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SILICA-BASED NANOPARTICLES IN LUNG CANCER THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF ANTITUMOUR, IMMUNOMODULATORY AND TRANSLATIONAL OUTCOME

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ABSTRACT

Background: Lung cancer remains the deadliest of all cancers worldwide, largely due to delayed diagnosis, fading treatment power, or harsh reactions from modern drugs. Instead of grand promises, silicon-based delivery systems – like mesoporous silica nanoparticles and porous silicon particles – are gaining attention for their ability to target tumours without harming surrounding cells. What sets them apart isn't mere transport – they alter how therapies engage with biological environments, quietly merging therapeutic action with monitoring potential. Progress continues in understanding how these carriers influence cell-level behaviour, where accuracy defines outcomes.

Objective: This review and meta-analysis aim to understand how silicon nanoparticles affect lung cancer by diving into lab-based research. Not limited to tumour responses, attention spreads towards changes in immune activity triggered by the particles. Tracking where these tiny substances travel inside organisms forms another layer, relying on evidence gathered from animals. Alongside benefits, possible risks emerge - especially around toxicity and buildup in tissues. Practical relevance isn't ignored; hints at future applicability surface quietly across the findings. Interpretation stays close to experimental outcomes without assuming immediate clinical leaps.

Method: A sweep through academic databases - PubMed, Scopus, Web of Science, Embase and Cochrane – took place, targeting work on silicon nanoparticle applications in lung cancer, spanning 2015 to 2025. Studies done in lab settings or animal models cut if they focused on those nanoparticles. Cell death rates, tumour growth control, shifts in oxidative stress markers and lifespan changes stood as central points of interest. For pooling results, random-effects modelling came into play, relying on Hedges'g when comparing averages, alongside hazard ratios wherever possible. Evaluation of study reliability drew from SYRCLE's tool, Cochrane's version 2.0 risk-of-bias framework, plus modified benchmarks suited to cell-level experiments.

Results: Out of thirty studies fitting the selection rules, just a tenth contributed numbers for pooled analysis. Treatments built on silicon nanoparticles strongly boosted cell death – effect size at 5.31, confidence interval stretching from 3.27 to 7.35 – and curbed tumour growth even more so, hitting 7.38 (CI: 3.12-11.64). Responses linked to oxidative stress and lifespan varied widely, shaped heavily by how each formula was put together. When tweaked chemically, these particles showed promise: they tamed immune reactions, reached specific tissues without spreading harmfully through the body, and broke down safely into orthosilicic acid, while showing lower overall damage to healthy systems. Still, flaws in the trial design and signs of exaggerated results from smaller reports surfaced repeatedly throughout the available research.

Conclusion: Still, the path from lab results to real-world use isn't straightforward – SiNPs show notable activity against tumours while influencing immune responses in early lung cancer tests. Their safety record looks acceptable; imaging and treatment functions combine well within one platform. Yet consistency across experiments remains uneven. Without uniform methods, drawing firm conclusions gets harder. Progress demands more rigorous, repeatable research before these particles can move into human trials.

KEYWORDS

Lung cancer, Meta-analysis, Tumours and Translational outcome.

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INTRODUCTION

Impact Statement

This thesis on silica-based nanoparticles (SiNPs) in lung cancer treatment is of great importance in several fields, including scientific research, medical practice, healthcare and population health. This

paper has demonstrated that the application of SiNPs holds immense potential in the treatment of tumours, the regulation of immune responses, and the preservation of favourable safety profiles and theranostic potential, which can be achieved through the future transplantation of such vectors.

Potential Beneficiaries

Nanotechnology Developers and Biomedical Researchers

Such findings will have a better implication for nanotechnology designers and biomedical researchers on how SiNPs can be programmed to realise their optimal therapeutic and diagnostic properties. The findings provide insight into the rational optimisation of particle size, porosity, and surface chemistry, thereby balancing efficacy and safety to establish effective nanomedicine platforms.

Pharmaceutical and Biotechnology Industries

Due to the potential commercialisation of SiNP-based formulations, these companies could utilise SiNPs as part of regimens with existing chemotherapeutic agents or immunotherapies, which may reduce the time to market products and enhance the competitiveness of the cancer market.

Health Providers and Patients

Healthcare providers and patients are ultimately the beneficiaries, as the creation of SiNP-based therapies can offer safer and more effective treatments, reduced systemic toxicity, improved tumour targeting, and enhanced monitoring with theranostic applications.

Policy Makers/Public Health Organisations

This evidence base can be leveraged to inform regulatory frameworks and guide investment in nanotechnology, thereby clarifying its direction towards the strategic objectives of enhancing cancer management and reducing the treatment burden.

Economic and Societal Benefit

Still, in an economic aspect, the application of SiNPs in treating lung cancer may, through its effectiveness in treatment, reduce the overall cost of health care by decreasing the rate of hospitalisation due to the drug toxicity. SiNPs could be used to make tumours more selective, which could reduce the dose of chemotherapy, decrease adverse events and reduce healthcare costs. This would also be beneficial to the pharmaceutical and biotechnology industries, as the new markets generated through the production of nanomedicine-based products are likely to create jobs, investments and long-term economic growth. At the societal level, lung cancer has been one of the significant causes of death globally and the possibility of SiNPs to enhance therapeutic outcomes is far-reaching. The impact on public health would be increased survival, decreased metastasis, and improved quality of life among the patients, which would reduce morbidity and mortality caused by cancer. Moreover, nanomedicine platforms facilitate the creation of global research partnerships, promote precision medicine, and help build confidence in the population to trust biomedical innovation.

Impact Pathway

The route to research impact is a straight line. Such outcomes are scientifically based to support future preclinical and translational research in the near future, especially to optimise nanoparticle formulations and routes of delivery. Biomedical scientists and developers can use this information and optimise SiNP systems to reach clinical readiness. The pharmaceutical and biotechnology industries can apply the findings in the medium term to conduct clinical tests, which are supported by regulatory bodies and public health organisations that have identified the potential of nanomedicine to meet the unmet needs of lung cancer. A successful translation into clinical practice can yield a significant long-term impact on patients, leading to safer, more focused, and effective therapies. Additional implementation would aid in reducing healthcare expenses, improving the economy, and increasing national and international cancer control programs.

Overall, this study demonstrates that SiNPs have transformative potential in treating lung cancer and could have direct beneficial effects on patients, the industry, and population health. These nanoparticles can transform the frontier of precision oncology due to their rational design, stringent testing and successful translation, which will not only improve economic growth but also benefit society.

Burden of Lung Cancer and Treatment Gaps

Lung cancer is the most frequent cause of cancer-related deaths and every year, there are approximately 2.2 million new cases, with most of

the deaths occurring in 1.8 million cases (Liu *et al*, 2023)[1]. NSCLC is present in 85% of cases and SCLC is present in 15% (Sabir *et al*, 2021[2], Youngren-Ortiz and Chougule, 2017[3]). The overall five-year survival rate is less than 20% despite multimodal treatment approaches, primarily due to late diagnosis, a high tendency to metastasise and tumour heterogeneity (Doroudian *et al*, 2021[4], Radhakrishnan *et al*, 2022[5]). The existing diagnostics, including CT scans and biopsies, are not effective in detecting tumours early enough, resulting in a delay in treatment (Rastogi *et al*, 2022)[6]. Traditional treatments also have a limited ability to target tumours, are systemically toxic and resistant to multiple drugs (Shen *et al*, 2016[7], Madni *et al*, 2017[8]). Although these targeted agents, such as EGFR and ALK, and immunotherapy, including checkpoint inhibitors, have greater efficacy, recurrence, resistance and immune-related toxicity limit their effectiveness (Wang *et al*, 2016[9], Huang *et al*, 2016[10], Yin *et al*, 2021[11]). These challenges underscore the need for innovative solutions that can integrate early detection, tumour-specific treatment and multimodal therapy to enhance survival rates (Dhingra *et al*, 2024[12], Reczynska *et al*, 2020[13], Vanni *et al*, 2017[14]).

Why Silicon/Mesoporous Silica Nanoparticles (MSNs)?

Silicon nanoparticles (mostly mesoporous silica nanoparticles (MSNs) and porous silicon nanoparticles (PSiNPs) are becoming an attractive method to deliver treatments to lung cancer. They can be readily engineered to possess customizable surface chemistry and a high surface area, which confers greater stability, longer circulation and better tumour penetration compared to conventional systems (Satyapal Rangaraj and Rajendran, 2017[15], Madni *et al*, 2017[8], Vanni *et al*, 2017[14]). Its primary advantage is that the SiNPs dissolve into non-toxic orthosilicic acid, which mitigates the issue of accumulation (Dhingra *et al*, 2024[12], Liu *et al*, 2023[1]). They can be functionalised to include targeting ligands, achieving greater tumour specificity of MSNs, such as cetuximab-modified MSNs targeting EGFR-mutant NSCLC (Pan and Shi, 2018[16], Wang *et al*, 2016[17]). Additionally, MSNs enable the release of drugs in response to tumour-related conditions as a reaction to stimuli (Tamarov *et al*, 2016[18], Vanni *et al*, 2017[14], Zhang *et al*, 2021[19]).

Along with drug delivery, MSNs and PSiNPs may also be used in theranostic therapy, and both treatment and imaging approaches, such as MRI and PET, can also be applied to monitor the distribution and effects in real-time (Srivastava *et al*, 2018[20], Yong *et al*, 2019[21], Reczynska *et al*, 2020[13]). Their bioreactivity improves the delivery properties of insoluble drugs in lung cancer therapy and silicon nanocarrier provides an important platform to improve therapeutic outcomes (Radhakrishnan *et al*, 2022[5], Rastogi *et al*, 2022[5], Wang, Makila *et al*, 2015[22], Wang Sarparanta *et al*, 2015)[17].

Therapeutic Modalities Enabled by SiNPs

Drug Delivery/Co-Delivery

Silicon nanoparticles, and in particular, MSNs, are an excellent platform for applying controlled and targeted drug delivery due to their ability to control pore size, surface area and the ease of surface modification. They are capable of loading hydrophobic or hydrophilic chemotherapeutics and delivering them in a controlled or stimulus-responsive manner to minimise systemic toxicity and maximise tumour accumulation (Madni *et al*, 2017[8], Doroudian *et al*, 2021[4]). Co-delivery systems also enhance efficacy, as evidenced by MSNs concomitantly loading chemotherapeutics with siRNA/miRNA to overcome multidrug resistance and provide synergistic cytotoxicity (Satyapal Rangaraj and Rajendran, 2017[15], Dilnawaz and Sahoo, 2018[23]). In particular, anticancer activity can be improved through the incorporation of nuclear-targeted MSNs, which transport doxorubicin to the nucleus, thereby eliminating the need for efflux pumps (Pan and Shi, 2018[16], Wang, Makila, *et al*, 2015[22], Wang, Sarparanta *et al*, 2015[17]).

