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Natural compounds promising way to treat Lung Cancer

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ABSTRACT:
The most deadly sort of cancer of all is lung cancer, which is quite serious. Natural substances including Formononetin, Matrine, Kaempferol, Trans-Resveratrol, and Apigenin are extremely effective anti-inflammatory and anti-cancerous compounds that can inhibit the signal transduction pathways for ERK-MAPK, JAK-STAT, p38, AMPK, PI3K/Akt, mTOR, STAT3, and wnt/-catenin. Inflammatory and proliferator enzymes such COX-2, caspase-3, MMP-9, MMP-2, NF-B, p53, Bcl-xL, Bcl-2, Mcl-1, miR-210, cyclin D1, iNOS, IL-1, TNF-, IFN-, IL-6, and IL-1 are inhibited by these APIs. The issues are caused by the aforesaid qualities' instability at the pH of the gastrointestinal system, which clearly demonstrates their anti-cancerous potential.At stomach pH, all substances either decay or lose their ability to cause cancer. Transferosomes are a type of new generation nanoparticle that is highly stable at 7.4 pH and has superior effectiveness and drug trapping potential than other types of traditional nanoparticle systems. If these APIs are included inside the transferosome's nano-vesicular structure, loaded in pMDI canisters like fluorocarbon polymerization (FCP) plasma coated canisters with a better propellant like HFA-134a, and delivered with the aid of spacers, it is possible to treat lung cancer affordably, effectively, with few side effects, and it also ensures that the cancer won't return.
Keywords: Formononetin, Matrine, Kaempferol, Trans-Resveratrol, Apigenin, Nano-particles.

INTRODUCTION:

Lung cancer has the highest mortality rate of all cancers. According to data published in 2020, lung cancer has the highest incidence rate (2.21 million new cases) and the highest mortality rate (1.80 million deaths)[1]; its mortality rate is almost twice as high as that of prostate cancer and female breast cancer combined. Smokers are 20 times more risky than non-smokers[2],with the most dangerous age group falling between 50 and 69. Hereditary risk for lung cancer is raised by 2.5 times. 20% of female fatalities and 32% of male fatalities are attributable to it. Blacks have a greater incidence rate than Caucasians; it has been noted for many years[3,4]. There are several variations of lung cancer.Adenocarcinoma (ADC), squamous cell carcinoma (SQCC), small cell carcinoma (SCC), and large cell carcinoma (LCC) are the most prevalent types of lung carcinoma; however, there are a few odd subtypes as well.

The recurrence risk of lung cancer is quite high following these difficult phases, and conventional lung cancer treatment methods like chemotherapy are incredibly expensive, have awful side effects, and are extremely ineffective. Non-invasive techniques made of natural ingredients are growing in popularity due to their reduced side effects, cost effectiveness, and accessibility.

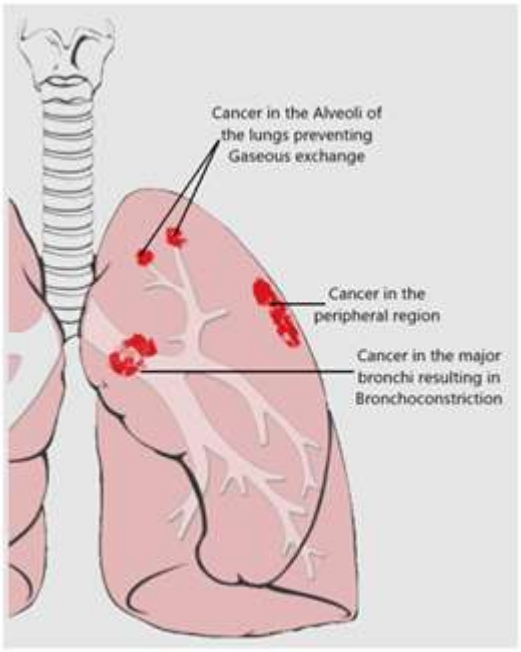

Fig 1: Sites of Lung cancer

Several forms of lung cancer:

- The invasive malignant epithelial tumour known as **Adenocarcinoma (ADC)**, often

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referred to as bronco-alveolar carcinoma, has glandular cells that can differentiate or create mucin. These typically start off smaller and more peripherally, in the glands that surround the lining of one of your organs. For 40% of all lung cancers, it is to blame [5,6].

