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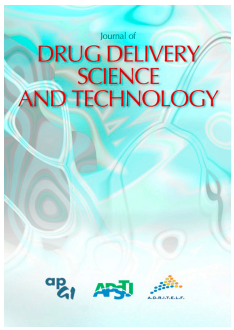

Anoverview of biomedical applications for gold nanoparticles against lung cancer

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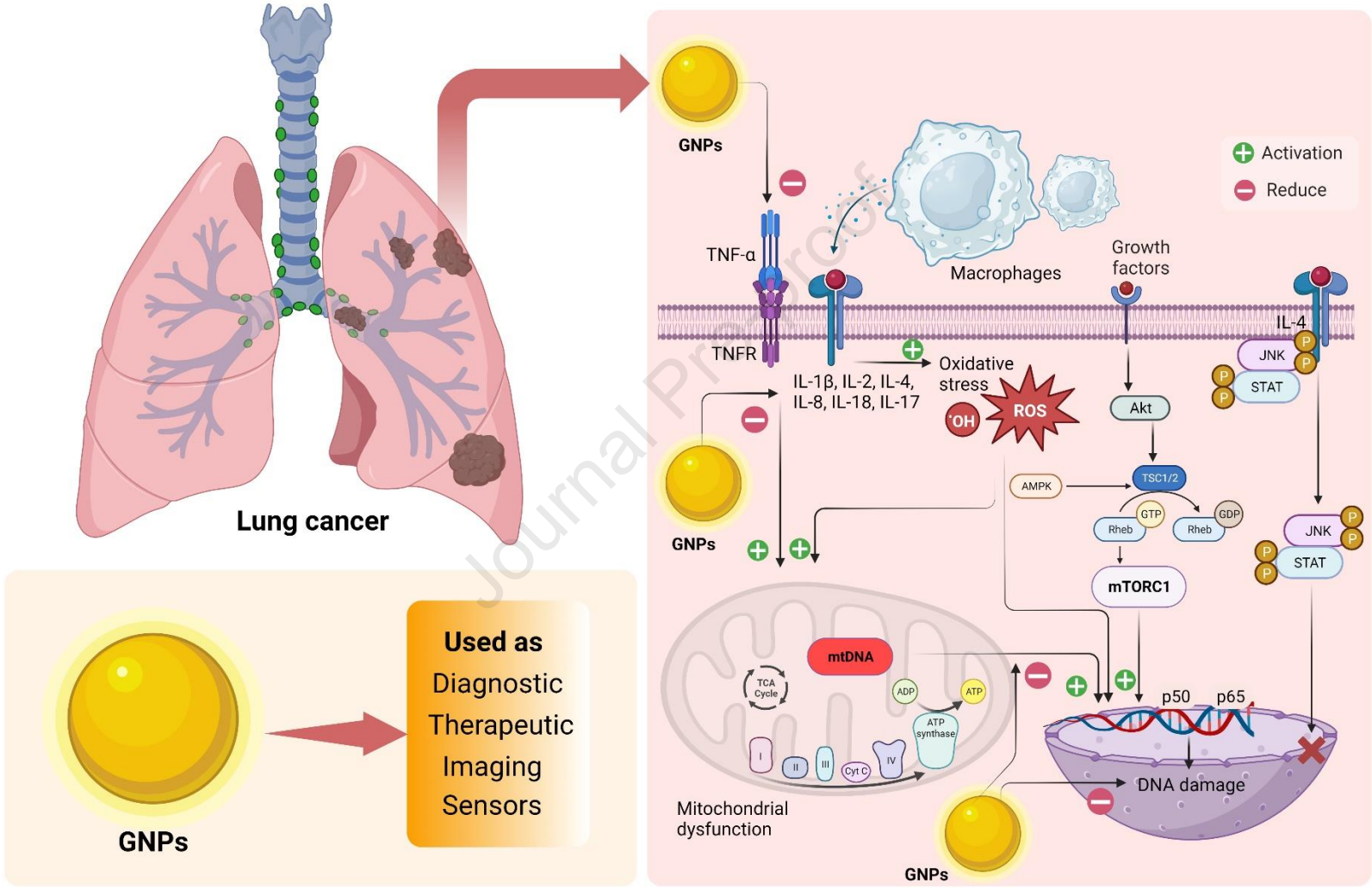
Unraveling the role of gold nanoparticles in lung cancer



An overview of biomedical applications for gold nanoparticles against lung cancer

Varsha Kumari[1,#], Sukriti Vishwas[1,#], Rajesh Kumar[1], Violina Kakoty[1], Rubiya Khursheed[1], Molakpogu Ravindra Babu[1], Vancha Harish[1], Neeraj Mittal[2], Pankaj Kumar Singh[3], Nahed S. Alharthi[4], Mohammed Ageeli Hakami[5], Faris F. Aba Alkhayl[6], Gaurav Gupta[7,8], Gabriele De Rubis[9,10], Keshav Raj Paudel[11], Manisha Singh[9,10,12], Milad Zandi[13], Brian G. Oliver[14,15], Kamal Dua[9,10,16**], Sachin Kumar Singh[1,10,*]

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Abstract

Lung cancer (LC) is the commonest class of cancer worldwide and is the reason for more deaths than any other type. Treatment of LC using conventional therapy has some limitations such as poor bioavailability and non-site release of drug causing various side effects. However, the use of nanotechnology makes it possible to offer efficacious treatment of LC by offering nanometer sized formulation that helps in better penetration of drug inside tumor cells and site specific drug release. Among various nanoparticles, gold nanoparticles (GNPs) has found unique and important application in the biomedical application of nanoparticles in various diseases, especially cancer. Owing to their high biocompatibility and stability against oxidation in vivo, tunable nano size, ease of functionalization with chemotherapeutic agents, capacity to enhance bioavailability and site specificity of entrapped drug, capacity to interact with visible light, make GNPs as special carrier for biomedical application in LC. GNPs can absorb infrared radiation and have optical qualities as well. In the present review, various aspects of LC and theranostic role of GNPs are comprehensively covered. These include prevalence, classification, economic burden, pathophysiology as well as commonly available therapies of LC. This was followed by advantages, synthesis, biomedical application of GNPs in treating LC as well as their fate in the body. Overall, the uniqueness of article relies on the fact that it covers all aspects of LC and all possibilities by which GNPs can offer their best role in management of LC.

Keywords: Lung cancer; Gold nanoparticles; Theranostic agents; Immunosensors; Surface plasmon resonance; Hyperthermal Therapy

1. Introduction

Lung cancer (LC) is a serious disease of high complexity wherein the cells lining the respiratory tract i.e., the bronchi, bronchioles, and alveoli start getting engulfed by carcinomas, commonly termed bronchogenic carcinoma [1]. Non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) are the two major classifications of LC [2]. The NSCLC constitutes around 85% of LC and SCLC constitutes around 15% of them [2]. These are located centrally or near the hilum and have neurosecretory granules in the majority of their tumor cells. Further, the NSCLC is categorized into adenocarcinoma (38.5%), squamous cell carcinoma (SqCCs) (20%), and large cell carcinoma (2.9%) [3]. Squamous cell carcinoma is commonly found in males who are continuous smokers. In this, epithelial dysplasia along with squamous metaplasia develops. Adenocarcinoma is also called scar carcinoma as it is associated with areas of chronic scarring and most commonly seen in females. Certain genetic changes have been observed that may lead to the progression of LC. These can happen due to the activity of growth-promoting oncogenes, upon mutation in the Kirsten rat sarcoma viral oncogene homolog (K-RAS) oncogene, and adenocarcinoma mutation occurs at the tyrosine kinase region of the epidermal growth factor receptor (EGFR) oncogene [1]. BRAF, MYC (master regulator of cell cycle entry and proliferative metabolism), and PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) families have also been reported to undergo mutations [1]. In the second case, tumor suppressor genes found on chromosome 3p get inactivated along with genes p53, Rb (retinoblastoma protein), and p16 leading to LC [1]. Hormones and Autocrine growth factors are seen to cause the initiation of mutations by activating the signaling pathways in LC and blocking apoptosis. Examples are the derivatives of nicotine [1]. In addition, inheritance is also one of the reasons for altered mutations seen in cases of LC. For instance, in the case of Li-Fraumeni syndrome, where a person is inherited to mutated p53gene that may lead to LC [1]. If a general scenario contemplating cancer is considered, it is no wonder to find that not only genetic reasons progress the disease but also the basic lifestyle of an individual, smoking, diet cycle, and reproductive behavior inflate the risk of causing it [4]. As the causes change rapidly there also comes a change in the region where the cancer cases gradually shift to. Pattern changes are vividly seen to shift from economically developed countries to some developing countries in South America, Asia, and Africa [4]. Especially, when smoking as an example is taken, which is one prime cause of LC. The pervasiveness of smoking among adult west men, considering the United States, is about 20%, more in comparison than in Indonesia, Greece, China, and Jordan [4]. LC remains to be

at the first position to take a life if a person gets into the clutch of this cancer disease in the United States and worldwide [5]. Precisely, 87% of all cancers related to the lung, such as bronchial, tracheal attributed to smoking [5]. It has also been reported that LC in more than 90% of afflicted people is fatal enough to take life [5]. While survival chances after being diagnosed with LC are directly proportionate with the stage at which the cancer is currently dwelling. The chances of survival could be ranging from 70% to less than 5%, for stage I to stage IV respectively [5]. Therefore, the most convenient way to reduce fatality due to LC is the cessation of smoking or altering smoking habits. Thus, glancing at the multitudinous approaches and treatments, LC remains a major, far and wide currently present global health issue. Certain exclusive approaches discount conventional treatments like surgery, radiotherapy, and chemotherapy [6]. As a novel perspective of utilizing the hidden capacities of nanoparticles has been put forward before the world. These nanoparticles, citing the example of gold nanoparticles (GNPs) are now being considered as one of the most victorious designs of action to be implanted to procure curative, restorative, indicative and detective approach access for death-dealing diseases like LC [7]. There are many attempts that various researchers have made to explore the utilization of GNPs in various diseases including LC.

GNPs have size in the range of 1 to 100 nm. They are biocompatible, easily get functionalized with ligands, capable of enhancing bioavailability of entrapped drugs as well as they are able to deliver those drug at targeted site [8,9]. These properties enable the GNPs as excellent nanoparticles for diagnosis, imaging, therapeutics as well as site specific delivery of entrapped drugs [10]. GNPs are available in various shapes such as rod shaped, spherical, star, flower like, wire, triangular, tetrahedral and octahedral shape [11]. These properties help the GNPs to be used as excellent theranostic agents. GNPs can interact with visible light and can produce heat upon interaction. Due to this they are also used as labelling agents and photo thermal agents and destruct the adjacent tumor cells by producing sufficient heat [12–14]. Furthermore, the GNPs are stable against oxidation [15]. and *in vivo* degradation [16]. These properties make them a potential diagnostic and therapeutic tool [17].

