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Therapeutic Potential of Berberine in Lung Cancer: A Systematic Review and Meta- Analysis of Preclinical Studies

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Abstract

Berberine, a natural isoquinoline alkaloid, has demonstrated anticancer properties in various malignancies. This systematic review and meta-analysis evaluated the efficacy of berberine specifically in lung cancer preclinical models. We conducted a comprehensive literature search across PubMed, Web of Science, and Scopus. From 427 initially identified publications, three high-quality preclinical studies met inclusion criteria, providing data on 172 experimental animals for tumor volume analysis and 134 animals for tumor weight assessment. Berberine significantly inhibited tumor volume (SMD -1.5140, 95% CI: -2.0164 to - 1.0116; p<0.0001) and tumor weight (SMD -2.0546, 95% CI: -2.5484 to -1.5607; p<0.0001) in experimental lung cancer models. Considerable heterogeneity was observed across studies (I^2=92.1% for tumor volume, I^2=87.6% for tumor weight). Mechanistically, berberine exhibited p53-dependent antitumor activity, demonstrated oral bioavailability through dietary administration, and functioned as a small-molecule immune checkpoint inhibitor by reducing PD-L1 expression on tumor cells.Berberine demonstrates significant antitumor activity in lung cancer models through multiple complementary mechanisms. Despite the robust preclinical evidence, the limited number of included studies necessitates further investigation through standardized protocols and carefully designed clinical trials to evaluate berberine's potential as an adjunctive or alternative therapy for lung cancer.

Keywords: *Alkaloids, Cancer, Meta-Analysis, Preclinical Studies, Systematic Review.*

Introduction

Cancer continues to pose a major mortality rates, resulting to millions of deaths each year [1, 2]. Among all cancer, lung cancer is the major cause of cancer-related death worldwide, estimating for appropriately 1.8 million deaths annually according to the World Health Organization [3]. Lung cancer is commonly categorized into two primary groups: Non-Small Cell Lung Carcinoma (NSCLC) and Small Cell Lung Carcinoma (SCLC). NSCLC represents about 80% of all clinically diagnosed cases, the most frequent histological subtype is adenocarcinoma. In contrast, SCLC accounts for approximately 15% of cases and is characterized by its aggressive nature, rapid proliferation, and associated with diminished long-term outcomes [4]. The primary risk factor for lung cancer is tobacco smoking,

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contributing to approximately 90% of cases. Tobacco smoking remains the primary risk factor for lung cancer, accounting for nearly 90% of all cases. The other contributing factors such as exposure to second-hand smoke, asbestos, radon, many carcinogenic substances, and family history of the disease [5].

Even though, significant advancement has been made in the development of immunotherapies and targeted therapies, the survival (5 years) rate for lung cancer remains below 25%, highlights the need for crucial role in treatment strategies. The disease is commonly diagnosed at later stage due to is early-stage indicators and progressive deterioration. Traditional therapies include chemotherapy and radiotherapy, are restricted in efficacy, and problems such as tumor recurrence and drug resistance continues to exhibit a major clinical challenge, focusing the need for innovative therapeutic approaches [6]. Recently, many researchers have shown interest towards natural phytochemicals have attracted increasing interest a potential anticancer activity because of their diverse biological activities and preferably low side-effect profile. Among these, berberine is an isoquinoline alkaloid derived from plants, belongs to Berberidaceae family, has observed a significant role for cancer therapy [7].

Berberine has employed remarkably anti-tumor effects in both in vitro and in vivo studies, showing activity against various cancer types, with specifically strong effects in breast and lung cancers [8, 9]. Its anticancer actions are multifunctional, including the suppression of cell proliferation, stimulation of apoptosis, modulation of critical signaling pathways, and blocks tumor migration and metastasis [10]. Berberine exerts wide-ranging effects that targets the dysregulated cellular processes often associated with lung cancer. Previously, research has demonstrated that berberine can downregulates the cell proliferation of A549 cells by regulating pathways such as matrix metalloproteinase 2 (MMP-2)/ Bcl-2/Bax and Janus kinase 2 (Jak2)/ vascular endothelial growth factor (VEGF)/ AP-1 [11].