- **Squamous cell carcinoma (SQCC)**, which is strongly associated with smoking. It invades the bronchial lumen exo-phytically, collecting mass intra-luminally, resulting in bronchus obstruction and atelectasis. SQCC often experiences metaplasia or dysplasia before developing into cancer. 25 percent of all instances involve it [7].
- **Small cell carcinoma (SCC)** is an exceedingly aggressive and lethal cancer that is brought on by cigarette smoking. There is no pre-invasive phase, and they typically form in the major bronchi or the periphery of the lung. It is composed of little cells of different sizes and shapes. It makes up 5–10% of the whole [8].
- The outermost part of the lungs is where **Large cell carcinoma (LCC)**, develops. The most aggressive kind of lung cancer, with cells that are bigger than normal cells and a strong propensity to migrate to distant locations such lymph nodes, In turn, pleural effusion occurs (fluids accumulate in the pleural cavity). 10% to 15% of all lung cancer cases are caused by it [9].

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.

Formononetin

An O-methylated isoflavone known as formononetin is found in a variety of plants, including red clovers (Trifoliumpratense L.), clovers, and the Chinese herb Astragalusmembranaceus (Fisch).Numerous pharmacological properties have been reported, including anticancer, anti-inflammatory, anti-oxidant, anti-allergic, anti-inflammatory, anti-proliferative, growth inhibitory, vaso-relaxant, neuroprotective, anti-apoptotic, and cardio-protective, mammary gland proliferative and anti-microbial activities [10,11].

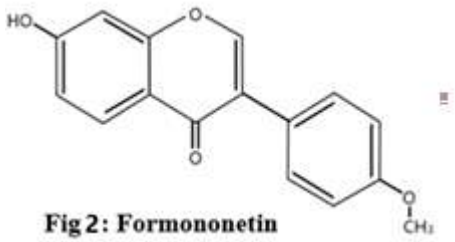

Fig 2: Formononetin

Anti-cancer potential

- The pro-inflammatory transcription factor NF-κB is inhibited by formononetin [12].
- Nitric oxide is produced in vitro less when NF-κB, a key transcription factor for the induction of nitric oxide synthase, is decreased.
- Formononetin showed that it could block the MAPK signalling pathway.
- Through the activation of the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 proteins, the MAPK pathways control the transcription of inflammatory genes. The MAPK signalling pathway is inhibited by these ERK, JNK, and p38, which prevents them from having any inflammatory effects [13].
- The generation of NO from iNOS, which is driven by IL-1β, is decreased by formononetin [14].
- Formononetin acts on COX-2 to lower prostaglandins.
- Additionally, formononetin inhibits the levels of IL6 and TNF-α [15].
- By preventing the release of histamine from the mast cells, formononetin acts as a mast cell stabiliser.

Matrine

Several types of cancer, Alzheimer's, rheumatoid arthritis, acute lung injury, ulcerative colitis, cardiac fibrosis, cerebral infarction, psoriasis, asthma, acute respiratory distress syndrome, and ankylosing spondylitis are among the conditions that matrine, which is derived from the root of Sophoraflavescens, has been shown to treat [16,17].

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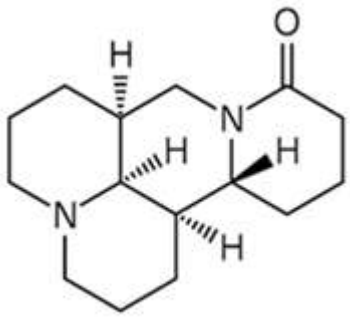

Fig 3 : Matrine

Anti-cancer potential

- Matrine protects against lung damage brought on by ulcerative colitis and suppresses the pro-inflammatory transcription factor NF-κB [18].
- Because it reduces neutrophil numbers and myeloperoxidase (MPO) and malondialdehyde (MDA) activity, it has anti-inflammatory properties [19].
- Matrine lowers the inflammatory mediators TNF-α, IL-1α, IL-1β, IL-8, and IL-6 that are responsible for the inflammation associated with asthma [20].
- It suppresses the expression of SOCS3 (a protein that monitors eosinophil levels) and the generation of reactive oxygen species (ROS).
- It lowers the concentrations of the pro-inflammatory cytokines ICAM-1 and COX-2.

