

Green Synthesis of Selenium Nanoparticle from Medicinal Plant Extract and its Potential in The Treatment of Lung Cancer

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Article History	Abstract
<p>Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 01 Dec 2023</p>	<p><i>Lung cancer is the leading cause of death globally with an estimated 238,340 people in 2023. Mukia madrespatana, a plant with ethnomedicinal properties, exhibits numerous therapeutic effects in traditional medicine. In recent years there has been a growing interest in utilizing selenium nanoparticles synthesized by green mediated approach involving the plant for treating various types of cancer. Despite notable advancements made in the past decade there are still inherent challenges associated with these treatment approaches. Notably, recent investigations have unveiled promising prospects in the realm of lung cancer treatment through the discovery of antitumor drugs derived from selenium, a trace element. Selenium nanoparticles can serve as a viable option for drug delivery systems, facilitating the precise control of protein kinase activity and they have been found to exhibit regulatory effects on immunity and have shown promise in enhancing immunotherapy for lung cancer.</i></p>
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1. Introduction

According to 2020 global cancer statistics, lung cancer has the highest incidence (11.4%) and fatality (18%)(Sung et al., 2021). Lung cancer patients had a 19% 5-year relative survival rate, while SCLC patients had 2% (Gazdar et al., 2017). Scientists worry about lung cancer's fast progression and high fatality rate (Ruzicka et al., 2019). Surgery, chemotherapy, and radiotherapy are the main lung cancer treatments. Surgery is a painful local therapy, chemotherapy and radiation produce nausea, vomiting, and bone marrow suppression, making them challenging to utilize in clinical settings. Even though lung cancer immunotherapies and gene mutation therapies have shown great promise, acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) is inevitable (Wang et al., 2022). Most patients lose TKI response within 1 year, their health worsens swiftly, and immunotherapy has a 20% response rate. Thus, therapeutic treatment needs safer and more effective methods(Verma et al., n.d.). The various stages of lung cancer has been represented in figure 1.

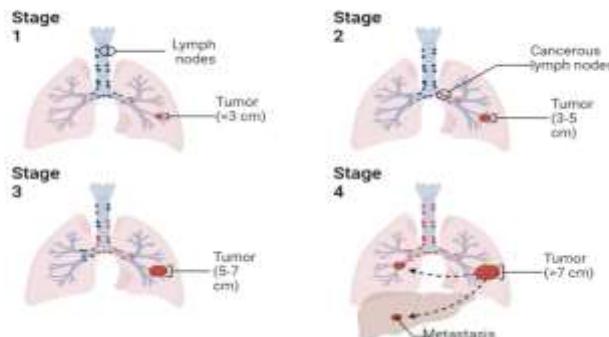


Figure1: Various stages of lung cancer progression

Mukia madrespatana (*M. madrespatana*) (L.) (Cucurbitaceae) is a plant commonly known as Madras pea banana. It exhibits a wide geographic diversity and is distributed in the tropical and subtropical regions of the Old World. Phytochemical studies of *M. madrespatana* revealed the presence of phenolic compounds, tannins, flavonoids, alkaloids and saponins (Pandey et al., 2013). The antioxidant activity of *M. madrespatana* is attributed to the presence of phytochemicals containing many hydroxyl (OH) groups, making them potent reducing agents. Many in vitro and in vivo studies have been carried out with plant models of *M. madrespatana* (Jayatilaka et al., 1990). The plant exhibits numerous pharmacological properties, including anti-arrhythmic, anti-asthmatic, antioxidant (Raja and Pugalendi, 2010), anti-histaminic, anti-inflammatory (Ramakrishnamacharya et al., 1996), anti-hypertensive, hepatoprotective (Thabrew et al., 1995) and anti-diabetic properties (Samad et al., 2020; Srilatha and Ananda, 2014) Figure 2.

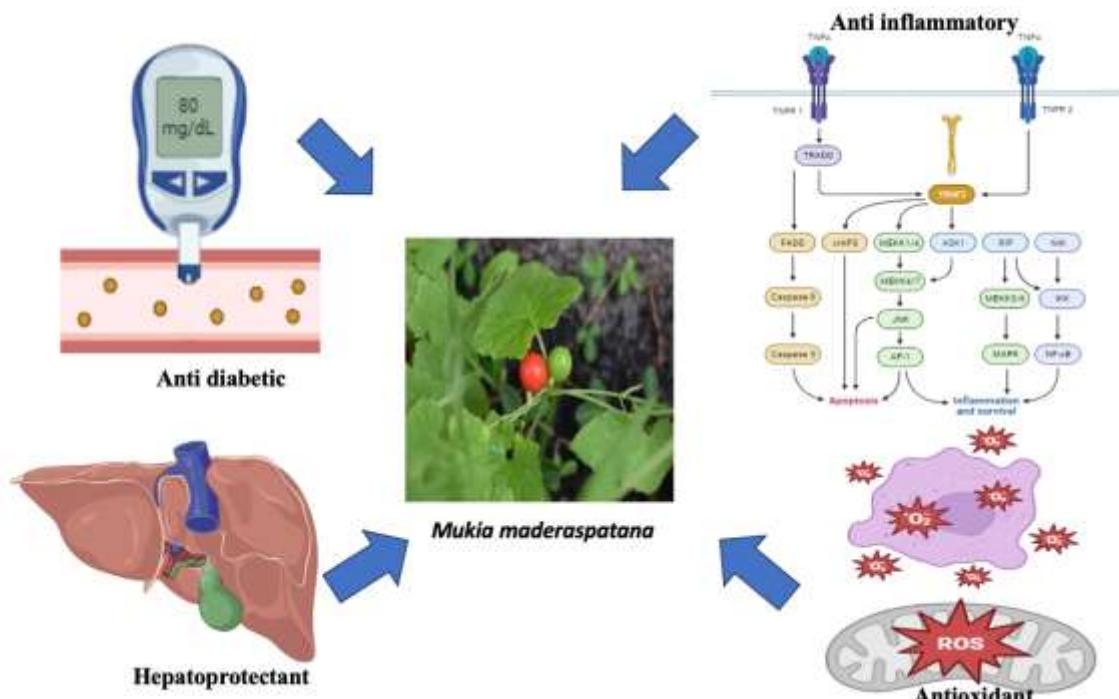


Figure 2: Pharmacological applications of *Mukia madrespatana*

Traditional treatments for lung cancer include chemotherapy, radiotherapy, or both. Each of these therapies has limitations, including indiscriminate killing of normal and cancer cells, soluble chemotherapeutic agents, rapid clearance from the blood before reaching the tumor site in, cancer cell radiation resistance, hypersensitivity of normal cells to radiation. In situ cryo-immune engineering (ICIE), gene therapy, immunological checkpoint inhibitor, drug recycling and therapy (Figure 3).