Owing to this multifaceted role of GNPs, wonderful reviews have been published in past three years by Barabadi et al. (2020) [18], Niloy et al. (2021) [19], Sehgal et al. (2022) [20]. For instance, Barabadi et al. reported a concise report on various studies reported by researchers till 2020 on anticancer activity of biosynthesized GNPs against LC cells and normal cells. All the studies reported in this review were based on MTT assay carried on A549 cell lines. The authors highlighted the biological source used to biosynthesize GNPs, their size and shape,

dose and IC50 value [18]. Continuing to this, Niloy et al. in 2021, reported a systematic review on theranostic use of GNPs in the treatment of LC wherein, they reviewed 61 studies wherein the GNPs functionalized with photosensitive agents such as miRNA, chemotherapeutic drugs, biomolecules, antibodies and peptides have shown good diagnostic and therapeutic efficacy against LC [19]. Sehgal et al., very briefly explained the role of GNPs and silver nanoparticles in the treatment of LC [20]. In the present review the main novelty relies on comprehensive coverage of entire aspects of lung cancer. These include prevalence of LC, classification of LC, economic burden of LC, factors affecting of LC, pathophysiology of LC, commonly available therapies for LC, limitations of existing therapies, advantages and application of GNPs in treating LC covering their use as therapeutic, diagnostic, sensing as well as theranostic agents. The fate of GNPs is also discussed in the current manuscript.

2. Prevalence of LC

There exists a dread with an average of 5-year viability rate among 15% of individuals diagnosed with LC in the United states of America (USA) [21]. The Cancer Statistics Centre of the American Cancer Society reported the new numbers of LC and death in 2022. The estimated new lung and bronchus cancer cases in males were 117,910 and in females, these were 118,830, whereas the estimated deaths were enumerated to be 68,820 in males and 61,360 in females (US 2022) [22] (Figure 1). According to World Health Organization (WHO), LC is the most usual cause leading to death due to cancer. Numerically, it snatches 1.76 million lives around the world per year [23]. International Agency for Research on Cancer appraises that there would be about 10 million deaths per year from LC by the year 2030 [1].

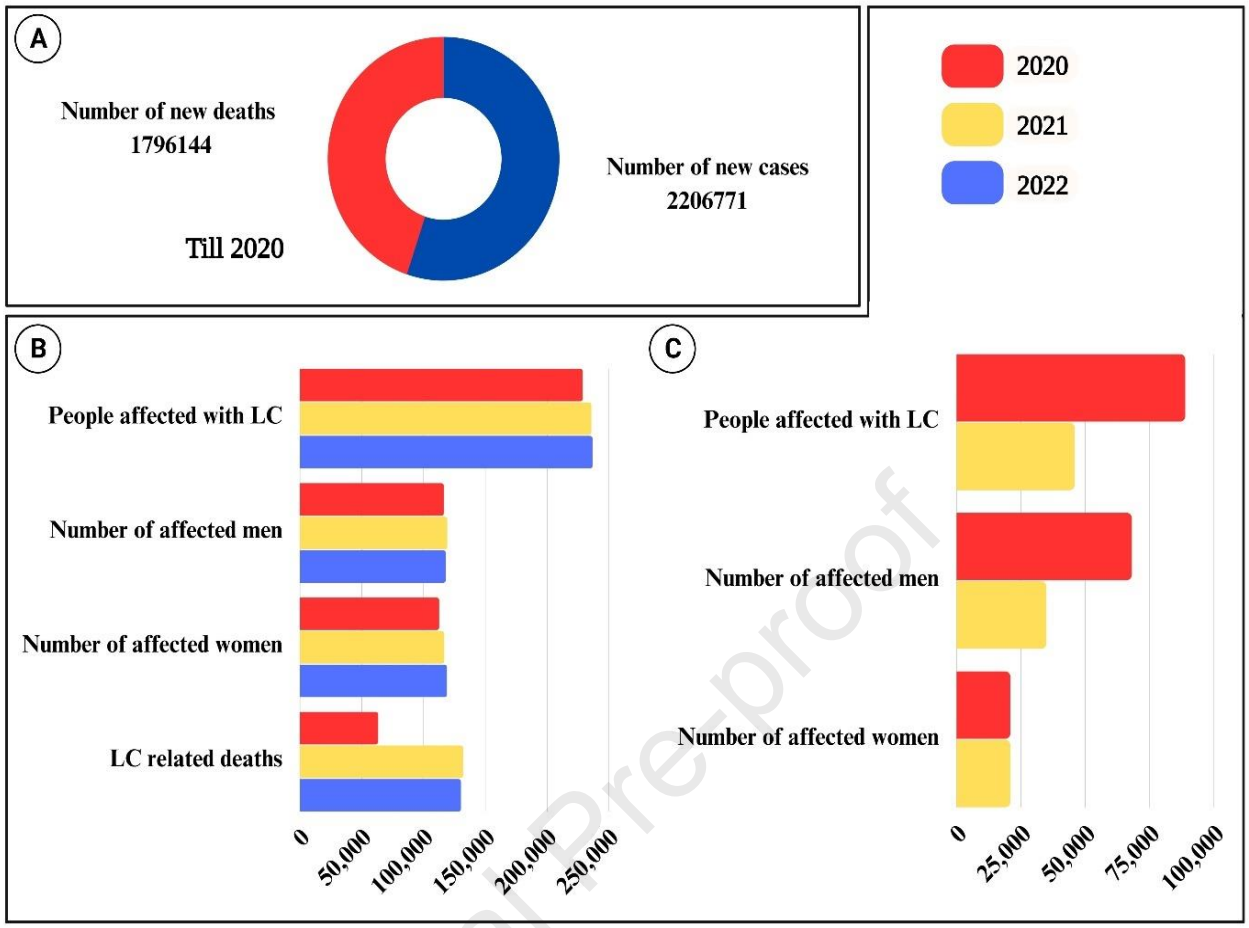

Figure 1: A. Prevalence rate of LC; Globally [24]; B. USA [23,25,26]; and C. India [27,28]

3. Classification of LC

3.1. Adenocarcinoma

3.1.1. Classification of Adenocarcinomas depending on invasiveness

According to the degree of invasiveness, adenocarcinomas are classified by the 2015 WHO as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma. Rate of disease-free survival when fully resected, of AIS and MIA is 100%. An adenocarcinoma with a scaly pattern and a diameter of less than 3 cm is referred to as an AIS [29]. The term "lepidic predominant adenocarcinoma, suspicious AIS" is used to describe a tumour if its diameter is greater than 3 cm. These tumours are uncommon and lack good classification. Adenocarcinomas that are regarded as minimally invasive have an invasion size of less than 5 mm and a diameter under 3 cm. Despite the fact that the invasion's size and the tumor's size fulfil the requirements for lymphovascular invasion, pleural invasion, or MIA [30].

3.1.2. Invasive adenocarcinoma variants

The majority of mucinous bronchioloalveolar carcinoma (BAC) contained invasive components; hence the term "mucinous BAC" is no more in use. Mucinous BAC was thus substituted with the term invasive mucinious carcinoma (IMA). In addition to IMA, invasive adenocarcinoma subtypes include foetal, enteric and colloid adenocarcinomas. Adenocarcinoma with a predominate constituent that has a resemblance with the cancer developing in the colorectal part and frequently exhibits caudal-related homeobox transcription factor 2 (CDX2) antibody is known as enteric adenocarcinoma [30].

3.2. Squamous cell carcinom (SqCCs)

SqCC is divided into three categories in the 2015 WHO classification: basaloid, non-keratinizing, and keratinizing SqCC. Basaloid SqCC had previously been classified as a large cell carcinoma. Basaloid SqCC immunohistochemistry, however, reveals "SqCC markers" (such as p40, CK5/6, and p63) and is classified as SqCC as a result [30].

3.3. Neuroendocrine tumors

A brand-new categorization for "neuroendocrine tumours" was created by the WHO in 2015. Neuroendocrine cancers that are invasive consist of the following three subtypes: SCLC, large cell neuroendocrine carcinoma of the lung (LCNEC), and typical and atypical carcinoid tumours. Pulmonary neuroendocrine cell hyperplasia of diffuse idiopathic origin relatively uncommon and non-invasive; as a result, its clinical significance is minimal. On the other hand, it is crucial in pathological and clinical practise to distinguish between a carcinoid tumour and a high-grade neuroepithelial tumor (HGNET), which includes SCLC and LCNEC. When compared to carcinoid tumours, which often have a non-malignant prognostication and oftenly affect patients who have never smoked cigarettes. HGNET is one of the utmost belligerent kinds and is characterised by the patient's past records of extensive and deliberate smoking [30]. LC classification is depicted in figure 2.

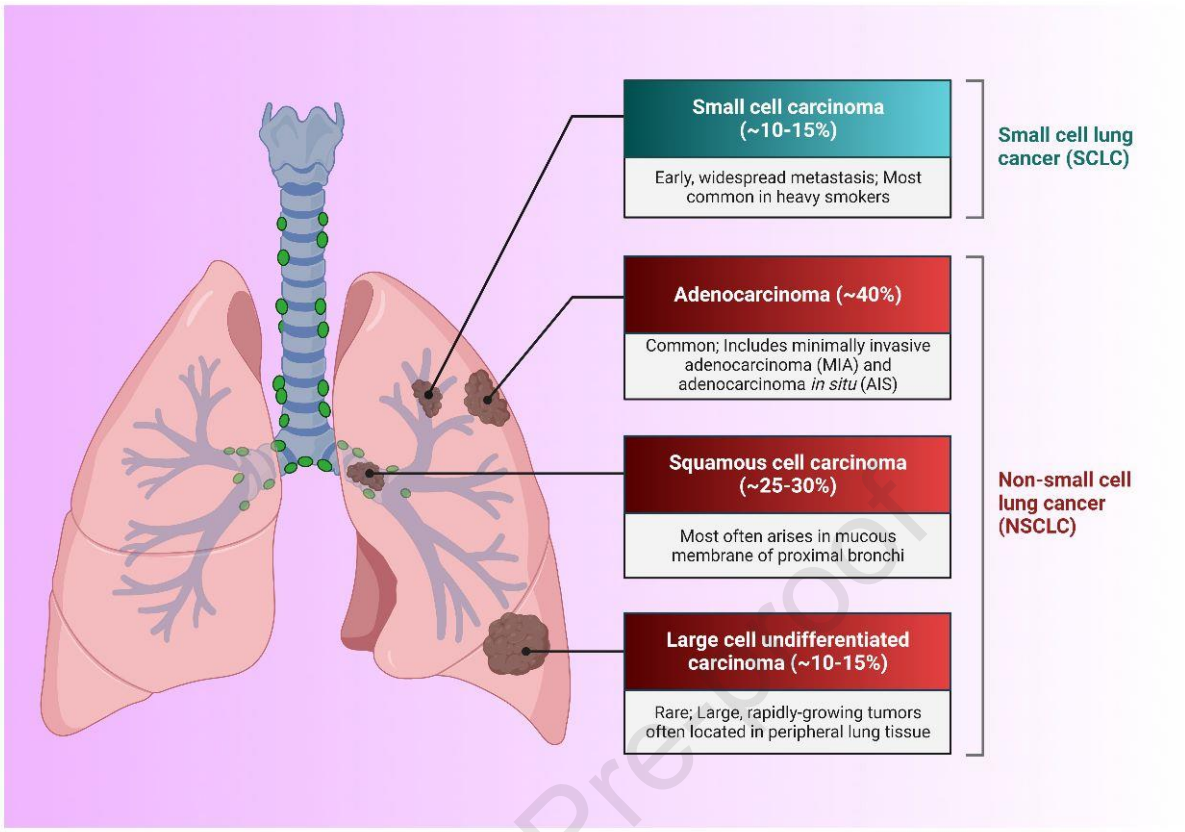

Figure 2: Classification of the LC

4. Economic burden of LC

There is a huge expenditure that dwells posing an economic burden in the case of LC with the hospitalization costs which may include surgery, primary treatment, radiotherapy, etc. The treatment costs comprise primary treatment, palliative care treatments, anti-cancer drugs, and supportive treatments needed. The direct costs include hospitalization costs and outpatient department diagnostics costs as well as the treatment for the separate diagnosis patient batch. The indirect costs include unemployment benefits, social transfer payments, social security, and social assistance. The method of treatment that has been followed also fluctuates the economic pile up due to LC. Thus, there not only just aids economic burden but also coalesces productivity loss and magnitudes of loss in national and global health overall. That is how the burden has changed over time. Therefore, such an onerous burden needs attention to increase intervention options to reduce the burden, evaluate health resource entanglement, spearhead novel technologies as alternatives, and execute nanoparticle strategies for the treatment approach. The average cost of cancer treatment is 36,812 Indian rupee (INR), which represents the whole financial burden of a sufferer in India. 40% of this overall cost is made up of