Kaempferol

Various plant components; including seeds, leaves, fruits, flowers, and even vegetables, contain kaempferol. Cardio-protective, neuroprotective, diabetic, inflammatory, anti-inflammatory, antioxidant, antibacterial, antitumor, and anti-cancer properties of kaempferol [21,22].

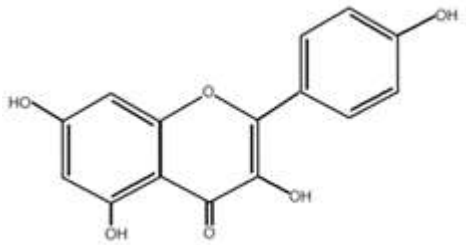

Fig 4: Kaempferol

Anti-cancer potential

- Cancer cells undergo apoptosis when exposed to kaempferol.
- The cell cycle is stopped at the G2/M phase.
- It inhibits phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and other signalling pathways [23].
- It expresses N-cadherin, E-cadherin, Snail, and Slug, markers associated with the epithelial-mesenchymal transition (EMT), as well as matrix metallopeptidase 2 (MMP-2), a marker associated with metastasis [24].
- By causing the activation of apoptosis-initiating enzymes such as cysteine proteases, caspases-3, 7, and 9, and poly (ADP-ribose) polymerases (PARP), it prevents the buildup of ROS.
- Kaempferol blocks the activation of AP-1, a transcription factor involved in the production of the COX-2 gene that is a downstream molecule controlled by MAPKs. As a result, it prevents COX-2 from being expressed as a result of UVB exposure [25].
- It prevents ERK, p38, and JNK phosphorylation brought on by UVB exposure.

Trans-Resveratrol

A member of the stilbene family of phytochemicals, resveratrol is pleiotropic. The secondary metabolites known as stilbenes are created by plants in response to stressful circumstances including fungal infections and UV radiation [26]. It has anti-cancer, anti-estrogenic, anti-inflammatory, anti-oxidant, anti-aging, anti-microbial, and anti-oxidant effects. Reversing multidrug resistance in cancer cells has also been found to be possible with resveratrol [27].

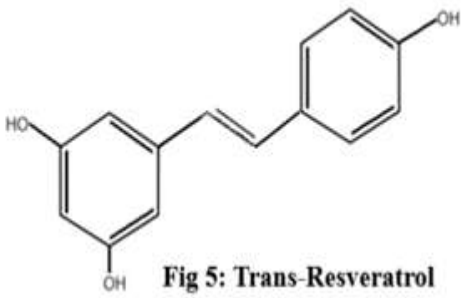

Fig 5: Trans-Resveratrol

Anti-cancer potential

- Resveratrol efficiently prevents the growth of skin cancers by inducing apoptosis, as shown by the stimulation of cytochrome C release, the expression of Bax, p53, and APAF-1, and the suppression of Bcl-2 [28].

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- Decreases the incidence of free radical scavenging.
- Reduces the expression of ODC and COX-2 (Ornithine decarboxylase) [29].
- Additionally, it lessens hyperplasia.
- It prevents IB-kinase activation, which in turn suppresses the expression of pro-proliferation genes such cIAP-2, survivin, cyclin D1, Bcl-xL, Bcl-2, XIAP, Bfl-1/A1, and TNF receptor-associated factor 2. (TRAF2) [30].
- Additionally, it inhibits COX-2, VEGF, MMP-3, MMP-9, and matrix metalloproteinase (MMP)-3. Resveratrol inhibits signal transducers and activators of transcription 3. (STAT3).
- It has an antioxidant effect by lowering lipid peroxidation and H_2O_2 levels in the skin.
- It also decreases the levels and expressions of hepatic TNF-α, IL-1β, and IL-6 [31].