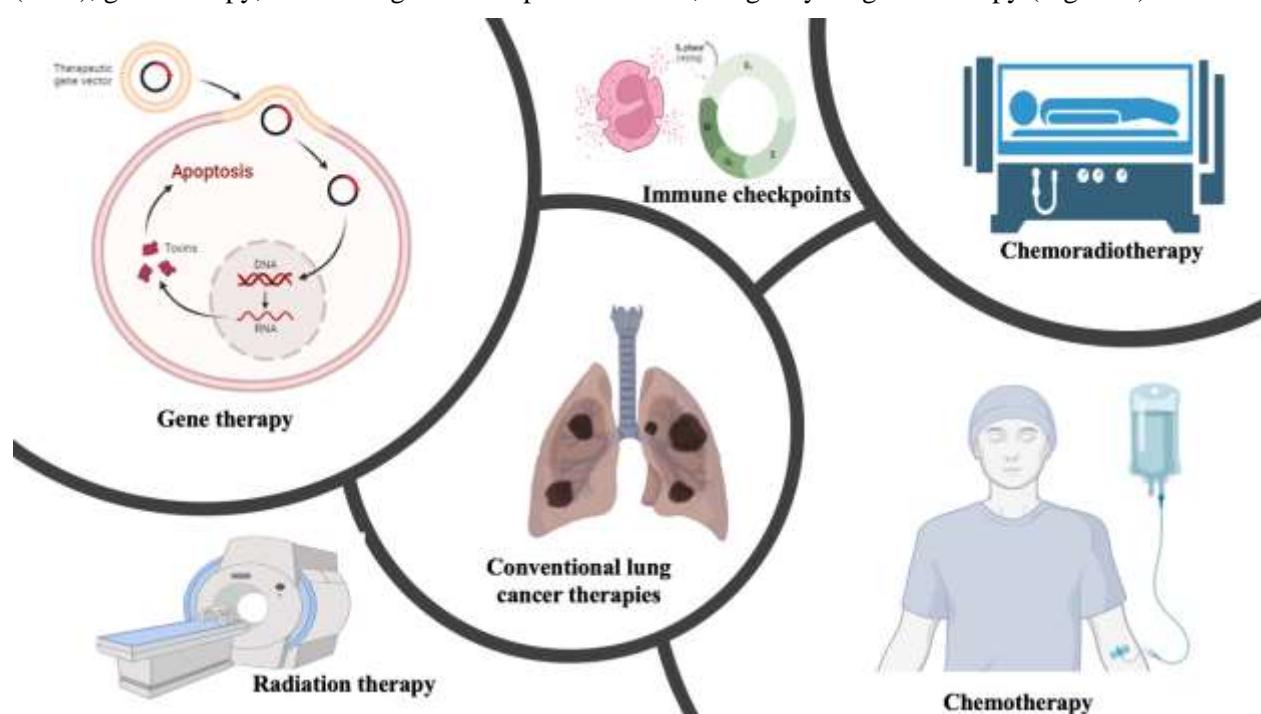
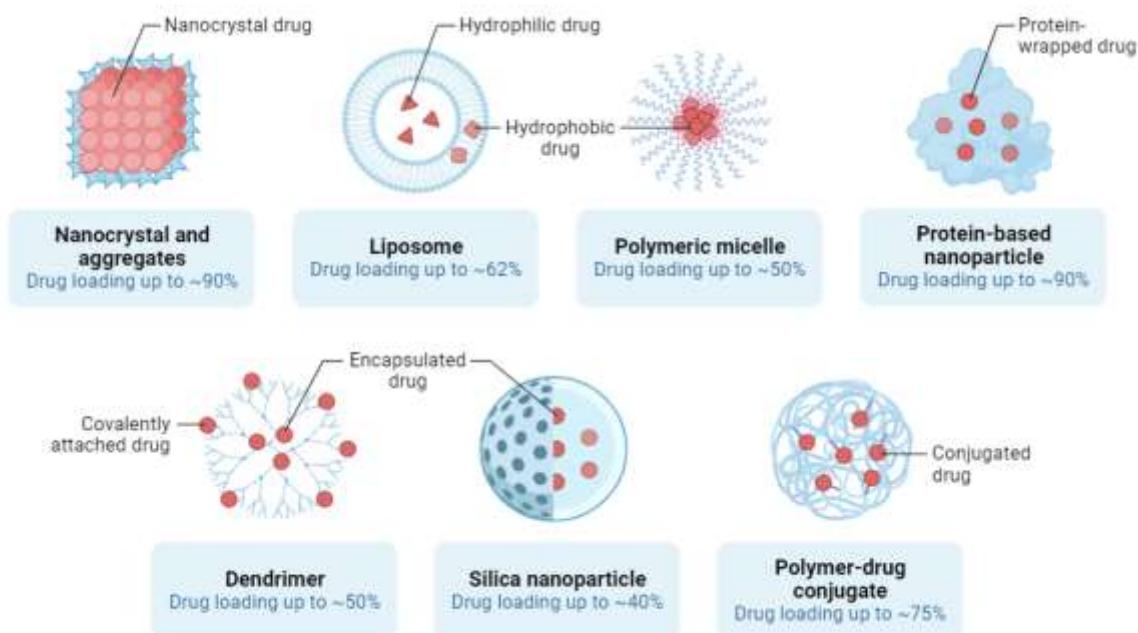


Figure 3: Traditional Lung cancer treatment

Nanotechnology has addressed many shortcomings of traditional medicine. Surface-modified nanomedicines, nanoparticles, and nanostructures have led to cancer cell death and radio sensitization. Tumor cells receive susceptible molecules from nano-enabled drug delivery systems, providing radiation therapy is more effective (Girigoswami and Girigoswami, 2023).