expenses incurred prior to visiting the hospital. There is very little published research on out-of-pocket expenses, in particular for the costs not associated with treating LC but related to its treatment that is incurred by individuals who have the disease. This refers to the costs associated with purchasing diagnostic and imaging equipment as well as transportation, accommodation, and boarding services for patients who attend primary and primordial level hospitals, since some expert healthcare professionals are only met in these sentinels. Over the period of 1992 to 2003, a US study by Cipriano and colleagues found that the average monthly cost for a patient with LC who was 72 years old in year 2000 was $645 in healthcare prior to diagnosis. A study conducted in 2007 at one of India's top universities, AIIMS, reported prices of 14597 INR. Using data from 5% of Medicare claims, a backward cohort study was performed by Lokhandwala and his team in the category of direct medical costs. That showed the average cost of a patient's entire diagnostic workup for LC was $7567. The diagnosis direct cost of the 113 patients involved in a study by Zarogoulidou and his team members in Greece was €117,939 [31].

5. Factors affecting of LC

There exist multiple risk factors that affect LC and its progression but the major factor that exists is tobacco smoking. It has been estimated that more than 1 million people die due to LC each year, out of which 90% of LC risks are only due to smoking [32]. It is enumerated to be 85% in men and 75% in women only due to smoking [33]. Smoking rapidly progresses the chronic inflammation to multiple forces promoting quick genetic alterations which mediate the macrophage recruitment, delayed neutrophil clearance, and increase in the ROS. All these processes conjointly accelerate the complexity and progression of lung carcinogenesis. Smokers dwell to suffer 15- 30 folds increased LC risk in comparison to the non-smoking mass [34]. A few other factors that implicate LC are:

1. Exposure to harmful radiations like radon gas. It is an inodorous, flavorless, radioactive gas produced in natural conditions during the radioactive rot of thorium and uranium. Human exposure to this gas has the potential to cause LC deaths in around 21,000 of the population exposed per year and in non-smokers, about 2900 deaths [35].

2. Exposure to metals like nickel, which gets released into the atmosphere during the mining process. It tends to bind the surfaces of compounds easily and sustains onto them. While breathing, drinking water, and intaking food nickel reaches inside the human body wherein it triggers the genotoxic and carcinogenic mutations leading to LC.

3. Pollutants in the environment float around the air and become a risk factor for the non-smokers leading to the development of bronchogenic carcinoma. People habituating near industrial areas are bleak of such circumstances.

4. Occupational exposure of people like workers who are working on a daily wage basis in the environment of arsenic, beryllium, asbestos, etc. They are very prone to be engulfed in LC as of continuous exposure to such compounds which behave as carcinogen.

6. Pathophysiology of LC

LC is complex phenomena which is not well clear. Several factors are responsible for the progression of LC such as inflammation, oxidative stress, mitochondrial dysfunction and abnormal releases of hormones and enzymes. Inflammation and their inflammatory mediators are one of the leading causes of cancer. Abnormal secretion of cytokines like interleukin (IL)-1β, IL-2, IL-4, IL-8, IL-18, IL-17, stromal derived factor-1/CXCL12-CXC and tumor necrosis factor (TNF)-α increase risk of malignancy to increase abnormal production of the cells. These inflammatory mediators alter other cellular functions which leads to increase the risk of LC. Like, activated IL-1β enhances phosphorylation of P65 by linking and activating IKβ kinase (IKK)α/β which further leads to upregulate the levels of NF-kB. Moreover IL-1β also upregulates PKCα-dependent c-JNK1/2, plasminogen activator (VPA) expression, P13K/AKT, growth factor receptors and play a very important role in progression of LC. It stimulates IJ- 15-hydroxyprostaglandin dehydrogenase (HPGD) and upregulates Mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase–protein kinase B/Akt (P13K/AKT), JAK- Signal transducer and activator of transcription 6 (STAT6) and Protein kinase C (PKC) pathways. Furthermore, oxidative stress is another major risk factor of LC. It promotes pulmonary inflammation and enhance mechanisms of carcinogenesis. Various factors such as consuming tobacco, smoking, environmental pollution, unhealthy lifestyle and stress are release level of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which further cause deoxyribonucleic acid (DNA) oxidative damage, macrophage stimulation and translation factors. Mitochondrial dysfunction is another major cause of LC. Increase production of ROS, RNS and various cytokines are responsible for mitochondrial oxidative damage which further leads to promotion of endoplasmic reticulum dysfunction, reduced protein synthesis as well as cause abnormalities. Studies also reported that increased intracellular ROS cause abnormalities in electron transport chain (ETC) and disable the function of complex 1-4. Pathophysiology of the lung cancer are presented in figure 3.

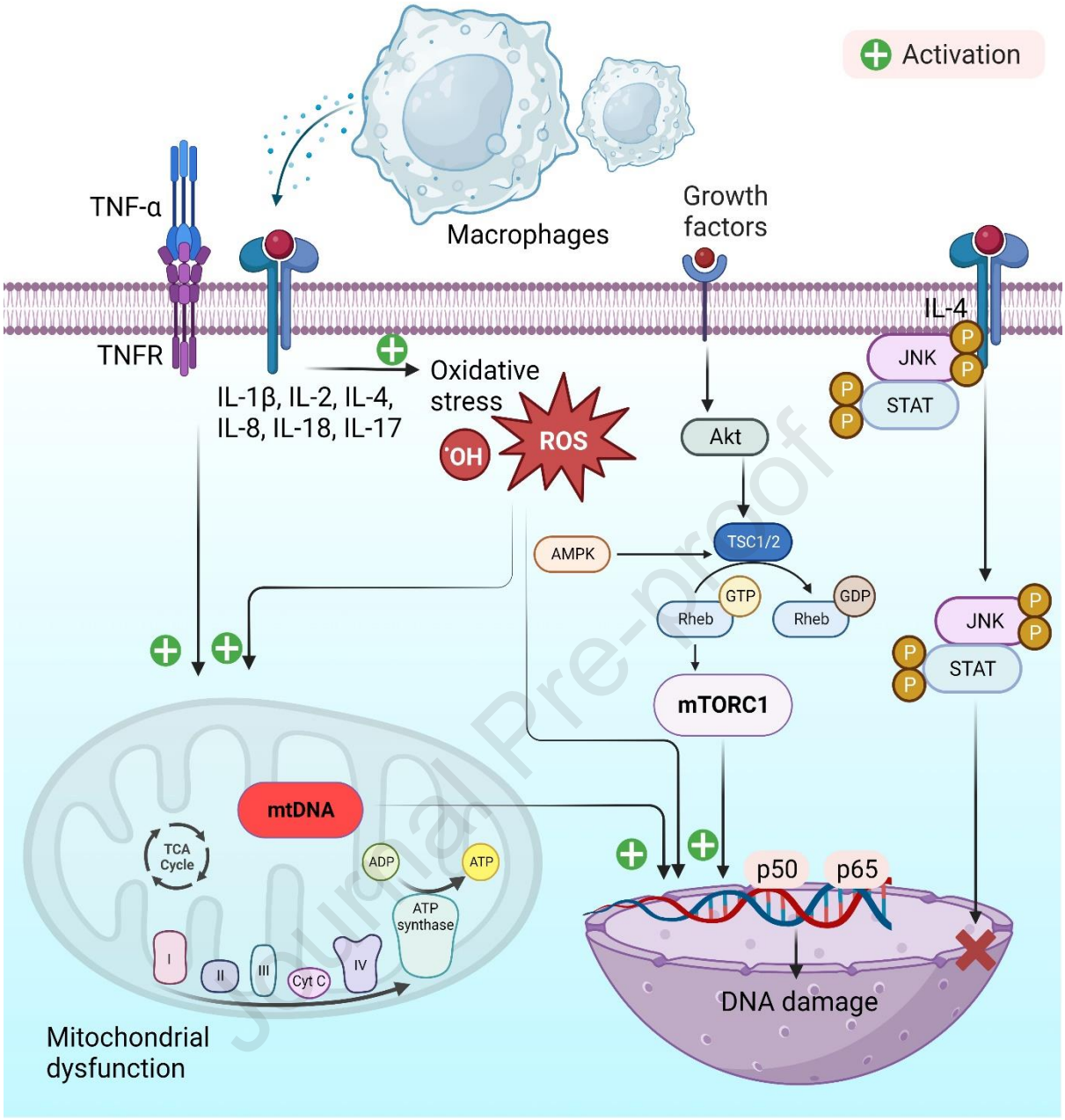

Figure 3: Pathophysiology of lung cancer

7. Commonly available therapies for LC

There are some commonly available treatment modalities present which have their probable benefits and potential risks to combat LC like surgery, chemotherapy, radiotherapy, and targeted therapy. The surgery depends upon the location and stage of LC as well as the patient medical conditions. Generally performed for an early NSCLC. It is considered the best option when the cancers are noninvasive. Thoracotomy, Lobectomy, video-assisted thoracoscopic surgery, segmentectomy, Pneumonoctomy, wedge resection are among the procedures done. [36]. In the case of, radiation therapy high intensity powerful X-rays are used to destroy cancer

cells. Helps to pull back growth of tumor cells before operating and after the surgery to kill the left-out cancer cells. It is used to relieve the symptoms of LC like pain and airway blockage. It is usually done via two methods; externally from outside the body and internally by planting radioactive material inside of the cancer cell. The techniques involved are external beam radiation, intensity-modulated radiotherapy, brachytherapy and stereotactic body radiation therapy [37]. In chemotherapy, the cancerous cells are aimed to shrink or stabilize, kill leftover cells, and relieve LC symptoms. This is used when surgery no longer remains an option. It is repeated in cycles that persist for up to weeks, given through an intravenous route. Chemotherapy was initially started a as single-medication chemotherapy trial in the 1960s with cyclophosphamide. With further research, it was discovered that the amalgamation chemotherapy was superior to single agents. Hence, combination anthracycline-based chemotherapy was introduced in the 1970s. Progressively, combination platinum-based chemotherapy came into effect in the 1980s of which paclitaxel and carboplatin, are currently the gold standard for the treatment of LC. From then on chemotherapy regimens became advanced and started being commonly used. Common chemotherapy regimens used to treat LC are, Carboplatin, Cisplatin, and Etoposide available as a generic drug, Docetaxel (Taxotere), Gemcitabine (Gemzar) [38].