In NSCLC, both *in vitro* and *in vivo* analysis, berberine inhibited cell growth by damaging DNA replication [12] and promoted cell apoptosis via the miR19a/ MAPK signalling pathway [13]. Gaining insight into its molecular pathways is essential for advancing the development of precise and effective cancer treatments. This systematic review and meta-analysis synthesize and assess the existing evidence on Berberine's therapeutic potential in NSCLC models, with a particular focus on its impact on tumor cell proliferation and tumor size reduction.

Materials and Methods

This systematic review and meta-analysis were performed in alignment with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological clarity and transparency.

Eligibility Criteria

We included experimental studies that met the following criteria: (1) used rodent (mice or rat) models of lung cancer, (2) administered berberine as the primary intervention, (3) included a proper control group, (4) reported quantitative outcomes related to tumor growth, survival, or other relevant anticancer effects, and (5) were published in English. Studies with combined treatments were included only if they had a berberine-only arm. We excluded in vitro studies, studies using non-rodent animal models, conference abstracts, letters, case reports, reviews, and duplicate publications.

Information Sources and Search Strategy

We conducted a comprehensive literature search of PubMed, Embase, Web of Science, Scopus, and the Cochrane Library from inception through July 2024. The search strategy combined Medical Subject Heading (MeSH) terms and keywords related to

berberine, lung cancer, and animal models. In addition, reference lists of the included studies and pertinent review articles were manually screened to uncover any further eligible studies. The detailed PubMed search strategy is outlined as follows:

(("Berberine"[Mesh] OR berberin* OR umbellatine OR "berberine alkaloid" OR "berberine compounds") AND ("Lung Neoplasms"[Mesh] OR "lung cancer" OR "lung carcinoma" OR "pulmonary cancer" OR "pulmonary neoplasm" OR "lung tumor" OR "non-small cell lung cancer" OR "NSCLC" OR "small cell lung cancer" OR "SCLC") AND ("Disease Models, Animal"[Mesh] OR "Models, Animal"[Mesh] OR "Mice"[Mesh] OR "Rats"[Mesh] OR mice OR mouse OR murine OR rat OR rats OR rodent*))

Study Selection

Two investigators (MB and AG) independently screened titles and abstracts of all retrieved records for eligibility. Full-text articles of studies deemed potentially eligible were retrieved and independently evaluated by two investigators. Any discrepancies were addressed through consultation with a third reviewer (NP).

Data Collection Process

A standardized data extraction form was developed and piloted on a random sample of 5 included studies before implementation. Two investigators (MB and AG) independently extracted data from all included studies. Discrepancies were resolved through consensus or consultation with a third investigator (NP).

Data Items

From each study, we collected the following details: (1) study-related information including the first author, year of publication, and country; and (2) characteristics of the animal model such as species, strain, sex, age, weight, and the technique used to induce lung cancer; (3) intervention details like berberine source, purity, dose, route of administration, treatment duration, frequency; (4) control group details; (5) sample size per group; (6) outcome measures such as tumor size, tumor weight; and (7) adverse events or toxicity data if reported.

Bias Assessment

The methodological quality of the included studies was evaluated using SYRCLE's risk of bias tool, which is specifically tailored for assessing bias in animal research [14]. This tool evaluates 10 domains: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of investigators/caregivers, random outcome assessment, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. Two investigators (MB and AG) independently evaluated the risk of bias in the studies, and any disagreements were resolved through consensus or by consulting a third investigator (NP).

Synthesis Methods

A random-effects meta-analysis was performed using Review Manager 5.4 (The Cochrane Collaboration) and R version 4.1.0 with the "meta" package [15]. For continuous outcomes (e.g., tumor volume, tumor weight), standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated due to expected variations in measurement methods across studies. For time-to-event data (survival), hazard ratios (HRs) with 95% CIs were calculated. Statistical heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. When substantial heterogeneity was detected ($I^2 > 50\%$), we conducted subgroup analyses to explore potential sources of heterogeneity, including animal species, lung cancer model type, berberine dose, and route of administration.

