BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Advances in Research on the Anticancer Properties and Mechanisms of Metformin in Lung Cancer

Yani Chen[1], Xianjun Wang[2,*]

[1]The Fourth School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou First People's Hospital, Hangzhou, Zhejiang, China
[2]Department of Laboratory Medicine, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou, Zhejiang, China
*Correspondence: wangxj0525@126.com (Xianjun Wang)

Abstract

Lung cancer is a leading cause of death globally with high mortality and morbidity. Patients are often diagnosed at an advanced stage. Metformin has become a primary medication used in the clinical management of type 2 diabetes mellitus (T2DM) due to its relative safety, low cost, and effectiveness, mainly exerting its hypoglycemic effect by inhibiting hepatic gluconeogenesis and insulin resistance. Research data indicate that metformin extends the distant metastasis-free survival (DMFS) and progression-free survival (PFS) of diabetic patients with lung cancer, improving overall survival rates. Metformin lowers the risk of tumour development through various mechanisms, including the adenosine 5'-monophosphate-activated protein kinase/liver kinase B1/mechanistic target of rapamycin (AMPK/LKB1/mTOR) pathway, insulin-like growth factor-1 receptor pathway, apoptosis, and autophagy. However, research findings are not entirely consistent. This article reviews the research progress of metformin in terms of lung cancer treatment within the past few years, aiming to provide a more comprehensive understanding of how metformin exerts its anti-cancer impact and how it can be clinically applied, as well as provide new insights for lung cancer treatment.

Key words: metformin; lung cancer; molecular mechanism; apoptosis; autophagy

Submitted: 5 June 2024 Revised: 11 July 2024 Accepted: 17 July 2024

Introduction

Based on information collected by the World Health Organization, cancer stands as a primary contributor to global mortality, claiming nearly 10 million lives in 2023 (Siegel et al, 2023). Lung cancer continues to stand out as the predominant reason behind cancer-linked fatalities (Siegel et al, 2023). Lung cancer is classified based on its pathological characteristics as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC), with NSCLC accounting for approximately 85% of all lung cancer cases. The majority of NSCLC patients receive a diagnosis at an advanced stage or with distant metastases, losing the opportunity for curative surgery, resulting in low five-year survival rates (Ettinger et al, 2021).

The incidence of diabetes mellitus (DM) has been increasing annually with changes in lifestyle, with type 2 diabetes mellitus (T2DM) accounting for more than 90% of all DM cases. Epidemiological data reveal a close association between T2DM and various malignancies (Gallagher and LeRoith, 2015; Wang et al,

How to cite this article:
Chen Y, Wang X. Advances in Research on the Anticancer Properties and Mechanisms of Metformin in Lung Cancer. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2024.0349

2017a). Metformin, commonly prescribed as a first-line treatment, is an oral medication used in the management of T2DM. In recent years, it has garnered significant attention for its potential antitumour properties (Coyle et al, 2016; Heckman-Stoddard et al, 2017; Lee et al, 2021). In cancer treatment, however, we must consider both short-term efficacy and potential long-term benefits or risks that may impact patients' long-term quality of life and overall outcome. Furthermore, the medical community is increasingly recognizing the potential of repurposing existing medications, such as metformin, as anticancer agents. This approach utilizes well-understood drugs to explore new therapeutic avenues, aiming to enhance treatment effectiveness and expand treatment options for cancer patients. Healthcare professionals play a crucial role by remaining vigilant, monitoring new developments, and addressing emerging therapeutic advances to ensure patients receive optimal care and benefit from advances in treatment strategies. This article examines recent literature to promote understanding of metformin's anticancer properties and mechanisms, with a specific focus on lung cancer.

Metformin's Impact on Lung Cancer

Correlation between Metformin Use and Lung Cancer Risk among Individuals with Diabetes

In a meta-analysis carried out by Yao et al (2019), which assessed the correlation between metformin use and lung cancer risk in diabetic individuals across 13 studies, research suggests a significant decrease in lung cancer risk associated with metformin use. In contrast to diabetic individuals not using metformin, those who do may experience a reduced likelihood of developing lung cancer. Kang et al (2021) monitored and followed 732,199 participants undergoing health examinations. The findings demonstrated a dose-response correlation between metformin use and lung cancer incidence (p = 0.008), suggesting a negative association between the use of metformin and the likelihood of developing lung cancer. Similarly, meta-analyses performed by Mazzone et al (2012), Zhu et al (2015), and Xiao et al (2020) similarly concluded that the use of metformin can mitigate the risk of lung cancer among individuals with diabetes.