The targeted therapy mainly focuses on damage reduction to healthy cells and interrupting cancer cell growth and functioning. This therapy is often used for patients having abnormalities in their diagnosed cancer cells. It includes medicine that treats cancer using the body's self-immunity developed from the immune system [38].Targeted therapy includes:

1. Inhibitors of the EGFR (epidermal growth factor receptor). In between 10% and 15% of LC cases, EGFR is present. When LC cells have EGFR mutations, researchers have discovered that EGFR-blocking medications may be beneficial in halting or reducing the growth of the disease. FDA-approved EGFR inhibitors include drugs like Afatinib, Dacomitinib, Erlotinib, Gefitinib, and Osimertinib [38].

2. Anaplastic lymphoma kinase (ALK) inhibitors. ALK is a protein that's involved in how cells grow. If present, this promotes the growth of cancer cells. ALK inhibitors aid in halting this procedure. ALK gene alterations are discovered in 4% of NSCLC patients. Currently, the following medicines that can be used to treat this genetic alteration are Alectinib, Brigantine, Ceritinib, Crizotinib, and Lorlatinib [38].

3. Medicines that block c-ros oncogene 1 (ROS1) fusion. Cell growth and differentiation issues might result from the rare ROS1 fusion or ROS1 rearrangement mutations. 1% to 2% of patients with LC had ROS1 fusion. Drugs that aim to modify the ROS1 gene include: ceritinib, crizotinib, entrectinib [38].

4. Treatment against angiogenesis which is the process of creating new blood vessels which are stopped by anti-angiogenesis therapy. Anti-angiogenesis medicines aim to "starve" tumors since they require the nutrients provided by blood vessels to grow and spread. For LC, anti-angiogenic medications can be an option taken in use, combining chemotherapy with the immunotherapy medication atezolizumab and bevacizumab, combined with the chemotherapeutic medication docetaxel, and ramucirumab [38] proves to be beneficial. Biologics can meet the need for highly targeted LC therapies but because of being expensive and not being able to show constant benefits, the use of biologics has not been accepted as the first line of treatment as targeted therapy for this deadly disease.

There are some biomarkers that are often accessible that assist in classifying patients based on illness progression, risk factors and bad outcomes. A list of serum proteins was produced utilizing carcinoidic epithelium and anomalously active in the fibrogenic process, which is most strongly connected with the advancement of IPF as in contrast with placebo groups, was developed as a result of the observational profile analysis. They were matrix metalloprotease-7 (MMP7), surfactant protein D (SP-D), 2 macroglobulins, and MMP. while substantial amounts of other proteins, such as cancer antigen 125 (CA-125), Macrophage migration inhibitory factor (MIF), carcinoembryonic antigen assay (CEA), were significantly linked to an increase in overall mortality, cancer antigen 19-9 (CA19-9) was particularly strongly associated with the development of disease [39].

8. Limitations of existing therapies

Patients afflicted with LC often suffer symptoms of shortness of breath, continuous cough, chest pain, wheezing, hoarseness, fatigue, weakness and weight loss, to boot these if there is a coalescence of the therapies that commonly exist for LC, will pose multiple other discomfort and inconveniences to the patient like, surgery creates room for possible complications along with excruciating pain. Radiation therapy gives rise to cough, sore throat, skin reactions, and tiredness. Chemotherapy makes patients undergo anxiety and depression, infection and bleeding, hair loss, gastrointestinal tract issues and nervous system changes. Targeted therapies

show common side effects of dizziness, constipation and changes in vision. Immunotherapy may lead to severe complications like pneumonitis, hepatitis and colitis [32,40].

9. GNPs

Past 3-4 decades GNPs have shown excellent results in drug delivery system. GNPs are classified under inorganic nanoparticles. Various clinical and preclinical studies have been reported where GNPs are used to treat various disease such as acquired immune deficiency syndrome (AIDS), neurological diseases, ulcer and heart diseases etc. They also exhibited excellent anticancer including LC. GNPs have gained lot of success due to their unique nature such as nano size range, good biocompatibility, enhanced bioavailability and easy functionalized with ligands [9,41]. Various surface coating, functionalization, and shape are mentioned in figure 4.

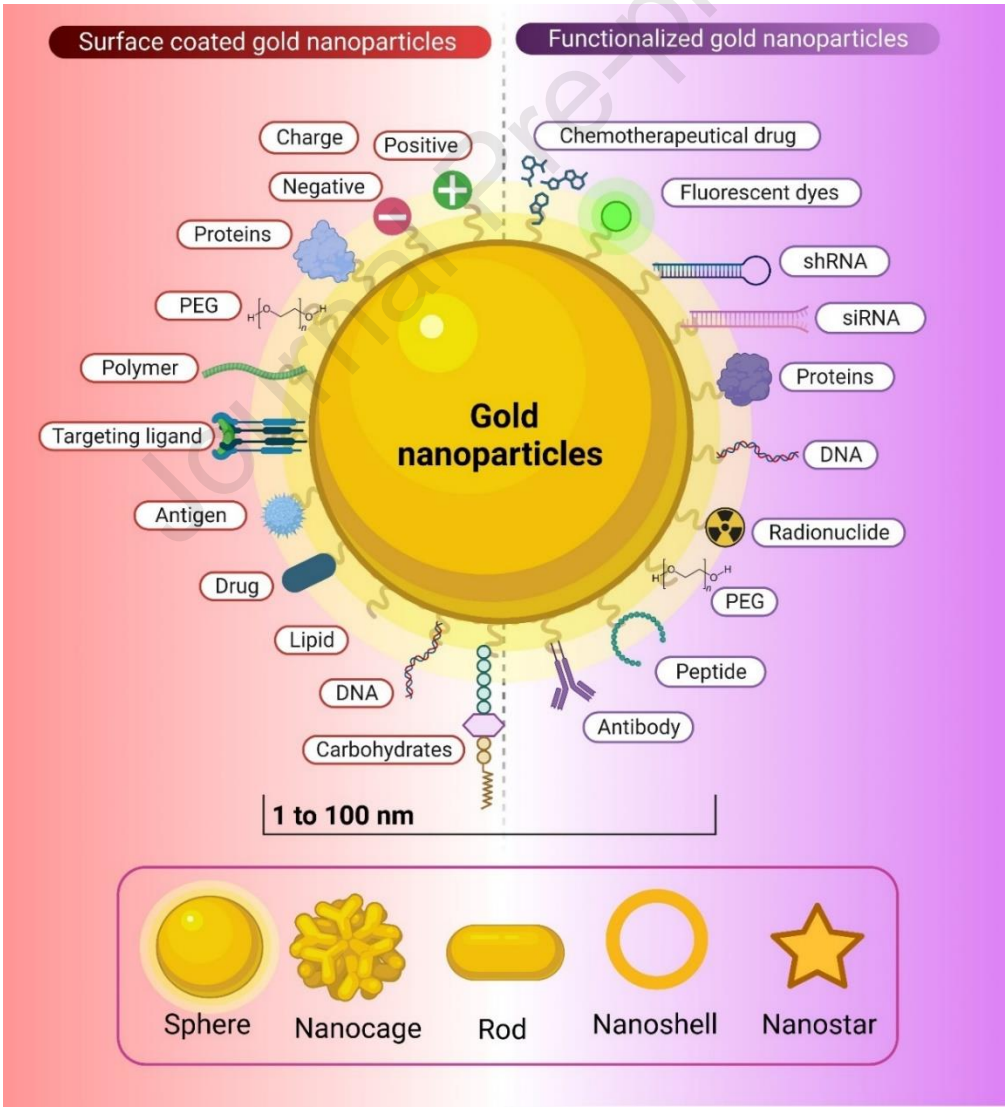

Fig. 4: Functionalization, surface coating, size and shape of GNPs

10. Need of GNPs to treat LC

LC is one of the major types of cancer having extreme fatality, the reason being its late diagnosis or detection in its last stages. Hence, if this delay in diagnosis can be cut down and can get hold within the initial stages of LC, its severe impact of it on the mass population can be prevented. Nanotechnologists have found some novel methods which boost early-stage tumor detection, better prognosis further improves survival rates. The huge potential of gold has been extracted in its nano amounts, the more we dig and zoom into the nano zone of gold the better capabilities have been seen projecting out. Nanotechnologists overhaul GNPs to pioneer as one of the emerging plans of action and strategy to treat the complex disease of LC. Gold is a chemically inert particle, has amazed scientists with its thrilling properties [9]. It has huge biocompatibility in the human body. Upon reducing its size from block gold to its nano size, there generates multiple folds increase in the surface per unit mass providing a large surface area for working onto by manipulating it according to the needs and demands of nanoscience. Its functions can be adopted for a variety of applications like diagnostics, immunosensors, serum tumor markers, geno-sensors, imaging, Computed Tomography (CT) and X-ray scans, MRIs, therapeutics, immunotherapies, plasmonic therapies, theragnostic [42,43]. Apart from working with GNP's exciting properties care must also be taken for its toxic effects. As it's found that GNPs illustrate some undesirable effects on healthy tissues as well. Therefore, it's the need of the hour to investigate and evaluate the fact that is any toxicity generated by these particles at the congregation at which they seem to exhibit curing tendencies. Similarly, these nanosized gold can prove to be the radio-active producing intracellular formation of ROS leading to cellular invasion, epigenetic modifications, organelle reorganization, and altered expression of proteins causing pulmonary toxicity [42]. Various methods are employed in the structuring and synthesis of these nanosized gold particles like biomolecules with amino group binding carboxylate tail group, alkyne-azide cycloaddition reaction, additions of functional groups like sugars, peptides, proteins and DNA strands.

These nanoparticles of gold while preparation is also acknowledged for their interactions with the biological cells and system, so it's well contemplated to take care of the materials taken in use to prevent any hindrance being caused in delivering and enhancing desired effects to the tumor cells. The surface charge and coating are likely to pose aggregation and delay circulation. To overcome this, a degree of controllable hydrophobicity is desirable which can be achieved by employing suitable polymers to coat GNPs. Polyethylene glycol (PEG) is the most extensively used polymer material to coat GNPs.