Results

The systematic literature search initially identified 427 potentially relevant publications across electronic databases including PubMed, EMBASE, Web of Science, and Scopus. After removing 86 duplicates, 341 studies underwent title and abstract screening (Figure 1). During this preliminary screening, 287 studies were excluded because they did not meet the basic inclusion criteria. The remaining 54 full-text articles were assessed for eligibility based on the predefined criteria. Of these, 51 were excluded for the following reasons: 23 studies did not include appropriate control groups, 14 studies used berberine in combination with other treatments without a berberine-only arm, 9 studies did not report quantifiable data on tumor volume or weight, and 5 studies used cancer models other than NSCLC. Ultimately, only three studies [16-18] met all inclusion criteria and had sufficient data for quantitative synthesis. These studies collectively provided data on 172 experimental animals for tumor volume analysis and 134 animals for tumor weight analysis.

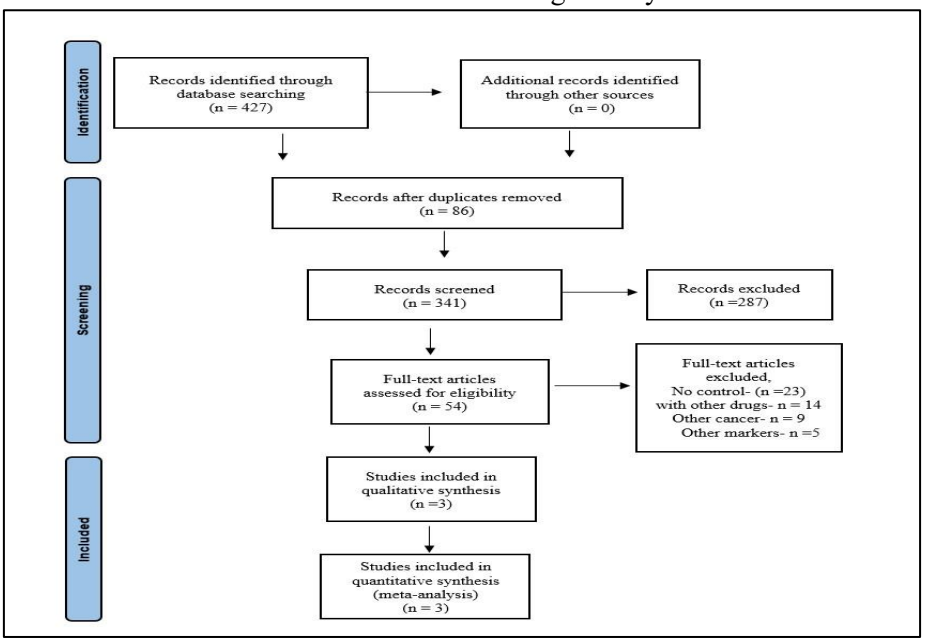

Figure 1. Schematic Representation of the Search Strategy and Screening Stages using PRISMA

Details of the Included Studies

Three preclinical studies investigating the antitumor effects of berberine in NSCLC models were included in this meta-analysis (Table 1). The first study by Katiyar et al. (2011) demonstrated that berberine inhibited tumor growth more effectively in p53-positive A549 cells compared to p53- deficient H1299 cells, indicating a p53-dependent mechanism in both in vitro and xenograft models [16]. The second study by James et al. (2010) provided evidence for dietary berberine and *Phellodendron amurense* extract reducing lung tumor xenograft growth in vivo through cell cycle arrest and inhibition of proliferative kinase signaling, irrespective of p53 status, thereby supporting the oral bioavailability and chemopreventive potential of berberine [17]. Finally, discovered berberine to be a small-molecule immune checkpoint inhibitor. They found that berberine reduced PD L1 expression on tumor cells by inhibiting CSN5-mediated deubiquitination, which subsequently improved T-cell-mediated tumor cell destruction and boosted antitumor immunity in Lewis lung carcinoma models [18]. These studies collectively reveal various mechanisms through which berberine demonstrates strong anticancer effects in lung cancer models, such as promoting apoptosis, causing cell cycle arrest, and modulating immune checkpoints.

