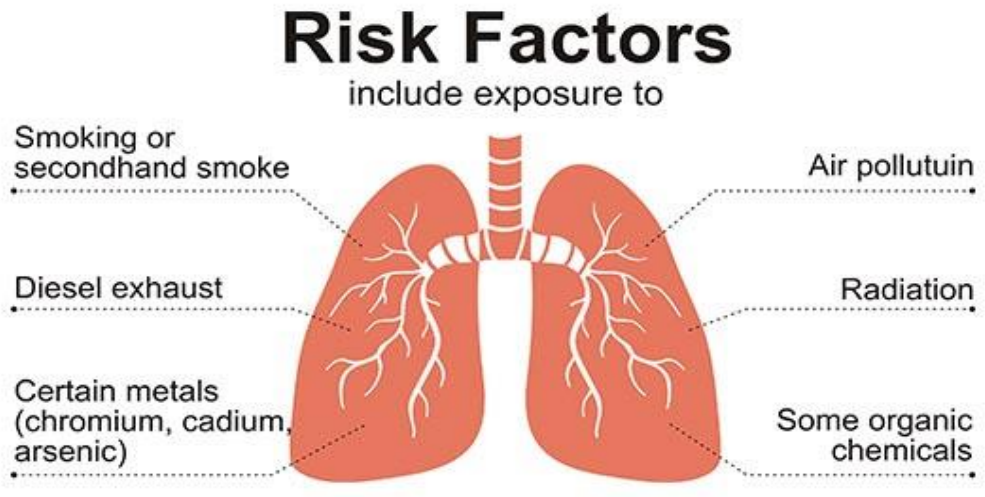

Fig. No. 1. Risk factors of lung cancer

With a measured 2 million new cases and 176 million deaths per year, lung cancer is one of the most often diagnosed malignancies and the major cause of cancer-related deaths globally. In the last two decades, significant advances in our understanding of disease biology, the use

of predictive biomarkers, and therapy enhancements have resulted in amazing progress and improved the outcomes of many patients (Thai et al. 2021).

Etiology of lung cancer

The mines had significant amounts of radon gas, and an etiologic link between radioactive gas exposure and lung cancer was hypothesized in the early twentieth century (Miller et al. 2005). A growing number of lung cancer cases have been reported in never-smokers, notably Asian women (Lam et al. 2004).

Lung cancer is most commonly caused by smoking. Smoking is thought to be responsible for 90 percent of lung cancer incidences. Male smokers are at the greatest danger. Exposure to other toxins, such as asbestos, increases the risk of cancer. Because of the intricate interplay between smoking, environmental, and genetic factors, there is no link between lung cancer and the number of packs smoked per year. Passive smoking increases the incidence of lung cancer by 20 to 30 percent (Alberg & Samet, 2003). Radiation for non-lung cancer treatment, particularly non-Hodgkins lymphoma and breast cancer, is another factor. Lung cancer has also been linked to metals like chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons. Independent of smoking, lung disorders such as idiopathic pulmonary fibrosis enhance the risk of lung cancer (Lorigan et al. 2005; Burns, 2000).

Epidemiology of lung cancer

Lung cancer is the most often diagnosed cancer in the world, accounting for 12.4 percent of all cancer diagnoses and the main cause of cancer-related fatalities. The American Cancer Society estimates that over 234,000 new lung cancer cases are diagnosed each year in the United States, with over 154,000 lung cancer-related fatalities. Lung cancer remained the biggest cause of cancer death worldwide in 2020, according to the Global Cancer Statistics report, with an expected 1.8 million fatalities (Siddiqui et al. 2021). The lung cancer epidemic seemed to be limited to the industrialized nations in the past. According to recent data, lung cancer is becoming more common, with nearly half of all new cases (49.9%) being identified in developing countries (Barta et al. 2019).

Pathophysiology

Lung cancer pathogenesis is extremely complex and poorly understood. Repeated exposure to carcinogens, such as cigarette smoke, is thought to cause lung epithelial dysplasia. If the

exposure is not stopped, it will cause genetic alterations and have an impact on protein production (Cagle et al. 2013).