11. Synthesis of GNPs

11.1. Biological method

Preparation of GNPs using plant was done which led to the green GNPs synthesis with sizes between 15 to 80 nm. This method uses HAuCl4 fruit juice decoction of citrus (Citrus limon, Citrus reticulate, and Citrus sinensis) which was employed as a precursor and reduced. Digestible mushroom was also employed in the light-powered manufacture of GNPs [44]. Using isolated fungi Fusarium solani in study, was cultured in yeast extract peptone dextrose broth and regulated at 28°C and 120 rpm on a shaker-type incubator for up to 9 days before being filtered through cheesecloth and repeatedly washed with double-distilled water. 100 ml of sterile water was added to the biomass and left alone for two days. After that, the whole amount of biomass was filtered using whatman paper filters. The sample's pH was then kept at 8.5 by adding 0.1 N NaOH, 1.0 ml of fungal reduction was put to 1 mM 4-aminobenzylamine and phosphoric acid (HAuCl4) (99 ml) solution, which was then incubated for 48 hours in the dark.

synthesis with a size within 40 and 45 nm was mediated by the fugal aqueous filtrate. Utilizing a range of analytical methods, the produced GNPs were evaluated and found to be extremely stable [45]. *P. aeruginosa* control strains and the two isolates were used. In 50 ml of nutrient broth medium, the bacteria were cultivated aerobically and then incubated for 24 hours of churning at 150 rpm and 37 °C. After the incubation, the overnight bacterial culture was separated at 5000 rpm for 5 minutes to get the afloat. In order to create GNPs, 50 ml of cell-free supernatant was combined with hydrogen tetrachloroaurate to achieve a final gold ion concentration of 1 mM. The ensuing resolution was then incubated at 37°C for 24 hours. Together with the experimental flask, the control (which contained only the supernatant and no gold ions) was run. The cell-free supernatant containing nanoparticle was recovered after 24 hours of incubation, via this method bacterial GNP synthesis were done [46]. When chloroauric acid was poured into the *C. parvula* aqueous extract, colloidal GNPs were created, which gradually began to turn the originally pale-yellow solution purple. After 48 hours of incubation, there was a total drop in gold nanoparticles. The surface plasmon resonance (SPR) vibration around metal particles caused the color intensity to increase during the nanoparticles formation. The glaze of purple showed that the GNPs have aggregated into clusters, which are huge spherical particles and are brought about by the density of gold ions. Because of their rapid and

easy production as well as strong metal potential for redox, green nanoparticle synthesis utilizing seaweed extract offers many benefits [47].

11.2. Chemical method

Abatement by citrate at 100°C is the conventional procedure, as described by Frens and radiochemist Turkevich. By heating a gold hydrochlorate solution in a double-walled reactor till it begins to boil that is connected by a bath thermostat, sodium tris-citrate starts reducing solution of gold hydrochlorate (Chempur, 99%). The mantle ensured that the reaction solution had a fairly uniform temperature distribution. Teflon-coated magnetic bars were used to stir the liquid vigorously. There were no temperature gradients in the liquid since there was no refluxing. 5 mL of citrate solution that had already been heated was added when the solution (95 mL) began to boil. In order to achieve various particle sizes, the citrate content was changed. The liquid was extracted after a specified amount of time (often 15 minutes) and brought to room temperature [48]. Utilizing naturally occurring GNPs, conducting multilayered films are constructed in triangle shapes by using 500 ml of sterile water to boil 100g of finely chopped, properly washed lemongrass (Cymbopogon flexuosus) leaf for 5 minutes. In an experiment, 45 ml of 10^3 M aqueous HAuCl4 solution was incorporated with 5 ml of this soup. By recording the ultraviolet-visible (UV-Vis) spectrum of absorption for this combination as a function of time taken to react till reaction max, the bio reduction of $AuCl_4$ ions was observed. The prill was created by centrifuging the brownish-red solution of colloidal gold at 3000 rpm. The pellet was then redissolved in 5 ml of purified water. This method increases the ratio of gold nanotriangles to spherical nanoparticles from around 1:1 in the solution put together to almost 3:1 after one centrifugation cycle, and ultimately 10:1 after three centrifugation and resuspension cycles [49]. At various pH levels, 0.1 mM gold (III), which produced from the salt of potassium tetrachloroaurate, was reacted with a sample of 10 mg of alfalfa biomass (Malone variety). The supernatants, which had been prepared with a pH value of 2.0, were then centrifuged at 3000 rpm to pellet the biomass, and they were then studied under a high resolution JEOL-4000 Fx-microscope with a cs of 1.0 mm and a JEOL 2010 microscope equipped with EDS analysis. The pictures were taken in high resolution mode with a defocus factor of 1f = 402 pixels (the Scherzer condition) [50]. For the chemical solution deposition of GNPs, a pure oxide sol and a solution of gold ions were prepared separately in order to synthesise gold-containing titanium dioxide (TiO_2) and zirconium dioxide (ZrO_2). Z_3H_2O was the precursor to Au31. The $HAuCl_4$ Z_3H_2O solutions were added to the oxide sol while being stirred, adding an appropriate ligand to facilitate the assembly of metal ion clusters.

452 THF (tetrahydrofuran) was employed as a solvent to create Au31-doped TiO_2 sols, and the
453 following molar ratios of the reactants were used: $Ti(OC_4H_9)_4$:THF : H_2O : acacH 5 1:5:4:0.8.
454 The customary process was used. First, acacH dissolved in 1-butanol or THF, used to chelate
455 the Ti precursor and the resultant solution was agitated for one hour. After adding the necessary
456 amount of water dissolved in 2-propanol to hydrolyze the Ti precursor, the sol was agitated for
457 an hour before the solution containing the metal was added. The resultant sol was agitated for
458 an additional hour. THF was once more used as the solvent for making Au3+-doped sols, and
459 the following molar ratios of the reactants were used: $Zr(OC3H_7)_4$:THF:H2O:acacH: 5:1, 5, 4,
460 and 1. TiO_2 and ZrO_2 sol preparation was completed in a glove box under a N_2 environment
461 with an H_2O concentration of 1 ppm [51]. The reaction of 231 nM HA (HA solution was
462 produced in toluene) with 97.2 mM solution of tetra butyl ammonium borohydride (TBAB) at
463 25ºC resulted in hexanoic acid stabilised GNPs (HA-GNPs). It was used to make TBAB
464 solution in DDAB. A 25 M dilution of AuCl4 made with stock of DDAB and a 2 mL solution
465 of standard produced in toluene were vigorously poured to the aforementioned reaction
466 mixture. To form HA-GNPs, the container was vigorously agitated for an hour at room
467 temperature [9].

468 *11.3. Physical Method*

469 A container, a gold plate, a lens with a 25 cm focus, a stirrer with a magnetic field, a second
470 harmonic 532 nm Q-switched Nd:YAG laser, and other materials were used to conduct the
471 experiment at room temperature. . In this investigation, a high purity, 99.99 percent pure gold
472 plate and a 99.9% inhibitor-free anhydrous form of (tetrahydrofuran) THF were employed.
473 After being secured to a support, the gold plate was submerged in 20 mL of THF. Above
474 mentioned laser beam with a pulse energy of 1200 mJ and a pulse duration of 10 ns was then
475 used to ablate it. The duration of the gold plate ablation, which used a 40 Hz repetition rate,
476 ranged from 7 to 30 minutes. THF solvent in the beaker was subjected to two conditions during
477 this procedure: stationary liquid medium and stirring. A magnetic stirrer was used for the first
478 scenario, and its speed was maintained at 400 rpm throughout the test. The creation of the
479 plasma plume was observed during the ablation procedure using light emission. The UV-visible
480 bandwidth, the bond strength, the shape, and dimension of the GNPs were all evaluated. The
481 prepared samples were characterized using various analytical techniques [9]. Tetra chloroauric
482 (III) acid, 15 mM, was dissolved in water. Tetraoctyl ammonium bromide, 35 mM in toluene,
483 was poured to the mixture (10 mL). As the toluene phase turned orange-brown upon mixing,
484 $AuCl_4$ ions moved to the top organic layer. Then, 15 min of cycle 1 centrifuging was repeated

three times at 14000 rpm. After removing the supernatant, vortex mixing was used for resuspension of the latex mesosphere in sterile unionized water. A tiny amount of the latex suspension was placed to a clean Si (111) substrate, and it was left to air dry for 20 minutes at room temperature (25ºC, 50% relative humidity). The closely packed spheres create an iridescent film on the surface on its own when the water evaporates as a result of capillary pressure during the drying process. Although a small layer of water is still present in some of the surface parts, water vapor is trapped and forms a liquid meniscus ring around the base of the spheres. The regions where water residues are found determine where octadecyl trichlorosilane (OTS) will adhere onto the facet. The scorched latex covering, acted as a patterned evaporative mask which was kept in a tiny volume of neat OTS in a sealed room. To produce OTS vapors, the specimen was prepared for eight hours at 70ºC in an oven. Vapor deposition does not affect the regions of the skin where latex fragments were present upon coming in contact with the substrate. The latex mesosphere coating was then eliminated by repeatedly sonicating and washing the sample with deionized water and ethanol. OTS molecule nanopatterns remain on the surface after the latex mask is removed, exposing arrays of ring-shaped nanostructures [9]. 500 mg of cotton was frozen and milled for half an hour at 30 Hz in the zirconia sample chamber at 77 K in the presence of six 10.06 mm zirconia balls. 5.1 103 M of metal solution was added to the chamber after 3 mL were ground, and the resulting mixture was then mixed at 5 Hz for 30 seconds. $HAuCl_4$, K_2PtCl_4, $AgNO_3$ (in H_2O), Co(C5H7O2)2were all solution of metals in acetonitrile. Following that, the mixture was placed in a polypropylene tube, reduced to 6 mL with the solvent used to create the corresponding metal solutions, and left in the shade for a day, a week or two weeks. The material was then rinsed with acetonitrile and dried to prepare cellulose metal tiny materials by ball milling of cellulose [9]. 1 ml of $HAuCl_4$ solution (5 mM) and 1 ml of Na_3Ct solution (25 mM) were dissolved in 18 ml of water and then added to a microwave oven chamber to react for 10 minutes at 210 W to create GNPs. Using a UV-vis spectrophotometer, the UV-vis absorption behaviors of gold nanoparticles were observed. The gold nanoparticles were studied utilizing zeta potential and transmission electron microscopy [9]. Numerous GNPs and their functionalization, reducing agents, catalytic reagent as well as characterization are highlighted in **Table 1.**

517 **Table 1:** Table indicating various functionalizing, reducing agents, and catalytic reagent used
518 in synthesis of GNPs as well as the size and shape obtained upon their synthesis

