International Journal of Scientific & Engineering Research, Volume 14, Issue 9, September-2023
ISSN 2229-5518

Repurposing Non-Cancer Drugs for the Treatment of Lung Cancer

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Abstract—Lung cancer (LC) possesses considerable malignancy and propensity for metastasis, resulting in it being the primary contributor to cancer-related fatalities globally, responsible for 18% of cancer-related deaths. Escalating rates of treatment failure, limited bioavailability, safety concerns, elevated expenses, and protracted drug development processes in cancer therapy have prompted the exploration of alternative avenues for drug discovery. Investigating established non-cancer medications for their potential anticancer effects offers a rapid route for advancing therapeutic strategies into clinical trials. The rationale behind repurposing non-cancer drugs for cancer treatment stems from the shared molecular pathways and targets that various diseases exhibit within cells. Consequently, drugs initially designed to combat diabetes, infections, inflammation, hyperlipidemia, psychiatric disorders, and parasitic infections are being reconsidered for lung cancer treatment. This review extensively discusses the repurposing of these drugs as potential treatments for lung cancer.

Index Terms—Lung cancer, Repurposed drugs, Anti-diabetic drugs, Anti-microbial drugs, Nonsteroidal anti-inflammatory drugs, Anti-hyperlipidemic Drugs, Penfluridol.

1 Introduction

LUNG cancer (LC) demonstrates a profoundly malignant and metastatic propensity, establishing it as the foremost contributor to worldwide cancer-related fatalities, encompassing 18% of such deaths [1]. Surgical resection of the tumor is considered the best treatment option for LC but is only feasible without metastasis. Unfortunately, nearly 55% of all LC cases are diagnosed only after detecting a locally advanced or metastatic tumor [2]. Additionally, a significant proportion of lung cancer patients experience cancer relapse with metastasis after undergoing surgical resection [3]. Once the cancer has spread, chemotherapy and targeted therapy should be employed [4].

For numerous years, platinum-based chemotherapies have stood as the prevailing treatment for lung cancer [2]. Recently, immunotherapy has emerged as a successful standard treatment in several cancers, either on its own or when combined with conventional therapies like radiotherapy and chemotherapy [5]. In non-small cell lung cancer (NSCLC), immune checkpoint inhibitors (ICIs) have been extensively examined in conjunction with diverse chemotherapies. This investigation has encompassed prospective Phase II and III clinical trials as well as retrospective studies, all of which have demonstrated encouraging outcomes. However, advancements notwithstanding, instances of resistance and relapse following extended periods of ICIs treatment have spurred researchers to delve into supplementary therapeutic avenues catering to the needsof lung cancer patients [6].

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Traditional drug discovery involves target discovery and validation, medicinal chemistry, and high-throughput screening. Using animal models, pre-clinical development evaluates compound efficacy, specificity pharmacology, drug interaction, and toxicology studies. However, the high-risk economic aspect of drug discovery in the pharmaceutical industry has led to oncological products being governed by marketing laws. Consequently, many newer cancer drugs are expensive for most patients globally and may not provide significant clinical benefits per current evaluation criteria [7], [8]. Furthermore, the journey of a single drug from discovery to widespread clinical use spans an average of 13 years. Notably, only 1 in 5,000 potential anticancer agents and a mere 5% of drugs entering phase I trials achieve approval from the U.S. Food and Drug Administration (FDA). These challenges have motivated researchers to explore alternative approaches for cancer drug development [9], [10].

Researchers have employed various strategies to expedite cancer drug development and reduce costs. The approach involves evaluating established non-cancer drugs that were previously approved for non-cancerous conditions. Due to earlier verified preclinical and Phase I studies, these drugs possess well-known targets, reliable biomarkers, and pharmacodynamic, pharmacokinetic, and toxicity profiles [11]. This approach, drug repurposing or repositioning, has gained significant attention over the last decade. Utilizing existing drugs with known safety profiles can rapidly progress into Phase II and III clinical trials, reducing costs significantly. Various effective methods have been employed to discover and incorporate non-cancer drugs into treatments related to lung cancer [12]. This review aims to briefly outline the repurposed drugs applied in lung cancer therapy, addressing their limitations and discussing novel endeavors to address these challenges.

