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Review Article

A PRAGMATIC APPROACH TO TREAT LUNG CANCER THROUGH LOADING THEAFLAVIN -3,3'-DIGALLATE AND EPIGALLOCATECHIN GALLATE IN SPANLASTIC

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ABSTRACT

Lung cancer has the highest mortality rate as compared to other cancers. The anti-proliferative and antioxidant potential of epigallocatechin gallate (EGCG) and Theaflavin -3,3'-digallate (TF3) can play a major role in treatment if delivered efficiently. To improve the chemical stability and medicinal potential of EGCG and TF3 in the respiratory tract, a spanlastic is developed which is composed of Tween-80, Span-60, and cholesterol which encapsulate EGCG and TF3 inside its vesicular structure and deliver it specifically to the target cancer cells. The cholesterol layer will produce efficient penetration while tween-80 and span-60 will help in easily deformability and lowers the interfacial tension hence, produces a small Z-average diameter which facilitates efficient penetration between layers of cells. The nano-vesicular structure ensures the APIs stability at alkaline pH (7.6) and also increases cellular antioxidant activity and Ferric reducing antioxidant powers values of APIs. Better encapsulation efficiency and safe consideration by MTT assay are major advantages of Spanlastic. The lung cancer cell loses the ability of apoptosis, which can revived with the help of a nano-vesicular system of EGCG and TF3 and in addition, there will be activation of several other properties such as cell arrest, activation of miR-210, suppression of cyclin D1, inhibition of MAPK, ERK, and JAK-STAT at their maximum potential. Furthermore, a special type of spacer and pMDI canister are developed in order to maximize the drug stability and efficiency of its delivery.

Keywords: Lung cancer, Epigallocatechin gallate, Theaflavin -3,3'-digallate, Nano-particles, Spanlastic.

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INTRODUCTION

Lung cancer has the highest mortality rate among all cancers. According to the research data of 2018, lung cancer has the highest incidence rates of 20.1 million new cases (12.22/100,000 individuals) and also the highest mortality rates of 1.76 million deaths; the death rate is 2 times of breast cancer in women and thrice of prostate cancer [1]. Smokers are 20 times more vulnerable than non-smokers [2]; the most prone age group is between 50 and 69.

The genetic risk of lung cancer is 2.5 times more [3]. It is a source of 32% of the casualties in men and 20% in women. It has been observed for many years that the incidence rate in blacks is more than in Caucasians [4]. There are several types of lung cancer such as Adenocarcinoma (ADC), Squamous cell carcinoma (SQCC), Small cell carcinoma (SCC), and Large cell carcinoma (LCC) are the major ones but there are also some rare types of lungs carcinoma.

The traditional techniques and chemotherapy used to treat lung cancer are highly expensive, has severe side effects and after going these exhausting stage, the reoccurring percentage of lung cancer is also very high. The proclivity of non-invasive techniques is increasing due to its lesser side effects, good cost effectiveness, and convenience [5].

Epigallocatechin gallate (EGCG) is a water-soluble flavonoid and is a major green tea catechin component among all with a molar mass of 458.4 $gmol^{-1}$ [6]. It has one of the best chemopreventive potency, but shows low bioavailability and is highly unstable hence the treatment is strenuous [7]. EGCG has low oral bioavailability (0.2–2%); max plasma EGCG concentration is 0.15 μM [8,9]. It is very unstable on pH 7.4; otherwise, it is next to an ideal anti-cancerous agent.

Theaflavin -3,3'-digallate (TF3) is also a flavonoid. The predominant constituent is highly soluble in water. These polymeric catechins are formed by the enzymatic fermentation of black tea leaves. It has lesser oral bioavailability (0.7–1%) with a molar mass of 564.499 $gmol^{-1}$. Like EGCG it is also less stable on pH 7.4 and has similar anti-cancerous potential as EGCG [10,11].