S. No.	Compound and functionalization	Reducing agent/ catalytic reagent	Size (nm)	Shape	Reference
1.	Chloroauric acid (Au^{+3}, $HAuCl_4$)	Ascorbic acid	10-20	Colloidal	[9]
2.	*Gracinia mangostana*	Compounds in Pericarp of G. Mangostana.	44.20 ± 16.99	Face center cubic(fcc) and spherical	
3.	*Hibiscus rosa sinensis*	Extract of hibiscus rosa sinensis	16-30	Spherical	
4.	*Plumeria alba* leaf	$NABH_4$	2.8 ± 5.6	Spherical	
5.	*Minosa pudica* leaf	$NABH_4$	12.5	Spherical	
6.	*Dalbergia coromandeliana* root	Methylene blue with $NaBH_4$ to Leucomethylene blue.	10.5	Spherical	[52]
7.	$HAuCl_{4(aq)}$	Tetra octyl ammonium bromide (TOAB)	1.5-5.2	Spherical	[53]
8.	Gold salt's seed Gold salt in presence of ascorbic acid and structure-directing Agents.	$NABH_4$	3.5-4 can grow up to 20-60	Nanorods	[54]
9.	*Sclerotium rolfsii*		25	Triangles, hexagonal, rods	[55]

10.	Hexanoic acid Solution + Tetra butyl Ammonium borohydride (TBAB)	--	4	Spherical	[9]
11.	Decanoic acid Solution (DA) + Tetra butyl ammonium borohydride (TBAB)	--	7	Spherical	
12.	*Hippomane spinosa*	Bioreduction of Chloroauric acid (HAuCl4)	80-90	Spherical	[9]
13.	*Nephentes khastana*	--	50-80	Triangular and spherical	

12. Key parameters of GNPs that are more determinant for LC

Mostly, gold is inert chemically, with a relatively higher biocompatibility in human beings. Reduction of particle size of gold results in increased surface area per unit mass and thus, offers a larger chemical surface for functional modifications. Gold also offers a variety of morphologies facilitating their applications in different areas [18]. The nano-size of material enables an interaction of electrons with the light at the surface of gold that results in the surface plasmon resonance (SPR). Incident light excites conduction electrons in metal as a result of which collective oscillation of these electrons takes place which is called as SPR which is mostly dependent on the size and shape of the structure. SPR enables their applications in medical field by modulation of the effect of electromagnetic waves focused around the material [57]. In view of that, it becomes important to comply with the biological/optical window by tuning the SPR absorption wavelength within the NIR region of the electromagnetic spectrum (650-1300 nm) as it facilitates deeper tissue penetration of light since other biological species are unable to absorb light in this range [58]. Charge and coating on the surface are the determinants of interaction between GNPs and biomolecules. Polymer coating provides

desirable hydrophobicity that helps repelling plasma proteins and thus, prevents aggregation and increases blood circulation time. PEG is the most used coating material for gold surface that limits the protein absorption on surface of GNPs and enhances the permeability and retention (EPR effect) in the tumour [59].

13. Role of GNPs to treat LC

13.1. GNPs as diagnostic agents

Diagnosis includes Imaging**,** which becomes crucial for early diagnosis, prognosis, and targeting tumor cell's location. GNPs prove to be advantageous among other conventional methodologies due to their versatility in reflecting a combination of multiple imaging modalities. The next important attribute is CT and X-ray scans**,** these techniques are useful in discovering and mounting of LC. The remarkable optical properties of GNPs increase the clarity of images of complexity to multiple folds in comparison to the conventional scans done. Along with this, patients can be tension free of the radiation as it's the lowest. The third diagnostic approach is fluorescence microscopy**,** done using the plasmon ring on the gold nanoparticle's surface and a fluorophore to overlap between their emission spectra will enhance the imaging capabilities called the fluorescence resonance energy transfer **(**FRET**)** phenomenon. The fourth one is MRI, an exemplary useful technique to carve the abnormalities in LC and diagnose them. Using, GNPs attached to gadolinium chelates, improve the diagnosis, execution, distinction and interactions with cancerous cells. GNPs have become a budding source of information to deal with life-threatening diseases, as mentioned by nano researchers. Their applicative function in the diagnosis of LC is of wide use due to their visual and physical qualities that are positive. The SPR property of GNPs is one of the striking features of its optical character. The SPR is a process that allows the gold's electrons to resonate in counter to the radiations striking it, further leading to two simultaneous actions, absorption of radiation as well as a scattering of radiation in the form of heat, light or radiations. This group of electrons undergoing oscillations because of energy absorption is called a plasmon. The utility of GNPs also increases to a high bar serving its purpose in the diagnosis of cancer. When they can be conjugated with numerous other bioactive moieties, specifically with thiol groups, and amine groups. They are eligible to lay out opportunities for important biomedical applications covering the area of therapeutics, targeting specific genes, bioimaging, sensing, MRI, and scanning [60].

In photothermal therapy (PTT), SPR phenomenon is taken into the consideration. PTT gets induced due to the excitation of photons at a particular temperature giving a physiological response. High temperature melts the tumor along with the gold. As GNPs easily convert light to heat due to the SPR phenomenon. It induces rapid tumor cell death (necrosis) without damaging surrounding tissues [61]. Certain studies have been performed which indicate the PTT used in the diagnosis of cancer. H Liu et al. (2008) have studies role of GNCPSs against Lewis LC (LLC) in mice and subjected to a modest dosage of NIR light (808 nm, 4 W $^{cm-2}$), our study found that LLC resulted in irreparable tissue damage. With an average inhibition rate of approximately 55% (P 0.005), the tumor sizes of the treated group with GNCPSs were considerably lower than those of the control groups. This work demonstrates the potential of GNCPSs for plasmonic photothermal tumor treatment [62]. Rupesh Jain et al. (Year) have reported improve the efficiency of photodynamic therapy for the treatment of LC, Liu et al. created R13 aptamer conjugated trimalonic acid modified C70 fullerene. Rupesh Jain et al. have also explained the action of photosensitizers. The photosensitizer is initially infused into the bloodstream or administered topically, where it soon accumulates at the tumor site, either gradually or aggressively. After that, the tumor is exposed to light radiation, which activates the photosensitizing molecule. The tumor cell dies as a result of the ROS that photosensitizer creates. That is how Photodynamic therapy (PDT) is an useful therapy for treating cancer [63]. PDT, is another diagnostic approach used for cancer treatment. The light source, photosensitizers and oxygen from the tissues are the requirements needed to comprehend the process of PDT. In this process, a photosensitizing agent like porphyrin is injected through intravenous administration and upon action, by light of specific wavelength, it causes ROS to be produced leading to the death of cancerous cell.

Fluorescence microscopy is the diagnosis technique that uses the plasmon ring on the gold nanoparticle's surface and a fluorophore to overlap between their emission spectra which will enhance the imaging capabilities called the fluorescence resonance energy transfer **(**FRET**)** phenomenon [64]. Man Wang et al. (2014) have an approach to make high-enhancement clean gold nanostar substrates that could have a stronger enhancing impact. The acquired substrates will allow us to effectively compare and discriminate between two LC cell lines [human type II alveolar epithelial cell line (AT II) and human lung adenocarcinoma epithelial cell line (A549)] and one normal lung cell line. Using SERS spectra. Hence, will help in early cancer detection and clinical cancer therapy [65]. When the SPR of GNPs and the fluorophore's

598 absorption and emission spectra overlap, it has been demonstrated that GNPs significantly
599 increase the excitation of fluorescence probes

600 *13.2. GNPs as sensors*

601 GNPs as immunosensors help in sensing of overexpressed antigens in tumor cells. GNPs have
602 multiple layers which tend to catch antibodies to generate optical signals that can be read. Next
603 are the serum tumor markers**.** The third approach involves the GNPs as genosensors, which
604 make the detection of nucleic acid easy, which is a challenging task during indications of LC,
605 in those cases specially designed spherical-shaped GNPs called genosensors are taken into
606 account that maximize the surface area to give high throughput, promising detections of
607 numerous microRNAs. We also have novel sensing methods, such as in biopsies, exhaled
608 Volatile organic compounds (VOCs) detection can be made easily. Any alterations hint
609 progression of carcinogenesis of LC. Therefore, exhaled VOCs from the breath will get
610 absorbed into a layer of GNPs prepared which will allow biomolecular detection. Another
611 group of fascinating biomarkers are overexpressed genes linked to tumors. Numerous potential
612 microRNAs that are critical to the growth of LC have recently been discovered using high-
613 throughput genomics approaches [66]. For instance, high levels of micro RNA-21 are thought
614 to be a sign of LC [67]. These molecules are known as microRNAs, which are tiny in between
615 19–25 nucleotide noncoding RNAs (ncRNA) that control protein or messenger RNA
616 expression by interacting with matching target messenger RNAs. This interaction either
617 inhibits or degrades mRNA [68]. Most biological processes, such as Regulation of the cell
618 cycle, cell death, vascular growth, cell differentiation, immune system management, and
619 transformation, are regulated by micro-ribonucleic acids (miRNAs), which are
620 phylogenetically conserved [69–71]. Shao su et al. (2016), stated that for label-free detection
621 of microRNA-21 (miRNA-21), which is a biomarker for lung malignancies, a highly sensitive
622 electrochemical biosensor is created. Using DNA probes to create hierarchical, flower-like gold
623 nanostructures, they were able to detect miRNA-21 with very low sensitivity applying
624 hybridization. Hence, it is concluded that the biosensor may be used to assess the amount of
625 miRNA-21 expression in human LC cell (A549) lysates and performed well in 100% serum,
626 indicating the possibility of using it for a variety of bioanalysis and clinical diagnostic
627 procedures. [67]. Additionally, long-noncoding RNAs, additional types of microRNAs linked
628 to LC, and circulating tumor DNA have all been better detected using gold nanostructures [72].
629 The so-called "Geno-sensors" or nucleotide-based sensing (NABSs) are biological tools that
630 may mark the nucleic acids (DNA or RNA) reaction based hybridization [73]. Sandwich and

competitive forms are preferable over direct ones to increase detection limits [73]. Geno sensors' recognition elements target nucleic acid patterns and probes, whose hybridization a direct format can view. The ss-DNA, probe-target DNA combination on the geno sensor's surface occasionally failed to lead to the aspired modifications to the transduction values. The ssDNA probe is immobilized on a transducer surface in the direct format, which depends on label-free detection, instead of the sandwich and other forms which combine a genetic target and a stranded DNA probe in an incubator. In an experiment, based on GNPs and microarrays, a quick and incredibly sensitive multiple protein detection assay was carried out. The benefit was that 12 samples could have biomarkers measured simultaneously. Compared to current assays, this requires fewer samples and less time. Unlike the traditional biomarker detection approach, numerous detection antibody molecules are attached to gold nanoparticle carriers, increasing the rate at which antigenic material molecules are combined and captured on the microarray analysis. Considering next, gold-precipitation staining amplifies the signals, considerably increasing the discernment level. W. Gao et al. (2016) in his experiment, performed an assay recruiting 106 LC patients along with 42 healthy people to analyse the presence of biomarkers for early diagnosis of LC. He emphasized upon the assay of many serum tumour markers, including carcinoembryonic antigen (CEA), cytokeratin 19 fragment antigen (CYFRA21-1), neuron specific enolase (NSE), and a novel biomarker Dickkopf-1 (DKK1). Where Capture antibodies bound to microarrays and detection antibodies carried on customised GNPs bridged four target proteins. As a result, by using $HAuCl_4$ and H_2O_2 to deposit gold, optical signals produced and were visible with a microscope or the unaided eye. When compared to sensitivity of single markers, combined detection of the four tumour markers significantly increased sensitivity to 87.74% for diagnosis of LC. Therefore, Based on GNPs and microarrays, a quick and extremely sensitive co-detection approach for numerous biomarker was created [74]. H. Daraee et al. in their research work, created and examined GNPs to track the sequence of hnRNPB1a as a biomarker for LC. The alterations in the samples' absorption spectra in the 250–750 nm region was used to establish the minimal level of detection (LOD) in solution, including DNA target and probe aggregation. After the target was detected, the results demonstrated that the percentage of dispersion increased with increasing hnRNP target concentration, and the technique's LOD was equivalent to 300 fmol/ml of the synthetic hnRNP target, demonstrating its great sensitivity. Hence, the outcomes were positive and could result in the advancement of technological knowledge that might serve as the foundation for the creation of LC diagnostic kits in future diagnosis. [75]. Due to the numerous benefits, they provide, using nanotechnology-based technologies, in particular the