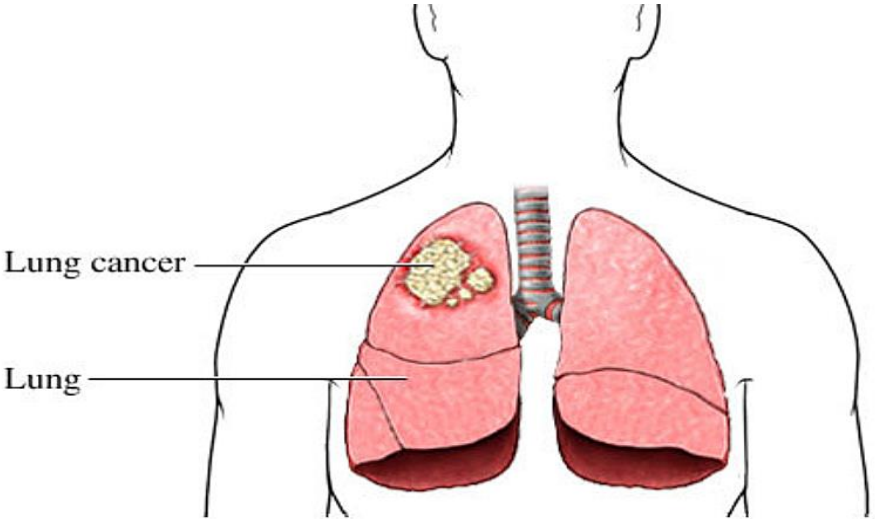

Fig. No. 2. Depiction of lung cancer

Lung tumors are classified histo-pathologically based on cellular and molecular subtypes, which is an important aspect of diagnosing and treating lung malignancies. Lung cancers are classified as follows per the World Health Organization (WHO) classification scheme of 2021-

- Precursor glandular lesions
- Adenocarcinomas
- Adenosquamous carcinomas
- Squamous precursor lesions
- Squamous cell carcinomas
- Large cell carcinomas
- Sarcomatoid carcinomas
- Lung neuroendocrine neoplasms
- Salivary gland-type tumors
- Neuroendocrine tumors
- Neuroendocrine carcinomas

- Other epithelial tumors

Carboplatin

Carboplatin differs from cisplatin chemically in that it is more water-soluble (40 mmol/L at 37°C) and has a slower rate of aquation (Harrap, 1985). Despite the differences in chemical characteristics, we show that carboplatin may be successfully encapsulated in a lipid formulation using a comparable approach, resulting in a formulation with significantly increased *in vitro* cytotoxicity against tumor cells compared to the free drug (Hay & Miller, 1998).

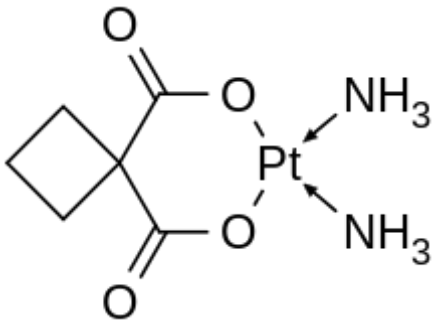

Fig. No. 3. Structure of Carboplatin

IUPAC Name: **Azanide; cyclobutane-1,1-dicarboxylic acid;platinum(2+)**

Molecular formula: $C_6H_{12}N_2O_4Pt$

Mechanism of action

Carboplatin primarily functions by attaching alkyl groups to nucleotides, resulting in monoadduct formation and DNA fragmentation when repair enzymes attempt to correct the defect. Carboplatin's activity is derived from DNA cross-linking from one base on one strand to another, which prevents DNA strands from separating for synthesis or transcription. Finally, carboplatin can cause a variety of mutations (Povirk &Shuker, 1994).