Apigenin

Grapefruit, parsley, onions, oranges, chamomile, and wheat sprouts all contain the flavonoid apigenin [32]. Antibacterial, antiviral, anti-proliferative, anti-inflammatory, antioxidant, antiangiogenic, and anticancer activities are only a few of its beneficial bioactive properties. It can also cure rheumatoid arthritis, autoimmune diseases, Parkinson's disease, and Alzheimer's disease [33].

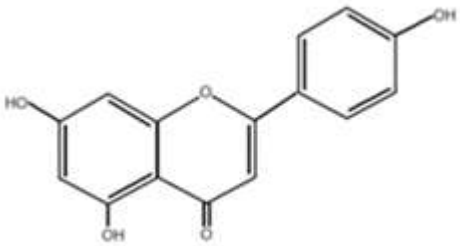

Fig 6: Apigenin

Anti-cancer potential

- Apigenin triggers apoptosis by altering the expression of the proteins Bcl-2, Bax, STAT-3, and Akt [34].
- It supports p38/MAPK and PI3K/Akt, two anti-inflammatory pathways.
- It also lowers COX-2 activity and inhibits the nuclear translocation of NF-κB and I-κB degradation [35].
- In human cell culture models, it interferes with the signalling molecules in the extracellular-signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK), and p38 pathways of the three main mitogen-activated protein kinase (MAPK) pathways to limit metastasis and angiogenesis [36].
- It is well recognised for inhibiting interferon gamma (IFN-γ)-induced phosphorylation of signal transducers and activators of transcription 1 (STAT1) in murine microglia, which reduces the production of cluster of differentiation 40 (CD40), tumour necrosis factor (TNF-α), and interleukin 6 (IL-6) [37,38].

Other natural compounds such as Theaflavins, Quercetin, Arctigenin, EGCG, Curcumin,and Cinnamaldehyde also promising products which are able to provide impactful therapeutic potential [39-43].

Different types of Niosomes used to deliver natural compounds

Transferosomes

A minimum of one inner aqueous compartment encompassed by a phosphatidylcholine and an edge activator is a particular feature of transferosomes, which are nano-vesicular carrier systems. These nano-vesicular carrier systems are able to load a significant quantity of API into them and can readily pass through the stratum corneum's pores [44].

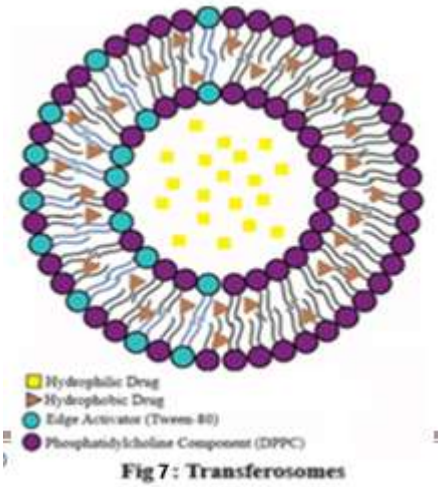

Fig 7: Transferosomes

Spanlastics

Spanlastics (Span + Elastic) was introduced in 2011. They are named Spanlastic because of its vesicles are primarily composed of Spans (Surfactants). Spanlastic entraps the drug inside its core cavity in the form of a bilayer. They

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are highly elastic and highly deformable and also amphiphilic. The elastic nature of these vesicles is because of the presence of edge activators on the surface of spanlastic [45-47].

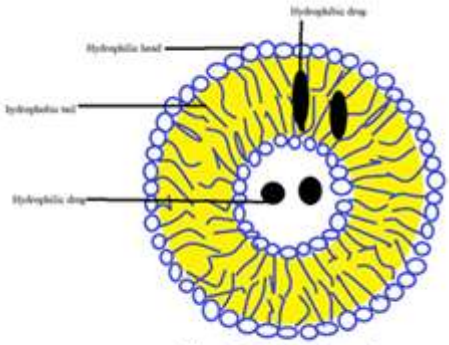

Fig 8: Spanlastics

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Author's Contribution:
Syed Saif Imam proposed the ideaand Ravi Sharmahave contributed data to the paper.

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

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