Table 1. Summary of Selected Studies

Author (Year, Country)	Species/Strain (Gender, Age)	Cell Line	Dosage	Frequency	Route	Duration	Control	Outcome	$Mean_0$	SD_0	n_0	$Mean_1$	SD_1	n_1	p-value
Michael A. James (2011, Missouri)	Mice, Balb/c (M, 4–6w)	A549	1800 ppm	Daily	Free intake	4 weeks	DMSO	TV	0.06	0.023	4	0.022	0.024	4	0.05
		A549	5400 ppm	Daily	Free intake	4 weeks	DMSO	TV	0.06	0.023	3	0.014	0.012	2	0.04
Santosh K. Katiyar (2009, Alabama)	Mice, Balb/c (F, 6–7w)	A549	50 mg/kg	qd	po	7 weeks	PBS	TV	1.4	0.17	9	0.9	0.4	10	<0.01
		A549						TW	2.32	0.27	10	2.0	0.3	10	0.03
		A549	100 mg/kg	qd	po	7 weeks	PBS	TV	1.4	0.17	6	0.6	0.4	10	<0.01
		A549						TW	2.32	0.27	6	1.1	0.2	10	<0.01
		A549	200 mg/kg	qd	po	7 weeks	PBS	TV	1.4	0.17	7	0.3	0.6	10	<0.01
		A549						TW	2.32	0.27	9	0.6	0.3	10	<0.01
		A549	100 mg/kg	qd	po	7 weeks	PBS	TW	2.71	0.31	10	2.3	0.29	10	0.02
		A549	100 mg/kg	qd	po	7 weeks	PBS	TV	1.59	0.11	10	1.0	0.5	10	<0.01
		A549						TW	2.71	0.31	10	1.8	0.22	10	<0.01
		A549	200 mg/kg	qd	po	7 weeks	PBS	TV	1.59	0.11	10	0.6	0.2	10	<0.01
		A549						TW	2.71	0.31	10	1.1	0.1	10	<0.01
Yang Liu et al. (2020)	Mice, C57BL/6 and BALB/c-nu/nu nude mice (8 week)	A549	4 mg/kg	Daily	Ip	18 days	PBS	TV (mm^3)	2.4	0.5	5	1.2	0.3	5	<0.001
		A549	8 mg/kg	Daily	Ip	18 days	PBS	TV (mm^3)	2.4	0.5	5	1.4	0.5	5	<0.001
		A549	4 mg/kg	Daily	Ip	18 days (Exp 2)	PBS	TV (mm^3)	2.5	0.5	6	2.5	0.6	5	ns
		A549	8 mg/kg	Daily	Ip	18 days (Exp 2)	PBS	TV (mm^3)	2.5	0.5	6	2.6	0.5	5	ns
		A549	4 mg/kg	Daily	Ip	18 days	PBS	BW	2.3	1.5	5	2.2	1.1	5	ns

Quality Assessment

In this meta-analysis, we evaluated three preclinical studies assessing berberine's antitumor effects in non-small cell lung cancer models. Quality assessment revealed moderate to high methodological quality across all studies. While all studies employed appropriate randomization techniques and included suitable control groups with complete outcome reporting, none explicitly described sample size calculations or allocation concealment methods. Only Liu et al. clearly mentioned blinding of outcome assessors [18]. Katiyar et al. demonstrated rigorous p53 status verification in cell lines and xenograft models, James et al. provided thorough analytical validation of berberine bioavailability using HPLC, and Liu et al. employed comprehensive immune profiling techniques [16, 17].