Impact of Metformin on the Survival Period of Lung Cancer Patients

Metformin, an oral medication, is used in the management of T2DM and is typically recommended as the initial therapeutic approach. An earlier study indicated that its use has an independent protective effect on lung cancer mortality, showing a negative correlation between metformin use and lung cancer risk (Kang et al, 2021). Xiao et al (2020) conducted a meta-analysis of 18 studies and concluded that metformin treatment is linked to decreased lung cancer incidence and improved survival rates. Zeng et al (2019) performed a combined analysis of 10 studies encompassing 4397 individuals and reported that the use of metformin significantly enhanced the survival rates of patients with lung cancer ($p < 0.001$). In retrospective studies, Xu et al (2018) noted significant increases in progression-free survival and median overall survival among those treated with metformin. Multivariate analysis revealed that metformin treatment independently predicted a more favourable long-term prognosis for diabetes patients with NSCLC ($p = 0.035$). Wink et al (2016) performed a retrospective cohort analysis investigating whether metformin use during concurrent chemoradiotherapy (cCRT) improved treatment outcomes in locally advanced NSCLC. They included 682 patients (59 metformin users and 623 controls) and revealed that metformin use correlated with enhanced distant metastasis-free survival (DMFS) and progression-free survival (PFS). This suggests that metformin use during cCRT for locally advanced NSCLC may improve DMFS and PFS, indicating it may be a valuable adjunctive therapy. In another study, a cohort of 22,324 Norwegian patients diagnosed with lung cancer was enrolled (Brancher et al, 2021), and the findings revealed that metformin could prolong the survival duration, significantly elevating the lung cancer-specific survival rate (LCSS) among those with regional squamous cell carcinoma (Brancher et al, 2021). In a recent meta-analysis comprising 6 studies involving 539 patients with SCLC and diabetes, it was found that individuals who used metformin exhibited significantly longer overall survival (OS) and disease-free survival (DFS) compared to those who did not use the medication (Fan et al, 2023). In conclusion, metformin, as a first-line treatment for DM, can effectively prolong the overall survival of lung cancer patients and prevent tumour recurrence, thus indicating a more favourable prognosis.

In a phase II randomized clinical trial, researchers compared standalone chemotherapy versus chemotherapy combined with metformin to treat patients with stage III NSCLC. This study included 167 eligible patients, and the results showed that the one-year progression-free survival (PFS) rate in the control group was 60.4% (95% Confidence Interval (CI): 48.5–70.4%) compared to 51.3% (95% CI: 39.8–61.7%) in the metformin group (hazard ratio (HR), 1.15; 95% CI: 0.77–1.73; $p = 0.24$). The one-year overall survival rate was 80.2% (95% CI: 69.3–87.6%) in the control group and 80.8% (95% CI: 70.2–87.9%) in the metformin group. The conclusion was that, while adding metformin to cCRT did not improve survival rates in inoperable stage III NSCLC patients, it was well-tolerated (Skinner et al, 2021). In a randomized phase II study that enrolled 164 advanced NSCLC patients, squamous cell carcinoma had significantly higher fluorodeoxyglucose uptake on baseline positron emission tomography (PET) image than non-squamous cell carcinoma NSCLC. Moreover, the addition of metformin to chemotherapy significantly improved survival rates in squamous cell carcinoma patients with high fluorodeoxyglucose uptake. This suggests a synergistic antitumour effect of metformin in tumours highly dependent on glucose metabolism (Lee et al, 2021). In a clinical trial of non-diabetic late-stage NSCLC patients, the addition of metformin to standard first-line chemotherapy resulted in a one-year PFS of 47% (95% CI: 25–88%) and a median overall survival of 15.9 months (95% CI: 8.4–not available (NA)), exceeding the historical control group's 15% one-year PFS and median overall survival of 13.9 months (95% CI: 12.7–NA). There were no significant differences in toxicity between the study groups (Marrone et al, 2018).

Meta-analysis revealed geographical differences in metformin's impact on lung cancer treatment outcomes. Subgroup analyses showed that in Asian countries, the OS hazard ratio (HR) was 0.52 (95% CI: 0.31–0.87; $p = 0.012$). In contrast, Western countries showed an OS of 0.86 (95% CI: 0.67–1.11; $p = 0.361$) (Tian et al, 2016).