Nanomedicine represents an emerging therapeutic approach that prioritizes drug delivery alternatives and maximizes therapeutic outcomes, all while minimizing potential harm to healthy tissue. Nanoparticles can be distributed (NPs) used in lung cancer management into two distinct classes: organic and inorganic nanoparticles (Figure 4 and 5). The following categories represent the main categories of organic nanoparticles: 1) liposome-cholesterol and phospholipid-based biofilm-like nanoparticles (NPs) 2) solid lipid nanoparticles (NPs). 3) Nanostructured lipid carriers (NLCs) which are a combination of solid fatty acids and liquid fatty acids. Polymer nanoparticles (NPs) are made from a variety of polymers, including sodium alginate, chitosan, gelatin, polycaprolactone, polylactide, and polylactic acid 5) Polymer micelles are colloidal nanoparticles formed by self-assembly of amphiphilic block copolymers. 6) Dendrimers are highly branched, symmetrical nanoparticles that exhibit radiative order (Markman et al., 2013). Inorganic nanoparticles can be classified into three distinct types: 1) Magnetic nanoparticles (NPs) refer to hyper paramagnetic materials with a diameter larger than 25 nm 2) Carbon nanotubes are characterized by their hydrophobic tubular shape of carbon atoms, ranging from 4 nm to 100 nm in diameter and 3) Quantum dots are colloidal nanoparticles (NPs) that exhibit atomic properties. There are three methods of passive targeting. One possible approach is to use the enhanced penetration-retention (EPR) effect in tumors to facilitate the accumulation of nanoparticles (NPs) in tumor tissue, but it should be noted that this approach is not feasible in the subjects (Doroudian et al., 2021).

**Figure 4:** Various nanoparticles for Lung cancer therapy

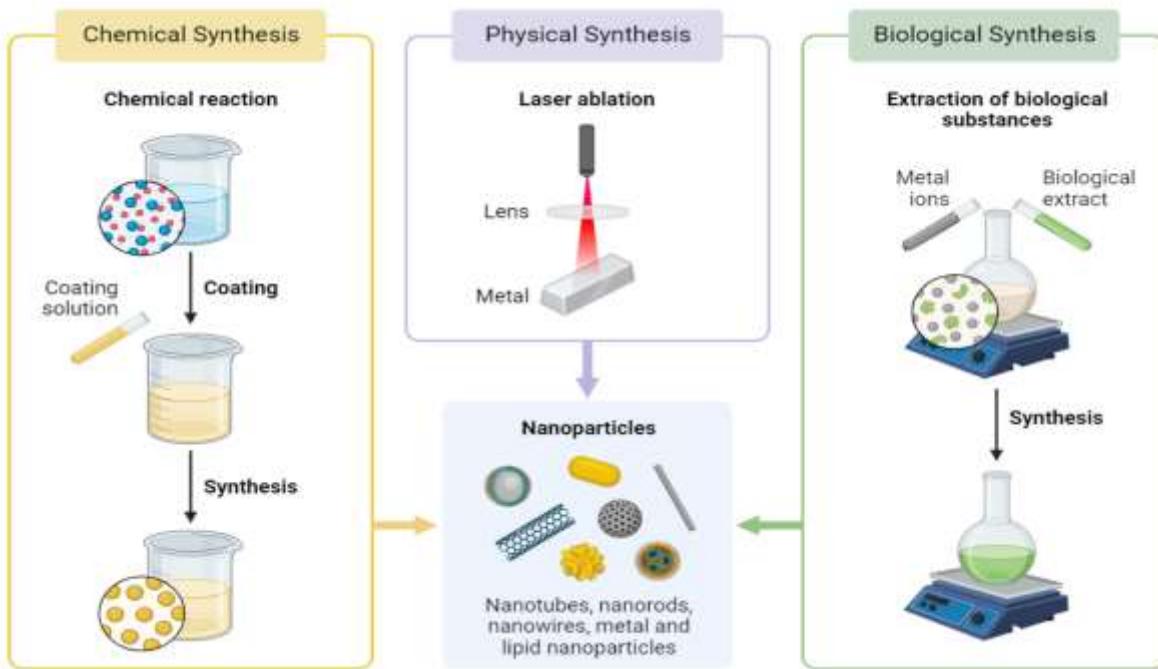


Figure 5: Types of nanoparticle synthesis

Studies show that individuals with malignant pleural effusion due to advanced lung cancer exhibit lower serum levels of selenium compared to their healthy counterparts (Song et al., 2021). This highlights the importance of Se plant. Recognized as a unique and essential trace element of selenoprotein Se that plays an important role in many human physiological processes it has been a topic of intense research in cancer therapy for many years (Li et al., 2016), studies have explored its potential as drug inhibitors in lung cancer -Se levels can significantly reduce lung cancer incidence in individuals (Feng et al., 2019) Another study has confirmed the important role of Se in limiting oxidative DNA damage and enhancing DNA repair, suggesting the importance of potential results in cancer development despite the increasing recognition of the importance of existing Se, Se supplementation, inorganic selenium (Inorg-Se) and organic selenium (Org-Se), are limited due to issues such as due to poor absorption and high toxicity They found that Se supplementation could reduce the risk of lung cancer when blood levels reached 106 ng/mL(Avery and Hoffmann, 2018). However, above this threshold (121.6 ng/mL) increases the risk of lung cancer and is associated with diabetes. Moreover, the use of SeMet has been shown to enhance radiosensitivity in human lung cancer cells without harming normal lung cells (Fritz et al., 2011). It should be noted that doses in cell assays may be significantly higher than those required for *in vivo* studies, and it is important to determine the appropriate *in vivo* dose (Lobb et al., 2018).