Immunotherapy/Immunomodulation

SiNPs are used in gene-based therapy and immune-modulating therapy because they help to stabilise and deliver siRNA and miRNA molecules to reprogram tumour signalling pathways. It was found that miR-200c repurified functionalised MSNs silenced oncogenes and prevented tumour growth and metastasis by delivering siPlk1 and miR-200c (Liu *et al*, 2023[1], Wathoni *et al*, 2022[24], Dilnawaz *et al*, 2018[23]). In addition to gene therapy, he/she can adopt the use of adjuvant vectors, such

as SiNPs, which entail loading immunostimulators or tumour-related antigens that elicit the activation of dendritic cells and T-cells. This broadens the prospects of MSNs in combination regimens, which involve chemotherapy and immune checkpoint inhibition (or cancer vaccines) to enhance the durability of response (Radhakrishnan *et al*, 2022[5], Wang *et al*, 2020[25]).

Theranostic/Stimuli-Responsive Platforms

An outstanding strength of silicon nanocarriers is their versatility for use in theranostics (combination therapy and diagnostics) in a single platform. It is used in magnetic hyperthermia with hybrid constructs, including silica-coated superparamagnetic iron oxide nanoparticles (SPIONs), where it is possible to use alternating magnetic fields to generate local heat and kill cancer cells, or in MRI contrast (Wang *et al*, 2016[17], Srivastava *et al*, 2018[20], Yin *et al*, 2021[11]). MSNs have also been conjugated with photosensitizers and sonosensitizers in photodynamic therapy (PDT) and sonodynamic therapy (SDT), which involve using reactive oxygen species (ROS) to kill tumour cells selectively (Zhang *et al*, 202[19], Lee *et al*, 2020[26], Srivastava *et al*, 2018[20]). Furthermore, lung-modified MSNs have also demonstrated potential in treating lung cancer locally, with a high local deposition potential and the ability to monitor and image without requiring any invasive procedures (Sally Yunsun Kim *et al*, 2015[27], Radhakrishnan *et al*, 2022[5], Srivastava *et al*, 2018[20]).

Safety, Biocompatibility and Biodegradation

Silicon-based nanoparticles (SiNPs) can be utilised in the medical sector due to their biodegradability, biocompatibility and safety. MSNs and PSiNPs degrade into an organic molecule named orthosilicic acid, which is excreted into the urine and does not accumulate over an extended time (Dhingra *et al*, 2024[12], Liu *et al*, 2023[1]). The *in vivo* literature suggests that therapeutic doses do not cause significant systemic toxicity and have minimal effects on haematological or biochemical parameters (Doroudian *et al*, 2021[4], Radhakrishnan *et al*, 2022[5]). The functionalisation of surfaces enhances hemocompatibility, decreases inflammation, and PEGylation extends circulation and lowers immune clearance (Shen *et al*, 2016[7], Reczynska *et al*, 2020[13]). The size, porosity and surface charge of nanoparticles affect their toxicity, and in high doses, oxidative stress is induced with smaller or highly charged particles (Lee *et al*, 2020)[26]. Nonetheless, optimised formulations exhibited high tolerability, clearance and reduced organ toxicity in preclinical models of lung cancer (Wang *et al*, 2016[17], Sally Yunsun Kim *et al*, 2015[27]). Overall, rationally engineered SiNPs have good safety, biocompatibility and biodegradability qualities, thus warranting their application as a therapeutic and theranostic platform.

Knowledge Gaps and Rationale

Silicon nanoparticles (SiNPs) are very promising in lung cancer treatment because they can be easily loaded with drugs, release them at a controlled rate and target the tumour. Their preclinical studies indicate that they can be applied in drug delivery, immunomodulation and theranostics; however, they have also revealed significant gaps that limit their translation to clinical applications. This compound has not been well-characterised in terms of its toxicity, biodistribution and long-term elimination in humans (Dhingra *et al*, 2024[12], Lee *et al*, 2020[26]). The unstable size of particles, porosity and surface chemistry also result in inconsistent safety profiles, which necessitate standard evaluation (Shen *et al*, 2016[7], Radhakrishnan *et al*, 2022[5]). However, SiNPs have remained relatively underdeveloped compared to known platforms of nanoparticles and have been slow to transition into clinical trials (Dilnawaz and Sahoo, 2018[23], Liu *et al*, 2023[1], Madni *et al*, 2017[8], Yong *et al*, 2019[21]). Combination Theranostic imaging and therapy systems are struggling to strike a balance between the sensitivity of imaging and the effectiveness of the therapeutic payload, with little clinical usefulness demonstrated (Wang *et al*, 2016[17], Srivastava *et al*, 2018[20], Reczyńska *et al*, 2020[13]). Additionally, the communication between the tumour microenvironment, immune system, and biological barriers, including mucus and alveolar clearance, is not well understood (Kim *et al*, 2015[27], Radhakrishnan *et al*[5], 2022, Nayl *et al*, 2022[28]). The importance of filling these gaps lies in the fact that lung cancer is the most common cancer that causes deaths. SiNPs, due to their biocompatibility, multifunctionality and potential for targeted

multimodal therapy, should be evaluated systematically for future clinical translation.

Research Questions

How effective is the therapeutic ability of silicon-based nanoparticles (SiNPs), such as mesoporous silica nanoparticles (MSNs) and porous silicon nanoparticles (PSiNPs), in preclinical models of lung cancer?

What are the advantages of SiNP-based platforms compared to traditional therapies in terms of drug delivery, co-delivery, immunomodulation, and theranostic applications?

What are the safety, biocompatibility, and biodegradation of SiNPs in the in vitro and in vivo models?

What is the impact of particle size, porosity, functionalisation, route of administration, etc., on the performance and toxicity of the SiNPs used in the treatment of lung cancer?

What is still lacking between the preclinical research and its translation into clinical practice in the treatment of lung cancer?

Aim and Objectives

Aim

To assess the therapeutic potential, safety and translational applicability of silicon-based nanoparticles (SiNPs) in the treatment of lung cancer by synthesising preclinical evidence.

Objectives

To determine and compile existing preclinical research that could establish therapeutic and theranostic combinations using SiNPs in the treatment of lung cancer.

To compare the SiNP platforms (MSNs, PSiNPs, SBA-15, amorphous/biogenic silica, and hybrids) with the conventional or free-drug controls on their efficacy and safety outcomes.

To determine therapeutic endpoints, such as apoptosis, ROS production, tumour inhibition, metastatic burden, and survival, in various models.

To assess the immunomodulatory, biodistribution, and biodegradation effects of SiNPs in administration.

To evaluate the risk of bias and the quality of the methods used in the included studies, and to determine the strengths and weaknesses of the experimental design.

To bring out the translational gaps and suggest future research directions in the area of clinical applications of SiNPs in the management of lung cancer.

METHODS

Design and Reporting

A systematic review and meta-analysis were conducted on silicon-based nanoparticles (SiNPs), including mesoporous silica nanoparticles (MSNs) and porous silicon nanoparticles (PSiNPs), in models of lung cancer. The protocol and analysis plan included eligibility criteria, outcomes, and subgroups, reported in a modified PRISMA format suitable for cell and animal studies. Key study designs featured drug-loaded MSNs for EGFR-mutant NSCLC, exosome-coated PSiNP theranostics, inhalable SBA-15 nanocomposites for lung metastases, and externally targeted PSi platforms with survival outcomes (Wang *et al*, 2016[17], Yong *et al*, 2019[21], Su *et al*, 2019[29], Tamarov *et al*, 2016[18]).

Information Sources

An extensive literature search was conducted in PubMed, Scopus, Web of Science, Embase, and Cochrane Library, as well as grey literature and clinical trial registries. This included in vitro lung cancer cell models (e.g., A549, PC9/PC9-DR) and in vivo murine or zebrafish models focusing on efficacy and immunomodulation (apoptosis, ROS, tumour growth, survival, cytokines). Examples included PC9-DR xenografts with cetuximab-capped MSNs and inhaled SBA-15 curcumin in B16F10 lung metastasis (Tamarov *et al*, 2016[18], Wang *et al*, 2016[17], Su *et al*, 2019[29], Lee *et al*, 2020[26]).

Search Strategy

The Boolean strategy used in the proposal was retained, with the replacement of disease/particle terms with a new scope. A representative PubMed string was:

("Lung Neoplasms" OR "Lung Cancer" OR "Lung Neoplasm" OR "Lung Carcinoma" OR "NSCLC" OR "Non-small cell lung" OR "SCLC" OR "Small cell lung cancer" OR "Pulmonary neoplasm") AND ("Silicon-based nanoparticle" OR "Nanoporous silica" OR "Silica nanoparticles" OR "SiNPs" OR "Silicon dioxide" OR "SiO_2" OR "Mesoporous

silica" OR "Mesoporous silica nanoparticle" OR "Mesoporous Silicon" OR "MSN" OR "MSNs" OR "Porous silicon" OR "PSi" OR "PSiNP" "SBA-15" OR "MCM-41") AND

("Drug delivery" OR "Targeted therapy" OR "Drug resistance" OR "Toxicity" OR "Therapeutic efficacy" OR "Immunomodulation" OR "Cytokine" OR "Immune response")

Any database was searched using the same logic (with appropriate field tags and truncations), without date restrictions, within the 2015-2025 window. Only literature with adequate methodology and quality of data (e.g., theses) and preprints was included.

Study Selection

All retrieved records were de-duplicated using a reference manager (EndNote/Zotero) and then uploaded to a systematic review platform for screening. Two reviewers independently evaluated titles and abstracts and the potentially relevant articles were moved to full-text evaluation. Differences were solved by discussing or consulting with a third reviewer. A PRISMA 2020 flow chart diagram (Figure No.1) was used to document and summarise the general selection process, specifying the number of studies found, screened, excluded and included.

Eligibility Criteria

Inclusion criteria included: (i) peer-reviewed articles published between January 2015 and June 2025, (ii) the research was on lung cancer models (*in vitro*, *in vivo* or clinical), (iii) the intervention used silica nanoparticles (SiNPs) or mesoporous silica nanoparticles (MSNs) or similar nanocarriers (PSi/SBA-15/SiO_2) to carry out treatment or diagnosis, and (iv) the results were at least one extractable endpoint, including apoptosis, ROS, tumour volume/inhibition (or metastatic burden), or time-to-event survival and when accessible, cytokines/immune readouts.

Exclusion criteria included non-peer-reviewed publications, articles outside the 10-year time range, non-English publications and studies unrelated to lung cancer or silica-based nanocarriers, as well as editorials, letters, and conference abstracts that did not contain complete reports. It ensured the rigour of the methodology and reduced bias, focusing on the most recent and clinically applicable evidence (Tamarov *et al*, 2016[18], Wang *et al*, 2016[17], Su *et al*, 2019[29], Lee *et al*, 2020[26]).

Data Extraction

A piloted, standardised extraction form captured by PICO framework:

Population (P): Preclinical lung cancer models, such as cell lines of human lungs (*in vitro*, e.g., A549, PC9, PC9-DR, BEAS-2B) and animal models (murine xenografts, syngeneic lung carcinoma, B16F10 lung-metastasis and zebrafish embryos).

Intervention (I): SiNPs or MSNs, PSiNPs, SBA-15, biogenic/amorphous silica, and silica-coated hybrids (as silicon-based nanoparticles) found applications in drug/co-delivery, theranostics, stimuli-responsive release, and inhalable/local delivery routes.

Comparator (C): Control groups, Vehicles or untreated vehicles, free formulations of drugs (e.g., curcumin API, standard cisplatin, gefitinib), and in the conventional delivery systems, the delivery system is not functionalised by using SiNP.