2REPURPOSED DRUGS

2.1 Anti-diabetic drugs (Metformin and Pioglitazone)

Metformin is a frequently prescribed oral anti-diabetic agent for type 2 diabetes. It acts through various mechanisms to reduce serum glucose levels, including increasing the effects of insulin, suppressing endogenous glucose production, and activating the enzyme adenosine monophosphate kinase. Furthermore, metformin enhances glucose disposal in peripheral tissues through increased non-oxidative utilization in skeletal muscles, exhibiting potential antitumor effects and reducing inflammatory responses [13], [14], [15].

In 2005, Evans et al. [16] demonstrated a reduced cancer risk among type 2 diabetes patients prescribed metformin, leading to subsequent numerous studies on metformin's potential in cancer therapy [17]. Recent significant reports have focused on the potential of combining anticancer drugs with metformin. Ko et al. [18] demonstrated that the combined therapy of metformin and trametinib led to a synergistic decrease in cancer cell viability when administered at lower doses, while it had an antagonistic effect at higher doses. Metformin exhibited a synergistic interaction with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), leading to reduced cell proliferation and enhanced apoptotic effects on EGFR-TKI-resistant cells while also delaying the emergence of resistance to EGFR-TKIs. [19], [20]. Moreover, immune checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab, and atezolizumab, combined with metformin, resulted in substantial stability in both NSCLC and SCLC [6], [21], [22]. Viveiros et al. [21] reported enduring disease stability in metastatic lung adenocarcinoma when incorporating metformin into the nivolumab treatment regimen. A year later, the same team exhibited a case of SCLC that displayed a notable, sustained response to the combination of metformin and nivolumab therapy for more than six months [22]. Detailed observations from studies combining anticancer drugs are summarized in Table 1.

TABLE 1
SYNERGISTIC INTERACTION OF METFORMIN WITH ANTICANCER DRUGS

-	Cancer Subtype	Anticancer drug	Observation	Reference
1	NSCLC	Trametinib	The combined therapy exhibited a synergistic reduction in cell viability when administered at low doses of both drugs (metformin 0.25 mM; trametinib 2.5 nM), whereas it resulted in an antagonistic effect at higher doses (metformin 4 mM; trametinib 40 nM).	[18]
2	NSCLC	EGFR-TKIs (Gefitinib and Osimertinib)	Metformin showed a synergistic interaction with EGFR-TKIs, resulting in decreased cell proliferation and augmented apoptotic effects on EGFR-TKI-resistant cells. The metformin-treated group displayed a significantly higher objective response rate (85.7% vs. 47.4%) and notably extended median progression-free survival and overall survival (21.6 vs. 9.2 months).	[19]
3	NSCLC	EGFR-TKIs	Metformin not only impeded the growth and induced cell death in lung cancer cells, especially those with EGFR-TKI resistance, but it also effectively combated and delayed the development of resistance to EGFR-TKIs.	[20]
5	Adenocarcinoma	Nivolumab	The addition of metformin to nivolumab regimen resulted in long-term disease stability coinciding of metastatic lung adenocarcinoma. This result might be correlated to enhancong anti-PD-1/PD-L1 activity of metformin.	[21]
6	SCLC	Nivolumab	Metformin along with nivolumab therapy resulted in a significant durable response of SCLC.	[22]
7	NSCLC	ICIs (nivolumab, pembrolizumab, atezolizumab)	Patients who underwent ICIs therapy along with metformin demonstrated an elevated response rate, as well as improvements in median progression-free and overall survial, in comparison to patients who solely received ICIs therapy.	[6]

Despite ongoing endeavors to explore the anticancer potential of metformin, limited clinical applicability has been hindered by its low bioavailability resulting from its highwater solubility and limited cell permeability [23]. The rational design of nanoparticulate drug delivery systems could significantly improve drug delivery efficiency [24]. Hyaluronic acid-cisplatin/polystyrene-polymetformin nanoparticles were developed byYang et al. [25]. These nanoparticles demonstrated efficient intracellular co-delivery and cleavage of metformin and cisplatin within tumor cells and tissues, ultimately leading to a synergistic antitumor effect. In a study conducted by Samadzadeh et al. [26], the electrospinning technique was employed to create nanofibers (NFs) using poly lactic-co-glycolic acid (PLGA) polymer, incorporating metformin. The PLGA NFs loaded with metformin exhibited notably higher cytotoxicity against A549 lung cancer cells than free metformin. Additionally, the metformin-loaded NFs effectively elevated intracellular ROS levels, resulting in apoptosis of cancer cells. Furthermore, PLGA/polyethylene glycol (PEG) nanoparticles co-loaded with metformin and silibinin developed by Javan et al. [27] showed a synergetic cytotoxic effect in lung cancer A549 cells. These magnetic nanoparticles inhibited the leptin gene and its receptor expression, consequently suppressing cancer

cell growth stimulated by leptin through the ERK1/2 pathway.