Pathways Targeting Lung Cancer

PI3K/AKT/mTOR pathways

The PI3K/AKT/mTOR pathway is recognized as a potential target in non-small cell lung cancer (NSCLC). This signaling pathway governs various cellular processes, encompassing cell proliferation, differentiation, apoptosis, gene transcription, and protein synthesis (Beevers et al., 2006; Hay and Sonenberg, 2004). In several cancers, including breast cancer, gastric cancer, and NSCLC, this pathway has been observed to activate upstream receptors (EGFR and PDGFR) and undergo mutations (Liu et al., 2017). Approximately 4% of NSCLC tumors expressing the PTEN protein, which inhibits the PI3K/AKT/mTOR pathways, exhibit mutations in PIK3CA (Kawano et al., 2006; Song et al., 2016). Efforts have been made to target the PI3K/AKT/mTOR pathways in NSCLC. For instance, a PI3K inhibitor (LY294002) has been reported to enhance NSCLC sensitivity to chemotherapy and radiation. Furthermore, the mTOR inhibitor temsirolimus (CCI-779), which targets molecules downstream of the PI3K pathways, has shown promising antitumor activity in phase I trials for NSCLC (Hidalgo et al., 2006). Other PI3K/AKT/mTOR inhibitors like everolimus (RAD001 or AP23573) are also undergoing preclinical trials. Studies have revealed that downregulation of miR-93 in NSCLC inhibits cell proliferation and apoptosis (Li et al., 2017), and miRNA-223 has been found to suppress cancer cells by targeting the EGFR/AKT2 pathway in NSCLC (Ma et al., 2019).

The PI3K/AKT/mTOR pathway has also been implicated in EGFR-TKI resistance (Fumarola et al., 2014; Vara et al., 2004). Loss of the PTEN gene, whose protein product operates downstream of the

PI3K/AKT/mTOR pathway, plays a significant role in erlotinib and gefitinib resistance in EGFR-mutated NSCLC. Several miRNAs have shown potential to counteract the inhibition of tumor growth, progression, and metastasis induced by the PI3K/AKT/mTOR pathway. MiRNAs can also regulate resistance in NSCLC by targeting this pathway. For instance, Wang and colleagues demonstrated that miRNA-328 overexpression confers cisplatin resistance to A549 cells via PTEN, while inhibiting miRNA-328 restores cisplatin sensitivity in NSCLC cells. Similarly, miR-21 has been shown to induce gefitinib resistance in NSCLC, and inhibiting miR-21 enhances sensitivity to gefitinib by modulating the PTEN/PI3K/AKT pathways (Wang et al., 2018). Additionally, miR-23a has been identified as an inhibitor of PTEN in NSCLC cells and downregulating miR-23a can reverse erlotinib resistance (Shen et al., 2014). Other miRNAs targeting the PI3K/AKT/mTOR pathways, such as miR-126, miR-203, and miR-34a, have been demonstrated to regulate drug resistance via PI3K/AKT signaling (Garofalo et al., 2012; Zhao et al., 2017; Zhong et al., 2010).

RAS-MAPK Signalling Pathway

The human RAS gene family, which includes KRAS, NRAS, and HRAS, encodes small G proteins (GTPases) located in the plasma membrane. These G proteins play a crucial role in regulating cell proliferation and progression through distinct pathways (Downward, 2003). Upstream membrane receptors, such as EGFR and FGFR, are associated with the RAS family, while downstream pathways like the RAS-MAPK and the PI3K-AKT-mTOR pathways are involved in cell differentiation and survival mediated by the RAS family (Garofalo et al., 2012). Among the RAS family genes, KRAS is the most frequently mutated one in lung cancer (Ricciuti et al., 2016). KRAS mutations are found in 20–40% of lung adenocarcinomas, constituting approximately 20% of cases in Western countries and 10% in Asian countries (Rosell et al., 2012). Some studies suggest that KRAS mutations may contribute to resistance to EGFR-TKIs in targeted therapies for NSCLC (Massarelli et al., 2007). Consequently, various agents are being explored to target the RAS pathway in NSCLC with the aim of overcoming drug resistance.

Numerous downstream receptors within the RAS pathways, including RAF, MEK, and mTOR, have been investigated as potential targets in NSCLC through multiple clinical trials. Sorafenib is an oral multikinase inhibitor that targets RAF and other receptors like VEGFR-2, VEGFR-3, and PDGFR-b (Wilhelm et al., 2004). Early clinical trials of sorafenib demonstrated promising efficacy, good tolerability, and stability in patients (Miller et al., 2012). However, subsequent clinical studies revealed limited efficacy in NSCLC, with objective response rates (ORRs) below 10% (Blumenschein et al., 2013; Papadimitrakopoulou et al., 2016). Similar results were observed in clinical trials of other BRAF inhibitors, which performed well in patients with BRAF mutations but not in those with KRAS-mutant lung NSCLCs (Ferrer et al., 2018). Clinical studies of MEK inhibitors, including selumetinib and trametinib, showed no significant benefits compared to pemetrexed-based or docetaxel-based chemotherapy in untreated NSCLC patients (Blumenschein et al., 2015). This lack of efficacy may be attributed to current Raf inhibitors recognizing only one binding site, leading to reduced binding affinity for other sites. Therefore, there is an urgent need for novel methods or target drugs to address these challenges in RAS-mutated patients.

Several genetic approaches have been developed to identify potential targets in NSCLC. Paula T. Hammond and colleagues attempted to combine siKRAS, miR-34a, and cisplatin to target the KRAS/P53 mutation in NSCLC. Their results demonstrated that this combination of miRNA and chemotherapy enhanced cancer cell line toxicity, increased treatment efficacy, and prolonged survival in mice (Gu et al., 2017). Other studies indicated that miR-202 enhanced the anti-tumor effect of cisplatin in NSCLC by targeting the Ras/MAPK pathway. MiR-202 was found to enhance cisplatin sensitivity in NCI-H441 and A549 NSCLC cells, inhibiting the Ras/MAPK pathway by targeting the KRAS gene (Sun et al., 2018).