Table 1. Summary of potential synergistic effects of metformin on various anticancer agents.

Therapy	Therapy class	Synergistic effect of metformin	Reference
Cisplatin	Platinum drugs	Improves the radiosensitizing effect Increases AMPK phosphorylation	(Riaz et al, 2019)
Cisplatin	Platinum drugs	Targets CD133 cancer stem cells	(Moro et al, 2018)
Gefitinib	EGFR-TKI	Suppresses IGF-1R signalling pathway	(Pan et al, 2018a)
Gefitinib	EGFR-TKI	Antiproliferative and proapoptotic Decreases MAPK and AKT phosphorylation	(Morgillo et al, 2013)
Erlotinib	EGFR-TKI	Attenuates the drug effect and postpones cancer cell death	(Xiao et al, 2017)
Erlotinib	EGFR-TKI	Reduces proliferation and induces apoptosis	(Wang et al, 2017b)
Rociletinib	EGFR-TKI	Inhibits NF-κB signalling	(Pan et al, 2018b)
Afatinib	EGFR-TKI	Downregulation of glycolytic, EMT markers, a significant decrease in glucose uptake, extracellular lactate, and a tendency towards increased OXPHOS subunit expression	(Barrios-Bernal et al, 2022)
Ionizing radiation	Radiation therapy	Activation of ATM-AMPK-p53/p21^{cip1} and inhibition of AKT-mTOR-4EBP1 pathways Reduces expression of angiogenesis Enhances expression of apoptosis markers	(Storozhuk et al, 2013)
Tenovin-6	SIRT1/SIRT2 inhibitor	*SIRT1* down-regulation	(Lee et al, 2019)
2-dDG	Glucose analogues	ROS, P-p38 and caspase-3 mediated	(Hou et al, 2016)
2-dDG	Glucose analogues	Inhibits the viability and clonogenicity of cancer cells	(Yakisich et al, 2019)
Buparlisib	PI3K inhibitor	Represses Mcl-1 and upregulates Puma in NSCLC cells Inhibits the PI3K/AKT signalling pathway, leading to activation of the FoxO3a/Puma signalling	(Shanshan et al, 2024)

Abbreviations: AMPK, adenosine 5’-monophosphate-activated protein kinase; IGF-1R, insulin-like growth factor-1 receptor; MAPK, mitogen-activated protein kinase; AKT, protein kinase B; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NF-*κ*B, nuclear factor kappa B; EMT, epithelial-mesenchymal transition; OXPHOS, oxidative phosphorylation; ATM, ataxia telangiectasia mutated; mTOR, mammalian target of rapamycin; 4EBP1, eIF4E binding protein 1; SIRT1/SIRT2, sirtuin 1/sirtuin 2; 2-dDG, 2-deoxy-D-glucose; ROS, reactive oxygen species; P-p38, phospho-p38 mitogen activated protein kinase; PI3K, phosphoinositide 3-kinase; Mcl-1, myeloid cell leukemia 1; NSCLC, non-small cell lung cancer; FoxO3a, forkhead box O3a; Puma, p53 upregulated modulator of apoptosis.

Zhong et al (2017) found that when stratified by country, the use of metformin was associated with improved survival in China (HR = 0.47; 95% CI: 0.32–0.70; $p < 0.01$; 95% prediction interval (PI): 0.32–0.70), whereas there was no such association observed in the United States (HR = 0.90; 95% CI: 0.64–1.28; $p = 0.57$; 95% PI: 0.36–2.28).

Combination Therapy of Metformin with Other Drugs

Metformin as a monotherapy has demonstrated potential in anticancer treatment, and studies have explored its synergistic effects when combined with other drugs. Table 1 summarizes the synergistic effects of metformin with other therapeutic agents.