usage of GNPs, may be a good tool for the identification of this condition. When compared to existing molecular detection techniques, these benefits include cost savings, speed, simplicity and accuracy, all of which may be shown and used in the future. The discoveries might result in the growth of technological understanding that will provide the groundwork for the production of LC diagnostic tools. In one of the early investigations, Mykhaylyk et al. investigated the absorption, distribution, metabolism and excretion characteristics of doxorubicin magnetic conjugate (DOX-M) nanoparticles utilizing a mouse model. Researchers in this work injected DOX-M formulations into the sinus eye vein of grown-up male rodents and administered a field of magnetic attraction over the left lung to see how effectively an irregular magnetic field affected the visual clarity of the magnetic DOX-M. They demonstrated how an irregular magnetic field dramatically altered the metabolism and absorption of the DOX-M combination. When compared to a control lacking a magnetic field, the application of a magnetic field led to a significant enrichment of DOX-M in the lungs and a depletion of the magnetic carrier in the liver. They demonstrated how using an alluring field might greatly enhance DOX-M's penetration in the lung [76]. Considering next study by Barash et al. wherein the published data served as a springboard for developing a bedside tool that might detect LC in its earliest stages and increase cure rates. H820, H1975, and A549 were the cell lines collected for the experiment. They detected 15 VOCs that exclusively exist in NSCLC and do not appear in the control medium, and 40 common VOCs (volatile organic compounds) that are present in >85% of NSCLCs and the control medium. Using this information, they created a variety of cross-reactivity sensors that are very sensitive, easy to use, and affordable, and exposed them to both NSCLC and the control media. Without applying any preconcentration techniques, PCA analysis of the array of sensors' responses revealed a 100% separation between the NSCLC clusters and the control medium. Hence forth, success in this project would eventually serve as a springboard for efforts for the quick identification of LC in fresh frozen tissues in surgical suites, where a binary diagnosis is essential for directing surgeons during operation [77]. Colloidal GNP is the most typical form of nanoparticle used in LFIS (lateral flow immunosensing). The LFIS method is based on immunological reactions in which an allergen is recognized by an antigen-specific antibody that has been labelled with different markers, including GNPs carbon dots, and quantum dots. On the basis of detection type, the LFIS can be divided into qualitative, semi-quantitative, or quantitative approaches. LFIS has developed into a crucial diagnostics technique due to its detection at low limits, high sensitivity, high specificity, durability, economic benefits and other qualities. Colloidal gold solutions made from GNPs have been utilized in studies to create immunochromatographic

699 strips and lateral flow devices that can detect various compounds and proteins. Numerous
700 analytes were identified by coupling colloidal gold with detection probes, including
701 immunoglobulin G (IgG) against Treponema pallidum, microbial transglutaminase (MTGase)
702 in samples of frozen foods, cortisol in homo sapiens, Staphylococcus aureus in food samples,
703 microalbuminuria diagnosis, and nitrofuran metabolites in fish sample [78].

704 *13.3. GNPs as therapeutic agents*

705 GNP based therapy involves improved drug delivery, utilizing GNPs to target the cancer site
706 due to their trans locative ability to bypass cell barriers, increased drug uptake and DNA repair
707 mechanisms. In contrast to the usual problems faced by the use of anticancer drugs of
708 resistance, decreased drug uptake, low specificity and pessimistic biodistribution of the drug.
709 Next is gene silencing therapy, in which cells may be effectively infected with siRNAs using
710 both time and resources that have been harnessed. Followed by Immunotherapies, which are in
711 use for patients suffering mutations as one reason for LC complexation. The approach of
712 immunotherapies involves the promotion and dendritic cell maturation in the lymph node
713 triggering antigen-specific lymphocyte response and local LC treatment. GNPs are efficiently
714 seen to increase dendritic maturation upon injecting coated nanocages. A prior study
715 demonstrated that the surface area of GNPs significantly influences their therapeutic impact
716 [79]. The cellular activities and reactions of GNPs with human LC cells are rather little
717 understood. Additionally, it is crucial to primarily concentrate on the effects of nanoparticles
718 on a particular cancer cell, to get an understanding of the root mechanisms involved. Zhengxia
719 Liu et al., (2014) examined the cytotoxicity and cell invasion propensity in A549 and 95D cells.

720 In vitro permeability study reported that GNPs easily cross and A549 and 95D cells through
721 sendocytosis pathways.

722 *In vitro,* following GNP treatment and demonstrated that LC cell may endocytose tiny GNPs,
723 which enhances cell invasion. It was observed that GNPs of 5nm and 10nm were easily
724 internalized into cytoplasmic vesicles by A549 and 95D cells respectively by means of general
725 endocytosis. The study alssso demonstrated that in two LC cell lines, tiny GNPs with a 2.5nm
726 radius are highly effective in preventing, expansion in volume encouraging apoptosis, the cell
727 cycle stops at the resting phase and G1 phase. In contrast, 10nm and its exponential size
728 nanoparticle like 20 nm and 40 nm GNP treated cells showed no noticeable signs of
729 cytotoxicity. Hence, it was also clear that GNPs and their distinct size-despendent
730 physiochemical characteristics have an amazing connection. [80]. The utilization of GNPs

coupled to CpG oligo-deoxynucleotides (CpG-ODNs) is one of the most obvious improvements. These vernacular CpG-ODNs are promptly destroyed by cell cytoplasm nucleases because they cannot cross the cell membrane into the cytoplasm. Due to its remarkable in vitro effectiveness, ODN-GNP is conjugated and employed for administration within the cells. Gold nanospheres within size range of 15–50 nm performs better than different nanoforms when GNPs are crosslinked with CpG-ODNs. In cancer immunotherapy, GNPs have also been utilized in conjunction with CpG-ODNs, tumor necrosis factor TGF, the protein PDL1 inhibitor, unique antibodies, and other tumor cell mortality factors and immunostimulants. Strong contacts between dendritic cells and GNPs produced immune system-boosting cytokines [81].

The Hyperthermal Therapy: The first report on the application of particles of gold to hyperthermal therapy was presented by Halas et al. (2003). They created 10-nm gold nano shells mounted on a silica surface and worked on their application in the near-infrared photothermal killing of cancer cells. Using the HER2 antibody, nano shells were employed to actively target breast cancer cells, and extravasation was used to congregate PEG-coated gold on silicon. Nano shells were passively targeted in a murine in vivo model. In the latter investigation, it was discovered that NIR irradiation increased the target area temperature by 40 to 50ºC, which specifically eliminated the carcinomas. Compared to controls, mice's likelihood of survival given this treatment was quite good. Therefore, it resulted in no surprise that particle morphologies other than nano shells can produce the therapeutic effect. [82]. In another study, S. Kumar et al. (2020) reported that gold nanoclusters (GNCs) have also been developed as a nanocomposite with fluorescent conjugated polymer-poly (2-methoxy-5-(2ethylhexyloxy)1,4-phenylenevinylene) (MEH-PPV), which is suitable for cancer studies due to its stable illumination, light picking, and receptive light response. It was observed that strong red fluorescence signals were detected after MEH-PPV@PEI-GNCs were incubated with human LC cells (A549), showing effective biodistribution in the cytoplasm. The created system was suitable with the target cells at different concentrations. According to a cytotoxicity investigation, upon irradiation, MEH-PPV@PEI-GNCs were able to cause cell death and resulted in a significant drop in cell viability.This is how a combined technology was employed for cancer cell imaging and photothermal destruction. This decrease was ascribed to GNCs' ability to produce localised high temperatures, which makes them ideal agents for photothermal elimination of cancer [83]. S. Rajeshkumar et al. in his experiment (2016) utilized HepG-2 and LC cell (A549) lines to test the anticancer effects of GNPs. Evaluation and comparison of in

vitro cytotoxic activity against the cell lines was done at various doses with the reference medication cyclophosphamide. The findings demonstrate the efficacy of cytotoxic action against cancer cells. The anticancer activity was significantly influenced by the quantity of GNPs present. 100µg, followed by 50µg, 25µg, and 1µg, provide good results in terms of performance against A549. The active physicochemical interaction of gold atoms with the functional groups of intracellular proteins, as well as with the nitrogen bases and phosphate groups in DNA, is what caused GNPs' cytotoxic effects [84]. S. viswanathan et al., used red seaweed Champia parvula in the biosynthesis of GNPs and researched about its anti-oxidant, free radical scavenging activity and anticarcinogenic properties that are effective against LC. Utilising Vitamin C as a reference, the anti-oxidant ability of Cp-GNPs was examined utilising the DPPH (2,2-Diphenyl-1-picrylhydrazyl), H2O2 (hydrogen peroxide), and FRAP (ferrous reducing assay power) radical scavenging assays. The MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) test was used to evaluate the anti-cancer efficacy of Cp-GNPs against LC cell lines (A549). At a CpGNPs concentration of 50 mg/mL, 46.7% viable cells were discovered. In A549 cells, the biosynthesized GNPs' IC50 value was discovered to be 36.08 mg/mL.Sincce, they included anti-oxidant-rich components, the biogenic Cp-GNPs demonstrated remarkable anti-oxidant along with free radical scavenging capacity. Hence, examination on LC (A549) cells, anti-cancer activity of Cp-GNPs was examined and high anti-cancer potential was found [47].

13.4. Theranostic role of GNPs for LC

GNPs have been extensively used for theranostic applications in cancer owing to the ease of synthesis, biocompatibility, and multifunctional characteristics [85]. Many researchers have utilized theranostic applications of GNPs in lung cancer. Knights et al. studied the effects of size of gold nanorods (GNR) on photoacoustic response, efficacy of pulse-wave plasmonic photothermal therapy, and photoacoustic imaging in a tissue-mimicking phantom for the progress of GNRs towards their clinical use. Under pulse-wave illumination, all GNRs exhibited toxicity at a laser fluence below the maximum permissible exposure to skin, and a maximum of 80 % cell-death showed by the smallest GNRs that favoured the feasibility of pulse-wave plasmonic photothermal therapy. GNRs combined with pulse-wave laser showed the potential theranostic application in the lung [86]. Nanospectra developed polyethylene glycol (PEG)-stabilized silica-gold nanoshells for the photothermal therapy to the solid tumors using near-infrared (NIR) light source [87]. In addition, AuroLase® was used for the photothermal ablation of primary or metastatic lung tumors (NCT01679470) [60]. Another

study reported by Ramalingam et al. exhibited the increased anti-cancer efficacy of doxorubicin (DOX) using polyvinylpyrrolidone (PVP) functionalized GNPs in lung cancer cells. PVP-functionalized GNPs were able to increases the generation of reactive oxygen species (ROS), up-regulation of tumor-suppressor genes, and apoptosis induction in lung cancer cells [88]. Peng et al. GNPs-based array of sensors which, in a high humidity atmosphere, could rapidly distinguish the breaths of lung cancer patients and that of healthy subjects. The results of study claimed that this technique could be used as a cost-effective and non-invasive diagnostic tool in lung cancer [89].