Pioglitazone is widely recognized as an antidiabetic medication, functioning as a synthetic ligand for the peroxisome proliferator-activated receptor (PPAR-γ) to regulate lipid and glucose metabolism within cells. Notably, this antidiabetic agent has garnered attention as a suppressor of cancer cell processes. Recent research by Kiran et al. [28] exhibited that the combined treatment involving pioglitazone and celecoxib significantly reduced the tumor weight of NSCLC. Additionally, this therapy improved patients' lifespan and mean survival time. Furthermore, Ciaramella et al. [29] unveiled that pioglitazone effectively diminished the NSCLC cell proliferation and invasion by inhibiting MAPT cascade and TGFβ/SMADs signaling pathways.

2.2 Anti-microbial drugs (Itraconazole and Bedaquiline)

Itraconazole is commonly prescribed to address fungal or yeast infections, and it has also exhibited anti-proliferative and anti-angiogenic properties in various cancers, including lung, breast, brain, prostate, and skin cancer [30], [31]. Particularly in lung cancer, itraconazole displays robust and selective inhibition against vital components of tumor-related angiogenesis both in vitro and in vivo, providing strong support for its clinical applicability [32]. In a small phase II study, Rudin et al. [33] combined itraconazole with standard chemotherapy, leading to higher overall and median progression-free survival rates. Specifically, the overall survival was extended to 32 months with itraconazole, compared to 8 months in the control group. Additionally, median progression-free survival times were 5.5 months with itraconazole and 2.8 months in the control group. Gerber et al. [34] reported that NSCLC patients with an Eastern Cooperative Oncology Group performance status of 0–2, exhibited a significant reduction in tumor volume when administered high-dose itraconazole. Moreover, itraconazole has beneficial effects in metastatic NSCLC regarding clinical benefit-, overall response-, and 1-year progression-free survival rate [35].

In recent years, diverse studies have possessed the anticancer effect of itraconazole linked to inhibiting the Hedgehog (Hh) signaling pathway [36]. The Hh signaling pathway is activated abnormally due to various factors such as overexpression of Hh ligands, receptor dysfunction, or disruption of transcription factors. These abnormalities have been linked to the development and advancement of different cancer types, including NSCLC and SCLC, through various pathways [37], [38], [39] (Figure 1).

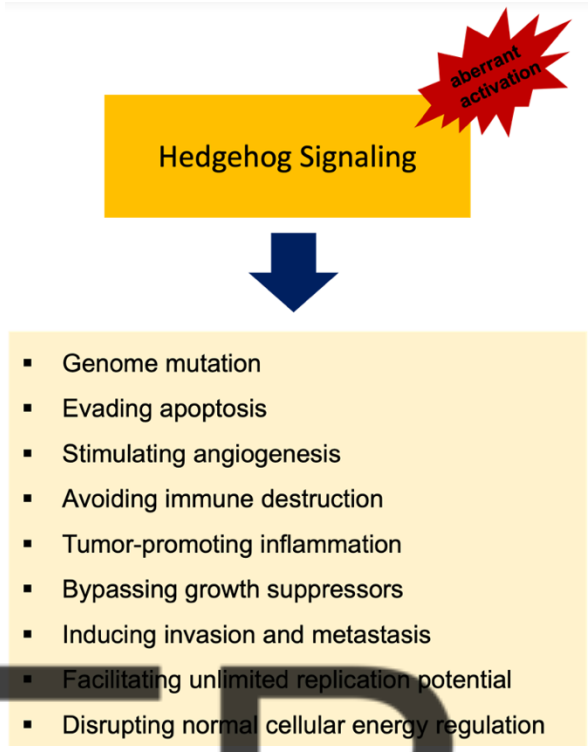

Fig 1. Associations between Hallmarks of Cancer and AberrantlyActivated Hedgehog Signaling

Apart from its impact on the Hh pathway, itraconazole also influences the Wnt signaling pathway, contributing to the advancement of lung cancer stem cells (CSCs). Chen and Zhang [40] demonstrated that itraconazole effectively decreased CD133 and ABCG2 expression in lung cancer cells that exhibited positive CSC markers by suppressing the Wnt signaling pathway. Additionally, itraconazole inhibited β-catenin and Wnt3 expression in cancer cells, both of which are key components that regulate the Wntsignaling pathway [40],[41].