EGFR pathways

EGFR belongs to the family of tyrosine kinase type I receptors and is located on the short arm of human chromosome 7 (Zhao et al., 2017). EGFR consists of 28 exons, forming a protein that resides on the cell membrane of various epithelial cells. It binds to epidermal growth factor and heparin-binding EGF, regulating cell growth (Zhong et al., 2010). Exon 20 insertions and exon 18-point mutations are less common than exon 19 deletions and exon 21 L858R substitutions in EGFR mutations in NSCLC (Downward, 2003; Zhou et al., 2014). Activation and regulation of EGFR and its downstream genes play a pivotal role in cell proliferation, apoptosis, and angiogenesis (Ricciuti et al., 2016). Various measures have been developed to target EGFR, including tyrosine kinase inhibitors (TKIs) and BRAF inhibitors (Massarelli et al., 2007; Wilhelm et al., 2004).

In recent decades, tyrosine kinase inhibitors have proven to be effective drugs in NSCLC, serving as valuable targeted therapies (Blumenschein et al., 2015). A range of agents targeting EGFR have emerged, such as gefitinib, erlotinib, cetuximab, and panitumumab (Blumenschein et al., 2015; Ferrer et al., 2018; Papadimitrakopoulou et al., 2016). Studies have demonstrated that the first-generation EGFR-TKIs, gefitinib and erlotinib, offer substantial benefits in terms of progression-free survival (PFS) compared to chemotherapy as first-line therapy (Gu et al., 2017). However, overall survival (OS) in advanced NSCLC patients remains largely unaffected by EGFR-TKI treatment after chemotherapy (Sun et al., 2018). Drug resistance typically develops in patients after 10–14 months of first-generation EGFR-TKI therapy (Xie et al., 2019). Mechanisms of drug resistance have been identified, including TK domain mutation (T790M), MET amplification, and RAS mutation (Kluge et al., 2011; Lai and Johnson, 2010). Among these mechanisms, TK domain mutation (T790M) is the most common acquired resistance mutation in NSCLC patients (Ono et al., 2013). Interestingly, some NSCLC patients with the T790M mutation have never undergone EGFR-TKI treatment, underscoring its potential as a target in NSCLC patients (Hu et al., 2016, 2014). Therefore, new approaches and therapies are needed to address drug resistance.

JAK–STAT pathways

The Signal Transducers and Activators of Transcription (STAT) protein family consists of seven distinct proteins, namely STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6, and STAT7, which activate various proteins by recruiting Janus kinases (JAKs). The JAK–STAT pathways are involved and activated in several solid tumors, including non-small cell lung cancer (NSCLC) (Lai and Johnson, 2010). These pathways play pivotal roles in cell differentiation, proliferation, and cancer progression. Among the STAT family members, STAT3 is the most extensively studied and has been implicated in malignancies of various types. In lung cancer, the STAT pathways regulate apoptotic genes, inhibit cell growth, and enhance the efficacy of EGFR-TKIs (Kluge et al., 2011). Reports have suggested that combining EGFR-TKIs or chemotherapy with JAK/STAT pathway inhibitors can enhance antitumor efficacy and reduce drug resistance in NSCLC (Chen et al., n.d.; Ono et al., 2013).

The potential of JAK/STAT pathway inhibitors in overcoming cisplatin resistance was investigated in NSCLC cell lines and tumor xenograft models. Studies demonstrated that a JAK2 inhibitor (ruxolitinib) impeded the growth of cisplatin-resistant H1299 cells and improved antitumor activity by inhibiting tumor growth and inducing caspase-3 expression in cisplatin-resistant tumor models (Hu et al., 2014)[44]. However, further research is necessary to fully evaluate the efficacy and safety of combination treatments with JAK2 inhibitors.

Additionally, Yibang Chen and collaborators explored the antitumor efficacy of combining a JAK-2 inhibitor (CYT387) with cetuximab in NSCLC models, both *in vitro* and *in vivo*. The results showed increased cellular toxicity when cetuximab was combined with CYT387 in resistant cell lines (H1975 and H1650). Furthermore, the combination of a JAK/STAT pathway inhibitor with cetuximab enhanced antitumor activity in resistant models. Thus, JAK–STAT pathway inhibitors have the potential to be a method for NSCLC therapy, either as standalone treatments or in combination with EGFR-TKIs [45].

Another study examined the role of Suppressor of Cytokine Signaling 3 (SOCS3) and miR-410 in regulating proliferation in NSCLC. SOCS3 negatively regulates the JAK–STAT pathways and was found to be decreased in NSCLC tissue compared to normal tissue. Treatment with anti-miR-410 and SOCS3 in lung cancer cells significantly reduced STAT3 phosphorylation. These findings suggest that miR-410 could potentially serve as a therapeutic target in NSCLC patients by regulating the JAK/STAT pathways. However, further studies and clinical trials are required to explore this potential in greater detail in the future. Another study investigated the potential role of miR-135 in NSCLC cells. Researchers discovered that miR-135 expression was elevated in NSCLC cells and that silencing miR-135 suppressed cell proliferation, invasion, and migration. Furthermore, inhibition of miR-135 upregulated TRIM16 expression through the JAK/STAT pathway, increasing sensitivity to gefitinib in NSCLC cell lines (Wang and Zhang, 2018) (Figure 6).