Outcomes: Primary outcomes: Apoptosis, ROS formation, tumour inhibition/volume change, and secondary and exploratory outcomes: Immunomodulation, biodistribution, toxicity, and biodegradation, theranostics efficacy, co-delivery synergy and safety/efficacy of biogenic or ultrafine silica system.

Variables were selected to guarantee meta-analytic coherence and mechanistic delineation. Extracted examples from previous nano-lung studies guided field selection (Tamarov *et al*, 2016[18], Wang *et al*, 2016[17], Su *et al*, 2019[29], Lee *et al*, 2020[26]). When data were absent or ambiguous, corresponding authors were consulted (if time allowed). Two reviewers independently performed the extraction and any discrepancies were resolved through mutual agreement.

Effect Measures and Synthesis

The continuous outcomes (apoptosis, ROS, tumour inhibition, survival) were compared using standardised mean differences (Hedges g, 95% CI), correlated with small samples. The results were presented as hazard ratios (HRs), which were calculated based on the same scale, using log (HR) and survival effects (SE) and then exponentiated. The estimates, confidence intervals (CIs), number of comparisons (k), between-study variance (τ^2) and

heterogeneity (I^2) were reported using random-effects models (DerSimonian-Laird tau^2) with inverse-variance weighting. Funnel plots and the Egger regression were used to evaluate the presence of publication bias when 10 or more studies were not present.

Subgroup analyses clustered the results based on model (*in vitro* and *in vivo*), payload (drug-loaded and bare MSN) and design (targeted and non-targeted MSN). The sensitivity tests used are leave-one-out tests to determine robustness and heterogeneity (I^2). If $k \geq 10$, small-study bias was tested; otherwise, descriptive funnels were used. Exploratory meta-regressions examined particle size, ligand targeting and external stimuli as key predictors of treatment response across various nanoparticle platforms.

Risk of Bias/Quality Assessment

Cochrane RoB 2.0 was used to evaluate randomised controlled trials, the Newcastle-Ottawa scale was used to evaluate observational studies, and SYRCLE was used to evaluate animal studies, based on randomisation, blinding and reporting. The reproducibility, dose and controls were used in evaluating *in vitro* studies. Studies were evaluated by two reviewers who reached consensus in areas of disagreement with third-party involvement. The funnel plot and Egger regression, where possible, were used to investigate publication bias, ensuring methodological rigour in all types of studies.

Ethics and Registrations

The review relies on published, secondary data; no human or animal experimentation was done. The work can thus be classified as low-risk according to institutional guidelines. The original proposal obtained ethical approval, and all procedures conducted here are in line with this approval. Registration of a protocol (e.g., PROSPERO/OSF) was also taken into account; the number of registrations will be reported if it is done. Otherwise, the entire protocol is revealed in the dissertation appendices.

Project Reference Number: P185374

Deviations

Any deviations of the pre-specified protocol (e.g., the extra subgroups requested by examiners, the altered inclusion cut-off dates depending on the data yield) were recorded, explained and reported in the Methods to maintain transparency. Post hoc switching of outcomes was not performed.

RESULTS AND DISCUSSION

Study Selection

PubMed, Scopus, Web of Science, Embase and the Cochrane Library were searched, yielding 1,250 records. An additional 120 records were included as grey literature and trial registry records (i.e., Google Scholar, ClinicalTrials.gov and the EU Clinical Trials Register). Following de-duplication, 1,100 records had survived; 820 were removed at the title/abstract stage and 280 full texts were evaluated. Among these, 250 were eliminated due to a lack of relevance, unsuitable interventions, inadequate outcomes, or duplication. Ultimately, 30 studies were included in the qualitative synthesis and 10 of these provided sufficiently harmonised data for the quantitative meta-analysis. The study selection process was conducted in accordance with the PRISMA 2020 guideline.

The figure illustrates the systematic review screening process, beginning with the database search and proceeding through the eligibility check, resulting in a total of 30 studies to undergo qualitative synthesis and 10 meta-analyses.

This strict filtering, combined with the requirement that only studies providing strong and interpretable data on the therapeutic efficacy, immune modulation, toxicity and biodistribution of silica-based nanoparticles in the lung cancer setting were retained, led to the synthesis and analysis of these studies.

Study Characteristics

This review is a comprehensive literature review of 30 preclinical studies examining silicon-based nanoparticles (SiNPs) (MSNs, PSi, SBA-15 and amorphous/biogenic silica) as therapeutic and theranostic agents in lung cancer. Ten studies were used to present similar information and conduct a meta-analysis of the outcomes of apoptosis, ROS, tumour suppression and survival. The most notable ones included hinokitiol-loaded calcium silicate (Shen *et al*, 2016[7]), thermo-responsive PSi (Tamarov *et al*, 2016[18]), exosome-based carriers (Yong *et al*, 2019[21]), cetuximab-modified MSNs (Wang *et al*, 2015, 2016)[17,22], co-delivery MSNs (Dilnawaz and Sahoo, 2018[23]), inhalable SBA-15

composites (Su *et al*, 2019)[29], ultrafine SiO_2 (Lee *et al*, 2020[26]), biogenic silica (Satyapal Rangaraj and Venkatachalam, 2018[15]) and anthraquinone-doped SiO_2 (Custodio *et al*, 2016)[30].

These selectivity and safety aspects were mainly studied *in vitro* on cell lines of NSCLC (A549, PC9/PC9-DR) and non-cancerous BEAS-2B cells (Shen *et al*, 2016[7], Lee *et al*, 2020[26]). Toxicity *in vivo* was investigated using xenografts, syngeneic Lewis lung carcinoma, B16F10 lung metastasis, and zebrafish (Tamarov *et al*, 2016[18], Su *et al*, 2019[29], Satyapal Rangaraj and Venkatachalam, 2018[15]). The vehicle, untreated controls, or free-drug arms were typically used as comparators, allowing for the direct measurement of the added value of the SiNP delivery systems against traditional formulations (Su *et al*, 2019[29], Wang *et al*, 2016[17]).

Customisable tunable cores (~ 50-200nm) and pore sizes (≈ 2-10nm) were utilised for loading, co-loading, or releasing drugs in response to stimuli in MSNs and PSi. Some of them are hinokitiol-loaded calcium silicate NPs (Shen *et al*, 2016)[7], cetuximab-capped MSNs in EGFR-mutant NSCLC (Wang *et al*, 2016)[17], siRNA-drug co-loaded MSNs (Dilnawaz *et al*, 2018)[23] and thermo-responsive PSi triggered by IR/RF (Tamarov *et al*, 2016)[18]. Others encompassed inhalable curcumin-SBA-15 (Su *et al*, 2019)[29], exosome-based carriers (Yong *et al*, 2019)[21], anthraquinone-doped SiO_2 to generate ROS (Custodio *et al*, 2016)[30], ultrafine amorphous SiO_2 to induce PI3K-AKT- ER stress apoptosis (Lee *et al*, 2020)[26] and biogenic silica that was utilised in A549 and zebrafish, which informed efficacy-toxicity balance (Satyapal Rangaraj and Venkatachalam, 2018)[15].

A systemic (IV) system was employed in targeted MSNs and select PSi designs, whereas SBA-15 composites were administered via inhalation/intratracheal routes to target the drug in pulmonary tissue (Su *et al*, 2019)[29]. The intratumoral dosing was also used in externally triggered PSi procedures to focus heating/release (Tamarov *et al*, 2016)[18]. Dosing was performed in a single exposure (triggered systems) and a multi-dose course (drug-loaded MSNs), with 24-72h of *in vitro* and 2-4 weeks of in vivo follow-up, based on *in vitro* and *in vivo* efficacy/survival, respectively.

Apoptosis (Annexin V/PI, TUNEL), ROS (DCF), caspase-3/7, mitochondrial depolarisation, tumour growth/volume, or the number of metastases, as well as overall survival (HRs or Kaplan-Meier), were the types of therapeutic readouts. There were inconsistent reports of immunomodulatory endpoints (e.g., TNF-α, IL-6 and IL-8) and histology (Ki-67 and cleaved caspase-3) (Su *et al*, 2019[29], Wang *et al*, 2016[17]). The safety assessments included hemolysis, normal lung cell viability (BEAS-2B), body weight/clinical signs, as well as biodegradation/clearance notes (Lee *et al*, 2020[26], Su *et al*, 2019[29]).

The ten studies offered extractable data (Mean/SD/N or HR with 95% CI) to be used in pooled SMD and HR meta-analysis to conduct subgroup analyses based on model (*in vitro* vs. *in vivo*) and payload (drug-loaded vs. bare) (Tamarov *et al*, 2016[18], Wang *et al*, 2016[17], Su *et al*, 2019[29]). The quality of reporting was not uniform, and randomisation or blinding were not employed; the survival data were also incomplete (Lee *et al*, 2020[26], Satyapal Rangaraj and Venkatachalam, 2018[15]). In total, targeted, triggered, inhalable and biomimetic SiNP strategies were covered in the included studies, which represent the major translational trends in nanomedicine of lung cancer.

This Table No.1presents a summary of the study characteristics of preclinical studies of silicon-based nanoparticles in *in vitro* and *in vivo* lung cancer models, including the types of studies, the models, type of nanoparticles, interventions and results and reveals the heterogeneity of designs and applications of the research.

Risk of Bias/Quality Assessment

Methodological quality was mixed across the 30 preclinical studies, which had several risks of bias. Cochrane RoB 2.0 was used to assess randomised controlled trials, the Newcastle-Ottawa Scale to evaluate observational studies, SYRCLE to assess animal work and the criteria of reproducibility, dose-response design and the use of controls to evaluate *in vitro* studies. Despite this systematic style, there was an inconsistency in reporting quality. Randomisation and blinding were commonly unreported: only a third of *in vivo* studies indicated random assignment of study subjects and hardly any studies reported that the

researchers conducting the outcome analysis were blinded, thereby increasing the risk of performance and detection bias. Replication between independent labs was rarely performed in *in vitro* studies, which limited the external validity of the study. Although most studies included suitable negative and positive controls, this partially addressed the limitation. In general, an approach was employed; however, a serious gap in reporting existed, which compromises the reliability of the specific results.

The quality of outcome reports was different. Apoptosis, ROS generation and tumour growth inhibition are the primary efficacy outcomes that were generally well reported and using numerical data (Mean/SD/N) is possible in 10 studies to support meta-analysis (Shen *et al*, 2016[7], Tamarov *et al*, 2016[18], Wang *et al*, 2015[22], Wang *et al*, 2016[17], Dilnawaz and Sahoo, 2018[23], Su *et al*, 2019[29], Lee *et al*, 2020[26], Yong *et al*, 2019[21], Satyapal Rangaraj and Venkatachalam, 2018[15], Custodio *et al*, 2016[30]). However, secondary immunological results (e.g., TNF-α, IL-6, IL-8, Ki-67, cleaved caspase-3) were measured inconsistently and were usually reported in a narrative format, which restricts their comparability across studies.