Despite revealing significant potential as an anticancer agent, itraconazole has limitations, such as poor water solubility, which hinders its clinical utility. Alhakamy et al. [30] developed chitosan-coated PLGA nanoparticles loaded with itraconazole and investigated their anticancer effects in lung cancer cells to address this limitation. Compared to the itraconazole solution, the itraconazole nanoparticles demonstrated more significant cytotoxicity and induction of apoptosis. At the molecular level, the itraconazole nanoparticles were more effective in promoting p53 and Bax expression, while reducing Bcl2 expression. Additionally, Zhang et al. [42] demonstrated that co-encapsulation of paclitaxel and itraconazole enhanced the effectiveness of inhibiting tumor growth, preventing recurrence, and reversing paclitaxel resistance. This effect was more significant than that achieved with paclitaxel monotherapy or combination therapy using separate paclitaxel and itraconazole micelles, attributed to the strong intermolecular interactions between the encapsulated agents.

Bedaquiline, an FDA-approved agent, is used to treat multi-

drug-resistant pulmonary tuberculosis by inhibiting the bacterial ATP-synthase. Often used alongside other antibiotics, bedaquiline exhibits significant efficacy against drug-sensitive and drug-resistant tuberculosis. Recent research has demonstrated its ability to impede mitochondrial respiration and glycolysis in lung cancer cells, leading to growth inhibition and angiogenesis suppression, ultimately curbing tumor progression [43]. However, bedaquiline possesses low water solubility and high permeability. These characteristics result in limited bioavailability and effectiveness, necessitating high, prolonged doses. Addressing these challenges, a study by Patil et al. [44] developed inhalable bedaquiline-loaded cubosome (BQLC) nanocarriers showing an encapsulation efficiency of 51.85 ± 4.83% (boasting a particle size of 150.2 ± 5.1 nm; zeta potential of (+) 35.4 ± 2.3 mV). The BQLC exhibited increased cytotoxicity and cellular internalization, demonstrating nearly a threefold reduction in IC_{50} compared to free bedaquiline treatment in human lung adenocarcinoma A549 cells. Similarly, Parvathaneni et al. [45] designed inhalablebedaquiline-cyclodextrin (BDQ-CD) complexes to enhance bedaquiline's solubility and anti-cancer efficacy in NSCLC cells. The complexation achieved a substantial ~2.8×103-fold solubility enhancement. The improved aqueous solubility contributed to an enhanced cytotoxic impact on H1299 cells.

2.3 Nonsteroidal anti-inflammatory drugs (Celecoxib and Indomethacin)

Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit analgesic, antipyretic, and anti-inflammatory properties by inhibiting cyclooxygenase (COX) enzymes [46]. Of particular interest is COX-2, which is linked to increased cell proliferation and decreased apoptosis; both are critical for promoting invasive tumor growth and metastasis. As a pivotal checkpoint, inhibiting COX-2 is crucial in combating these processes [47].

Celecoxib, a specific COX-2 inhibitor, is recommended by the FDA as a primary analgesic for individuals suffering from osteoarthritis and rheumatoid arthritis. It also holds FDA approval for managing acute pain in adult women and primary dysmenorrhea [48]. In most lung cancer cases, the anticancer mechanism of COX-2 inhibitor is associated with inducing apoptosis by reducing BAX, BCL-xL, NF-kB, and caspase-9 expression [49]. A combination therapy of celecoxib and afatinib, a second-generation irreversible ErbB family inhibitor commonly used for NSCLC treatment, resulted in a synergistic improvement in radiotherapy sensitivity for A549 cells by inhibiting COX-2 and EGFR expression [50]. Indomethacin, one of the NSAIDs, functions as a nonselective inhibitor of cyclooxygenase enzymes and addresses mild to moderate acute pain while relieving symptoms associated with arthritis or gout. Research carried out by Sarvepalli et al. [51] discovered notable COX-2 inhibition and caspase induction within all NSCLC groups treated with indomethacin. Simultaneously, several studies have proposed the potential engagement of NSAIDs in COX-2-independent pathways for lung cancer. Liu et al. [52] demonstrated that celecoxib is bound to 3-phosphoinositide-dependent protein kinase-1 (PDK-1), effectively suppressing the PDK1/Akt pathway. In addition, the inhalation of celecoxib induced cytotoxic and apoptotic reactions in human NSCLC cells in vitro, as evidenced by the increased expression of PPAR-γ and p53 [53].