As anti-lung cancer

In the treatment of metastatic bladder transitional cell carcinoma (TCC), the platinum/gemcitabine combination and MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) are two first-line regimens with similar anti-tumor activity (Masse et al. 2000). Because of the severe toxicity of MVAC, platinum/gemcitabine has generally replaced MVAC as the first-line chemotherapy strategy for bladder cancer. Carboplatin is a platinum

analog of the second generation. Carboplatin has a lower toxicity profile than first-generation cisplatin, with less nephrotoxicity and neurotoxicity. This is especially intriguing in bladder cancer patients, as many of them have renal insufficiency and cardiovascular co-morbidities, making cisplatin treatment impossible. Cisplatin or carboplatin in conjunction with gemcitabine has been used to treat a variety of different cancers (Bajetta et al. 2003; Hudson & Lester).

Recent research showed that when the bladder cancer cell line 5637 was treated with gemcitabine followed by carboplatin or concurrent carboplatin/gemcitabine, synergism was detected. When cells were treated with carboplatin and then gemcitabine, moderate antagonism was detected. The combined effect of these two medicines, according to cell cycle studies, was cell cycle disruption (Wang et al. 2010). Even though a larger concentration of carboplatin is required, the carboplatin-DNA adduct production is nearly identical to that of cisplatin (Knox et al. 1986). Carboplatin (Paraplatin), a cisplatin derivative, has significantly less nonhematologic toxicity than cisplatin, while myelosuppression may be slightly higher. The growing adoption of carboplatin-based regimens to treat small-cell lung cancer has come from the reduced toxicity and equivalent efficacy of carboplatin. Overall response rates for carboplatin as a single-agent treatment for small-cell lung cancer were around 60% for previously untreated patients and 17% for those who had previously received treatment in phase I and II trials (Ettinger, 1998).

Carboplatin is a cisplatin analog that lacks much of the parent compound's renal toxicity, neurotoxicity, and ototoxicity. Carboplatin is an active drug in small cell lung cancer, according to the outcomes of trials presented in this review. Although there are no prospective randomized trials to establish this, carboplatin regimens appear to have an equivalent activity to cisplatin regimens in combination regimens for SCLC. To determine carboplatin's final involvement in SCLC, more trials examining dosage response relationships and colony-stimulating factors (CSFs) are needed. Non-small cell lung cancer (NSCLC) is also responsive to carboplatin, with an overall response rate of little under 10%. Its single-agent survival is comparable to that of non-carboplatin-containing combos (Bunn, 1989).

These studies are one of the first to show that genetically altered mice models may be used to determine the best combinations of conventional chemotherapeutics. Importantly, we show that the combination of rosiglitazone and carboplatin is a more effective anticancer treatment than either agent alone; this has practical consequences because we show that both medicines

may be provided without increasing overall toxicity. Finally, chemosensitivity and chemoresistance include a variety of processes. The ability of the rosiglitazone/carboplatin combination regimen to reduce tumor growth in multiple genetically modified animal models of lung carcinogenesis in a synergistic manner suggests the possibility of a broadly successful anticancer therapy (Girnun et al. 2008).

Phytosomes

Phytosomes are a combination of a natural substance with naturally occurring phospholipids, such as soy phospholipids. The interaction of stoichiometric quantities of phospholipid with the chosen polyphenol (such as simple flavonoids) in a nonpolar solvent produces this complex (Bombardelli et al. 1989). The creation of hydrogen bonds between the polar head of phospholipids (i. e. phosphate and ammonium groups) and the polar functional groups of the substrate has been proven to be the main phospholipid-substrate interaction based on their physicochemical and spectroscopic data. Phytosomes are enhanced herbal products that are more easily absorbed, utilized, and thus generate greater outcomes than traditional herbal extracts (Franco & Bombardelli, 1998).

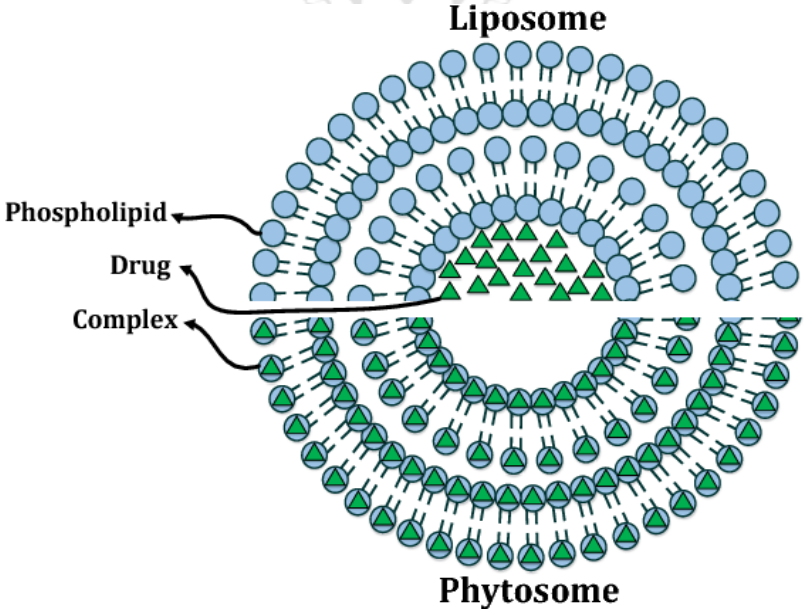

Fig. No. 4. Depiction of the structure of Phytosome Vs Liposome

Phytosomes as anti-lung cancer

The formulation's in vitro release pattern revealed a biphasic release pattern, with an initial burst release within 2 hours followed by a protracted release. The considerable drop in the

IC50 value of TQ-phytosomes (4.31 2.21 M) against the A549 cell line revealed a noteworthy increase in dose-dependent cytotoxicity. TQ-phytosomes had a different effect in cell cycle analyses, with cancer cells accumulating in the G2-M and pre-G1 stages. Additionally, the annexin V staining approach demonstrated enhanced apoptotic induction and cell necrosis of TQ-phytosomes via caspase-3 activation. TQ-phytosomes dramatically increased ROS formation in A549 cells in a study of reactive oxygen species (Alhakamy et al. 2020).

Phytosomes are a type of vesicular drug delivery system that transports bioactive substances obtained from plants across the cell membrane. Phytosomes are micelles with a core that encapsulates plant extracts and an exterior surface that conjugates the targeted proteins. Drug carriers are passively targeted by vesicular drug delivery systems, which evade the immune system. However, in the case of tumor therapy, phytosomes with a molecular weight of more than 40 kDa and a nanometric size range of 100–1200 nm actively target tumor cells because of their improved penetration and retention impact. Active targeting specifically delivers the pharmaceuticals to the site of action, while passive targeting boosts the bioavailability of the drugs. The two are combined in phytosomes to deliver the bioactive ingredients (Azeez et al. 2018).

Anti-tumor, anti-inflammatory, antinociceptive, anti-obesity, thermoregulatory effects, cardioprotective, anti-asthmatic, anti-diabetic, anti-oxidant, hepatoprotective, and powerful CNS activity are among the phytoconstituents' pharmacological properties. Various drug delivery methods, including liposomes, niosomes, transferosomes, ethosomes, phytosomes, colloidosomes, and others, have been created to transport drugs to the site of action without requiring their metabolism. Phytosome applications such as improving bioavailability, acting as anti-cancer and antioxidant, transdermal administration, and wound healing potential have all been studied (Chivte et al. 2017).

CONCLUSION

Nowadays, lung cancer has become one of the leading cancer types worldwide. Many well-approved treatments are available to cure lung cancer but medical research is massively working to evaluate some more reliable anti-cancer potential with easy availability. They must be cost-effective to fulfill the needs in developing countries. Carboplatin and phytosomes have been evaluated as anti-lung cancer in various animal models. In conclusion, it was possible to obtain a sustained release profile with much improved anticancer potential using TQ by this phytosomal nanocarrier platform a novel drug delivery (NDDS) system.

SOURCE OF FUNDING

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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