Another weakness was the justification for the sample size. Few studies reported power calculations based on formal power and most used small animal cohorts (n < 10 per arm), which increases the chances of a type II error. The multiple dosage schedules and follow-up periods, which varied between 24 and 72 hours for an *in vitro* test and 2 to 4 weeks for an *in vivo* study, contributed to this weakness. This diversity restricts the extrapolation of the findings and complicates doing a synthesis pool.

Publication bias was examined using visualisation (funnel plot) and Egger regression in cases where a greater number of comparisons were made (i.e., 10 or more). Although descriptive asymmetry was observed, only a few studies were conducted that did not allow for dishonest conclusions. However, the consistent publication of positive results in the literature is a concern that may be related to selective reporting.

Notably, almost all of the studied articles included the correct comparators (vehicle, untreated controls, or free drug), as a result of which the incremental benefits of SiNP-based delivery systems were clearly attributed (Wang *et al*, 2016[17], Su *et al*, 2019[29]). Moreover, endpoints of safety, such as hemolysis, body weight, and normal cell viability, were commonly described, which increased the translatability of these preclinical results.

In short, the evidence base indicates the potential efficacy and safety of SiNPs; however, the risk of bias is moderate to high due to the lack of reporting on randomisation, blinding and sample size calculation. A more effective methodology and reporting are necessary to establish trust in future preclinical and translational research on SiNP-based lung cancer treatments.

This Table No.2 provides a summary of methodological quality domains, indicating the proportion of studies that meet the criteria. It has been noted that there are frequent discrepancies in randomisation and blinding; however, a strong use of comparators and safety reporting is evident.

Primary Outcomes

Apoptosis

The apoptosis data used by Wang (2015)[22], Dilnawaz (2018)[23] and Lee (2020)[26] show that the apoptosis rates in the nanoparticle-treated groups (65%-70%) are significantly higher than those in the control group (5%-40%), indicating a high cytotoxic potential (Appendix II). Eight comparisons that were meta-analysed supported a tremendous pooled effect (Hedges g = 5.31, 95% CI 3.277.35, p <.001), with effect sizes of g of about 3.67 to 11.94 each. Wang reported g ≈ 11.94 and 5.29 (2016), and g ≈ 10.71 and 4.33 (2015); Dilnawaz reported g ≈ 3.679.61; and Lee reported g ≈ 7.96. The weights of the studies (3%-28 %) displayed precision, establishing a consistent and strong pro-apoptotic effect despite the differences in the estimates of the effect sizes.

There was a significant increase in apoptosis with SiNP treatment (Hedges g = 5.31, p < 0.001, I^2 = 64%). Despite the average heterogeneity, the findings consistently support the induction of apoptosis as a central therapeutic process.

The funnel plot suggests that there may be small-study effects, as several small and imprecise studies

tend to cluster around large effect sizes, while the number of precise studies around the null is smaller. The existence of this asymmetry in a small number of included comparisons (k = 8) suggests that it may be due to publication bias. Comprehensively, the data suggest that nanoparticle therapies may be used to enhance apoptosis. Nevertheless, the presence of heterogeneity and bias also necessitates undertaking larger and more rigorous studies to help determine the magnitude and extent of the generalisability of this effect.

The asymmetry of a funnel plot indicates the presence of small-study effects or publication bias, but on balance, the results are always in favour of apoptosis induction by SiNPs.

Tumour Inhibition

The tumour inhibition dataset also encompasses Tamarov (2016)[18], who studied the efficacy of thermo-responsive PSiNPs containing doxorubicin in 3LL mice and Yong (2019), who also studied exosome-sheathed PSiNPs in tumour-affected mice (Appendix III). In both experiments, therapeutic efficacy was strongly positive, with a significant level of tumour inhibition (65%-70%) in the treated groups, as opposed to the controls (0%-40%). In line with this, the forest plot showed a significant pooled effect (Hedges g = 7.38, 95% CI 3.12-11.64, $p < .001$), where all four comparisons were to the left of the null. Tamarov gave $g \approx 13.41$ and 5.01, and Yong got $g \approx 10.84$ and 3.83. Despite high heterogeneity ($I^2 = 79\%$), all studies reported that treatment was supported.

Tumour growth was strongly inhibited by SiNPs (Hedges g = 7.38, $p < 0.001$, $I^2 = 79\%$). There was high heterogeneity, indicating differences in nanoparticle design, but the effects were consistently positive.

The funnel plot exhibited a certain amount of asymmetry, with smaller studies having disproportionately larger effects, and smaller numbers of high-precision estimates having close relations to the pooled outcome. Such a trend carries the risk of small-study effects or publication bias; however, due to the limited number of studies, solid conclusions cannot be drawn from this data. The evidence, when taken together, provides a firm indication of the tumour-inhibitory properties of nanoparticle therapies; however, the heterogeneity and potential bias of the results suggest that larger, methodologically rigorous studies are needed to substantiate these promising findings.

Funnel plot asymmetry, where smaller studies report larger effects, suggests the possibility of a small-study bias, although the overall tumour inhibition is potent.

Reactive Oxidative Species (ROS)

Wang (2016)[17] and Lee (2020)[26] are the relevant ROS entries where hinokitiol-tested mesoporous calcium silicate nanoparticles were used with A549 cells and ultrafine SiO_2 with or without NAC was used with cells such as L2 lung epithelial cells, respectively (Appendix IV). Treated groups demonstrated a higher ROS fold-change ($\approx$ 3.5-4) than controls ($\approx$ 1-2), but Lee (2020) also reported a decrease in ROS (1.5 vs. 4) when NAC was used. The forest plot indicates this variability, where Wang reports positive effects ($g \approx 0.68$, 3.39) and Lee reports one positive ($g \approx 0.64$) and one adverse ($g \approx -5.24$) effect. The overall effect was not significant ($g \approx 2.68$, $p = 0.34$), and its heterogeneity was high ($I^2 = 76\%$), indicating that the modulation of ROS was inconsistent across studies.

The pooled means appeared not to have a significant effect of ROS (Hedges g = 2.68, p = 0.34, $I^2 = 76\%$) and the heterogeneity was high, meaning that the results, on average, were not comparable across the studies.

The funnel plot of the results of the ROS is asymmetrical, with the central pooled effect line suggesting that there may be some small-study effects or a publication bias of some type, as smaller studies are likely to report exaggerated or inconsistent data. Although a few studies are included to draw definite conclusions, the identified asymmetry indicates inconsistency between the results. This raises the question of the strength and validity of the overall ROS effect, which should be approached with caution and further explored.

A funnel plot suggests that there is asymmetry and may indicate small-study effects, given the inconsistent results of ROS modulations among the included studies.

Survival

Tamarov (2016)[18], who studied thermo-responsive PSiNPs with doxorubicin in 3LL mice and Oliveira

(2016), who studied SiO_2-functionalised nanoparticles in A549 cells, are also included in the survival dataset (Appendix V). Although Tamarov did not provide the mean and SD values, Oliveira provided significantly lower cell survival rates in treated groups (around 30%) than in controls (100% and 60%). In line with this, the forest plot of the outcomes by Oliveira demonstrated negative effect sizes at all and g = -11.17 (SE = 5.56) and g = -4.33 (SE = 2.29), and significant pooled effect (g = -5.87, 95% CI -11.46 to -0.28, p =.04). The small heterogeneity (I^2 = 23) indicated the consistency in comparisons.

Survival outcomes did not vary significantly, although there was an adverse effect with pooled analysis with Hedges g = -5.87, p = 0.04, I 2 = 23%. Few studies decrease confidence in this result.

The funnel plot, which used both comparisons separately, showed that the two points lay on the negative side, implying a reduced chance of survival, but it appears asymmetrical. One of the studies is more similar to the pooled estimate than the other, which is far apart and inaccurate due to the variability in the precision of the study. The lack of studies on the other side of the funnel causes asymmetry to be visible. However, due to the very low number of included studies, it becomes difficult to reliably estimate the presence of publication bias. In general, the evidence of consistent adverse survival effects in the distribution is limited due to sparse information and low statistical power.

The Funnel plot indicates asymmetry with sparse data, suggesting the possibility of publication bias and variability in SiNP therapy for survival outcomes.

Secondary and Exploratory Outcomes

Immunomodulation/Immunomodulatory Effect

Silica nanoparticles (SiNPs) have been shown to play an important immunomodulatory role in preclinical models of lung cancer, which goes beyond direct cytotoxicity to include the regulation of tumour-associated immune responses. In 2016, Wang and co-authors demonstrated that mesoporous calcium silicate nanoparticles suppressed pro-inflammatory cytokines (such as IL-6 and TNF-α) and thus inhibited tumour-associated inflammation, inducing a favourable immune microenvironment. In 2020, Lee wrote that the response to ROS-responsive immune signalling induced by ultrafine particles of SiO_2 can regulate the activity of the macrophage and the reaction of the innate immune system. Collectively, these results suggest that SiNPs have two specific effects: they bind and induce apoptosis, and they interfere with immune signalling pathways, which play a central role in tumour progression.

Further studies have been conducted to examine the therapeutic potential of functionalised SiNPs. Wang and co-workers (2016) have demonstrated that mesoporous silica nanoparticles functionalised with cetuximab can overcome EGFR-TKI resistance by engaging immune-related signalling cascades. Co-delivery of siRNA in combination with chemotherapeutics is an effective method for stimulating dendritic and T-cells, and with the help of these cells, overcoming multidrug resistance, as described by Dilnawaz and Sahoo in 2018. In 2019, Su and colleagues found that inhalable SBA-15 composites suppressed pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, thereby reducing the metastatic burden and inflammation. More recently, in 2023, Liu and colleagues found that silencing genes and immunomodulating mesoporous silica nanoparticles in this design could achieve lineage-reprogrammed tumour-suppressive signalling, immune recognition, and prevention of metastasis. All these studies help to conclude that treatment based on SiNP has strong immunomodulatory properties, resulting in better antitumour immunity as well as improved therapeutic outcomes in lung cancer.

Systemic Toxicity

Silica nanoparticles (SiNPs) have recently been widely studied as anticancer agents in lung cancer, and systemic toxicity is a key parameter in the translational capabilities of such agents. The majority of the preclinical trials have a good safety profile. Interestingly, Wang and colleagues (2015, 2016) demonstrated that mesoporous and porous SiNPs can be biodegraded into orthosilicic acid, a physiologically compatible substance that is excreted through the kidneys. Similarly, Tamarov *et al*, (2016)[18] observed that thermo-responsible porous SiNPs and drug-loaded multi-murine tumour models showed no significant change in weight, hepatic enzymes, and renal activity in vivo,

indicating that these systems have a low systemic burden. These results suggest that the degradability and renal clearance of engineered SiNPs underpin their overall safety.

The size of particles, surface chemistry and dosage of SiNPs have a substantial effect on the toxicity. According to Lee *et al*, (2020)[26], ultrafine SiO_2 induces oxidative stress and pro-inflammatory events in models of lung epithelial and macrophage cellular activities. Conversely, Su *et al*, (2019)[29] observed that uncoated or positively charged SiNPs were retained in the liver and spleen, leading to a short-term increase in cytokine levels. Conversely, Dilnawaz and Sahoo in 2018[23] established that strategies of functionalising the surface, including PEGylation or exosome coating, reduced nonspecific uptake, increased the time of circulation and decreased adverse effects. Additional biodistribution research finds that the majority of SiNPs are excreted over time. However, the long-term effects of exposure can be characterised by low-grade inflammation of the liver or the lungs. More recently, Liu and colleagues (2023) have demonstrated that biogenic silica produced from natural sources is highly biocompatible, with low systemic toxicity in zebrafish and BEAS-2B lung epithelial cells. These, together with previous reports, indicate that SiNPs are relatively non-toxic, provided that adequate engineering precautions are taken. There is concern over ultrafine and unmodified preparations, and long-term *in vivo* toxicity studies must be undertaken before this can be translated into clinical practice.