TF3 and EGCG have an excellent anti-proliferative effect but unstable at respiratory tract pH [12,13]. Loading TF3 and EGCG inside a spanlastic nano-vesicular structure can increase the bio-stability of the drug by many folds. Spanlastic is chosen to be the carrier because of its high permeability and high deformability [14]. The spanlastic is composed of tween 80 and span 60 and the outer surface is further coated with cholesterol (spanlastic will be produced through ethanol injection method) [15]. Inside it EGCG, TF3 will be present in a liquid solution made up of ethanol. Further, this system will be tested for its cytotoxic effects, pH effects, cellular antioxidant activity (CAA), ferric reducing antioxidant power (FRAP), apoptosis, cancer colonies (A549 and HLC-1) shape, size, and zeta potential. Extraction of EGCG will be done from drying of green tea leaves, and extraction of TF3 will be done from oxidative coupling reaction ECG and EGCG via o-quinones. The drug will be delivered through pMDI in addition to spacers for better drug consumption [16]. Due to this novel drug delivery system the drug directly reaches the receptor in the lungs bypassing the liver reducing t1/2 increasing clearance rate and bioavailability.

EGCG

Green, black, and oolong tea, all come from the same plant, *Camellia sinensis* L. of the *Theaceae* family [17]. EGCG major component of green tea is one of the excellent chemo preventive agent and shows anti-proliferative effect more than 5-flurouracil [18] and can be used in the treatment of prostate cancer [19], lung cancer [20], colorectal cancer [21], and breast cancer [22]. It has properties such as neuroprotective [23,24], anti-diabetic [25], anti-bacterial [26], anti-atherosclerotic [27], cardio-protective [28], anti-viral [29], anti-oxidant [30], anti-inflammatory [31], anti-proliferative [32], and anti-obesity [33]. The antioxidant activity of EGCG is more than that of Vitamin C and Vitamin E (maybe 25 times more) [34].

WORKING OF EGCG AGAINST CANCER

EGCG upregulates the expression of miR-210 (key cancer preventive) by binding HIF-1αwhich inhibits proliferation and anchorage-independent growth of lung cancer [35]. Overexpression of EGFR causes tumorigenic processes. EGCG inhibits HGF-induced c-Met phosphorylation enhances the anti-proliferative potential EGFR inhibitors which further causes repression in the growth factor receptor signaling in ADC [36]. EGCG suppresses cyclin D1 and induces p21 expression which reduces the cell growth or promotes cell arrest and by this, it reduces the cancer cells [37]. The process of apoptosis is blocked in cancer cells which stimulates abnormal growth of the cell. EGCG induces intracellular reactive oxygen species (ROS) and oxygen distress which causes a breakdown in cancer cellular DNA thus initiating the process of apoptosis [38]. EGCG activates the AMPK signaling pathway which inhibits lung cancer cell proliferation, colony formation, migration, and invasion (AMPK inhibits essentially all anabolic pathways that promote cancer cell growth) [39,40]. EGCG downregulates the expression of nuclear factor kappa B (NF-κB) and NF-κB target genes are induce cancer by proliferation (MYC, Cyclin D1), metastasis (MMP2 and TWIST1) inflammation (cyclooxygenase-2 [COX2], and TNF-α), and survival (Bcl-XL, BCL-2) [41].

THEAFLAVINS

Theaflavins are major component of black tea [42], this polyphenolic compound have diverse health benefits such as antiviral [43], antibacterial [44], anti-osteoporotic [45], anticancer [46], anti-atherosclerotic [47], anti-inflammatory [48], anti-obesity [49], and anti-dental caries properties [50]. Likewise EGCG, theaflavins are also present in low concentrations [51]; hence, it is a cumbersome process to extract theaflavin, and also it is difficult to use in the medical field because of its highly unstable nature. Theaflavins have similar antioxidant potential as EGCG [52].

THEAFLAVIN WORKING AGAINST CANCER

Theaflavin exhibited substantial cell arrest at the G2/M phase which inhibits proliferation and cell division of cancer cells [53]. Theaflavin inhibits or delays hyperplasia and dysplasia [54]. 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 [55,56]. 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 proenzyme caspase-3 which catalyses the specific cleavage of many important cellular proteins which plays an important role in apoptosis [57]. Theaflavins suppresses inducible signal transducer and activator of STAT3 (transcription 3) phosphorylation which further downstream anti-apoptotic proteins (Bcl-2 and Survivin). Theaflavin also down regulates invasion-related proteins (MMP-9, MMP-2) [58].

DIFFERENT TYPES OF LUNG CANCER

ADC

ADC also known as bronco alveolar carcinoma is an invasive malignant epithelial tumor differentiation or mucin production by the tumor with glandular cells. These are usually more peripherally located and tend to be smaller, start in the glands that line the inside of one of the organs [59]. A Tepidic pattern of spread is observed with an alveolar septal Tumors (<3 cm) and a small invasive component (<5 mm); enlargement can be seen often which causes bronchus obstruction and atelectasis. It accounts for 40% of all lung cancers [60].