Table 2. Role of GNPs against LC

S No.	Method of preparation	Drug	Type of LC cell line	Outcome	References
THERAPEUTIC APPLICATIONS					
1.	Green synthesis	Pleuropterus multiforus	A549	• Reduced cytotoxicity level • Migrated of hazardous tumor growth protein • Promoted DNA damage in cancer cells • Activated protein expression specially caspase 3, P53, P38	[90]
2.	Green synthesis	Padina tetrastromatica	A549	• The average particles dimeter of GNPs was observed 8-10 nm • Increased production of oxidative stress and elevate level of ROS in cancer • Reduced cell viability	[91]
3.	Green Synthesis	*Lantana montevidensis* (LM)	A549	• An *in-vivo* toxicity investigation was conducted, all medications were administered to C57BL6 black mice through the intraperitoneal route (IP). • Suppressed cancer cell growth in comparison to the free LM extract and conventionally synthesized GNPs	[92]

				• Increased cellular ROS production • G2/M in A549 was arrested which resulted in apoptosis	
4.	Biogenic production	*Champia parvula* (Cp)	A549	• GNPs exhibited scavenge free radicals' production in cancer cells • Downregulated 80.2%, DPPH scavenging activities at a dose of 50 mg/mL.	[47]
5.	Sonication	biocompatible collagen (BC)	A549	• Reduced growth of tumar cells to 70% for BC-GNPs and maximum • Collagen gold at 2.5 ppm, decreased cancer cells population of S-phase • 60% (p 0.01) of the tumour weight was reduced by the collagen nanogold carrier, compared to 20% (p 0.05) by the lip-ofetamine carrier.	[93]
6.	Chemical route	Glucose capped GNPs (Glu-GNPs)	A549	• Increased ROS, cytotoxicity, cytokinesis to stop, and apoptosis in cancer cells	[94]
7.	Chemical reduction	Citrate- and polyethylene imine (PEI)-functionalised GNP	A549	• Induced apoptosis which is concentration dependent • Reduced cellular growth and altered nuclear morphology • Decreased in cellular membrane size	[95]
8.	Chemical synthesis	DOX@PVP-GNP PVP: Polyvinylpyrrolidone	A549	• Early and late apoptosis induction and overexpression of tumor suppressor genes in LC cells	[60]
9.	Stirring and centrifugation	Curcumin-containing CD/PEG-conjugated GNPs (cur-CD-GNPs)	A549	• Produced sustained release profile • Promoted cancer cells growth	[96]

		CD:cyclodextrin			
10.	Stirring	Kaempferol (K)	A549	• Increased DNA damage to the A549 cancer cell • Produced less toxicity to the normal human cells • Nucleus condensed and fragmented seen as per theconfocal imaging of DAPI-stained samples • Nuclear breakage signalling apoptosis • Exhibited cytotoxicity at a relatively low dosage (12.5 g/mL) in LC celles	[97]
SENSOR BASED APPLICATIONS					
1.	Copper-free click chemistry	DNA based GNPs	A549	• Decreased cell viability less than 70% • Two fluorescent red and green signals corresponding to the identification of both keratin 8 and vimentin mRNAs were seen during nanoparticle dimers were incubated with A549 cells	[98]
2.	Chemical reduction	Polyethylene glycol (PEG)	A549	• Reduced cell proliferation between 4 to 20% • Activated *in vitro* surface-enhanced raman scattering (SERS)	[99]
3.	Green synthesis	GNPs-based sensors	A549	• GNPs used to detect LC cells	[100]
4.	microwave-hydrothermal method	Colloidal carbon	A549	• Reduced cell viability in A549 cells and more than 80% of cells were still viable after 48 h which showed high biocompatibility that is suited for sensing with A549 cells	[101]

DIAGNOSTIC APPLICATIONS					
1.	Seed-mediated and seedless growth	Doxorubicin	A549	• Sensitized DNA double-strand and breaks • Reduced cancer cells	[102]
3.	Incubation	Photothermal bubbles created around GNP	A549	• Photothermalysis • Reduced cell viability nearlly 8%	[103]
5.	Physical method	Using GNPs-conjugated aptamer ENO1 antibodY was targeted.	A549	• Solid-phase microextraction with gas chromatography/mass spectrometry was combined that helped in identifying volatile organic compounds acting as biomarkers	[104]

14. Fate of GNPs in the body

Kadhim et al. investigated the toxicity of GNPs in-vitro (rat embryonic fibroblast cell lines) and in-vivo (mice model). MTT assay was used to investigate cytotoxic activity of GNPs against the cell line and intraperitoneal injection of GNPs at a concertation 100 mg/Kg was used for in-vivo study. Post-GNPs treatment, no cytotoxicity and morphological alterations were observed against rat embryonic fibroblast cell lines at concentration of 1, 5, and 10 µg/ml. Similarly, no changes were visible in histopathological studies. The research findings suggested the biocompatible nature of GNPs both in-vitro and in-vivo [105]. Another study reported transmission electron microscopy study of the uptake of ca. 16 nm surface modified GNPs by human fibroblast cells (HeLa cells). It was inferred that delivering the nanoparticles in form of liposomes or by surface modified nanoparticles can significantly bypass the well-known endosomal route of cellular uptake [106]. According to Goodman et al., anionic GNPs were non-toxic whereas cationic GNPs showed moderate toxicity for erythrocytes, when used at the same concentration. They also studied the effect of GNPs with different surface charges on embryo development in zebrafish and reported non-charged GNPs without adverse effects while anionic GNPs were observed to provoke the behavioural abnormalities in the larva. Yang et al. observed fourfold more toxicity of aggregated cationic GNPs in human dermal fibroblasts as compared to non-aggregated particles [107].

Nanoparticles clearance generally takes place through liver and kidney depending upon their size. When the size of GNPs is greater than renal filtration cutoff, their excretion from the blood

takes place by the reticuloendothelial system (RES) to get accumulated in the liver. Urinary excretion filters out the small sized-particles in a few hours to days post-administration. Hepatobiliary excretion removes the GNPs in a few hours to weeks after their administration. On the other hand, RES traps non-degradable GNPs for more than 6 months. Thus, the liver, kidney, and spleen are the major organs responsible for elimination of GNPs from the body [108].

15. Conclusion and future perspective

High-caliber GNPs are becoming increasingly important in a range of high-technology applications and biomedical applications. However, there still lies a challenge. Using conventional gold in block form could be extremely strenuous, as, an antibody cannot be very appropriately linked to it in that form compared to its nanoform. Acknowledging the revolution that was brought to provide a solution is related to development of functionalized nanoparticles. Functionalization offers a proprietary surface coat to the nanoparticle that further makes the nanoparticles extremely stable and helps in their active targeting. Thus, functionalized GNPs can be conveniently covalently linked to an antibody as well as oligonucleotides. Consequently, providing a therapeutic and diagnostic approach to working. Additionally, colloidal gold has the most consistent and stable shape. Gold's property of forming bonds with amine and thiol groups easily allows GNPs to be tagged with ligands. Ligands are molecules that attach to the outside of a nanoparticle and bind preferentially to receptors on tumor cells. Another property that GNPs prevail in related to their plasmon gold nanoform. Plasmon GNPs are particles made of gold that are having optical properties. They even differ in their color and appearances from block gold that are normally golden in color, reflecting shiny light and giving luminescence. Based on their size GNPs appear to be red, yellow, green, and purple in color, which changes on the basis of their size and shape. It gets even more magnificent when we look at their electrons which are also nano-small, even smaller than light. Thus GNPs can fit in between the wavelengths of light. Therefore, whenever a light wave passes out over the GNPs, the electric field causes the free electrons on the surface of the GNPs to move. It causes electrons present on the surface of the particle to oscillate SPR. These nanoparticles thus, acquire the ability to unzip DNA, and site-target tumor cells by being coated with specific molecules designed to attach cancerous cells. These gold-loaded cancer cells are targeted using low-power laser light. The unique advantage of this technique is that only the cancer cells experience heavy gold loading while surrounding cells with much lower loading are less

affected by the treatment. These special properties of GNPs make them special and a good candidate for their biomedical application against LC.

Despite these advantages the GNPs have to address major bottlenecks related to their in vivo application. As GNPs work on cancer cells through EPR effect that help them to enter into tumor cells via their leaky vasculature. They remain within the tumor for longer time due to poor lymphatic flow. In addition, the size and shape of GNPs play important role in passive targeting of cancerous cells. Hence, a better control on size and shape is required during their synthesis to achieve desired targeting of GNPs to tumor cells. Usually, GNPs having size less than 200 nm is required for excellent EPR effect, however, size less than 50 nm enhances faster extravasation of GNPs from tumor cells through fenestrations. This leads to poor retention/stay of GNPs inside tumor cells leading to ineffective treatment. Hence, size and shape controlled synthesis of GNPs is very important in order to get optimum size that could offer better permeation as well as retention of GNPs inside tumor cells. This becomes a critical factor when the GNPs have to be synthesized at commercial scale as the major challenge is faced during scale-up process. The stability of GNPs is another challenge that is required to be addressed. The proper selection of type and concentration of stabilizer is important to develop stable GNPs. Furthermore, the functionalization of GNPs to the therapeutics/biomolecules using proper ligands lead to active targeting of GNPs to cancerous cells. The optimization of formulation and process variables affecting active functionalization of GNPs to ligands should be done through quality by design approach. This would help in achieving GNPs having good active targeting properties.

Further, in vitro and in vivo correlation of functional ability of GNPs is required by correlating their effect on cell lines and within the body as there exists variation due to disease physiology and heterogeneity among humans. The preclinical performance of GNPs related to therapeutic efficacy, safety, biodistribution, and pharmacokinetics should be done on suitable animal model of LC and compared with the results of in vitro studies. The in vivo preclinical study should be carried out on multiple animal models of LC in order to get reproducible results and better correlation with human physiology. Considering these factors in future studies would definitely enable GNPs as very good candidates for their biomedical application in LC.

Conflict of interest: Declared none

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Research highlights

- There are about 1.76 million deaths due to LC per year.
- Existing therapies are less effective due to their poor permeation and retention in LC cells
- GNPs are biocompatible, easily get functionalized, and stable to in vivo oxidation
- GNPs can enhance bioavailability and site specific delivery of drugs to LC cells
- Surface plasmon resonance and optical properties enable GNPs as sensors and imaging agent

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: