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Review Article

Old molecules, new hope: A scoping review and bibliometric analysis of drug repurposing for lung cancer

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ABSTRACT

Drug repurposing has gained prominence in oncology by enabling the investigation of approved drugs for new therapeutic purposes. In lung cancer, this strategy may reduce the time and costs associated with drug development. This study aimed to map the landscape of *in silico*, *in vitro*, *in vivo*, and clinical research on drug repurposing for lung cancer, while identifying key molecular targets and research gaps. A systematic search was conducted in PubMed, Embase, and Web of Science, following Joanna Briggs Institute and PRISMA-ScR guidelines. Two reviewers independently selected and extracted the data. A total of 58 studies, published between 2010 and 2024—mainly from the United Kingdom (19%) and United States (17%), were included. Most studies used *in vitro* models (53%), followed by *in vivo* (31%) and *in silico* (16%), with frequent combinations of methods. The most investigated drug classes were antibiotics (10%), antipsychotics (9%), antidiabetics (8%), anthelmintics (6%), and antihistamines (6%). Frequently studied drugs included niclosamide, metformin, atorvastatin, and doxazosin, targeting pathways such as PI3K/AKT/mTOR, apoptosis, and autophagy. Bibliometric analysis revealed increasing scientific output, with emphasis on combination therapies, cellular mechanisms, and technologies like molecular docking and nanosystems. These findings highlight the growing relevance of drug repurposing in lung cancer, especially in accelerating effective therapy discovery using approved compounds. Progress in this field depends on integrating diverse methodologies and fostering interdisciplinary collaboration. As a next step, rigorous clinical trials are essential to confirm the efficacy and safety of promising repurposed agents in oncology.

1. Introduction

Despite decades of research and substantial investments, lung cancer remains the leading cause of cancer-related death globally, with 2.48 million new cases and 1.81 million deaths reported in 2022 [1,2], reflecting its substantial clinical, social, and economic impact on patients and the healthcare system. Approximately 85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC), a biologically and clinically heterogeneous group of tumors with marked variability in size, local extension, and nodal involvement, with adenocarcinoma being the most common histological subtype [3].

While significant advances in molecular profiling and targeted therapies were achieved, consistent and durable responses in lung cancer remain challenging. An overall 5-year survival for NSCLC across all stages remains relatively low - estimated at around 25%, and dropping to less than 10% in advanced or metastatic disease [4]. This limited improvement reflects the disease's biological complexity and the frequent emergence of resistance to treatment, often driven by activating mutations in genes such as *epidermal growth factor receptor* (*EGFR*) and *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) [5].

Although significant progress has been made in cancer biology and pharmacology, especially with the advent of immuno- and target therapies, developing new cancer drugs is a time-consuming, expensive, and uncertain process. Estimates suggest that the time from early-stage discovery to regulatory approval ranges from 11.4 to 13.5 years, with development costs per drug varying between $161 million to $1.8

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billion [6,7]. Additionally, fewer than 5% of candidate molecules progress to Phase I trials, and those that do typically result in highly costly therapies with limited accessibility. [8]. Within this challenging scenario, drug repurposing emerges as a promising strategy - not only to reduce development time and costs, but also for capitalize on existing pharmacological active compounds whose antitumor potential may have been previously underrecognized [9].

Drug repurposing, also known as drug repositioning, is the process of discovering new therapeutic uses for existing approved drugs beyond their original purposes. In the field of oncology, this strategy can help avoid early-stage toxicological challenges and speed up the transition to clinical applications. Moreover, repurposed drugs, especially when combined with standard treatments, can improve therapeutic outcomes through synergistic effects or by targeting alternative pathways [10,11]. Reinforcing the relevance of such approach, previous studies have broadly addressed cancer management drug repurposing, highlighting its potential to reduce time, costs, and risks associated with new therapies development, drug repurposing has emerged as a promising alternative to the traditional model of new drug discovery. While the average cost to bring a new molecular entity to market can exceed US$2.8 billion, the development of a repurposed drug is estimated to range between US$8.4 million and US$300 million representing up to 85% in savings. Examples such as thalidomide, originally approved for erythema nodosum leprosum and later repurposed for multiple myeloma, and the Bacillus Calmette-Guérin (BCG) vaccine, initially developed for tuberculosis and subsequently approved for superficial bladder cancer, illustrate this potential for cost reduction. Both drugs underwent development processes supported largely by public institutions or with minimal involvement from pharmaceutical companies, contributing to significantly lower investment compared to conventional drug development pathways [12]. *In silico*, *in vitro*, and *in vivo* strategies have been widely applied to screen compounds with antitumor action. However, given the high incidence, mortality, and molecular complexity of lung cancer, it is essential to synthesize the evidence in a more targeted way for this specific neoplasm [13,14], as is the case with NSCLC.

With the rising interest in drug repurposing strategies and the increasing volume of related publications, a comprehensive synthesis of the evidence is essential. This study aims to map the current landscape of drug repurposing in lung cancer by conducting a scoping review of preclinical and clinical studies, alongside a bibliometric analysis of the publications to highlight major research trends and identify existing gaps in scientific literature.

2. Methodology

This scoping review was conducted following the Joanna Briggs Institute's recommendations for scoping reviews, and the data were reported according to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines, available in supplementary material [15,16]. The study protocol is available at OSF https://doi.org/10.17605/OSF.IO/6MKPX.

2.1. Search strategies and eligibility criteria

The search strategy was conducted in the PubMed, Embase, and Web of Science databases with terms and synonyms related to “lung cancer” and “drug repurposing”, combined using the Boolean operators “OR” and “AND”. The search strategies are described in the Supplementary Material (Table S1). Retrieved records were exported to Rayyan for duplicate removal [17]. No timeframe or language limits were applied during the search March/2024.

The eligibility criteria were based on the guiding question: “How has the drug repurposing strategy been used to treat lung cancer?”. Articles eligible for inclusion investigated drug repurposing strategies aimed at identifying new pharmacological treatments for any form of lung cancer. Selected studies evaluated non-antineoplastic exploring *in silico, in vitro, in vivo*, and clinical trial methodologies (being published as peer-reviewed articles). Reviews, case reports, errata, study protocols, conference abstracts, books, and book chapters were excluded.

2.2. Study selection

All the steps of study selection and data extraction were independently performed by reviewers, with discrepancies resolved through discussion with a third reviewer. Initially, the titles and abstracts of retrieved articles from the databases were screened. Full-text of potentially eligible studies were then assessed to confirm alignment with the inclusion criteria. Reasons for exclusion at the full-text stage were: Reasons for exclusion at the full-text stage were lack of focus on lung cancer, use of antineoplastic drugs, absence of drug repurposing approach, non-original research or use of non-eligible methodologies. Eligible articles underwent systematic data extraction and synthesis.

2.3. Data extraction and synthesis

Included articles had their data extracted using Microsoft Excel® sheets, including information regarding author/year of publication, country, drug, therapeutic class, type of lung cancer, targets/mutations, methodology, and key findings. As this was a scoping review, the methodological quality of the included studies was not assessed.

A narrative synthesis of the results of the included studies - structured around the target population and drug classes, as well as descriptive statistics-was used to present the findings of the scoping review (GraphPad Prism software, version 8).

2.4. Bibliometric analysis

A bibliometric analysis of publications was conducted to identify patterns and trends in the scientific literature on drug repurposing for lung cancer treatment. The analysis covered the same period as the scoping review and used identical search strategies applied to the same databases (PubMed, Embase, and Web of Science). Data were extracted without applying any screening or eligibility filters, encompassing the entire dataset retrieved. The analysis was performed using R (version 4.4.2) within RStudio® (version 2024.09.1), employing the *bibliometrix* package [18,19].

The content analysis primarily included the following metadata: article's title, abstract, authorship details DOI, journals, keywords, publication years, total citations, and cited references (Supplementary Material – Fig. S1). The data were analyzed using the Biblioshiny graphical interface, which enabled the generation of visual outputs such as graphs and maps. Titles, abstracts and keywords of the ten most-cited articles were examined to identify influential studies, explore thematic connections, and reveal both developments and gaps within the field. This quantitative approach complemented the scoping review, providing a more comprehensive understanding of the research landscape.

3. Results and discussion

3.1. Scoping review findings

A total of 723 records were retrieved from the databases after duplicates removal. Of these, 631 records were excluded during screening for not meeting the inclusion criteria. Of the 92 full-text articles assessed for eligibility one was inaccessible, and 33 were excluded for specific reasons (see ***Supplementary Materials Table S2***), resulting in 58 studies included in this scoping review (Fig. 1), with detailed information on study characteristics, author, title, year, country, drug, therapeutic class, type of cancer, targets/mutations, cell lines, methods, dose (Inhibitory Concentration 50- IC50, Growth Inhibition 50 - GI50, mg/kg), and main findings presented in Supplementary Material Table S3 [20–77].

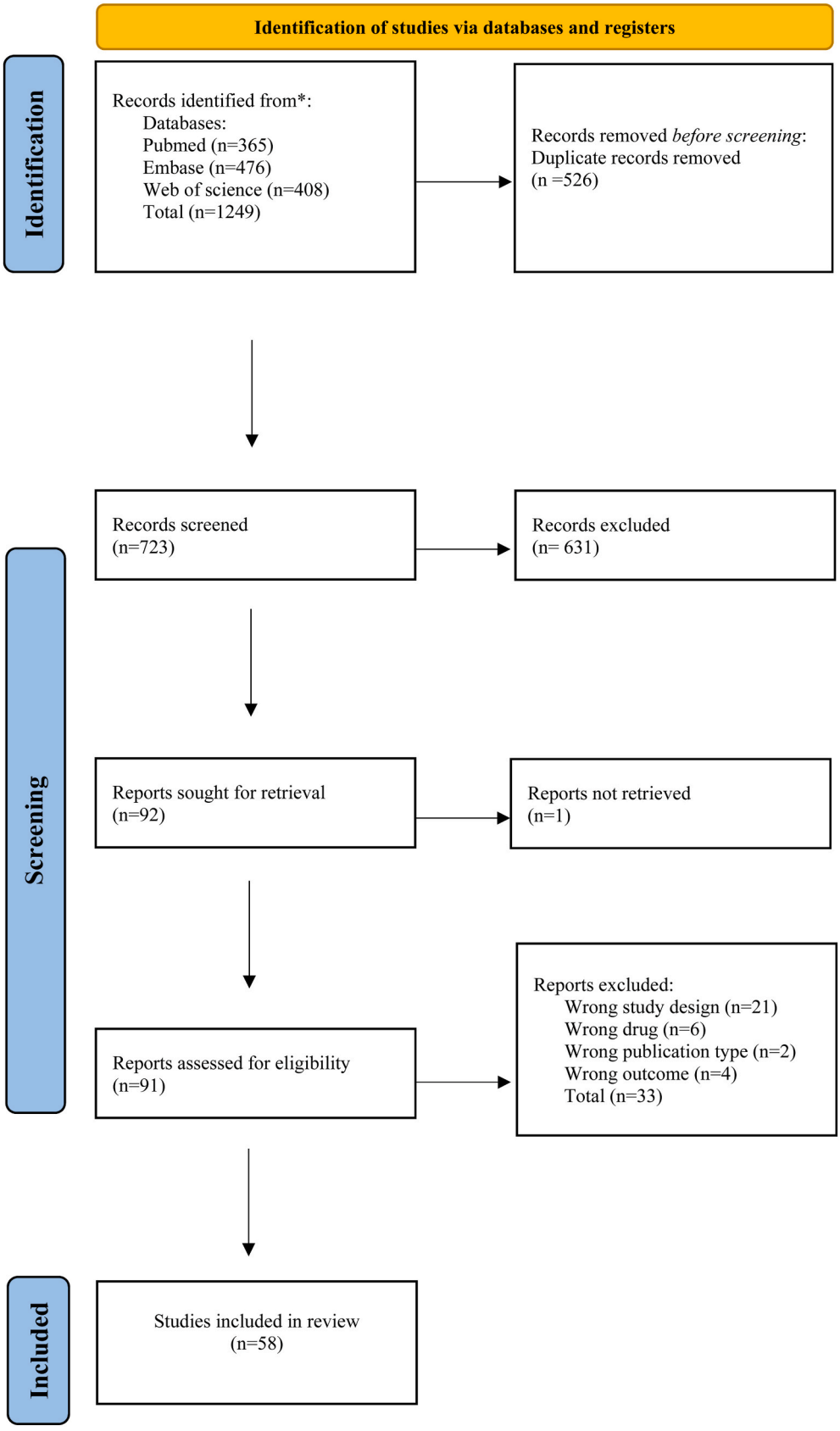

Fig. 1. Scoping review flowchart [15].

The 58 studies, published between 2010 and 2024, show a marked increase in output since 2016 - peaking in 2023 (n = 12 studies) - likely driven by methodological and regulatory advancements in oncology aimed at streamlining approval pathways for existing compounds with established safety profiles (Fig. 2A). In fact, innovations in computational technologies in the past decade have enabled the efficient virtual screening of existing compounds, significantly reducing both the time and costs associated with early-stage drug discovery [10]. At the same time, the increased use of alternative approaches to animal testing - such as organ-on-a-chip technologies and human-derived cell models - has made preclinical research more ethical and physiologically relevant [78,79]. Countries such as the United Kingdom (18.9%), the United States (17.2%), and Switzerland (13.7%) emerge as the leading contributors to research in lung cancer, while some European and Asian countries exhibit a modest contribution (Fig. 2B). This aligns with the global trend, where countries like the United Kingdom, United States, and Switzerland dominate scientific output in biomedical fields. A potential explanation for this pattern lies in their long-standing science policies that emphasize performance-based research funding, international publication incentives, and strong academic evaluation systems. These countries also benefit from robust public and private investments in research, institutional support for high-impact publications, and a competitive academic environment that fosters international collaboration, contributing to higher publication rates in cutting-edge areas such as drug repurposing for lung cancer [80,81].

Regarding methodological approaches, 52.8 % of the studies applied *in vitro* techniques; 27.5% used *in vivo* models, and 16.0% explored *in silico* tools. Only 3.4% of the selected studies were designed as clinical trials. Notably, approximately 50% of the articles utilized a combination of methodologies, indicating a clear trend towards methodological complementarity (Fig. 2C). Combining these techniques enhances translational relevance by validating computational predictions with cellular and animal models, thereby improving robustness, minimizing false positives and pitfalls, and boosting the potential of repurposed drug

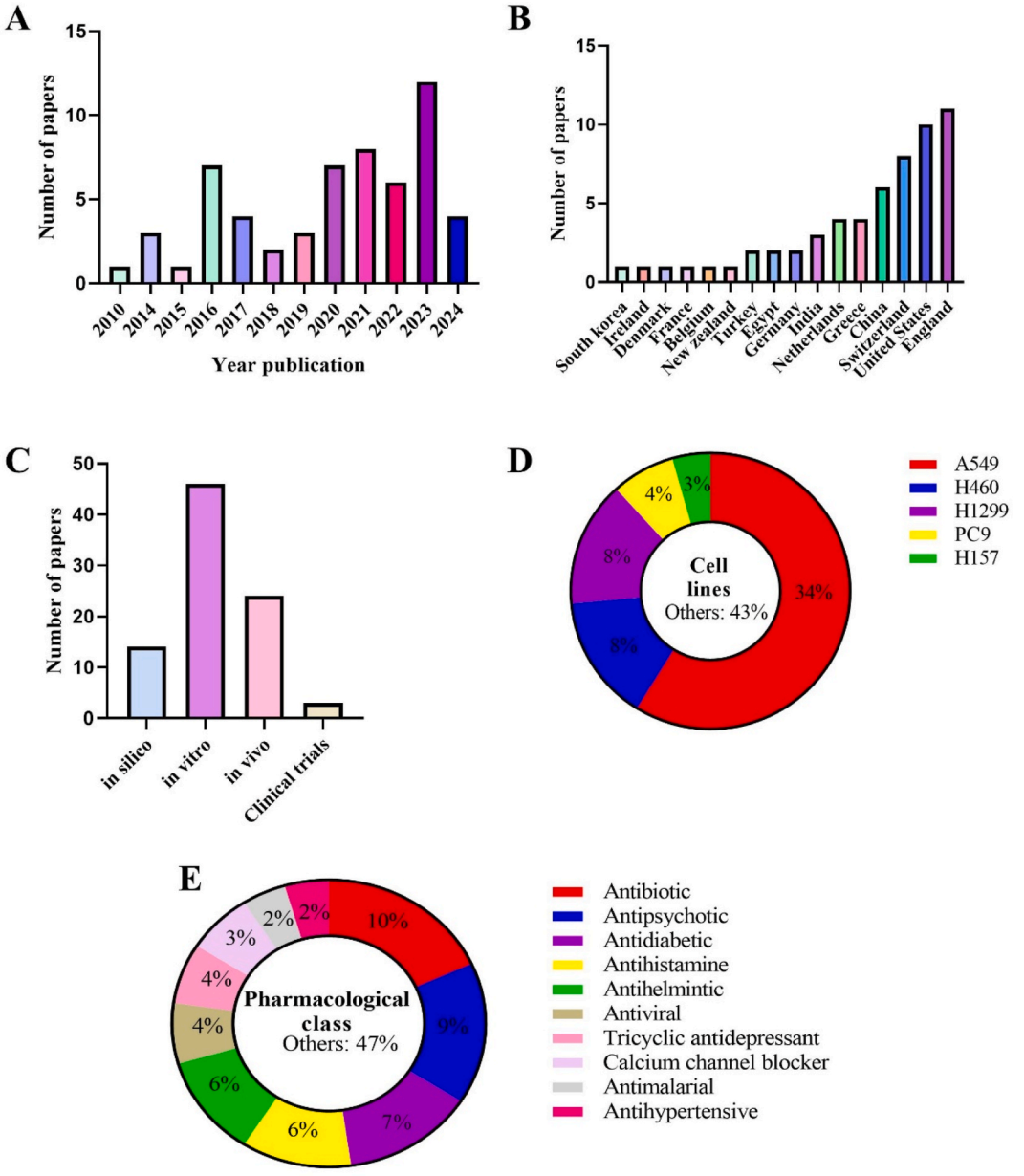

Fig. 2. Characteristics of the articles included in the study. A = Number of articles by region of publication; B = Number of articles published over the years; C = Employed methodologies; D = Top 5 most used cell lines; E = Top 10 pharmacological classes.

candidates [82]. While *in silico* analyses provide efficiency and cost-effectiveness in identifying targets and performing molecular docking, *in vitro* assays shed light on cytotoxicity and mechanisms of action, and *in vivo* models verify therapeutic efficacy and pharmacokinetics within a physiological environment [83,84]. The simultaneous application of these approaches addresses the shortcomings of any individual method, reduces false positives, and enhances the translational potential of repurposed candidates [85].

Within the *in vitro* investigations, lung cancer cell lines were used in drug repurposing studies (Fig. 2D), with the A549 the most frequent (n = 40; 34%), followed by H460 and H1299 (n = 10; 8% each), PC9 (n = 5; 4%), and H157 (n = 3; 3%). Although focused on a limited number of well-characterized lung cancer cell lines, these models represent the most clinically relevant subtypes, capturing key genetic and phenotypic features of the disease. Using multiple cell lines enhances biological relevance and better reflects tumor heterogeneity; however, it also introduces methodological variability that can complicate direct comparisons between studies. Balancing representativeness with experimental consistency is therefore essential to ensure robust and translatable results. Moreover, given that genetic profile (e.g., EGFR, KRAS, or TP53) significantly influences drug sensitivity and affects reproducibility and translational potential, implementing standardized experimental designs and transparent rationale for cell line selection are essential [86].

The therapeutic classes identified in the studies were diverse, with 48% distributed across various categories, showing the multidisciplinary nature of drug repurposing efforts in lung cancer. Antibiotics (n = 8; 10%) and antipsychotics (n = 7; 9%) were the most frequently reported, followed by antidiabetics (n = 6; 8%) and antihistamines (n = 5; 6%) (Fig. 2E). Similarly, a wide range of therapeutic targets was identified across the studies, including protein targets (with EGFR being reported in 12 studies), oncogenic pathways, such as the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) signaling pathway, and key physiological processes such as Reactive Oxygen Species (ROS) generation, Interleukin-6/Interleukin-8 (IL-6/IL-8))regulation, apoptosis, autophagy, and cell proliferation. This broad diversity of targets reflects the complexity and heterogeneity of lung cancer, and the multiple therapeutic strategies explored in drug repositioning [87,88]. See complete information of the included studies in Table S4 and Table S5 of the Supplementary Material.

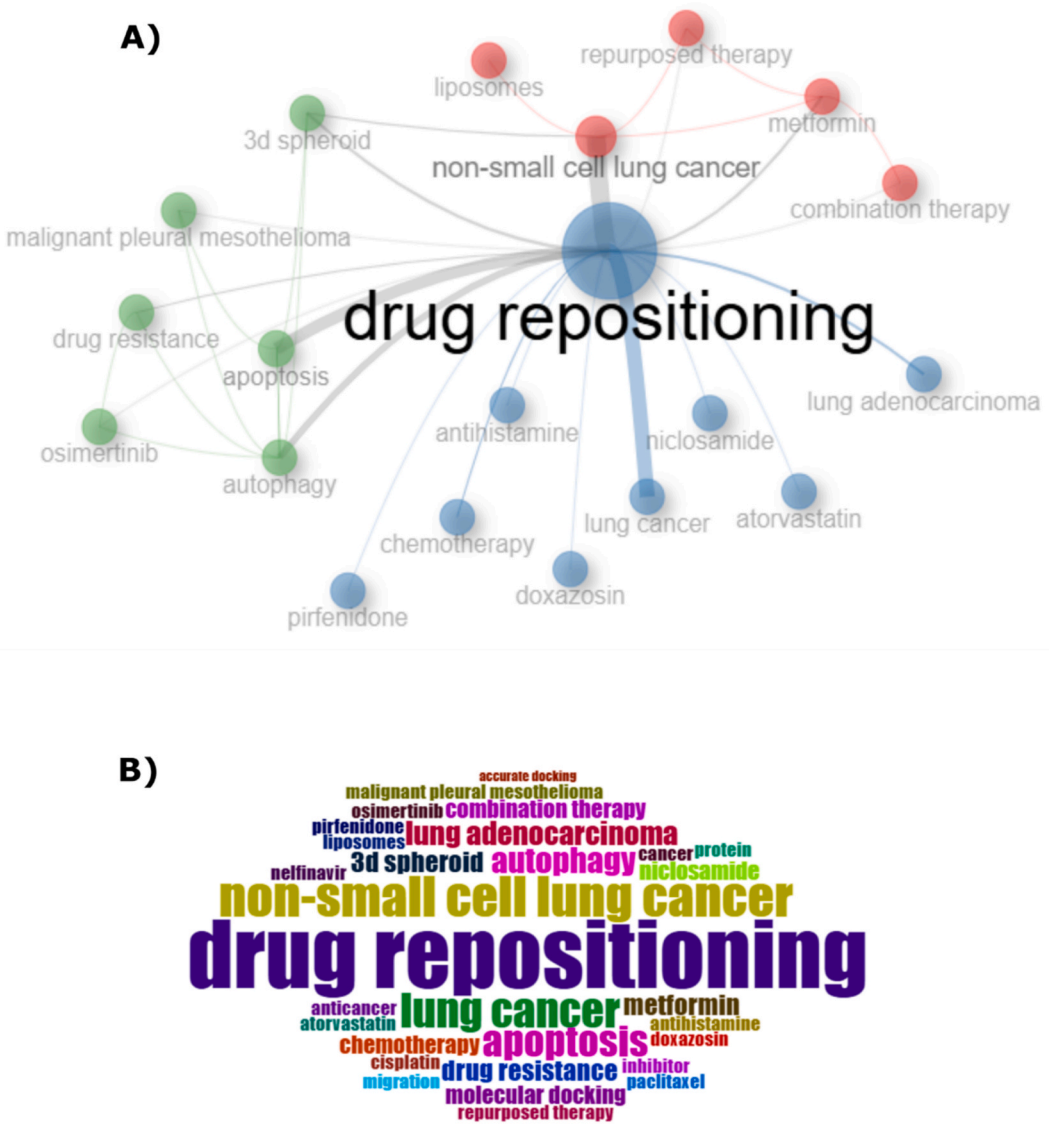

Fig. 3. Key clusters (A) and keywords (B) of articles published between 2010 and 2024.

3.2. Bibliometric analysis

As a complementary approach to the scoping review, bibliometric analysis was conducted to provide a deeper understanding of drug repurposing in lung cancer (including most studied areas and current gaps) and guide future research priorities. By quantitatively analyzing metadata - such as keyword co-occurrences, publication trends and citations, this method uncovers influential studies, emerging topics, and knowledge gaps [89].

Fig. 3A illustrates the co-word network of the included studies highlighting the main thematic connections in the field. Three major keyword clusters (represented in blue, green, and red) reflect distinct research domains in lung cancer, including therapeutic strategies, biological pathways, and specialized approaches (e.g., computational methods). Fig. 3B shows the most frequent keywords, with "drug repositioning" leading (n = 43), followed by "non-small cell lung cancer" (n = 15) and "lung cancer" (n = 11).

The blue cluster focuses on lung cancer and related therapies, with "drug repositioning" (central term) closely linked to "non-small cell lung cancer" (red cluster), which represents the most prevalent subtype of lung cancer. Related terms include "chemotherapy", "lung adenocarcinoma", and repositioning candidates as "atorvastatin", "niclosamide", "doxazosin", and "pirfenidone" - drugs investigated for their potential to modulate key cancer-related pathways such as proliferation, apoptosis, and inflammation [34,44,90,91]. The presence of individual drug names (e.g., doxycycline, rifabutin) instead of broader terms like "antibiotic" reflects a limitation of co-word networks, which prioritize frequency and connectivity. As a result, highly cited drugs may overshadow their pharmacological class, underestimating the broader therapeutic landscape [92].

The green cluster emphasizes drug resistance and key cellular processes such as "apoptosis," "autophagy," and "drug resistance," reflecting efforts to understand how repurposed drugs can modulate survival pathways in resistant tumor phenotypes. Resistance to conventional therapies in lung cancer is often linked to evasion of apoptosis, autophagy activation, and compensatory signaling [93]. The presence of "osimertinib" highlights its role in overcoming resistance in EGFR-mutant NSCLC, suggesting its use as a reference or in combination strategies [94]. This cluster points to a growing interest in repositioned drugs not only for their cytotoxic potential but also for their potential to reverse resistance and enhance targeted therapy efficacy.

The red cluster reflects a focus on "combination therapy" and advanced drug delivery. It highlights the strategic use of "repurposed therapy" alongside different delivery systems (such as "liposomes") to enhance specificity and reduce toxicity in NSCLC treatment. The placement of "non-small cell lung cancer" within this cluster, rather than the blue one, suggests its strong association with studies emphasizing therapeutic synergies and formulation innovations.

The findings from the cluster analysis and word cloud (Fig. 3) are reinforced by the TreeMap of the 30 most frequent bigrams in research titles (Fig. 4). The term "drug repositioning" dominates, appearing in 26.9 % of titles, followed by "non-small cell lung cancer" (10.3%), "lung cancer" (7.6%), "apoptosis" (6.2%), and "autophagy" (4.1%). Other recurring keywords include "metformin" (2.8%), "lung adenocarcinoma" (3.4%), "3D spheroid" (2.8%), and "drug resistance" (2.8%). Emerging computational methods are also reflected in "molecular docking" (2.1%) underscoring the growing role of *in silico* approaches in drug discovery. Traditional chemotherapeutics, "cisplatin" and "paclitaxel" (1.4% each), alongside repurposed drugs like "doxazosin", "atorvastatin", and "nelfinavir" (1.4% each), illustrate the breadth of candidates under investigation. Terms such as "liposomes" and "inhibitors" (1.4% each) further emphasize advances in drug delivery systems and targeted therapies. Specific research areas are indicated by mentions of "malignant pleural mesothelioma", "migration", "protein" (all 1.4%), reflecting focused efforts on specific mechanisms. Collectively, these patterns demonstrate a coherent and multidimensional research landscape in lung cancer drug repurposing, delineating strategic priorities and emerging directions.

The consistent mention of metformin, cited in four studies included in the scoping review conducted alongside this article, points to a growing interest in exploring its antitumor potential beyond glycemic control [95]. Evidence suggests that metformin exerts anticancer effects through mechanisms including AMP-activated protein kinase (AMPK) activation, mTOR inhibition, cell cycle arrest, and suppression of insulin/IGF-1 signaling. It also induces mitochondrial dysfunction by altering oxidative metabolism, reduces angiogenic factors like vascular endothelial growth factor (VEGF), and modulates epigenetic regulation of pro-apoptotic genes such as p53 [95,96]. Its ability to modulate tumor metabolism and enhance sensitivity to chemotherapy and targeted therapies (combined with its low cost, well-established safety, and

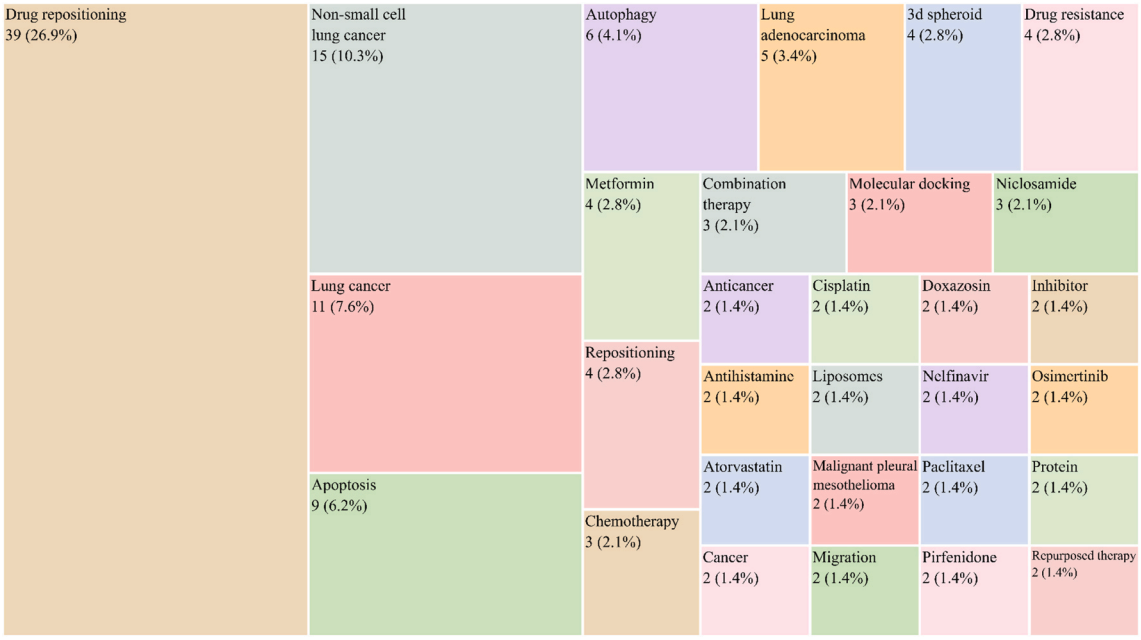

Fig. 4. A tree map of the 50 most frequently used bigrams of research titles.

pleiotropic mechanisms) positions it as a strong candidate for combination strategies in NSCLC [95,96]. Although current data are preliminary, emerging studies support its integration into precision oncology, especially for molecular subgroups with limited options [97,98].

Other mentioned drug, atorvastatin, was originally developed as a lipid-lowering agent by inhibiting HMG-CoA reductase. Recently, it has demonstrated antitumor effects in NSCLC through multiple mechanisms, such as oxidative stress, by reducing antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and total antioxidant capacity (TAC), while increasing malondialdehyde (MDA) levels, leading to cellular damage and apoptosis. Atorvastatin also downregulates VEGF and heme oxygenase-1 (HO-1), inhibiting angiogenesis and weakening cellular defenses against oxidative stress [90,99]. Additionally, it suppresses the MAPK pathway, and sensitizes mesenchymal tumor cells with high ITGB3 expression to chemotherapy by inhibiting the NF-κB signaling pathway, reducing NF-κB transcriptional activity and lowering anti-apoptotic gene expression (e.g., BCL-xL), thereby overcoming drug resistance [99]. The combination of atorvastatin and metformin has demonstrated marked synergistic effect, enhancing apoptosis, increasing the proportion of cells in the sub-G1 phase, and reducing cell viability to 15.6%, compared to 50-63% observed with monotherapies [90]. Another promising drug is niclosamide that has originally been approved as an anthelmintic [34,63]. In oncology, it seems to act as a radiosensitizer by enhancing apoptosis in cells exposed to radiation through activation of the p38 MAPK/c-Jun pathway, which increases ROS and induces cell death [100]. Additionally, it suppresses tumor growth by inhibiting the oncoprotein CIP2A, leading to reactivation of the tumor suppressor PP2A, resulting in oncogenic proteins dephosphorylation, such as Akt, c-Myc, and ERK1/2, reducing cell proliferation and causing mitochondrial dysfunction through increased mitochondrial ROS [101]. More recently, niclosamide has been shown to decrease PD-L1 expression by inhibiting STAT3 phosphorylation, thereby enhancing $CD8^{+}$ T cell cytotoxicity and improving the efficacy of anti-PD-L1 immunotherapy in combination treatments [34].

Doxazosin was also fairly explored in the included studies as an option for NSCLC. This is an alpha-1 adrenergic receptor antagonist originally used for hypertension and benign prostatic hyperplasia [44,60]. Its multifaceted action includes inducing autophagy, which restores sensitivity to the EGFR inhibitor osimertinib at non-toxic concentrations [60,102]. Doxazosin also targets cancer stem cells, potentially reducing tumor recurrence and metastasis. Additionally, it inhibits vasculogenic mimicry in 3D NSCLC models by suppressing vessel-like structure formation and downregulating markers such as VEGF-A, VE-cadherin, EphA2, MMP-2, and MMP-9, while blocking the EphA2/AKT/mTOR pathway and laminin-5γ2 cleavage, processes essential for tumor invasion and migration. This drug also promotes apoptosis by downregulating survival pathways like PI3K/AKT/mTOR and modulating EMT markers such as vimentin and fibronectin, thus reducing tumor aggressiveness [60,102].

Fig. 5 shows a thematic map based on author keywords, organized by development and relevance, highlighting current priorities and future directions in lung cancer research. Motor themes such as “autophagy”, “drug resistance”, and “chemotherapy” are well-developed and central. Themes like “drug repositioning” and “apoptosis” are relevant, but still ess extensively studied. Niche themes, including “metformin”, “combination therapy” and “atorvastatin” reflect focused, but less central research. Emerging or declining themes such as “3D spheroids” and “molecular docking” indicate early-stage or diminishing interest.

A targeted analysis of the ten most-cited studies in the bibliometric dataset (Supplementary Material – Image S2) was also performed using citation frequency as an indicator of scientific impact. This approach highlights influential contributions that have shaped the understanding and application of drug repurposing in lung cancer. Table 1 summarizes the main characteristics of these studies, which collectively highlight diverse therapeutic strategies (ranging from antidepressants, antibiotics, antifibrotics to antiparasitics) and molecular targets, underscoring the versatility of non-oncologic drugs in overcoming resistance and enhancing treatment efficacy through the modulation of apoptosis,

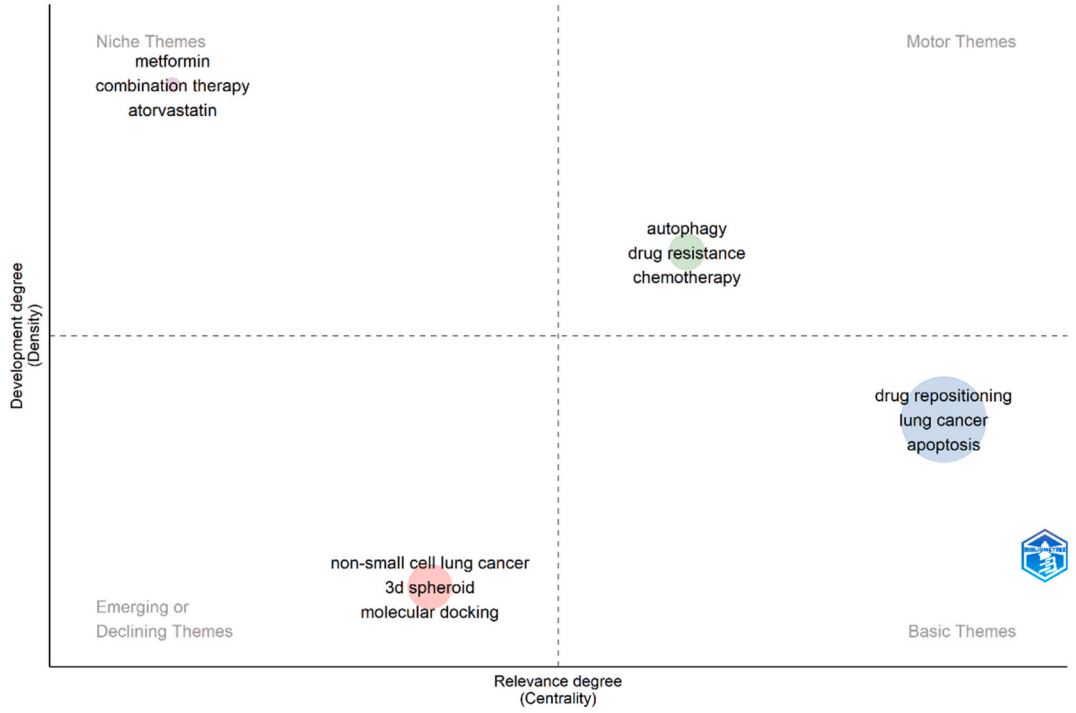

Fig. 5. Thematic map of the main topics related to drug repositioning for lung cancer. The quadrants represent different types of themes based on density (development degree) and centrality (relevance in the field): motor themes (upper right), basic themes (lower right), niche themes (upper left), and emerging or declining themes (lower left).

Table 1
Most cited articles on drug repositioning for lung cancer.

Reference	Number of citations	Drug	Type Cancer	Target/Mutation	Methodology	Main Findings
Jahchan et al. (2014) [43]	261	Imipramine, Promethazine, Clomipramine, Tranylcypromine, Pargyline	SCLC	Pathways related to G protein-coupled receptors (GPCR) and calcium signaling pathway and MAPK/JNK pathway	*In silico, in vitro,* and *in vivo*	TCAs like imipramine activated GPCR/MAPK pathways and induced cell death in SCLC, including cisplatin-resistant tumors.
Li et al. (2016) [103]	116	Auranofin	NSCLC	PI3K/AKT/mTOR pathway	*In vitro* and *in vivo*	Auranofin inhibited TXNRD, STAT3, NF-κB, and PI3K/AKT/mTOR, showing anticancer activity in lung cancer cells.
Ellegaard et al. (2016) [25]	95	Loratadine, Astemizole, Ebastine, Clemastine, Desloratadine, Terfenadine	NSCLC	Formation of LGALS1 (galectin-1), indicating lysosomal damage.	*In vitro*	CADantihistamines like loratadine reduced mortality in advanced NSCLC by enhancing chemotherapy through structural action and tissue distribution.
Van Nuffel et al. (2015) [104]	87	Clarithromycin	NSCLC	IL-6 and TNF-α, TIMP-2 and TGF-β	*In vivo*	Clarithromycin inhibited autophagy, IL-6, and angiogenesis, showing antitumor effects and increased survival in NSCLC
Luo et al. (2019) [34]	69	Niclosamide	NSCLC	PD-1/PD-L1	*In vitro* and *in vivo*	Niclosamide inhibited STAT3 phosphorylation, reduced PD-L1, increased apoptosis and T-cell infiltration, enhancing PD-L1 blockade.
Jiang et al. (2018) [105]	57	Sertraline	NSCLC	EGFR and KRAS (AMPK/mTOR)	*In vitro* and *in vivo*	Sertraline combined with erlotinib activated autophagy via AMPK/mTOR, showing antitumor effect in EGFR TKI-resistant NSCLC.
Parvathaneni et al. (2020) [55]	56	Pirfenidone	SCLC	PI3K-AKT-mTOR	*In vitro*	PFD–D-Lip formulation reduced colony growth 1.5–2 times in NSCLC cells, highlighting inhalable liposomal pirfenidone as a promising strategy.
Song et al. (2016) [106]	55	Levofloxacin	NSCLC and SCLC	EGFR and KRAS	*In vitro* and *in vivo*	Levofloxacin induced mitochondrial dysfunction, oxidative stress, inhibited complexes I and III, reduced ATP, and showed anticancer activity in lung cancer.
Stachnik et al. (2014) [107]	47	Zoledronate and Risedronate	NSCLC	HER-driven	*In vitro* and *in vivo*	Bisphosphonates (zoledronate, risedronate) bound HER1/2 kinase, reduced tumors, and enhanced TKIs, including resistant cases.
Lee et al. (2014) [63]	42	Niclosamide	NSCLC	p38 MAPK-*c*-Jun	*In vitro*	Niclosamide activated p38 MAPK-*c*-Jun pathway, increased apoptosis and radiosensitivity dose-dependently, enhancing radiotherapy.

*SCLC (Small Cell Lung Cancer); NSCLC (Non-Small Cell Lung Cancer); GPCR (G Protein-Coupled Receptors); MAPK (Mitogen-Activated Protein Kinase); JNK (c-Jun N-terminal Kinase); PI3K (Phosphoinositide 3-Kinase); AKT (Protein Kinase B); mTOR (Mammalian Target of Rapamycin); TXNRD (Thioredoxin Reductase); STAT3 (Signal Transducer and Activator of Transcription 3); NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells); LGALS1 (Galectin-1); IL-6 (Interleukin 6); TNF-α (Tumor Necrosis Factor Alpha); TIMP-2 (Tissue Inhibitor of Metalloproteinases 2); TGF-β (Transforming Growth Factor Beta); PD-1 (Programmed Cell Death Protein 1); PD-L1 (Programmed Death-Ligand 1); EGFR (Epidermal Growth Factor Receptor); KRAS (Kirsten Rat Sarcoma Viral Oncogene Homolog); AMPK (AMP-Activated Protein Kinase); HER1/2 (Human Epidermal Growth Factor Receptor 1/2); TKI (Tyrosine Kinase Inhibitor); p38 MAPK (p38 Mitogen-Activated Protein Kinase).

autophagy, oxidative stress, immune evasion, and synergy with existing therapies Studies were published between 2014 and 2020, presented between 42 and 261 citations, and assessed mostly NSCLC.

The most cited article was prepared by Jahchan and colleagues (2014) identified tricyclic antidepressants (imipramine, promethazine) as selective inhibitors of small cell lung cancer (SCLC) growth via disruption of neuroendocrine autocrine signaling and induction of apoptosis, validated across sensitive and resistant models *in vitro* and *in vivo* [43]. Similarly, Jiang et al. (2018) repurposed the antidepressant sertraline to enhance the efficacy of the tyrosine kinase inhibitor (TKI) erlotinib in treatment-resistant NSCLC cell lines (A549, H522, H1975, PC9, and PC9/R), acting through AMPK/mTOR-dependent autophagy. The combination demonstrated synergistic antiproliferative effects in resistant cells and significantly improved survival in murine models [105].

Li and colleagues (2016) (the second most cited paper) proposed auranofin, a gold-based antirheumatic, as an inhibitor of the PI3K/AKT/mTOR pathway (through the suppression of AKT, mTOR, p70S6K, and 4EBP1 phosphorylation) inducing apoptosis and necroptosis in NSCLC in *in vivo* mouse xenograft models. Favorable pharmacologic profiles were also reported across ten NSCLC cell lines (Calu3 and HCC366 showing high sensitivity to treatment; $IC_{50} < 1$ μM), supporting the potential for rapid clinical translation [103].

In another highly cited article, Ellegaard and coworkers (2016) showed that cationic amphiphilic antihistamines (e.g., loratadine, astemizole) selectively accumulate in NSCLC cell lysosomes, inducing lysosomal membrane permeabilization and cell death. In A549, H1299, H661, and A549-MDR cell lines, these agents sensitized tumors to docetaxel and vinorelbine at submicromolar concentrations (indicar o range). Epidemiological data from Danish registries further linked loratadine use to reduced mortality in metastatic NSCLC patients, especially when combined with chemotherapy [25].

Van Nuffel and collaborators (2015) analyzed preclinical and clinical evidence on the use of the antibiotic clarithromycin, a macrolide, as an adjuvant agent in various types of cancer (quais). The drug demonstrated antitumor effects through autophagy inhibition, immune activation ($CD8^+$ T cells, NK cells), and antiangiogenic activity. In Lewis lung carcinoma models (C57BL/6 mice), it reduced tumor nodules and enhanced cisplatin/vindesine efficacy when administered with delayed timing. In vitro and *in vivo* studies, along with clinical data, showed improved outcomes - especially in hematological cancers when combined with agents like lenalidomide and dexamethasone - supporting further clinical evaluation of clarithromycin in NSCLC [104].