Due to limited aqueous solubility, there have been suggestions for combinatorial therapies involving celecoxib with other drugs. The combined treatment of low concentrations of celecoxib and curcumol demonstrated increased sensitivity compared to using each drug independently, with the synergistic effects attributed to the activation of caspase-9/caspase-3 and G1 cell cycle arrest, suppression of NF-κB activity, and inhibition of PI3K/AKT signaling pathways, ultimately leading to apoptosis [54]. The combination of low doses of celecoxib with sorafenib, a vascular endothelial growth factor receptor inhibitor, induced apoptosis by reducing the expression of apoptosis-inhibiting genes, including survivin and Bcl-2 [55]. On the other hand, Emami et al. [56] developed PLGA nanoparticles loaded with celecoxib, possessing spherical shapes and particle sizes ranging from 153 to 192 nm, to enhance their cytotoxicity for treating lung cancer. These PLGA nanoparticles displayed enhanced cytotoxicity against A549 tumor cells, although this effect was observed only at higher concentrations than celecoxib alone.

2.4 Anti-Hyperlipidemic Drugs (Statins)

Statins are the most effective medications for reducing low-density lipoprotein (LDL) cholesterol levels. These medications share structural similarities with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and function by competitively inhibiting HMG-CoA reductase, an enzyme critical in this process[57]. Beyond their cholesterol-lowering capabilities and consequential cardiovascular risk reduction, statins have shown promise in lung cancer prevention and treatment [58]. Various studies have shown that statins can trigger apoptosis in various tumor cell types. The mechanisms behind this apoptotic induction are closely linked to their dual roles in mevalonate synthesis suppression and HMG-CoA reductase inhibition [59]. Notably, statin treatment has been linked to increased expression of pro-apoptotic agents such as Bax, Bak, and Bim, coupled with diminished levels of apoptosis-inhibiting molecules like Bcl-2. Furthermore, through suppressing pro-angiogenic elements such as vascular endothelial growth factor, statins exert an inhibitory effect on tumor angiogenesis [60].

Both preclinical and clinical data have demonstrated that statins possess anti-proliferative, anti-invasive, and pro-apoptotic properties. Walther et al. [61] showed that lovastatin decreased cell viability and DNA fragmentation initiation in lung cancer. This study observed elevated intracellular lactone levels that triggered apoptotic cell death by upregulating COX-2 while augmenting the production of PGD2, which activates peroxisome proliferator-activated receptor γ (PPARγ). At the molecular level, simvastatin demonstrated its capacity to induce apoptosis in p53-mutated cells alongside inhibiting cell growth and proliferation [62]. Recent evidence has emphasized fluvastatin's anti-proliferative and chemotherapeutic properties in lung cancer. Overexpression of HMG-CoA reductase (HMGCR), a rate-limiting enzyme in the mevalonate pathway, is observed in NSCLC tissues compared to normal tissues. Zhang et al. [63] revealed that fluvastatin-induced

HMGCR knockdown hindered tumorigenesis, curtailed cell growth, and prompted apoptosis.

2.5 Penfluridol

Penfluridol, commonly known to treat schizophrenia and psychotic patients with similar symptoms, was discovered in 1968 by Janssen Pharmaceutica. This drug is one of the first generations of diphenylbutylpiperidine antipsychotics, a class of commonly used antipsychotic drugs [64]. Penfluridol's antipsychotic effects arise from its ability to block dopamine receptors, with a notable emphasis on D2 receptors [65]. Recently, penfluridol has been revealed to exert oncostatic effects in various cancer types, including lung, colon, breast, pancreatic, and brain cancer. Penfluridol might suppress cancer cell proliferation, impede metastasis and invasion, induce cancer cell death, and hinder angiogenesis and cancer cells to avoid immune destruction [66] (Figure 2).

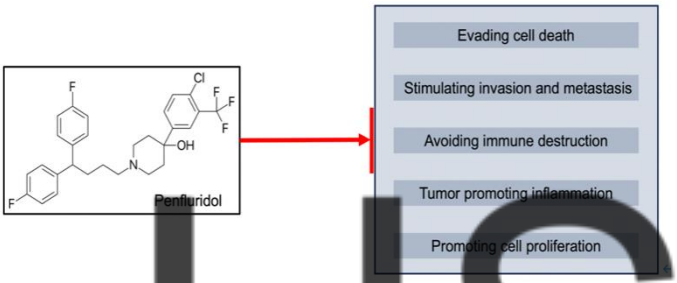

Fig 2. The hallmarks of cancer inhibited by penfluridol.