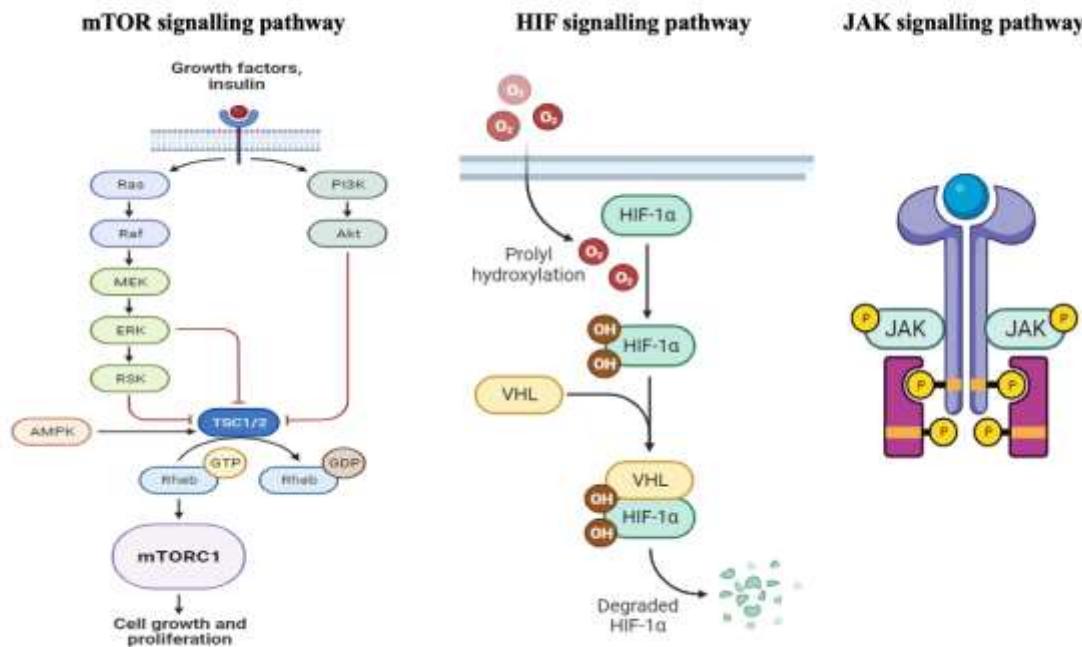


Figure 6: Signalling pathways for targeting Lung cancer

Medicinal plants in the treatment of lung cancer

Plant derived substances have played a crucial role in the treatment of cancer. Hartwell, in his publications, documented the existence of more than 3000 species possessing anticancer properties (Graham et al., 2000). The exploration of plant sources for anticancer agents began in the early 1950s over time, medicinal plants have been utilized as a precursor for creating new anti-cancer drugs with various structural characteristics in the field of synthetic, combinatorial and biotechnological sciences. Currently, more than 60% of the anticancer drugs in use are derived from natural sources and the healing properties of these plants are attributed to the presence of low molecular weight substances called secondary metabolites such as alkaloids, flavonoids, steroids and terpenoids (Cragg and Newman, 2005; Khan, 2014). These plant derived anticancer agents are known for their reduced side effects compared to the conventional chemotherapy drugs. Approximately two-third of cancer therapies are derived from plant bases sources categorized by their specific mechanism of action(Iqbal et al., 2017). A notable example is thymoquinone, a bioactive compound extracted from plants which acts as a reactive oxygen species inducer (Ahmad et al., 2017) (Table 1).

Brucea javanica, a plant belonging to the Simaroubaceae family, has demonstrated its anticarcinoma effects in addressing brain metastasis as a complication of lung cancer. The findings from this research revealed that when a combination of radiotherapy and intravenous (i.v.) injection of 10% *Brucea javanica* emulsion was administered, patients experienced notably extended median survival duration (15 months in the treatment group versus 10 months in the control group). Furthermore, the quality of life for these patients in the treatment group was significantly improved compared to those in the radiotherapy-only group (control). These results strongly indicate that the use of *Brucea javanica* emulsion in conjunction with radiotherapy has a synergistic effect in the treatment of brain metastasis occurring as a complication of lung cancer (Guo et al., 2022). Another study involving this herbal extract demonstrated that preoperative intravenous emulsion of 10% *Brucea javanica* oil may enhance the surgical treatment of non-small cell lung cancer (NSCLC) (Nie et al., 2012).

In studies related to antitumor activity in lung cancer models, the Celastraceae family was the most frequently mentioned, followed by the Araliaceae, Euphorbiaceae, and Fabaceae families. Among these, *Maytenus serrata* from the Celastraceae family exhibited antitumor activity in its fruit, root, and stem wood. Within the Araliaceae family, *Eleutherococcus senticosus* and *Panax ginseng* red type were the species evaluated. Among the four studies conducted on *P. ginseng* red type, one demonstrated its antitumor activity against lung adenoma induced by various carcinogenic agents. These studies on *P. ginseng* involved the use of the ethanol-insoluble fraction obtained from the fractionated water extract. The induction of tumors was achieved through a single subcutaneous (s.c.) injection of benzo[α]pyrene (BP), and treatment with *P. ginseng* significantly reduced the incidence of lung tumors. Investigations into the mechanisms of action revealed an increase in the proliferation

of splenocytes and the generation of activated killer cells in vitro, suggesting immunomodulatory effects (Yun et al., 1993).

Table 1: Medicinal plants for the treatment of Lung cancer
Plant derived anti-cancer agents in clinical use

Plant name	Plant part used	Mechanism of action	Reference
<i>Catharanthus roseus</i>	Whole plant	Microtubule depolymerization and mitotic spindle destabilization ultimately lead to cell cycle arrest and cell death	(Pham et al., 2020)
<i>Aplidium cyaneum</i>	Antarctic tunicate	Induction of apoptosis in cancer cells by activation of caspase. In addition, they also act by targeting the VEGF(Vascular endothelial growth factor) signal pathway and extracellular degradation of the matrix	(Olofinsan et al., 2023)
<i>Sanguinaria Canadensis</i>	Roots	Suppression of cell growth and induction of apoptosis by downregulating the JAK/STAT pathway. Moreover, it induces apoptosis through the production of reactive oxygen species (ROS)	(Xu et al., n.d.)
<i>Cananga odorata</i>	Barks	Blocking of G2 to M phase transition of the cell cycle and induction of caspase activation and apoptosis in human lung cancer cells	(Tan et al., 2015)
<i>Stephania tetrandra</i>	Roots	Suppress cell growth and induces apoptosis by inhibition of by activation of intercellular adhesion molecule-1 (ICAM-1)/hypoxia inducible factor (HIF)-1 α HIF-1 α /vascular endothelial growth factor (VEGF) pathways	(Li et al., 2023)
<i>Boerhaavia diffusa</i>	Whole plant	Inhibits the expression of matrix metalloproteinase-2 and vascular endothelial growth factor (VEGF), resulting in cell death	(Saraswati et al., 2013)
<i>Strychnos nux-vomica</i>	Seeds	Induce apoptosis by blocking G0/G1 phase of the cell cycle through downregulation of Cyclin D1 and Cyclin E expression. In addition, they cause cell death by inhibition of COX2 expression and release of Prostaglandin E2 (PGE2)	(Deng et al., 2006)

Vinca alkaloids represent one of the earliest classes of agents employed in the cancer treatment, which is the second most commonly utilized agents in clinical practice (Mann, 2002). These alkaloids are derived from *Catharanthus roseus* and have been widely used in the treatment of lung cancer. The primary vinca alkaloids are vincristine, vinblastine and vinflunine. They primarily bind to tubulin and disrupt the activity of microtubules, primarily those composing the mitotic spindle apparatus leading to the cell cycle arrest at the metaphase stage(Zhang and Kanakkanthara, 2020).