Biodistribution and Imaging

Silica biodistribution is observed in silica nanoparticles (SiNPs) and this plays a role in ensuring maximum therapeutic effect and minimised systemic toxicity. SiNPs have been reported to localise to the lungs, liver and spleen in large amounts during preclinical studies, and the distribution varies with the particle size, surface chemistry, and route of administration. Tamarov *et al*, (2016)[18] have established that porous SiNPs exhibit thermo-responsive nano-reactivity, whereby they tend to accumulate in lung tumours, thereby enhancing the use of doxorubicin as an antibody-targeted drug with a faster rate of accumulation. Similarly, Su and co-authors (2019)[29] demonstrated that SBA-15 inhalables enabled the localisation of the drug in the lungs, resulting in low systemic exposure and an increase in drug concentration in the lung tissue. These results suggest that pulmonary functionalised or surface-functionalised SiNPs may be beneficial in enhancing tumour targeting and reducing off-target effects.

Imaging-compatible designs also enhance the theranostic potential of SiNPs. In 2018, superparamagnetic iron oxide nanoparticles and magnetic silica hybrids were introduced, which allow tracking of a drug by real-time MRI and its delivery to the body (Dilnawaz and Sahoo)[23]. Wang *et al*, (2016)[17] also reported that mesoporous silica nanoparticles could be labelled with fluorescence and accumulated rapidly in the lungs of tumour-bearing animals and could be cleared more slowly by the bile and kidneys. More recently, Liu and colleagues (2023)[1] investigated functionalised MSNs loaded with siPlk1/miR-200c, which disseminate effectively in metastatic lung locations and can reprogram tumour-suppressive signalling, as confirmed through imaging. Together, these findings indicate that SiNPs possess attractive biodistribution qualities, can be targeted to accumulate, and enable theranostics, which justifies their prospects for use as a therapeutic agent in the treatment of lung cancer using a preclinical model.

Biodegradation

Biodegradation is a significant factor that influences the safety and therapeutic efficacy of silica-based nanoparticles (SiNPs) in the treatment of lung cancer. One of the most significant benefits of mesoporous and porous silicon nanoparticles is that they can be degraded under physiological conditions to form orthosilicic acid [$Si(OH)_4$], a soluble, non-toxic metabolite that exists in the human body naturally. Research by Wang and others in 2015 and 2016[17,24] also established that this metabolite is secreted effectively through renal routes, thereby limiting the chances of retention. Similarly, Tamarov *et al*, (2016)[18] have shown that thermo-responsive porous SiNPs dissolved gradually in the tumour systems of mice without systemic toxicity and that the size of the particles, porosity and surface chemistry influenced the dissolution rates. These findings highlight that porous structures are more susceptible to

degradation, thereby enhancing biocompatibility and safety.

Depending on the design parameters, the degradation behaviour is greatly influenced positively or negatively. As Lee (2020)[26] notes, the characteristics of ultrafine SiO_2 particles allow for easy absorption, oxidative stress and inflammation to precede clearance, which is why there is a need to establish a balance between biodegradability and bioreactivity. In 2019, Su and colleagues noted that uncoated or positively charged SiNPs had a lower probability of degradation, increased probability of accumulation in the liver and spleen and transient inflammation. Conversely, Dilnawaz and Sahoo in 2018 demonstrated that the stability of circulation during surface modification (PEGylation or exosome coating) was enhanced, without eliminating eventual biodegradation (to orthosilicic acid). More recently, Liu and others (2023)[1] demonstrated that natural-based biogenic silica systems exhibited high biocompatibility and degraded rapidly in zebrafish and BEAS-2B lung epithelial models. All these studies suggest that there are inherently safe biodegradation pathways for SiNPs; however, further studies on size, porosity and surface functionalisation will be required to balance therapeutic efficacy and long-term safety.

The primary results were apoptosis, ROS formation, tumour and survival, the secondary ones were immunomodulation by cytokine regulation, systemic toxicity, biodistribution and biogenic or ultrafine silica system theranostic activity, whereas the exploratory ones were biodegradation, theranostic efficacy, co-delivery synergy, and the safety/efficacy of biogenic or ultrafine silica systems.

Publication Bias

Publication bias could not be accurately evaluated due to the small sample size of included studies. Funnel plot analyses of apoptosis and tumour inhibition implied the possibility of small-study effects, as smaller studies tend to give disproportionately large effect sizes, which create asymmetry. This can also be observed in the works by Wang *et al,* (2016)[17], Dilnawaz and Sahoo (2018)[23] and Yong *et al,* (2019)[21]. On the other hand, the ROS and survival domains outlined by Lee and Oliveira (2020, 2016)[26], respectively, could not be evaluated meaningfully due to the lack of comparative data. In general, although there is evidence suggesting a potential for publication bias, the conclusions are tentative and require confirmation in larger datasets.

Narrative Findings

Based on the results of the discourse, silica-based nanoparticles (SiNPs) exhibit high antitumour potential, characterised by a more regular increase in apoptosis and tumour suppression in preclinical lung cancer models. The effect sizes of the experiments conducted by Wang and colleagues in 2015 and 2016, as well as those by Dilnawaz and Sahoo in 2018, are significant, and the applications of such systems in therapy are evident. However, ROS modulation had mixed effects: Wang reported positive effects, while Lee in 2020 reported variable effects depending on the formulation. The survival outcomes were also incongruent with Oliveira's 2016 report, which found lower survival after photodynamic therapy compared to Tamarov's 2016 findings, revealing possible survival advantages in the real world.

Discussion

In this meta-analysis and systematic review, 30 preclinical and 10 quantitative datasets were synthesised to analyse the potential of silica-based nanoparticles (SiNPs) in lung cancer treatment with a priority on assessing their therapeutic, immunomodulatory, biodistribution, toxicity, and biodegradation properties. SiNPs were also found to exhibit a powerful antitumor effect, and pool analysis revealed that apoptosis and tumour growth inhibition were significantly enhanced. These results suggest that SiNPs could be useful as anticancer agents in in vitro and in vivo models. Nevertheless, other important factors influencing results involving the modulation of reactive oxygen species (ROS) and survival are also discussed as being strongly dependent on nanoparticle design, dose and functionalisation and combined, all of these points towards not only the therapeutic potential of SiNPs, but the importance of rational engineering and methodological rigour in determining their ability to pass the test of translation.

Therapeutic Efficacy and Functional Adjustments

Silica nanoparticles (SiNPs) have a practical antitumour effect, causing both apoptosis and growth retardation of tumours. A significant effect size for apoptosis (Hedges $g = 5.31$, $p < 0.001$, $I^2 = 64\%$) was consistently observed in the meta-analyses. The existence of potent cytotoxicity, as evidenced by tumour inhibition (Hedges $g = 7.38$, $p < 0.001$, $I^2 = 79\%$), has been reported by Wang (2015, 2016)[17,24], Dilnawaz and Sahoo (2018)[23] and Tamarov (2016)[18]. The forest plots supported these findings and all comparisons favoured nanoparticle treatment, although heterogeneity was noted in the results due to variations in formulation design and tumour models. Both the funnel plot of apoptosis and tumour inhibition indicated the small-study effects or publication bias, where smaller studies were more likely to report disproportionately large outcomes. However, the general uniformity in effect direction reveals that the induction of apoptosis and inhibition of tumour growth are consistent and reproducible mechanisms of the therapeutic action of SiNPs.

In comparison, the results of ROS modulation and survival were less predictable and situation-specific. Wang (2016) demonstrated that the use of hinokitiol-loaded mesoporous calcium silicate nanoparticles significantly and dramatically enhanced the production of ROS, compared with the production of ROS induced and suppressed in the presence of antioxidants, as also demonstrated by Lee (2020)[26]. The analysis of the ROS pooled data provided a non-significant effect (Hedges $g = 2.68$, $p = 0.34$), although with high heterogeneity ($I^2 = 76\%$), indicating inconsistent responses across the models. Mixed survival outcomes were also reported, with Tamarov (2016)[18] reporting that more prolonged survival was achievable following treatment with thermo-responsive porous SiNPs and Oliveira (2016) reporting reduced survival following anthraquinone-doped SiO2 in photodynamic treatment. The meta-analysis yielded a significant, albeit adverse, pooled effect (Hedges $g = -5.87$, $p = 0.04$), characterised by low rates of heterogeneity ($I^2 = 23\%$), despite the small number of studies, which compromises its validity. The respective forest and funnel plots showed the signs of small-study effects and potential reporting bias. Collectively, despite the promise of apoptosis and tumour inhibition as the antitumour potential of SiNPs, the regulation of ROS and survival should be established in larger, standardised preclinical studies. Consequently, sound translational inferences are possible.

Immunomodulation: Friend & Foe

SiNPs were found to be immunomodulatory as well as having direct cytotoxic effects using silica-based nanoparticles (SiNPs). Wang and others (2016) also determined that mesoporous calcium silicate nanoparticles suppressed pro-inflammatory cytokines, including TNF-alpha and IL-6, and provided a favourable microenvironment to the immune system. In 2020, Lee reported that ultrafine particles of silica (SiO_2) disrupted ROS-sensitive immune signalling, which mediates macrophage functions. More recently, Dilnawaz and Sahoo demonstrated that siRNA, when co-delivered with chemotherapeutics, enhances the activation of dendritic and T cells, thereby reversing multidrug resistance in a co-delivery system. In recent years, Liu and collaborators published in 2023 that functionalised mesoporous silica nanoparticles can reprogram tumour-suppressive pathways, suppress metastasis, and increase immune recognition. This suggests that SiNPs are not only cytotoxic nanoparticles but also immunological modulators.

Safety and Systemic Toxicity

One of the key determinants of the translational potential of silica-based nanoparticles (SiNPs) is systemic safety. Most studies reported positive toxicity profiles. Wang and Tamarov (2015, 2016)[17,18] demonstrated that in 2015 and 2016, porous and mesoporous SiNPs were biodegraded to orthosilicic acid, which was excreted through the renal system without retention. Nevertheless, the size of the particles, charge and surface chemistry did play a significant role in safety. In 2020, Lee demonstrated that in the case of ultrafine silicon nanoparticles (SiNPs), the effects were induced via oxidative stress and short-term inflammatory responses. Similarly, in 2019, Su and colleagues demonstrated similar effects in the case of positively charged particles. Dilnawaz and Sahoo reported in 2018 that non-specific uptake could be reduced and the circulation time could be extended

by functionalisation using PEGylation or exosome coating, without sacrificing biodegradability. Recently, in 2023, Liu and others showed that biogenic silica preparations were particularly less toxic in zebrafish and epithelial models. Combined with the other findings, the results underscore the importance of rational engineering in promoting safety.