The effects and mechanisms of penfluridol in relation to lung cancer remain unclear. However, several studies established the anticancer activity of penfluridol against lung cancer. Wu et al. [67] determined that penfluridol exhibits in vitro cytotoxic potential (IC_{50} (μmol/L) of 2.45/48h) and can inhibit tumor growth in vivo. The study identified a dose-dependent reduction in total cholesterol within tumor tissues, suggesting penfluridol's anticancer mechanism might involve cholesterol homeostasis dysregulation. Ashraf-Uz-Zaman et al. [68] observed penfluridol's cytotoxic effect at high dosages, with an IC_{50} (μmol/L) of 4.3/24h. However, these dosages considerably exceeded those employed in antipsychotic therapy, prompting concerns about the potential onset of central nervous system side effects in patients undergoing intensive pharmacological treatment. Hung et al. [69] suggested nontoxic concentrations of penfluridol, which significantly reduced lung adenocarcinoma cells' migration, invasion, and adhesion. The study proposed matrix metalloproteinase-12 (MMP-12) as a potential target for penfluridol in modulating cancer cell adhesion and motility. By inhibiting the urokinase plasminogen activator (uPA)/uPA receptor/transforming growth factor-β/Akt axis, penfluridol downregulated MMP-12 expression, subsequently reversing MMP-12-induced epithelial-mesenchymal transition. Xue et al. [70] demonstrated that penfluridol curtailed the viability of lung cancer cells by inducing G0/G1 phase arrest, decreasing cyclin-CDK complex levels, and increasing p21/p27 expression. Additionally, penfluridol disrupted mitochondrial membrane potential and escalated reactive oxygen species levels, pointing towards a potential mitochondria-mediated intrinsic apoptosis pathway.

Considering the emergence of autophagy as an alternative cancer drug delivery strategy due to resistance arising from impaired apoptosis [71], Hung et al. [72] proposed that penfluridol instigates endoplasmic reticulum (ER) stress-mediated autophagosome accumulation, causing ATP energy depletion. Through this mechanism, penfluridol suppressed NSCLC cell proliferation. By impeding autophagic flux, penfluridol led to non-apoptotic cell death, characterized by autophagosome-related protein LC3 B-II accumulation. A subsequent study disclosed that penfluridol suppressed mitochondrial oxidativephosphorylation by targeting the SIRT1/PGC-1α axis, reducing ATP production, especially in mutant KRAS-expressing NSCLC cells [73].

2.6 Other Drugs

Repurposing of anti-helminthic, anti-retroviral, and anti-malarial drugs for NSCLC treatment is proposed, yet clinical studies still need to be made evident. The potentials of these drugs in lung cancer therapy are summarized in Table 2.

TABLE 2
REPURPOSED DRUGS SHOWING ANTICANCER PROPERTIES

	Property	Repurposed drug	Effects	References
1	Anti-helminthic	Mebendazole	Induction of apoptosis and mitotic arrest by depolymerizing tubulin.	[74]
		Niclosamide	Downregulation of PD-L1 expression.	[75]
			Diminishing the nuclear localization of STAT3 in radioresistant cancer cells.	[76]
2	Highly active anti-retroviral	Efavirenz and Lopinavir/Ritonavir	Induction of S-phase arrest. Decrease of cancer cell viability.	[77]
3	Anti-malarial	Atovaquone	Reduction of tumor hypoxia	[78], [79]

3 Conclusion and Future Outlooks

Despite the increasing survival rates, lung cancer remains the foremost contributor to cancer-related fatalities worldwide. The convergence between drugs designed for distinct conditions and the shared pathways within various lung cancer subtypes underscores a promising avenue. Harnessing the concept of drug repurposing offers a rapid and cost-effective approach to introducing novel treatment options for lung cancer patients, potentially enhancing survival rates.

At the intersection of dynamic advancements in precision medicine and the transformative potential of artificial intelligence, a broader range of drugs becomes amenable to repurposing in a focused and systematic manner. Through a genuinely customized medicine approach, the overarching ambition is to create interventions precisely tailored to the unique attributes of individual tumors. This strategy aspires to factor in patient-specific tumor characteristics, ultimately enhancing survival rates, quality of life, and overall cost-effectiveness within personalized medicine. To unveil the full scope of possibilities within lung cancer treatment, future research should delve into comprehensive investigations, integrating in vivo experiments and clinical trials whenever feasible.

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