Taxanes represent a promising class of anticancer drugs originally derived from the Yew tree, they exert their anticancer effect by stabilizing the microtubules, leading to the cell cycle arrest and abnormal mitosis. Among them paclitaxel, a natural compound obtained from the bark and leaves of *Taxus brevifolia* and docetaxel, a semi synthetic derivative, are predominantly used in the treatment of lung cancer. Cabazitaxel, is a derivative of docetaxel that demonstrates cytotoxic activity against the tumors with less toxicity compared to the major one, also the compound has the ability to penetrate the blood brain barrier amongst all the other ones (Kotsakis et al., 2016; Oudard et al., 2017).

Resveratrol is a polyphenolic phytoalexin, specifically stilbenoid compound. numerous studies have provided evidence that resveratrol can inhibit the growth of lung cancer. Also, the compound has proven to show significant reduction in the tumor growth and the spread of lung cancer in mice with

highly metastatic Lewis lung carcinoma tumors. The mechanism of action is by the inhibition of DNA synthesis, blocking neovascularization and the suppression of angiogenesis(Ko et al., 2017).

Camptothecins is a quinolone alkaloid compound derived from *Camptotheca acuminata* which acts by complexing with type I DNA topoisomerase preventing the cleavage and relegation of DNA leading to a DNA break and cytotoxicity. Currently two synthetic drugs derived from the compound has been approved by FDA and the list are irinotecan and topotecan. Irinotecan is prescribed in the treatment of advanced cancer and topotecan is used in the treatment of recurring small cell lung cancer(Ardizzone, 1995).

Selenium nanomedicine

Selenium holds a prominent position among essential dietary supplements in the human diet. It plays a vital role in the synthesis of numerous antioxidant proteins, which act as effective scavengers of reactive oxygen species, including the important enzyme glutathione peroxidase. Consequently, selenium has garnered attention for its ability to counteract and provide resistance against various diseases triggered by oxidative stress, such as arthritis, tumors, as well as heart and brain disorders. Selenium nanoparticles (SeNPs) have emerged as promising nutritional supplements with distinct advantages, including enhanced degradability, reduced toxicity, and the capacity to be gradually eliminated from the body. SeNPs represent a unique form of selenium with remarkable prophylactic and therapeutic properties, featuring dual synergistic effects that involve delivering therapeutic cargo and enhancing anticancer activity. Recent investigations have extended the applications of nano-sized selenium to encompass a wide spectrum of biological activities, including their role as anticancer agents (Sakr et al., 2018) (Figure 7).

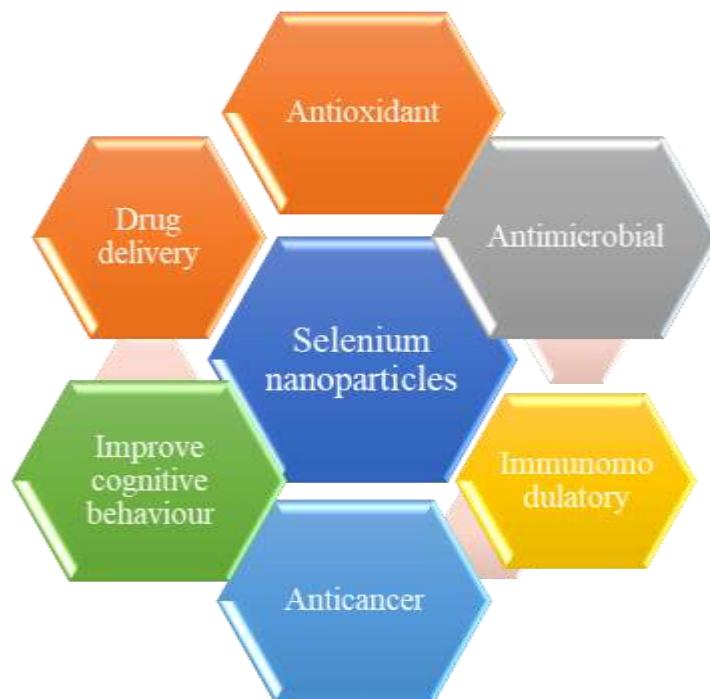


Figure 7: Biomedical applications of selenium nanoparticles

Inorganic selenium in lung cancer treatment

Initially, many early studies focused on inorganic selenium (Inorg-Se) and provided substantial evidence showcasing it's in vitro antitumor effects. Inorg-Se agents exhibit cytotoxic properties capable of directly eliminating cancer cells and restraining their abnormal growth (Selenius et al., 2008). Furthermore, Inorg-Se demonstrates the ability to promote the differentiation of cancer cells, potentially reducing tumor invasiveness and improving the prognosis for lung cancer patients (Xu et al., 2014). Additionally, Inorg-Se has been found to enhance the response to chemotherapy (Asfour et al., 2007) and reduce the systemic toxicity associated with cancer chemotherapeutic drugs (Ohkawa et al., 1988; Rao and Rao, 1998). Research has also indicated that Se not only counteracts renal and cardiac toxicity by elevating intracellular superoxide dismutase (SOD) and glutathione peroxidase (GPX) levels and activities, inhibiting peroxide-induced nuclear factor kappa beta (NF- κ B) activation, but also stimulates the production of immunoglobulins and antibodies, which can enhance the overall systemic immunity of patients (Baldew et al., 1991).