SQCC

SQCC is strongly associated with smoking. It grows exophytically into the lumen of bronchi which accumulates mass intra-luminal, causes bronchus obstruction and atelectasis. SQCC usually passes through metaplasia or dysplasia before transforming into carcinoma some SQCC show cauliflower-like intraparenchymal mass. SQCC accounts for 25% of lung cancers (Figs. 1-7) [61].

SCC

It is caused due to cigarette smoking and it is highly malignant proving it to be most fatal. They mainly arise in the periphery or the major bronchi of the lung with no pre-invasive phase. It comprises small cells with no particular shape or size. Studies suggested that they are generally associated with ectopic hormone production and it majorly originates from neuroendocrine progenitor cells (which are present in the lining of bronchial epithelium). It accounts for 5–10% [62].

LCC

It generally grows in the outer region of the lungs. Cell size is larger than a normal cell with prominent large nucleus, it has high tendency to spread to the lymph nodes and distant sites; most aggressive among all lung cancer. It leads to pleural effusion (fluids accumulate in the pleural cavity). It accounts for 10–15% of all lung cancers [63].

Some rare type of lung cancers

- Adenosquamous carcinoma (a hybrid of ADC and SQCC) [64]
- Large cell neuroendocrine carcinoma (an aggressive subtype of non-small cell lung cancer) [65]

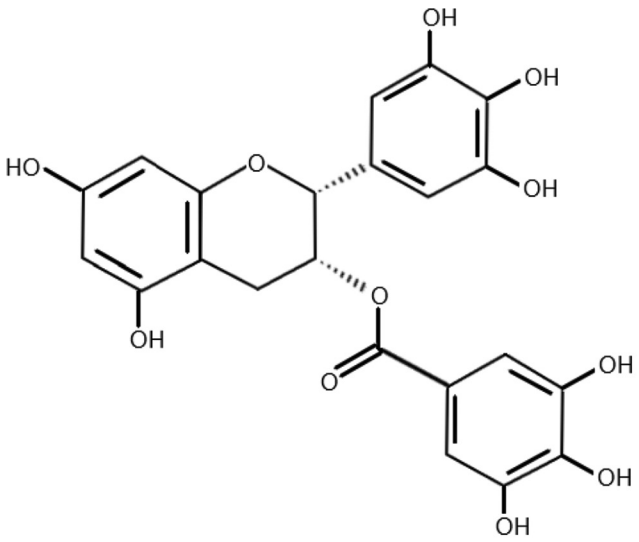

Fig. 1: Structure of epigallocatechin gallate

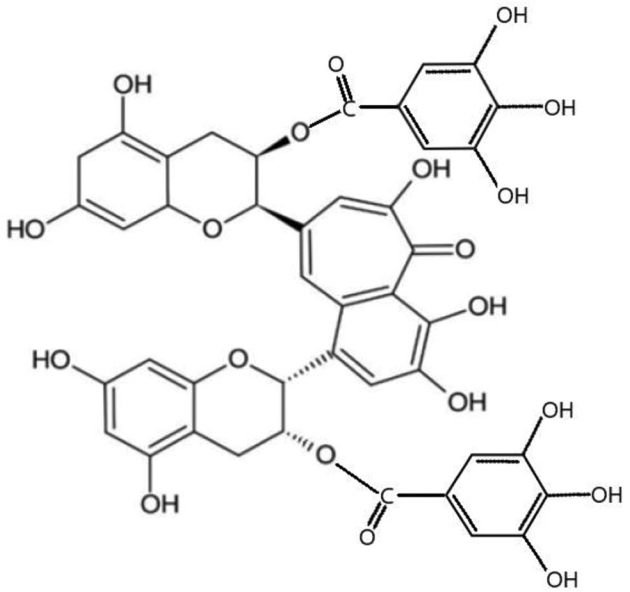

Fig. 2: Structure of Theaflavin -3,3'-digallate

- Salivary gland-type lung carcinoma [66]
- Lung carcinoids (more common in young individuals)
- Mesothelioma (develops in mesothelium)
- Mediastinal tumors [67].

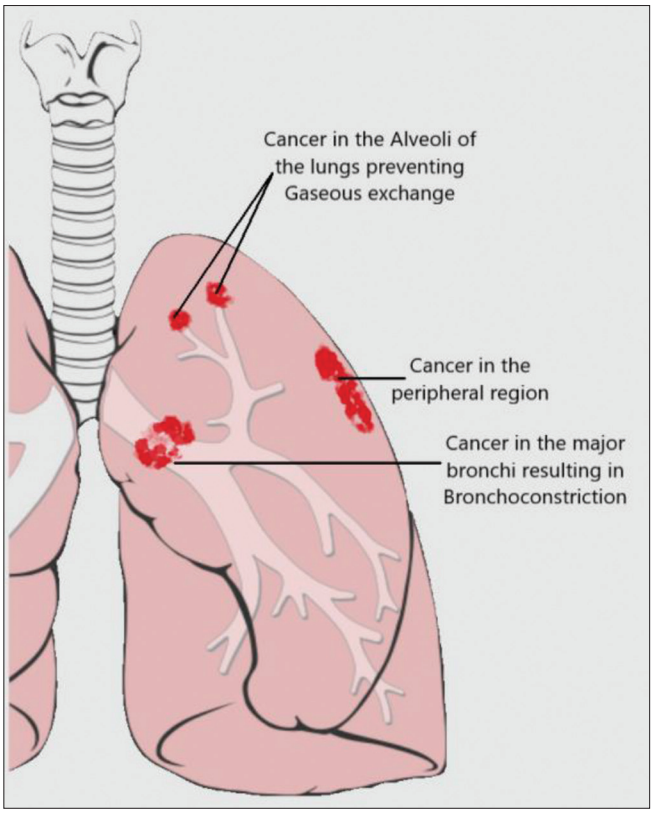

Fig. 3: Cancer at different locations of Lungs

MECHANISM OF PENETRATION OF DRUGS ONTO THE CANCER CELLS

When the drug reaches at the cancer cells, it interacts with mucus layer causes deformability in the outer layer of nano vesicle without damaging the drug entrapped in it, this deformability helps in effortless penetration in mucus and epithelium layer. In general, cancer occurs at the glands ADC or in the layers of the cell LCC, SQCC, and SCC. After penetrating mucus and epithelium layer, some amount of the nanoparticles breaks down and releases the drug onto the ADC which is on glands cells, while other penetrates deep inside the layers to the different types of cell carcinoma and then similar breakdown of spanlastic and release of drug process occurs.

The drug then binds with the receptors of cancer cells and produces their anti-proliferative and anti-inflammatory effects thus, causing reduction in the cancer cells.

PATHWAY AND PHARMACOKINETICS OF DRUG

The drug is stored in pMDI canisters and delivered through spacers. Spacers are used to facilitate drug delivery. The drug systematically covers the pathway from the mouth passing through the pharynx to the trachea then enters into the lungs. A small amount of drug may absorb from the mouth and further went for the first-pass metabolism.

Cancers generally occur at major bronchi, the surface of alveoli, and the periphery of the lungs. The drug can easily reach these sites because of nanoparticle's high deformability and high permeability which are developed by edge activator, non-ionic surfactant, and cholesterol.

The half-life of EGCG is 3.4±0.3 h [68] (half-life of pure EGCG is 2.25 h) and half-life of TF3 is 3–4 h [69], their half-life is very low so fewer chances of accumulation. Spanlastics never get accumulate and if rarely accumulate it is tested negative for MTT assay for its cytotoxicity effects [70]. The absorption rate of EGCG and TF3 is poor but it enhanced by many folds when delivered by spanlastics. In between 15 and 20 h the 4th t1/2 will be achieved means elimination of EGCG and TF3 is done.

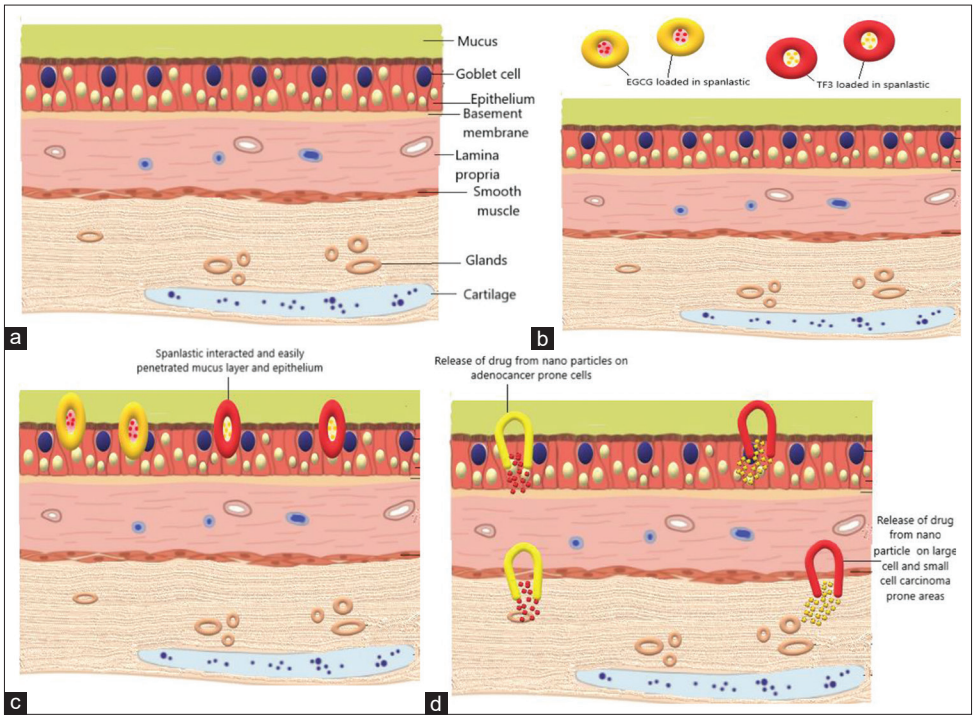

Fig. 4: (a) Layers of lungs, (b) Arrival of Epigallocatechin gallate and Theaflavin -3,3'-digallate nano particles at lungs layer, (c) Easily penetrating the mucus layer and the epithelium by spanlastics, (d) Breakdown of spanlastic and release of drug onto the target cells

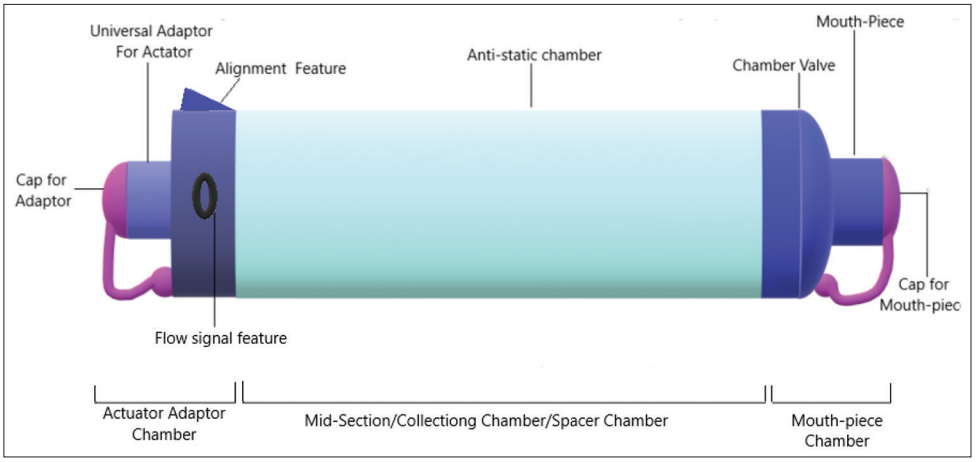

Fig. 5: Deep-air Spacer

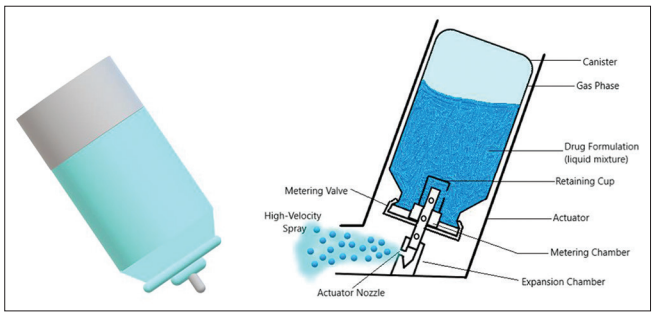

Fig. 6: Fluorocarbon polymerization plasma coated Canisters and pMDI drug delivery diagram

The clearances rate of pure EGCG is 72.5 ml × min/kg, and the apparent distribution volumes (Vd) is 22.5 dl/kg [71]. The clearances rate of TF3 is 0.17±0.02 L × h/kg, and the apparent Vd is 1.26±0.43 L/kg [72]. Further, these values are not of novel drug delivery systems; hence, t1/2 of these drugs will be reduced as of their original value there may be seen some increase in the volume of distribution and clearance rate.

BASIC REVIEW OF ARFA DRUG

EGCG and TF3 have anti-inflammatory and anti-oxidant properties and acts as efficient anti-cancerous agents. It produces oxidative distress and ROS activities causing a breakdown in cancer cellular DNA, which inhibit proliferation and anchorage-independent growth of lung cancer. However, it is highly unstable in respiratory pathway pH.

In ARFA drugs, EGCG and TF3 are mixed in ethanol to make a stable liquid solution. It is covered by non-ionic surfactants then it is covered by edge activator then by ethanol and finally a lipid layer (cholesterol) all these layer increases efficacy, entrapping efficacy, the negative net charge on the surface, deformability, bioavailability, biostability, and permeability of the drug by several folds. With the help of pMDI facilitated with spacers to increase drug consumption in the lungs and easily cross mucus membrane reaching the cancer site. After reaching the cancer site the spanlastic nano-vesicle breaks down and there is a systematic release of drug and is seen which further attaches to the receptor site causing apoptosis in cancer cells. The elimination of TF3, EGCG, and the rest of the nano-vesicular structure is very efficient with very little chance of accumulation or side effects.

In some special cases in which the patient is unable to eliminate the drug from the lungs. A less potent solution of salbutamol will be given to release the mucus by which the drugs will also get out without accumulating in the Lungs.

SPACER

A special spacer is designed for the treatment of lung cancer. The spacer is designed to deliver the ARFA drug and also to deliver the Salbutamol drug through pMDI. In some cases, in which the patient is unable to excrete out the cell debris, Salbutamol will help in it also it does not interact with nano-particle which hence will not destroy the integrity of the medication.

- The container size of the anti-static chamber will be 400 mL which perfectly fits like a medium to deliver both drugs
- The surface both inner and outer plus the caps whole body of the spacer is made up of Polycarbonate which provides more strength and durability also cost-efficient.

Both sides of the spacer have caps that provide better protection against any foreign contamination.

PROPELLANTS

Propellants are liquefied gases use to facilitates the delivery of formulation in proper form having vapor pressure greater than atmospheric pressure. HFA-134a is used as a suitable propellant for ARFA drugs [73].

PMDI CANISTERS

The outer layer of canisters is made up of aluminum and the inner layer is coated with fluorocarbon polymerization plasma which prevents drug degradation and ensures drug safety.

THE TECHNIQUE TO PREPARE EGCG AND TF3 LOADED IN SPANLASTIC SYSTEM

Different steps involved in the preparation:

1. Materials required
2. Extraction of components and preparation of TF3
3. The preparation of the system
4. The preparation of cancer colony
5. The test of the system against cancer colonies
6. Test of system on different pH and check for biostability.

MATERIALS REQUIRED

Green Tea leaves, Absolute ethyl alcohol, FeCl3, Triton X-100 ($C_{14}H_{22}O$), DMSO,Tween-80, Cholesterol, Deionized water will be decarbonized by boiling and bubbling N_2, Annexin-V-FLUOS Staining Kit, Human Cancer Cell line (A549 for small and LCC and HLC-1 for ADC), TPTZ (2,4,6-tri(2-pyridyl)-s-triazine), 1% penicillin/streptomycin, 10% fasting blood sugar (FBS), prandial blood sugar (PBS), 10% buffered formalin, Stains used will be hematoxylin and eosin, HCl, NaOH, NaCl, Acetate buffer, and Propidium Iodide.

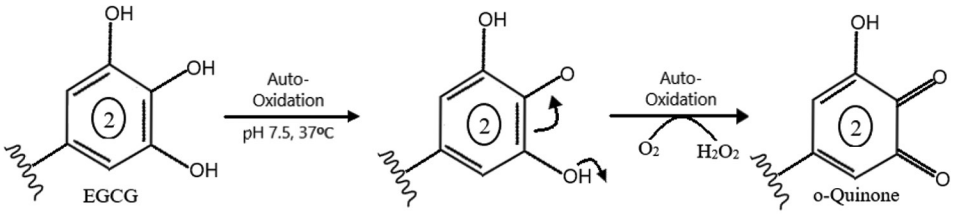

Fig. 7: Auto-oxidation of 2 ring of Epigallocatechin gallate into o-Quinone

EXTRACTION OF COMPONENTS AND PREPARATION OF TF3

- Extraction of EGCG: The best suitable method of extraction for EGCG and ECG is the hot extraction method by dry leaves of green tea. It is a two-step method. First, leaves are exposed to 50 and then, to 80; the net amount of EGCG extracted is between 500 and 600 g/ml and also a good amount of ECG is produced.
- Preparation of TF3
  Theaflavins are generally found in trace amounts in black tea (maximum amount of TF3 is found in Assam teas, i.e., 0.42–1.13 g/100 g). There are two ways by which we can extract theaflavins one is directly from black tea which is an expensive and exhausting process because of TF3 low availability in black tea.

The other way is, by oxidative coupling reaction through o-quinones (At pH of 7.4 and temp 37°C, EGCG is auto-oxidized and converted to o-quinone through nonenzymatic dehydrogenation of phenolic hydroxyl groups at ring no 2) by combining two compounds with hydroxyl groups at ring no.2, to prepare TF3; EGCG and ECG undergo oxidative coupling reaction [74].

EXTRACTION OF COMPONENTS AND PREPARATION OF TF3

The reaction involves the oxidation of the B ring of the catechin molecule to the quinone, which will react with the quinone of a gallocatechin through a Michael addition followed by carbonyl addition across the ring and subsequent decarboxylation to form theaflavins.

METHOD OF PREPARATION OF EGCG AND TF3 LIQUID SOLUTION SYSTEM

To prepare a liquid medium of these tea phenols 90% concentrated Ethanol is mixed with them. In both containers, a similar amount of tea phenols are placed as the ratio of these two phenols is 50:50. Then, a similar amount of ethanol is added to both systems (ex: in 100mg of EGCG or TF3 similar numerical value of 100 ml of ethanol will be added). The mixing will be done with the help of a bath sonication technique which will equally distribute the drug.

THE PREPARATION OF THE SYSTEM

- The ethanol injection method is used to prepare the spanlastic system as it fetches a great quality and quantity of spanlastic as compared to other methods of preparation, also the method is economical
- Both EGCG loaded in spanlastic and TF3 loaded in spanlastic are prepared separately with similar ways and components
- Span-60 mono-stearate (It is a non-ionic surfactant that lowers the interfacial tension and Laplace pressure P; which makes the concentric structure of Spanlastic stable) is dissolved in a solution of EGCG and TF3 and then sonicate the solution for few minutes
- The solution will then be shifted to preheated aqueous phase fixed ratio solution of Tween-80 (It is an edge activator which increases lipid bilayer flexibility and permeability, it generally have a high HLB value, it lowers the interfacial tension between the bilayer and hence increases the deformability) and cholesterol (increases efficacy) and then stirred on a magnetic stirrer at 1000–1400 rpm.
- The drawback to this method is the removal of residual ethanol which is very difficult as it forms an azeotropic mixture with water, hence molecular sieves are used
- The Z-average diameter and polydispersity index of the spanlastic will be determined by dynamic light scattering as the characterization is necessary
- This characterization will determine the shape and size of the spanlastic (shape and size of the spanlastic may change during the digestive process)
- Change of shape and size can be seen under the TEM imaging
- Encapsulation; one of the reasons for choosing spanlastic over other different types of niosomal preparations is that spanlastic can hold more amount of drugs inside its vesicular system
- For the differentiation between the encapsulated EGCG and TF3 and free EGCG and TF3, the Ultracentrifugation technique will be used and the dispersions will be released with Triton X-100
- The amount of total encapsulated EGCG and TF3 and free EGCG and TF3 were quantified by reversed-phase high-performance liquid chromatography
- The encapsulation will be determined by the formula of

$$EE\% = \frac{1 - C\,(\text{free})}{C\,(\text{total})} \times 100$$

Where C(free) is the concentration of free EGCG and free TF3 and C(total) is total EGCG and TF3 concentration prepared.

THE PREPARATION OF CANCER COLONY AND TESTING THE SYSTEM

- A549 for small and LCC and HLC-1 for ADC
- A549 cells were cultured in 25 mL DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FBS and 2 mM L-glutamine for complete media. Cells were grown in 5% CO2 in an air-humidified incubator at 37°C. The media was replaced every 2 days, and cells were passaged when they were nearly 80% confluent. Experiments on the culture media are done when the confluent levels pass above 90%. The medium will be undergone for the Trypsinization process and cells are removed from the medium by a wash with PBS and addition of EDTA (for lysis)
- HLC-1 cancer cell line
  A mixture of blooded pleural fluid and heparin will be centrifuged and the sediment will be suspended in Eagle's minimum essential medium and loaded on top of Ficol and 60% urograffin solution. Then, cells will be again suspended in RPMI-1640 supplemented with 20% FBS and incubated at 37°C for 30 min. After extracting out the medium, the floating cells not adhering to the surface were collected and cultivated at 37° in 5% CO2. Culture media were RPMI-1640 and Ham's F-12 supplemented with 20% FBS and 60 µg/ml Kanamycin.

TESTING OF THE EGCG LOADED IN SPANLASTIC ON DIFFERENT CRITERIA

- Testing of the vesicular system against different pH
  The vesicular system will be tested against pH 6.2 and 7.6; these 2 different pH will be chosen because it represents the overall gap in the pH of the whole mouth to bronchi to alveoli
- Testing of the vesicular system against different temperatures
  The temperature of the body varies from 97°F (36.1°C) to 100.4°F (38°C) at normal. The vesicular system must be stable at this temperature

- FRAP will determine the antioxidant potential of the drug. To make FRAP reagent acetate buffer will be mixed with TPTZ in HCl and $FeCl_3.6H_2O$. Then after the preparation of FRAP, the sample will be added to the FRAP and the results will be observed under the UV–vis spectrophotometer
- CAA
  For the calculation of CAA fluorescent readings will be observed. The formula for calculation of CAA is

$$\text{CAA unit} = 100 - \frac{(\int S - \int B)}{(\int C - \int B)} \times 100$$

Where ∫ S is the integrated area under the sample fluorescence versus time curve, ∫B is the integrated area from the blank curve, and ∫ C is the integrated area under the control curve

- MTT assay can also be used to detect the cytotoxic effects of the spanlastic system
- Detection of apoptosis
  For the Detection of apoptosis the Annexin V–FLUOS staining assay will be performed. In this, the cells are covered by Annexin-V-FLUOS labeling solution containing a diluted solution of Annexin V-FITC and Propidium Iodide. In the dark, the differentiation will occur and by using fluorescence microscopy we can check for apoptosis. Necrotic cells take up Propidium iodide and stain red, while apoptotic cells stain green

- X-RAY diffraction method
  The X-ray diffraction method will determine the integrity of the vesicular system inside the respiratory system. Furthermore, the anions and cations stability will be observed at different bands
- Zeta-potential and electrophoretic mobility
  Both have to be calculated and if there is a relatively high surface charge of spanlastic then it will more likely to interact with negatively charged cell membranes and be taken up by the cells easily.

RESULTS

EGCG and TF3 nano vesicular systems are prepared through ethanol injection method with Span 60 as non-ionic surfactant and tween-80 as edge activator with an outer covering of lipid (cholesterol). Both the EGCG-spanlastic system and TF3 spanlastic system were tested on several bases such as for shape and size TEM imaging will be used, for surface charge and zeta potential poly-dispersity index is measured. Testing against cancer cell lines will be done on A549 for SCC, LCC, and HLC-1 for ADC. MTT test will be done to detect the cytotoxic effects of the nano vesicular system. Stability will be tested on pH 7.6 and temperature at 37°C.

CAA, FRAP, and apoptosis (Annexin V–FLUOS staining assay) will also be calculated. After all these testing it can be said that EGCG and TF3 loaded in spanlastic will be a revolutionary cure for lung cancer.

CONCLUSION

Nanoparticles are used in novel drug delivery systems because of their high permeability and resistance against different body conditions. Spanlastic is one of the finest nano-particle because of its drug entrapping efficiency and cell-penetrating ability.

TF3 and EGCG have quite effective anti-cancerous potential but unable to produce these effects in the body due to their instability at pH 7.4 but if loaded in spanlastic they can utilize their potential against cancer cells; even they can perform more than their potential.

The side effects that occur in the traditional cancer therapy will not occur here also the treatment will be safe, economical, and of a shorter period. Patient compliance will also increase as the technique is non-invasive. Accumulation of drugs will not be seen also the psychological problems faced by patients will be reduced.

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AUTHORS CONTRIBUTIONS

Both the authors contributed equally in conceptualizing the theme as well as finalizing the draft.

CONFLICTS OF INTEREST

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

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