Platinum Drugs

Cisplatin, a frequently employed chemotherapy agent in lung cancer treatment, often encounters reduced effectiveness as resistance develops in managing NSCLC. Evidence suggests that metformin can halt mitochondrial oxidative phosphorylation (OXPHOS), consequently restoring drug sensitivity in lung adenocarcinoma (Wang et al, 2024). In a study by Riaz et al (2019), H460 (sensitive to cisplatin) and NSCLC cell lines A549 (resistant to cisplatin) were subjected to cisplatin, metformin, or a combination of both prior to exposure to ionizing radiation. Clonogenic assays revealed that the concurrent administration of metformin and cisplatin demonstrated enhanced synergistic effects on the radiation response in H460 and A549 cells, respectively (Riaz et al, 2019). Pharmacological blocking of adenosine 5'-monophosphate-activated protein kinase (AMPK) with Compound-C indicated that metformin enhanced cisplatin radiosensitization in H460 cells through an AMPK-dependent pathway, whereas no such effect was observed in A549 cells (Riaz et al, 2019). This suggests that metformin combined with cisplatin could amplify the effectiveness of radiotherapy in NSCLC. In another investigation, metformin plus cisplatin were observed to counteract Kristen rat sarcoma viral oncogene/liver kinase B1 (*KRAS/LKB1*) co-mutant tumours and impede or delay the onset of cisplatin resistance by targeting $CD133^{+}$ cancer stem cells (Moro et al, 2018). In a prospective phase 2 clinical trial, 14 individuals diagnosed with stage III B or IV lung adenocarcinoma received carboplatin plus pemetrexed with metformin treatment. It was assumed that incorporating metformin into the chemotherapy regimen for progressed NSCLC would be beneficial, but compared to previous phase III clinical trials, it did not significantly improve clinical efficacy (Parikh et al, 2017). In a retrospective study, Wen-Xiu et al (2018) also found that metformin treatment shows no significant impact on the overall survival of NSCLC patients undergoing platinum-based chemotherapy.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI)

Gefitinib, a first-generation inhibitor of the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), demonstrates efficacy against NSCLC cells exhibiting sensitivity to epidermal growth factor receptor (EGFR) mutations (Pan et al, 2018a). However, Li et al (2019) found that the addition of metformin to gefitinib does not improve the PFS or OS of Chinese patients. Some researchers have studied the effects of gefitinib and metformin on NSCLC and observed that combination therapy significantly inhibits proliferation and promotes apoptosis in the wild-type *LKB1* NSCLC cell line (Morgillo et al, 2013). Xiao et al (2017) investigated erlotinib, another first-generation EGFR-TKI, and concluded, based on cell viability assays, that metformin did not potentiate erlotinib's inhibition of NSCLC cell proliferation *in vitro*. However, in another study, Wang et al (2017b) discovered that metformin reduced NSCLC cell proliferation by inducing apoptosis and sensitized resistant lung cancer cells to erlotinib (Wang et al, 2017b) and rociletinib (Pan et al, 2018b). By investigating the impact of concurrent administration of metformin and the second-generation tyrosine kinase inhibitor (TKI) afatinib, both alone and in combination, on acquired resistance to EGFR-TKIs in NSCLC cell lines, researchers found that combination therapy-induced EGFR pathway inhibition by suppressing epithelial-mesenchymal transition (EMT) and reducing glycolysis, demonstrating higher cytotoxicity than afatinib alone (Barrios-Bernal et al, 2022).

Radiation Therapy

Storozhuk et al (2013) used A549, H1299, and SK-MES lung cancer cell lines in their study. In an A549 mouse xenograft model, the concurrent administration of metformin and radiotherapy resulted in a more pronounced suppression of tumour cell growth compared to radiotherapy alone, indicating that metformin may enhance tumour cell sensitivity to radiotherapy. Similar conclusions were drawn in another study (Riaz et al, 2019), where metformin was found to increase the sensitivity of H460 and A549 NSCLC cells to combined treatment with cisplatin and ionizing radiation, with better efficacy observed in A549 cells and lower sensitivity to cisplatin. In a retrospective analysis by Wink et al (2016) involving 682 patients with type II to III advanced NSCLC who had received chemoradiotherapy and had diabetes, metformin treatment was observed to exert no notable influence on OS or local recurrence-free survival (LRFS). However, it effectively prolonged PFS and DMFS. In a randomized clinical trial, the addition of metformin to radiotherapy and chemotherapy resulted in worsened treatment outcomes and increased toxicity (Tsakiridis et al, 2021). Similarly, Skinner et al (2021) found that while the tolerance to the addition of metformin to radiotherapy and chemotherapy was good, it did not improve the survival rate of patients with unresectable stage III NSCLC.

Other Drugs

Sirtuin1 is a protein involved in tumour development and progression. Lee et al (2019) noted that combining tenovin-6 (sirtuin 1 inhibitor) with metformin exhibited superior efficacy in impeding NSCLC cell proliferation and suppressing sirtuin 1 (SIRT1) compared to either treatment alone. Both NSCLC cell lines with and without *LKB1* expression showed reduced cell growth, indicating that this effect is independent of *LKB1*. Hou et al (2016) found that metformin or 2-deoxy-D-glucose (2-dDG) alone decreased the viability of A549 cells, but the combined treatment exhibited greater cytotoxicity than either drug alone. The authors hypothesized that metformin decreased the necessary dosage of 2-dDG, implying that metformin could function as an additional treatment to alleviate the potential adverse effects of 2-dDG. Yakisich et al (2019) reported that the combined use of metformin and 2-dDG could synergistically impact cell viability, clonogenic formation, and chemotherapy sensitivity. The study by Wang et al (2024) indicated that metformin and buparlisib synergistically inhibit the growth of NSCLC cells and induce apoptosis. This could potentially offer a novel approach for treating NSCLC.

Mechanisms of Action

Adenosine 5'-Monophosphate-Activated Protein Kinase/Liver Kinase B1/Mechanistic Target of Rapamycin (AMPK/LKB1/mTOR)

Liver kinase B1 (LKB1), a pivotal regulator of AMP-activated protein kinase (AMPK), functions as a tumour suppressor protein. Mutations leading to the inactivation of the *LKB1* tumour suppressor gene occur in 20% of NSCLC cases (Shackelford et al, 2013). One theory suggests that metformin reduces glucose levels and impedes cancer cell proliferation by activating LKB1 and suppressing mammalian target of rapamycin (mTOR) (Zhang et al, 2017). However, some investigators found that metformin-mediated tumour suppression may not require the activation of LKB1 (Guo et al, 2016). In their research, metformin notably suppressed cell proliferation, prompted cell cycle inhibition at the G0-G1 phase, and heightened apoptosis in both LKB1-positive H1299 and LKB1-deficient H460 NSCLC cells (Guo et al, 2016; Moro et al, 2018). These findings imply that the growth-inhibitory effects of metformin may be contingent upon AMPK activation rather than *LKB1*. Similar results were observed by researchers in their investigation of the effects of metformin at a low dosage on NSCLC cells (Storozhuk et al, 2013). Moreover, Dicer's involvement in the emergence of gefitinib resistance in lung cancer patients promotes NSCLC autophagy and resistance to cisplatin by downregulating let-7i-5p expression, consequently hindering the activation of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway (Li et al, 2021).

Insulin-Like Growth Factor-1 Receptor (IGF-1R)

Malignant cells frequently demonstrate increased glucose uptake and glycolysis to fulfill their heightened metabolic requirements for rapid protein synthesis and cell proliferation. Investigators examined the effect of metformin on the insulin-like growth factor-1 receptor (IGF-1R) pathway (Cao et al, 2015). Their data suggested that the anti-IGF-1R monoclonal antibody figitumumab (CP) inhibited SCLC cell proliferation through the downregulation of IGF-1R, without significant downstream signal activation. When combined with metformin, CP significantly enhanced its efficacy in inhibiting SCLC. Subsequently, this research team examined the anticancer effectiveness of metformin in NSCLC cells by using the same methodology and found that the survival capacity of NSCLC cells was reduced after treatment with metformin (Cao et al, 2016). Metformin reduces IGF-1, insulin receptor, and AKT activation in lung cancer tissues, inhibits the phosphorylation of mTOR, and suppresses protein synthesis to achieve its antitumour effect (Memmott et al, 2010).

Apoptosis

Some investigators have reported an increase in apoptosis rates in NSCLC cell lines after treatment with metformin (Guo et al, 2016; Luo et al, 2019). Riaz et al (2019) treated cells with metformin and cisplatin, followed by irradiation doses of 0 Gy, 4 Gy, and 20 Gy, and used the caspase-3 method to detect apoptosis rates in cells irradiated for 48 hours. They observed that metformin had no impact on apoptosis in H460 cells, while A549 cells were highly resistant to apoptosis, with an apoptotic cell rate of less than 3% regardless of the treatment. Thus, they concluded that apoptosis is not involved in metformin radiosensitization. In a separate investigation, the researchers employed the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay to evaluate cell viability, revealing that metformin dose-dependently suppressed A549 and H460 cell growth. Additionally, it significantly initiated poly adenosine diphosphate (ADP)-ribose polymerase cleavage and caspase-3 activation, both indicative of apoptosis, thereby implying its capacity to induce apoptosis in NSCLC cells (Luo et al, 2019).

Autophagy

Autophagy, a conserved cellular mechanism, entails the enclosure of malfunctioning proteins and organelles within dual-membrane cytoplasmic vesicles called autophagosomes. This process is vital for supplying nutrients and energy sources and supporting tumour growth, particularly under circumstances such as starvation, hypoxia, and immune challenges (Kang et al, 2017). Hexokinase 2 (HK2) has been demonstrated to stimulate autophagy under conditions of glucose deprivation, and its elevated expression in diverse cancers is correlated with unfavourable prognoses (Kang et al, 2017). In one study (Kang et al, 2017), metformin could inhibit autophagy by suppressing nickel chloride ($NiCl_2$)-induced levels and hexokinase 2 (HK2) activity. In a recent study, the effects of the third-generation EGFR inhibitor osimertinib on autophagy in NSCLC cells were investigated, alongside an examination of whether metformin's regulation of autophagy enhances sensitivity to the inhibitor (Chen et al, 2019). They discovered that osimertinib triggered prosurvival autophagy in H1975 and PC-9GR cells, whereas metformin heightened the sensitivity of these cells to osimertinib by suppressing autophagy (Chen et al, 2019). The potential mechanism involves metformin inducing prolonged activation of AMPK, which can time-dependently suppress autophagy.

Other Mechanisms

In one study, researchers investigated the expression patterns of gap junction proteins in NSCLC. Their findings suggested that metformin could potentially impede tumour advancement by curtailing the expression of these proteins in NSCLC (Yu et al, 2024). Ning et al (2024) investigated the chemoprotective effects of metformin combined with atorvastatin against drug-induced lung cancer in mice and concluded that combination therapy significantly inhibited lung cancer through the inflammatory pathway. Research in Lewis lung cancer C57BL/6J mice has provided relevant evidence indicating that metformin synergizes with anti-PD-L1 antibodies to enhance anticancer effects by modulating the gut microbiota (Zhao et al, 2024).

Perspectives

Lung cancer continues to pose a significant global challenge. In the past few decades, various methods for treating lung cancer, such as radiotherapy, chemotherapy, and surgery, have greatly revolutionized the medical field, and the emergence of immune-targeted therapy has also greatly promoted personalized treatment. However, the emergence of resistance limits the effectiveness of various drugs, making the search for adjunct drugs that can enhance drug efficacy of significant clinical importance.

This review summarizes the relationship between metformin and the treatment of lung cancer, focusing on aspects such as disease risk, survival period, as well as the value of combining metformin with other drugs and treatment methods (Fig. 1). Currently, there is no universally accepted diagnostic or grading standard regarding the anticancer effects of metformin on lung cancer. The reasons for this can be traced to several factors. Firstly, existing research exhibits variations in several aspects. Some studies are prospective clinical trials with strict randomization and control groups (Marrone et al, 2018; Skinner et al, 2021). In contrast, others are retrospective observational studies relying on existing data analysis, which imposes greater limitations on patient groups (Tian et al, 2016; Zhong et al, 2017). Studies with large sample sizes and long durations provide more reliable and widely applicable results, whereas those with small sample sizes and short durations may introduce bias. Metformin, commonly used as an antidiabetic agent for T2DM treatment, has been explored in studies investigating its impact on lung cancer in this population (Yao et al, 2019). Conversely, another study has considered non-diabetic populations (Marrone et al, 2018). Diabetes itself may influence the development and prognosis of lung cancer, a distinction that needs careful consideration in analysis. Variations in metformin dosages and treatment durations across different studies may also affect evaluations of its efficacy in lung cancer treatment (Lee et al, 2021; Skinner et al, 2021). In future studies, more attention should be paid to the long-term effects of metformin in treating lung cancer, with priority given to determining the minimum effective dosage and maximum safe concentration of metformin for its anticancer effects, as well as potential influences of different cell lines on metformin activity.

Primary outcomes observed in phase II trials include PFS, overall survival, time to local/regional recurrence, time to distant metastasis, and adverse events. To standardize the evaluation of metformin's efficacy in cancer treatment in future research, potential standards such as Response Evaluation Criteria in Solid Tumours and specific biomarkers, such as levels of AMPK activation, insulin-like growth factors, and autophagy-related indicators, should be considered.