Overall, Inorg-Se stands out as a promising and cost-effective antitumor agent, as validated by laboratory studies. However, Inorg-Se needs to bind with organic ligands in the gastrointestinal tract

before it can be absorbed by the human body, and it can readily bind with vitamins within the body (Fernández-Martínez and Charlet, 2009). Due to various factors competing for organic ligands in the intestinal tract, the absorption rate, stability, and bioavailability of Se are relatively low (Pedrero and Madrid, 2009). Additionally, Inorg-Se possesses some level of toxicity, and excessive local overdose can lead to irreversible harm (Ye et al., 2021).

Hence, considering the potent antitumor efficacy of Se but the limited utilization of Inorg-Se, researchers have endeavoured to address the shortcomings of Inorg-Se by developing organic selenium (Org-Se) and selenium nanoparticles (SeNPs). For instance, Inorg-Se can undergo conversion to Org-Se through natural transformation (involving biochemical mechanisms in organisms like plants, animals, and microorganisms) and artificial synthesis (utilizing chemical methods) (Huang et al., 2020; Yang et al., 2020), while SeNPs are crafted using nanotechnology (Yan et al., 2018). Consequently, Se products characterized by lower toxicity and enhanced stability have been successfully synthesized.

Selenium nanoparticles (SeNPs) offer distinct advantages compared to other nanomaterials due to selenium's promising role in stabilizing the immune system and activating defense responses. The utilization of SeNPs and their supplements not only holds pharmacological significance but also primes the body's immune system to effectively combat pathogens. The phyto-synthesis of SeNPs yields nanomaterials of diverse sizes, shapes, and biochemical characteristics, and it offers advantages over conventional physical and chemical methods owing to its biocompatible, eco-friendly nature and *in vivo* actions. Moreover, certain selenium-based drug delivery systems have been developed by engineering SeNPs with functional ligands to facilitate targeted drug delivery (Hosnedlova et al., 2018).

Organic Selenium in Lung Cancer Treatment

Organic selenium (Org-Se) can be easily stored in tissues, absorbed, and rapidly utilized by the human body after absorption. Studies have demonstrated its association with various cell death pathways, such as cell cycle arrest, autophagy, apoptosis, and necrocytosis, indicating its potential in anticancer applications. One well-known Org-Se compound, ebselen, possesses antioxidant and anti-inflammatory properties and acts as a GPX mimetic and peroxynitrite scavenger. Ebselen inhibits thioredoxin activity in tumor cells, regulates downstream pathways, and induces tumor cell apoptosis, contributing to its antitumor effects (Chen et al., 2019). Additionally, Org-Se, similar to inorganic selenium (Inorg-Se), can reduce the systemic toxicity of cancer chemotherapeutic drugs (Hu et al., 1997).

Current research in our group primarily focuses on antitumor targets and mechanisms related to Org-Se. New targets have been identified through chemical biology techniques, confirming the interactions among p53, Org-Se, and TrxR targets. Furthermore, the sensitizing effect of Org-Se on radiation therapy (RT) and chemotherapy has been extensively evaluated, providing valuable insights into its anticancer effects (Liang et al., 2014).

Org-Se primarily exists as selenomethionine, which participates in protein synthesis and is easily stored, absorbed, and utilized in tissues. Compared to Inorg-Se, Org-Se exhibits reduced toxicity and better biocompatibility, although challenges such as potential systemic toxicity persist. Research suggests that both forms have sub chronic toxic effects, and although Org-Se production is complex and costly, efforts are being made to enhance its safety and potency (Cruz et al., 2019). Nanotechnology offers a solution by enabling the preparation of nanosized Org-Se, reducing toxicity, and enhancing its safety. Consequently, virtually nontoxic, and highly potent selenium nanoparticles (SeNPs) have emerged in the medical field, becoming a promising area of research in cancer treatment (Nonsuwan et al., 2018).

Nanoparticle Composites For Lung Cancer Treatment

Nanocomposite materials consist of minuscule inorganic particles, metals, semiconductors, rigid particles, and the like, all of which are produced through appropriate fabrication methods. Recent studies have revealed that nanocomposites, including selenium (Se) nanocomposites, hold potential in medical applications, particularly in the context of cancer treatment (Feldman, 2016). Se nanoparticles (SeNPs) possess distinctive attributes, and when used as therapeutic agents, they exhibit excellent tissue penetration while causing minimal harm to the body.

Some of the Se nanocomposites currently under investigation encompass porous Se@SiO₂ nanocomposites, Cu₂-XSe nanocrystals coated with silica and transformed into Se quantum dots, and PVP-etched structures (Liu et al., 2016). These nanocomposites effectively hinder the proliferation of cancer cells through a mechanism mediated by reactive oxygen species (ROS). Another noteworthy

example is the Au@Se core-shell nanostructure, synthesized through a seed-mediated approach involving the formation and conjugation of Se shells onto gold nanorods (Au NRs) (Chang et al., 2017). When combined with X-ray therapy, Au NRs can induce cell apoptosis by influencing the expression of p53 and genes associated with DNA damage, thereby triggering an excessive production of intracellular ROS and significantly enhancing their anticancer efficacy.

Se dioxide (SeO₂) nanoparticles and Se dioxide/titanium dioxide nanocomposites (Se/Ti (I), (II), and (III)) have also demonstrated potential in cancer treatment (Ahmed et al., 2019). These nanocomposites are biologically safe due to their controlled release of Se, ensuring a favorable therapeutic effect while minimizing toxicity (Liu et al., 2016). The outlook for the successful application of these nanocomposites in medical contexts appears highly promising.

2. Conclusion

Innovations in lung cancer diagnosis detection, imaging and treatment using nanoparticle (np) based medicine are infinite. Understanding tumour biology, the microenvironment and malignant cell NP interactions is essential to developing specific medication delivery techniques for tumour and lung metastases. However, *in vivo* toxicity and biological distribution of NPs are important because many are still in pre-clinical stages and challenging to produce with varied functions and uniform size distribution for improved performance. Nanotechnology must be reproducible, simple to prepare, low cost and exceptional functional and structural features. This review briefly highlights the findings in this sector and can help us understand the huge potential for treating lung cancer patients with precise medicine in the future.

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