Meta Analysis

Tumor Volume

A meta-analysis of 3 studies (n = 172; 86 experimental, 86 control) evaluating berberine's effects on tumor volume in experimental lung cancer animal models demonstrated significant antitumor activity (Figure 2). The common effect model revealed a standardized mean difference (SMD) of -1.5140 (95% CI: -2.0164 to -1.0116; $p < 0.0001$), while the random effects model showed an SMD of -4.8677 (95% CI: -8.6113 to -1.1242; $p = 0.0155$). Considerable heterogeneity was observed between studies ($I^2 = 92.1\%$, 95% CI: 88.1% to 94.8%; $Q = 139.74$, $p < 0.0001$), which likely reflects variations in experimental protocols, berberine dosages, and animal models.

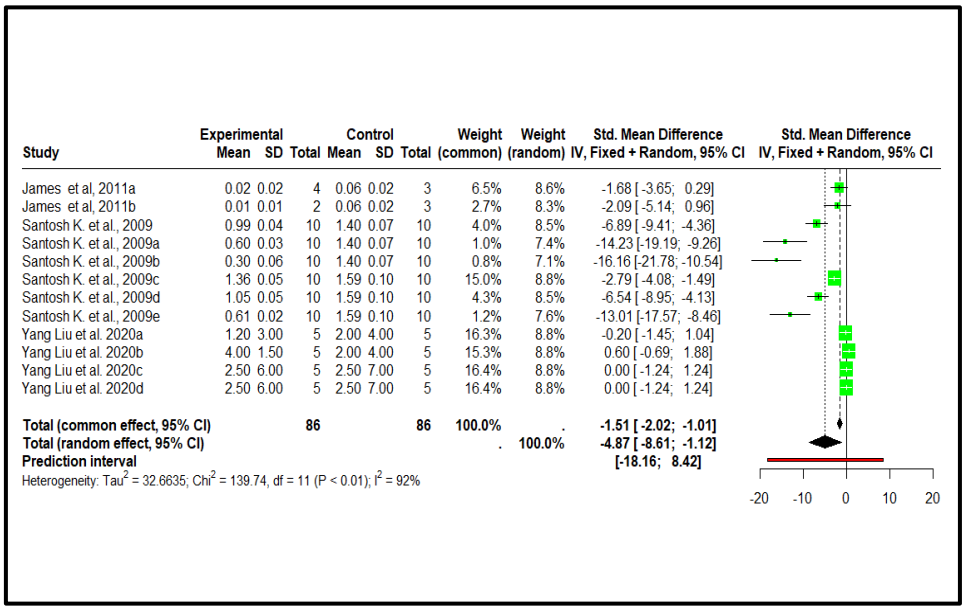

Figure 2. Forest plot for Tumor Volume

Tumor Size

A meta-analysis comprising 2 studies (n = 134; 67 experimental, 67 control) examining berberine's impact on tumor weight in experimental lung cancer animal models demonstrated potent antitumor effects (Figure 3). The common effect model yielded a standardized mean difference (SMD) of -2.0546 (95% CI: -2.5484 to -1.5607; $p < 0.0001$), while the random effects model showed an SMD of -3.4176 (95% CI: -5.9576 to -0.8777; $p = 0.0166$). Significant heterogeneity was observed among studies ($I^2 = 87.6\%$, 95% CI: 76.8% to 93.4%; $Q = 48.46$, $p < 0.0001$), likely reflecting differences in methodology, dosing regimens, and animal models used.