In the future, research on the use of metformin in lung cancer treatment will face both challenges and opportunities. Firstly, there is a need for a better understanding of the exact regulatory mechanisms of metformin in the occurrence and development of lung cancer, including its effects on cellular signalling pathways and modulation of the tumour microenvironment. This will help to more accurately determine the indications for metformin in lung cancer treatment and poten-

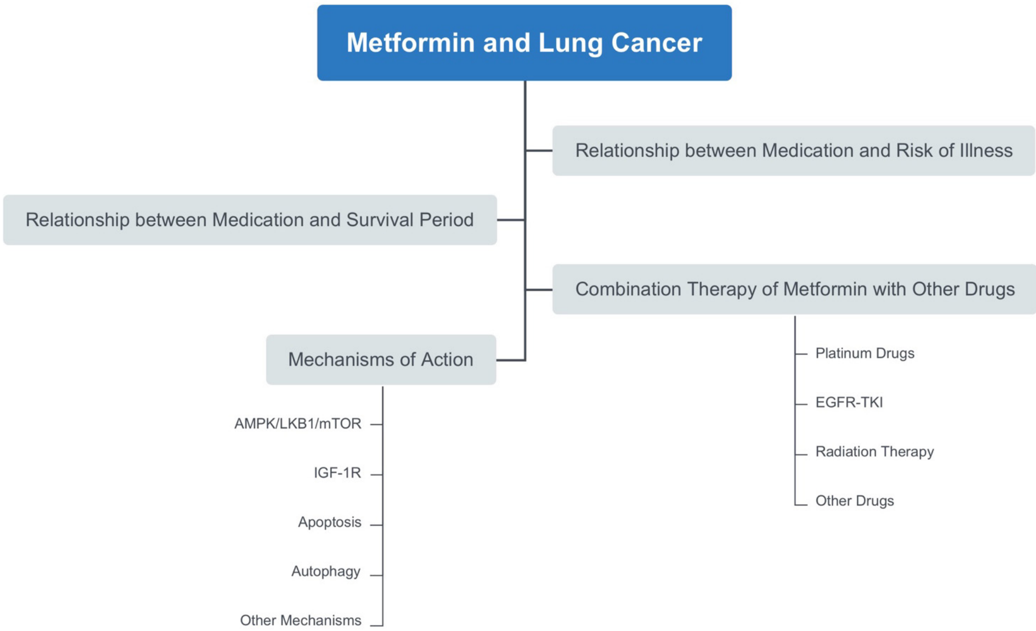

Fig. 1. Mind map of this review. LKB1, liver kinase B1.

tial combination therapy strategies. Secondly, future research needs to emphasize personalized treatment, tailoring metformin treatment plans based on factors such as patients' genetic characteristics, tumour subtypes, and metabolic status to enhance treatment efficacy and reduce adverse events. Additionally, the design and execution of clinical trials will be a key focus of future research. Large-scale clinical trials will help validate the effectiveness and safety of metformin in lung cancer treatment and provide stronger evidence for its clinical application.

Conclusion

In summary, metformin, as one of the most commonly used antidiabetic medications worldwide, has been confirmed in terms of its economy, safety, efficacy, and tolerability. Metformin in combination with other treatments generally exhibits synergistic effects, but some studies have yielded contradictory results, possibly due to significant heterogeneity and confounding factors among the studies, necessitating more rigorous research. Additionally, an increasing amount of evidence suggests that metformin may have anti-lung cancer properties, though its mechanism of action is still debated, such as activation of the AMPK/LKB1/mTOR pathway, IGF-1R pathway, promotion of cell apoptosis, inhibition of autophagy. With ongoing clinical trials, metformin therapy for lung cancer holds much clinical potential and may provide more effective treatment options for this population.

Key Points

- Metformin combined with other methods in the treatment of lung cancer often demonstrates a synergistic effect.
- The anti-lung cancer mechanism of metformin remains controversial, although it likely involves activation of the AMPK/LKB1/mTOR pathway, IGF-1R pathway, promotion of apoptosis, and inhibition of autophagy.
- There are currently no universally recognized diagnostic or grading criteria for the antitumour effects of metformin on lung cancer, and future research should standardize relevant evaluation systems.
- More attention should be paid to the long-term effects of metformin in the treatment of lung cancer.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

YC and XW designed the review topic. YC collected the relevant literature and drafted the manuscript. XW reviewed and revised the manuscript. Both authors contributed to important editorial changes of important content in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

Funding

The review was supported by the Medical Science and Technology Project of Zhejiang Province (NO. 2020KY209).

Conflict of Interest

The authors declare no conflict of interest.

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