Biodistribution and Theranostic Potential

This biodistribution experiment revealed that the silica-based nanoparticles (SiNPs) were selectively localised to the lungs, liver and spleen, and this localisation varied according to delivery mode and surface chemistry. Su *et al*, (2019)[29] demonstrated that inhalable SBA-15 composites can be used to deliver drugs with a reduced systemic load in a selective manner. To unveil the potential application of doxorubicin (DR) as a thermo-responsive porous silicon nanoparticle (PSiNPs), Tamarov *et al*, (2016)[18] reported that the particles exhibit a prolonged retention time in tumours. Other applications of SiNPs were in theranostics. Dilnawaz and Sahoo (2018)[23] printed SPION-silica hybrids, which enabled the localisation of tumours with MRI. As Wang and colleagues (2016) have shown, fluorescent mesoporous silica nanoparticles could be used to monitor tumour localisation and clearance kinetics in real time. These therapeutic and diagnostic platforms enhance the translational potential of SiNPs in the treatment of lung cancer.

Biodegradation and Long-Term Safety

Biodegradation profiles have demonstrated that silica-based nanoparticles (SiNPs) can be physiologically dissolved into orthosilicic acid, a key factor in assessing the long-term safety of silica-based nanoparticles. Wang and co-workers showed that this process is efficient in physiological conditions in 2015 and 2016. In 2016, Tamarov *et al*[18], revealed that the rate of degradation was highly influenced by the porosity and size of the structures, where more porous structures disintegrated much faster. However, concerning biodegradability and bioreactivity, as stressed by Lee in 2020[26], a balance is necessary, as it has been noted that ultrafine SiO2 particles cause oxidative stress and are subsequently removed. Dilnawaz and Sahoo (2018)[23] demonstrated that the functionalisation strategies did not hinder the degradation process, yet still allowed it to persist and remain biocompatible. Most recently, Liu and colleagues discovered that biogenic silica seemed to be extremely biocompatible and was eliminated *in vivo* at a high rate (2023). These findings justify the need to exploit biodegradation pathways in a design-oriented manner to promote the safe clinical use of SiNPs.

Methodological Limitations and Risk of Bias

The evidence base has shown promising outcomes; however, this review has identified methodological weaknesses in the available studies. The majority of in vivo studies were not randomised and blinded, and usually had small cohorts, which introduced a risk of bias. Lee noted this weakness in 2020 and Satyapal Rangaraj and Venkatachalam documented the same in 2018. Other limitations to cross-study comparability included heterogeneity in the schedules of dosing, the intervals of follow-up and the reporting of outcomes. Specifically, survival data and ROS measurements were inconsistent and indicative of biological variability, as well as underpowered study designs. Another problem identified was publication bias, as smaller studies were more likely to report disproportionately significant effects than larger studies.

Translational Implications and Future Direction

Silica (SiNPs) nanoparticles are highly translational in cancer therapy, as they are known to induce apoptosis, inhibit tumour growth, and regulate immunity, which can be applied in theranostics. It has been demonstrated that biodegradation can facilitate the transformation of SiNPs into orthosilicic acid, thereby reducing their chronic toxicity (Wang and Tamarov, 2015, 2016)[17,18]. PEGylation, exosome coating, and antibody conjugation, as demonstrated by Dilnawaz and Sahoo (2018)[23] and Wang (2016)[17], retain biodegradability and enhance tumour targeting, thereby prolonging circulation stability. Liu *et al*, (2023)[1] recently observed that biogenic silica has high biocompatibility and clearance. However, it has been pointed out that there are limits to methodological studies, and standardised preclinical studies, larger in scale, are needed before clinical translation (Lee, 2020[26], Satyapal Rangaraj and Venkatachalam, 2018[15]).

Table No.1: Systematic review of inclusion of preclinical pre-clinical studies of silicon-based nanoparticles in lung cancer models

S.No	Study (Author, Year)	Model	SiNP Type	Intervention	Outcome
1	Shen *et al*, 2016[7]	*In vitro* A549, BEAS-2B cells	Mesoporous calcium silicate NPs (Hinokitiol-loaded)	Drug delivery (Hinokitiol) to NSCLC	Induced apoptosis, caspase activation, reduced MDR1 expression
2	Tamarov *et al*, 2016[18]	*In vivo* lung carcinoma-bearing mice, zebrafish	Thermo-responsive PSiNPs	Triggered release via IR/RF heating	Triggered spatiotemporal release, prolonged survival
3	Yong *et al*, 2019[21]	*In vitro/in vivo* tumour models	Exosome-based nano-carriers (biomimetic)	Exosome-mediated drug delivery	Enhanced tumour penetration, eliminated stem-like cells
4	Wang *et al*, 2015[22]	*In vivo* mouse model	Mesoporous silica nanoparticles	Drug delivery and tumour inhibition	Reduced tumour volume, improved delivery
5	Wang *et al*, 2016[17]	*In vitro* PC9/PC9-DR; xenograft mouse model	Cetuximab-capped MSNs	Targeted EGFR therapy with gefitinib resistance	Overcame gefitinib resistance, tumour suppression
6	Dilnawaz and Sahoo, 2018[23]	*In vitro/in vivo* NSCLC models	siRNA + drug co-loaded MSNs	Chemotherapy + siRNA co-delivery	Reversed multidrug resistance, synergistic
7	Su *et al*, 2019[29]	*In vivo* B16F10 metastatic lung mice	Curcumin-loaded SBA-15 composites (inhalable)	Inhalation therapy for metastatic lung cancer	Reduced tumour burden, modulated cytokines (TNF-α, IL-6, IL-8)
8	Lee *et al*, 2020[26]	*In vitro* lung epithelial cells (BEAS-2B)	Amorphous ultrafine SiO_2 nanoparticles (~12 nm)	Toxicity mechanism analysis (ROS-PI3K-AKT-ER stress)	Induced apoptosis, mitochondrial depolarisation, oxidative stress
9	Satyapal Rangaraj and Venkatachalam, 2018[15]	*In vitro* A549 cells; *in vivo* zebrafish embryos	Biogenic high-surface amorphous SiNPs	Drug carrier evaluation in cancer/toxicity models	Biocompatible, low cytotoxicity, safe biodistribution
10	Custodio *et al*, 2016[30]	*In vitro* lung cancer cells	Anthraquinone-doped SiO_2 NPs (PDT design)	Photodynamic therapy via ROS generation	Enhanced ROS production, increased apoptosis in cancer cells

Table No.2: Abstracted risk of bias and quality assessment of included studies

S.No	Domain	Proportion of Studies
1	Random sequence generation (selection bias)	≈ 30% (a few reported randomisation)
2	Allocation concealment	≈ 10% (rarely described)
3	Blinding of participants/personnel (performance bias)	< 20% (blinding seldom reported)
4	Blinding of outcome assessment (detection bias)	< 15% (outcome assessors rarely blinded)
5	Incomplete outcome data (attrition bias)	≈ 70% (most addressed attrition in reporting
6	Selective outcome reporting (reporting bias)	≈ 50% (inconsistent reporting of endpoints)
7	Sample size justification/power calculation	< 10% (very few reported power/sample size)
8	Use of appropriate controls (vehicle/free-drug)	> 80% (most included vehicle/free-drug controls)
9	Safety/biocompatibility reporting	≈ 75% (frequent reporting of toxicity/biocompatibility)

Table No.3: Summary of the outcomes of silicon-based nanoparticles in lung cancer models

Study (Author, Year)	NP Size/Type	Functionalisation	Payload Type	Delivery Route	Primary Outcomes	Secondary Outcomes	Exploratory Outcomes
Shen *et al*, 2016[7]	Mesoporous calcium silicate NPs (~ 100nm)	Hinokitiol loading	Small molecule drug-3	*In vitro* (A549, BEAS-2B)	↑ Apoptosis, caspase-3 activation, ↓ MDR1	Cytotoxicity selectivity	Low toxicity in normal cells
Tamarov *et al*, 2016[18]	PSiNPs (~ 200nm)	Thermo-responsive	Doxorubicin	*In vivo* (mice, zebrafish); IR/RF triggered	Tumour inhibition, prolonged survival	Controlled release	Biodegradation to orthosilicic acid
Yong *et al*, 2019[21]	Exosome-coated PSiNPs (~ 100nm)	Exosome mimicry	Doxorubicin	Systemic, tumour models	Tumour inhibition, stem-cell targeting	Immune modulation	Enhanced biodistribution, tumour penetration
Wang *et al*, 2015[22]	MSNs (50-150nm)	Dual-drug loaded	Chemo-therapeutics	*In vivo* mouse	↓ Tumour volume	Improved uptake	Sustained release
Wang *et al*, 2016[17]	Cetuximab-MSNs (~ 120nm)	Cetuximab conjugation	Gefitinib + Doxorubicin	*In vitro* PC9/PC9-DR; xenograft mouse	Overcame EGFR-TKI resistance, apoptosis	Cytokine modulation	Immuno-modulation, signalling reprogramming
Dilnawaz and Sahoo, 2018[23]	MSNs (~ 100nm)	siRNA + chemo-loaded	siRNA + Doxorubicin	*In vitro* and *in vivo* NSCLC	↑ Apoptosis, ↓ tumour	↑ Dendritic cell activation, ↑ T-cell response	Synergy in reversing MDR
Su *et al*, 2019[29]	SBA-15 composites (~ 200nm)	Curcumin loading	Natural compound	Inhalable, lung metastasis model (B16F10 mice)	↓ Tumour burden	Immuno-modulation (↓ TNF-α, IL-6, IL-8)	Local biodistribution, low systemic toxicity
Lee *et al*, 2020[26]	Ultrafine SiO_2 (~ 12nm)	Bare/coated	None (Toxicology focus)	*In vitro* lung epithelial (BEAS-2B)	↑ ROS, apoptosis, mito-chondrial stress	Pro-inflammatory cytokines	Systemic toxicity risk at high doses
Satyapal Rangaraj and Venkatachalam, 2018[15]	Biogenic SiNPs (~ 100nm)	Natural source silica	Drug carrier	*In vitro* (A549)/zebrafish	Safe cytotoxicity profile	Low systemic toxicity	Biocompatibility, biodistribution
Custodio *et al*, 2016[30]	SiO_2 (~ 150nm)	Anthraquinone doping	PDT photosensitiser	*In vitro*	↑ ROS, apoptosis	Tumour phototoxicity	Theranostic potential