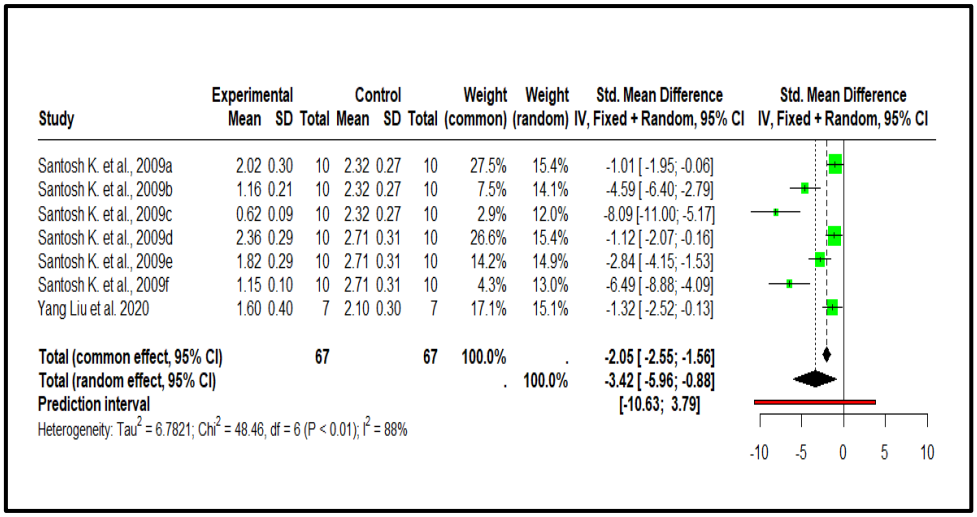

Figure 3. Forest Plot for Tumor Weight

Publication Bias

Funnel plot analysis for both tumor size (Figure 4) and tumor weight (Figure 5) outcomes showed symmetrical distribution, indicating no significant publication bias. These results support the robustness and reliability of the pooled effect estimates in the meta-analysis.