Niclosamide has been repurposed for NSCLC through distinct yet

complementary therapeutic strategies. Luo and colleagues (2019) demonstrated its efficacy as an adjuvant to immune checkpoint blockade therapy by inhibiting STAT3 phosphorylation, thereby reducing PD-L1 expression in tumor cells. This modulation enhanced T-cell activation, increased lymphocyte tumor infiltration, and elevated granzyme B release. Accordingly, these effects were validated in NSCLC cell lines (A549, H1299 and H460) and *in vivo* murine LLC model, resulting in significantly improved immunotherapy responses and prolonged survival. In another study, niclosamide acted as a radiosensitizer agent by potentiating ionizing radiation-induced apoptosis via ROS generation and p38 MAPK and c-Jun pathways activation in H1299 cells [34,63].

The study of Parvathaneni and collaborators (2020) repurposed pirfenidone (PFD), an antifibrotic agent, for localized NSCLC. To enhance efficacy and reduce systemic toxicity, PFD was loaded in inhalable cationic liposomes. The formulation demonstrated greater cytotoxicity than free PFD against four NSCLC cell lines (A549, H157, H460 and H4006), presenting 1.5- to 2-fold higher colony formation inhibition, enhanced penetration in 3D spheroids, and suppression of angiogenesis and cell migration, potentially via AKT/β-catenin signaling. The optimized liposomes exhibited suitable aerodynamic properties for pulmonary delivery and increased ex vivo action, highlighting this approach as a promising for NSCLC therapy [55].

Bisphosphonates (e.g., zoledronic acid) were investigated by Stachnik and coworkers (2014) as inhibitors of the HER1/2 signaling pathway in NSCLC and triple-negative breast cancer. These agents bind the HER1 kinase and enhance the efficacy of TKIs such as erlotinib, even in cells harboring the resistance-inducing T790 M mutation. The study combined computational modeling with *in vitro* and *in vivo* approaches, showing strong translational potential. However, clinical applicability remains limited due to the high bone affinity of bisphosphonates, which impairs their bioavailability in soft tumor tissues - highlighting the need for reformulations to improve delivery systems [107].

Lastly, Song and colleagues (2016) showed that levofloxacin exerts antitumor action in both NSCLC and SCLC models. The drug induced mitochondrial dysfunction by disrupting electron transport chain complexes I and III, increasing ROS production and promoting apoptosis. These effects were validated by *in vitro* assays in different cell lines (A549, H460, H3255) and in xenograft models. While the findings sparks the potential of antibiotic repositioning in oncology, limitations include a lack of data on tumor selectivity and resistance models, as well as concerns about systemic toxicity at higher doses, warranting further clinical investigation [106].

4. Conclusions

This scoping review, supported by a bibliometric analysis, demonstrates drug repositioning as a strategic, and increasingly prominent approach for lung cancer treatment, particularly NSCLC. Over the past years, there has been a marked increase in research output, alongside a qualitative shift toward more advanced investigative approaches. Emerging themes such as nanosystems and computational tools (e.g., molecular docking) reflect the growing integration of technological innovation with efforts to address unmet clinical needs in this field. The methodological diversity - dominated by *in vitro* studies and complemented by *in silico* and *in vivo* research - reflects a synergistic, multidisciplinary effort to identify new therapeutic uses for approved drugs. Similarly, the use of a variety of cell lines (e.g., A549, H460, H1299) representing various lung cancer types and subtypes, underscores attempt to capture the disease's biological complexity. Multiple therapeutic classes, including drugs as niclosamide, metformin and atorvastatin, are being explored, often alongside standard treatments, targeting critical oncogenic pathways like PI3K/AKT/mTOR, MAPK, apoptosis, autophagy, and immune evasion.

The alignment of the synthesized preclinical evidence presented in this review with the expanding body of research underscores the urgent need to advance well-designed clinical trials in the field.

By providing a comprehensive and up-to-date review while mapping current trends and gaps in the field, our study can guide future research priorities, foster interdisciplinary collaboration, and inform public health strategies aimed at accelerating access to effective repurposed therapies for lung cancer.

CRediT authorship contribution statement

Wellington Martins de Carvalho Ragassi: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Fernando Miguel Stelmach Alves:** Writing – original draft, Methodology, Formal analysis. **Raul Edison Luna Lazo:** Writing – review & editing, Investigation, Data curation. **Fernanda Stumpf Tonin:** Tonin, Writing – review & editing, Methodology, Investigation, Data curation. **Roberto Pontarolo:** Writing – review & editing, Supervision, Resources, Conceptualization. **Marcel Henrique Marcondes Sari:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Luana Mota Ferreira:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2026.112048.

Data availability

No data was used for the research described in the article.

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Glossary

AKT -: Protein kinase B
AMPK -: AMP-activated protein kinase
BCG -: Bacillus Calmette - Guérin
CAT -: Catalase
EGFR -: epidermal growth factor receptor
GI50 -: Growth Inhibition 50
GPCR -: G Protein-Coupled Receptors
HER1/2 —: Human Epidermal Growth Factor Receptor 1/2
IL-6 -: Interleukin 6
IL-8 -: Interleukin-8
IC50 -: Inhibitory Concentration 50
JNK -: c-Jun N-terminal Kinase
KRAS -: Kirsten rat sarcoma viral oncogene homolog
LGALS1 -: Galectin-1
MAPK -: Mitogen-Activated Protein Kinase
MDA –: Malondialdehyde
mTOR -: Mammalian Target of Rapamycin
NF-κB -: Nuclear Factor kappa-light-chain-enhancer of activated B cells
NSCLC -: Non small cell lung cancer
p38 MAPK —: p38 Mitogen-Activated Protein Kinase
PD-1 —: Programmed Cell Death Protein 1
PD-L1 —: Programmed Death-Ligand 1
PI3K -: Phosphoinositide 3-kinase
ROS -: Reactive Oxygen Species
SCLC -: Small Cell Lung Cancer
SOD -: Superoxide Dismutase
STAT3 -: Signal Transducer and Activator of Transcription 3
TAC -: Total Antioxidant Capacity
TGF-β -: Transforming Growth Factor Beta
TIMP-2 -: Tissue Inhibitor of Metalloproteinases 2
TKI —: Tyrosine Kinase Inhibitor (Inibidor de Tirosina Quinase)
TNF-α -: Tumor Necrosis Factor Alpha
TXNRD -: Thioredoxin Reductase