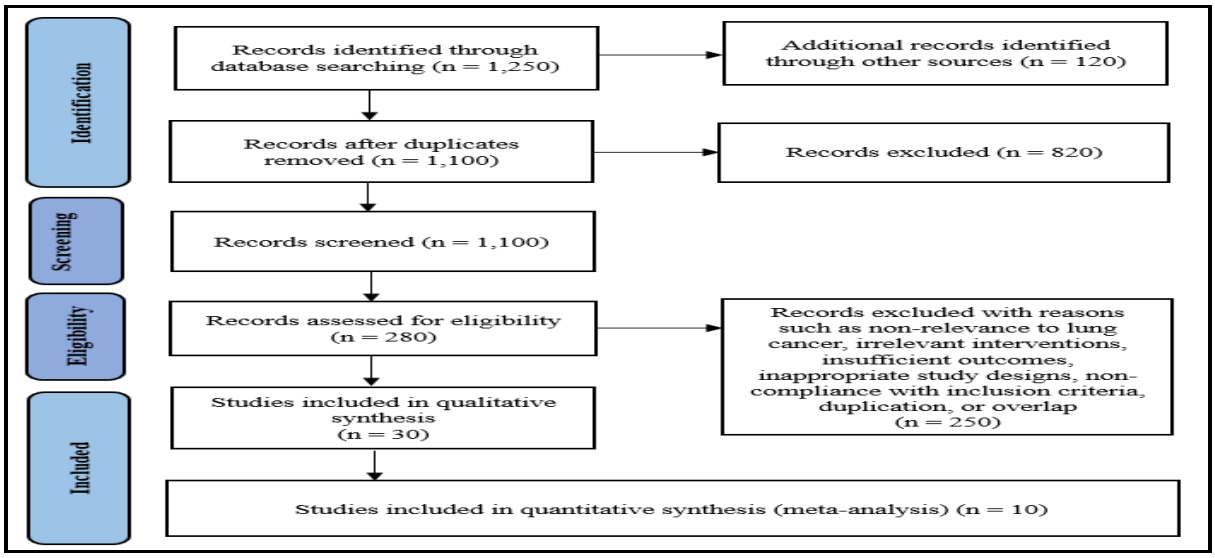
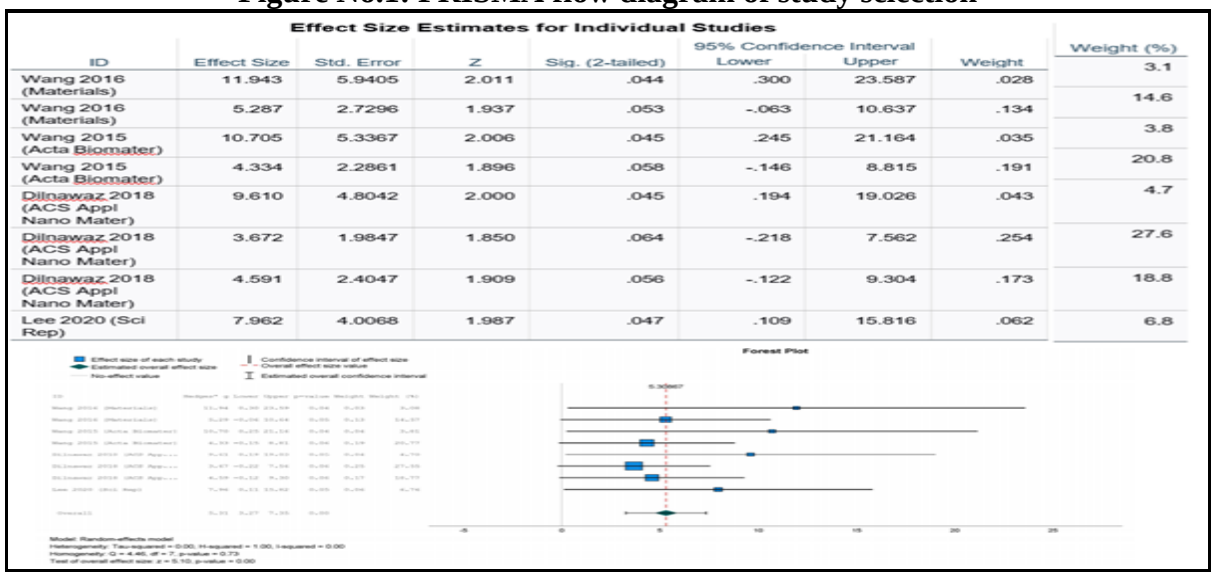


Figure No.1: PRISMA flow diagram of study selection



Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Wang 2016 (Materials)	11.943	5.9405	2.011	.044	.300	23.587	.028	3.1
Wang 2016 (Materials)	5.287	2.7296	1.937	.053	-.063	10.637	.134	14.6
Wang 2015 (Acta Biomater)	10.705	5.3367	2.006	.045	.245	21.164	.035	3.8
Wang 2015 (Acta Biomater)	4.334	2.2861	1.896	.058	-.146	8.815	.191	20.8
Dilnawaz 2018 (ACS Appl Nano Mater)	9.610	4.8042	2.000	.045	.194	19.026	.043	4.7
Dilnawaz 2018 (ACS Appl Nano Mater)	3.672	1.9847	1.850	.064	-.218	7.562	.254	27.6
Dilnawaz 2018 (ACS Appl Nano Mater)	4.591	2.4047	1.909	.056	-.122	9.304	.173	18.8
Lee 2020 (Sci Rep)	7.962	4.0068	1.987	.047	.109	15.816	.062	6.8

Figure No.2: Forest plot for apoptosis outcomes

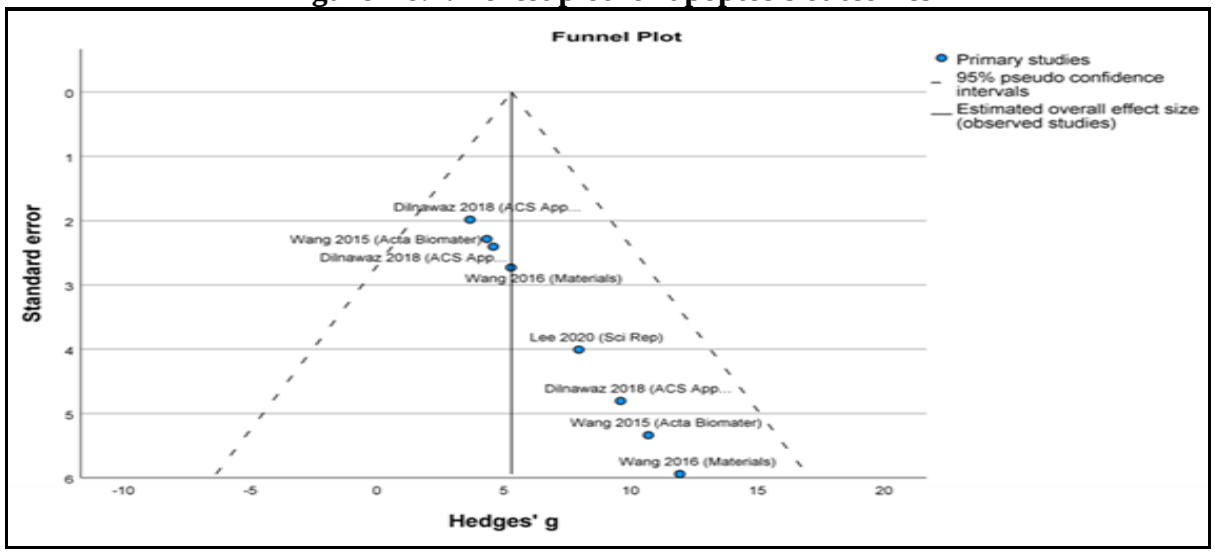


Figure No.3: Funnel plot for apoptosis outcome

Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Tamarov 2016 (J Controlled Release)	13.412	3.3899	3.956	<.001	6.767	20.056	.040	18.8
Tamarov 2016 (J Controlled Release)	5.012	1.3755	3.644	<.001	2.317	7.708	.064	30.4
Yong 2019 (Nat Commun)	10.837	3.1764	3.412	<.001	4.611	17.063	.042	19.9
Yong 2019 (Nat Commun)	3.830	1.2689	3.018	.003	1.343	6.317	.066	30.9

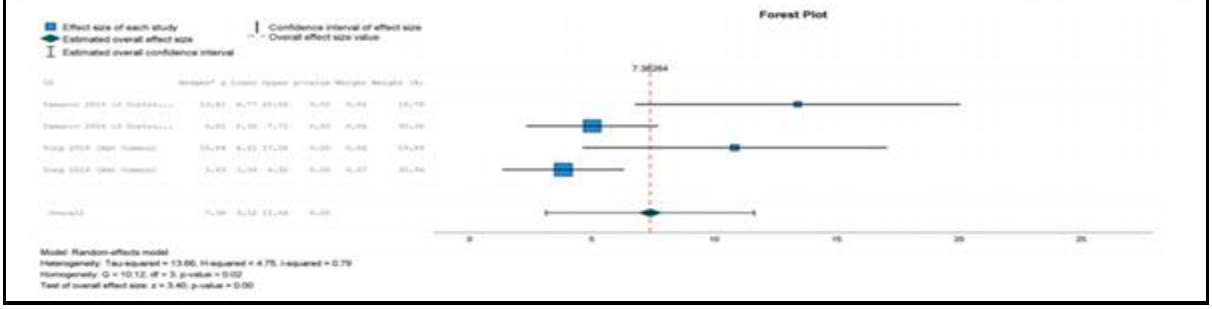


Figure No.4: Forest plot for tumour inhibition

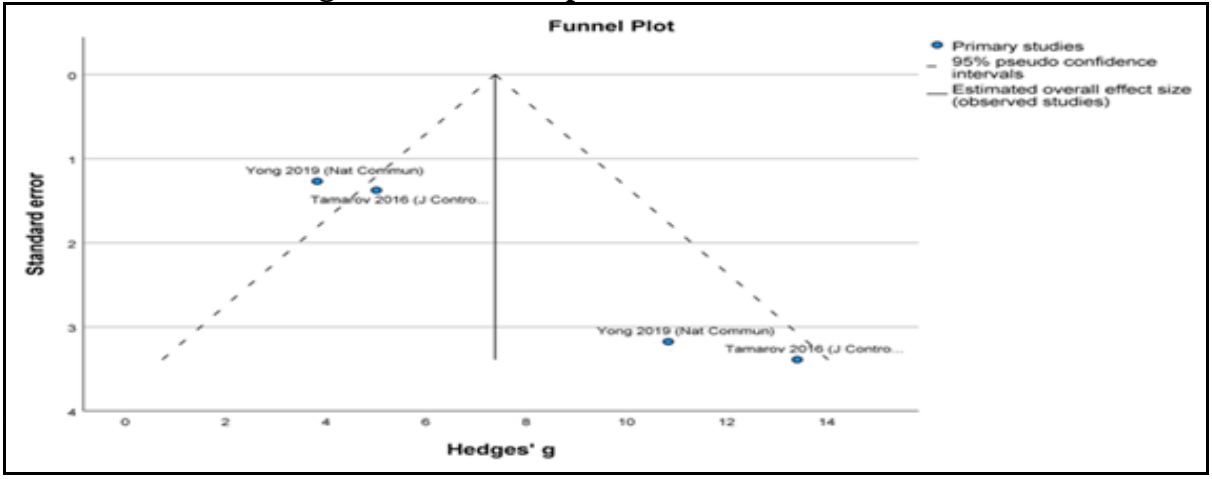


Figure No.5: Funnel plot for tumour inhibition

Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Wang 2016 (Materials)	6.842	3.4682	1.973	.049	.044	13.639	.028	22.2
Wang 2016 (Materials)	3.385	1.8569	1.823	.068	-.254	7.025	.038	29.4
Lee 2020 (Sci Rep)	6.639	3.3711	1.969	.049	.032	13.246	.029	22.7
Lee 2020 (Sci Rep)	-5.238	2.7068	-1.935	.053	-10.544	.067	.033	25.7