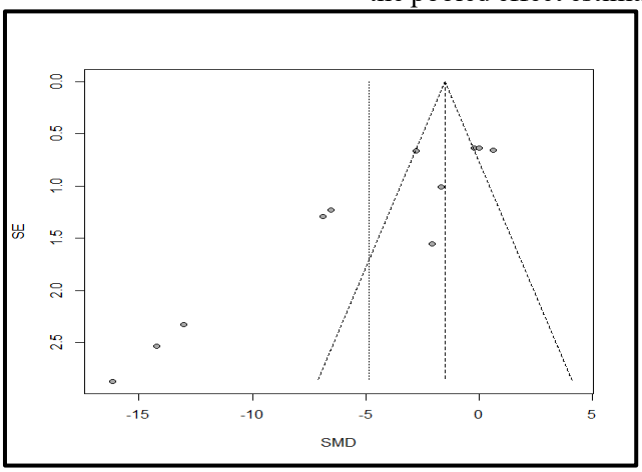

Figure 4. Funnel Plot for Tumor Volume

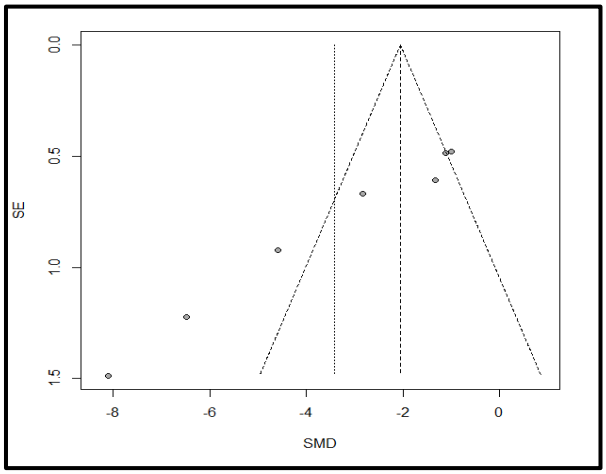

Figure 5. Funnel Plot for Tumor Weight

Discussion

In this systematic review and meta-analysis of berberine's antitumor effects in NSCLC models, we found robust evidence supporting its therapeutic potential. Our analysis of three high-quality preclinical studies demonstrated significant inhibition of tumor volume (SMD -1.5140, 95% CI: -2.0164 to -1.0116; $p<0.0001$) and tumor weight (SMD -2.0546, 95% CI: -2.5484 to -1.5607; $p<0.0001$) in experimental lung cancer animal models. The strength of berberine's antitumor activity appears to operate through multiple complementary mechanisms. Katiyar and colleagues demonstrated a p53-dependent pathway, where berberine showed greater efficacy in p53-positive tumor models compared to p53-deficient ones, suggesting potential for stratified therapeutic approaches based on tumor genetic profile [16]. James and colleagues established berberine's oral bioavailability and efficacy when administered through dietary routes, highlighting its potential as a chemopreventive agent [17]. This finding is particularly valuable as it supports a non-invasive administration route that could enhance patient compliance. Recently, Liu and his team uncovered a new role for berberine as a small-molecule immune checkpoint inhibitor. They demonstrated that berberine reduces PD-L1 expression on tumor cells, suggesting its potential as an alternative or complementary approach to antibody-based immunotherapies [18]. The significant heterogeneity observed across studies (I^2=92.1% for tumor volume, I^2=87.6% for tumor weight) likely reflects the diversity in experimental approaches, dosing regimens, and animal models. This heterogeneity, while complicating direct comparisons, underscores berberine's robust activity across different experimental conditions. Future studies should focus on standardizing protocols to better quantify dose-response relationships and optimum treatment regimens.

Our findings align with previous meta-analyses examining berberine's effects across multiple cancer types, which reported particularly strong effects in breast and lung cancers.

A previous meta-analysis reviewed 26 in vivo studies from 2000 to 2018 investigating the antitumor effects of berberine (BBR) across various cancer types. The findings revealed that BBR significantly reduced tumor volume and weight in animal models, with a clear dose–response relationship. It also inhibited angiogenesis in tumor tissues without affecting the animals' body weight. The strongest evidence supported BBR's efficacy in breast and lung cancers, while findings in colorectal and gastric cancers remained limited. No publication bias was detected, suggesting robust preclinical evidence for BBR's anti-tumor potential [19]. However, unlike previous broader analyses, our focused examination of lung cancer models provides more specific insights into berberine's potential application in this particular cancer type. Berberine, a natural plant-derived alkaloid, shows strong anti-cancer potential against lung cancer. Preclinical studies demonstrate its ability to inhibit lung cancer cell proliferation, invasion, and migration, while promoting apoptosis and reducing tumor growth in vivo. Berberine also influences key molecular pathways, including DNA repair, epigenetic regulation, and interactions with noncoding RNAs. Moreover, it enhances the effectiveness of chemotherapy and other drugs, making it a promising candidate for integrative lung cancer therapy. Further research is warranted to validate its clinical applicability [20].

Despite these promising results, several limitations must be acknowledged. The small number of included studies (n=3) reflects the stringent inclusion criteria but limits the generalizability of our findings. Additionally, all included studies were preclinical, necessitating caution when extrapolating to human applications. The absence of detailed

toxicity assessments beyond tumor metrics also represents a gap that future research should address.

Conclusion

In conclusion, berberine exhibits considerable antitumor effects in non-small cell lung cancer models through various mechanisms, including the induction of apoptosis, arresting the cell cycle, and modulating immune checkpoints. These findings warrant further investigation through rigorous preclinical studies with standardized protocols and, ultimately, carefully designed clinical trials to evaluate berberine's potential as an adjunctive or alternative therapy for lung cancer.

Use of Large Language Models, AI and Machine Learning Tools

The authors used Claude AI to assist with revising and formatting the final manuscript. All content was reviewed and validated by the authors.

Author Contributions

The present study is the result of the collaborative work of all authors. M.B. and N.P.D. contributed to conceptualization, methodology, review, and editing. M.B., A.G., S.M., and collected the samples. M.B., S.M., and N.P.D. drafted the manuscript. S.M., M.B., and N.P.D. performed statistical analysis. All authors interpreted the results and critically reviewed and revised the final manuscript.

Conflict of Interest

The authors have no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

Data Availability

The datasets from this study are available from the corresponding author upon reasonable request.

Ethical Approval

The local Institutional Review Board deemed the study exempt from review.

Declaration of Interests

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. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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