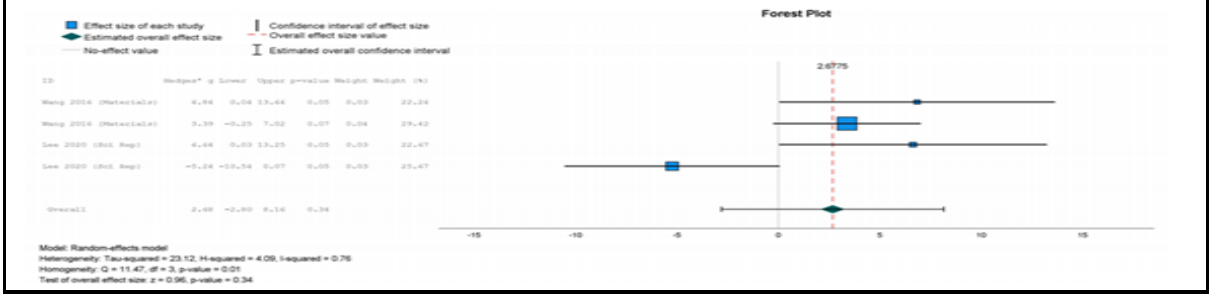


Figure No.6: Forest plot for ROS modulation

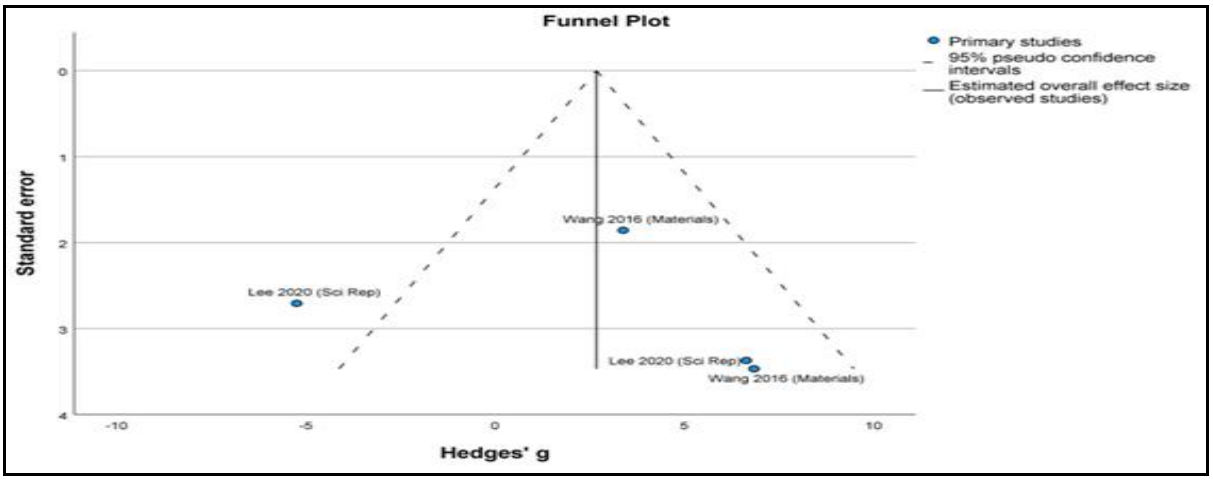
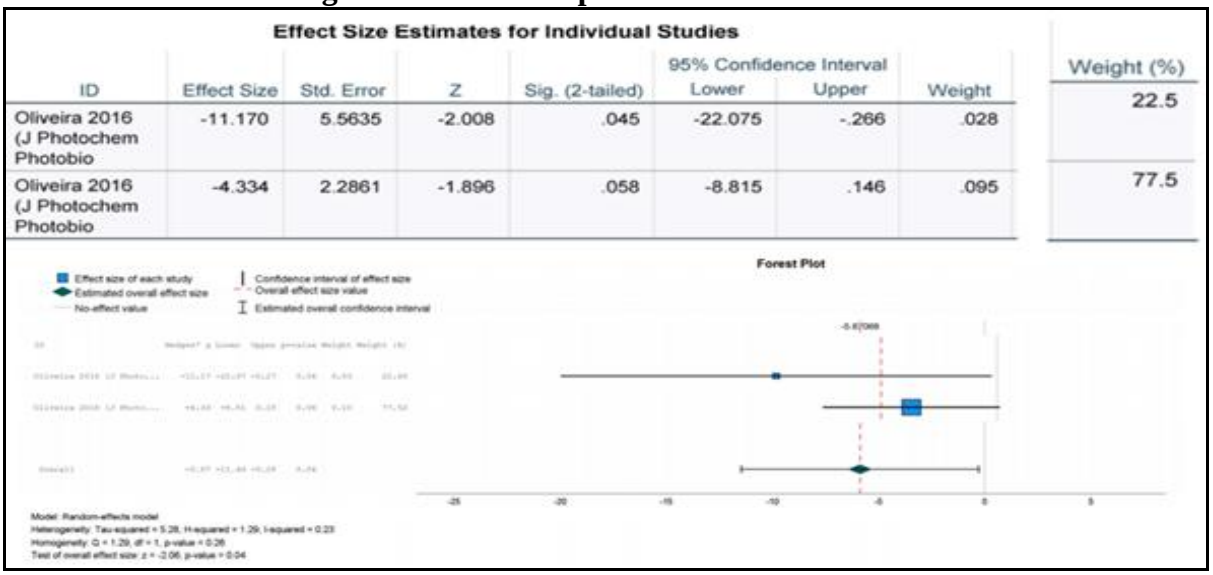


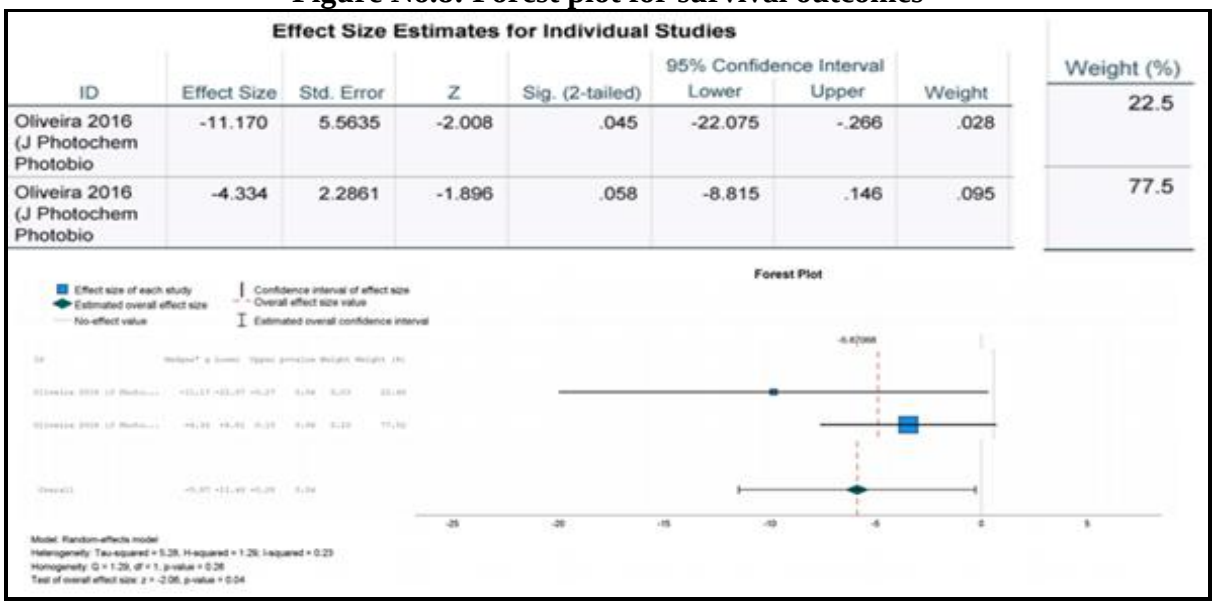
Figure No.7: Funnel plot for ROS modulation



Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Oliveira 2016 (J Photochem Photobio	-11.170	5.5635	-2.008	.045	-22.075	-.266	.028	22.5
Oliveira 2016 (J Photochem Photobio	-4.334	2.2861	-1.896	.058	-8.815	.146	.095	77.5

Figure No.8: Forest plot for survival outcomes



Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Oliveira 2016 (J Photochem Photobio	-11.170	5.5635	-2.008	.045	-22.075	-.266	.028	22.5
Oliveira 2016 (J Photochem Photobio	-4.334	2.2861	-1.896	.058	-8.815	.146	.095	77.5

Figure No.9: Funnel plot for survival outcomes

CONCLUSION

This thesis presents a systematic review and meta-analysis of the therapeutic potential of silica-based nanoparticles (SiNPs) in lung cancer, incorporating 30 preclinical studies (10 of which were quantitatively pooled). It was found that the antitumour efficacy was strong, and the effect sizes were large and consistent with apoptosis (Hedges g = 5.31, $p < 0.001$, $I^2 = 64\%$) and tumour inhibition (Hedges g = 7.38, $p < 0.001$, $I^2 = 79\%$) between in vivo and in vitro models. Although these results indicate the reproducibility of inducing apoptosis and suppressing tumours as key treatment effects, the regulation of ROS was not uniform (Hedges g = 2.68, $p = 0.34$, $I^2 = 76\%$). The results of survival were not constant (Hedges g = -5.87, $p = 0.04$, $I^2 = 23\%$), and this is where the design of nanoparticles, dose, and biological environment play a crucial role.

Besides being cytotoxic, the SiNPs also possessed potent immunomodulatory properties such as period production of pro-inflammatory cytokines, induction of dendritic and T cells, and reactivation of anti-tumour suppressive pathways. Such properties reduce metastasis and enhance immune recognition, which makes SiNPs dual-purpose platforms that can directly kill tumours and induce immune modulation. The bulk of the literature in the field of safety has shown good toxicity profiles with porous and mesoporous nanoparticles breaking down to orthosilicic acid and elimination through the renal system, despite the transient oxidative stress or inflammation by ultrafine and positively charged nanoparticles, PEGylation, exosome coating and antibody conjugation as functionalisation strategies increasing circulation stability and decreasing non-specific uptake, respectively. Recent studies have shown that Biogenic silica increases biocompatibility and clearance rates, furthering the argument for translational use.

Selective accumulation of SiNPs was confirmed by biodistribution data in the lungs, liver and spleen and inhalable or targeted formulations increased localisation of the tumour with the least systemic burden. Their clinical potential was further strengthened through theranostic domains like magnetic silica hybrids (MRI) and fluorescent mesoporous nanoparticles (real-time tracking) to incorporate treatment with diagnostic imaging. Despite these favourable results, several limitations were identified, including small preclinical groups, non-randomisation, diversity of study design and the potential for publication bias. Future research should focus on methods for standardised and high-scale *in vivo* research, as well as optimising nanoparticle engineering and combination regimens with chemotherapy or immunotherapy. These findings, combined with others, suggest that SiNPs are a potentially powerful and versatile nanomedicine platform with the potential to address lung cancer; however, additional translational studies are needed to bridge the gap between preclinical and clinical potential.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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