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Pueraria Lobata and Puerarin in Lung Cancer: Molecular Mechanisms, Anticancer Cancer Potential and Translational Challenges

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ABSTRACT

Lung cancer is among the leading causes of cancer-related morbidity and mortality worldwide and therapeutic resistance, treatment-related toxicity and disease relapse are still major challenges for clinical outcomes. Pueraria lobata and its main isoflavonoid, puerarin, are receiving increasing attention because of their diverse pharmacological activities and possible effects on biological pathways relevant to tumor development. This narrative review summarizes the botanical characteristics, phytochemical constituents, molecular mechanisms, experimental anti-cancer activities, potential combination with conventional lung cancer treatments, pharmacokinetic properties, safety issues, and translational challenges of P. lobata and puerarin. Experimental studies, mostly in non-small cell lung cancer (NSCLC), suggest that puerarin may reduce tumour-cell viability and proliferation, induce apoptosis, block cell-cycle progression and inhibit cell migration and invasion. Mechanistic evidence suggests involvement of pathways such as miR-342/CCND1, PI3K/Akt/mTOR, MAPK/ERK, NF-κB, oxidative stress and apoptosis-related signaling. Moreover, inhibition of tumor growth has been demonstrated in vivo xenograft studies. The potential interaction of puerarin with chemotherapy, targeted therapy, radiotherapy and immunotherapy offers a platform for further research, but evidence for clinically significant therapeutic synergy is still limited. Poor water solubility, low oral bioavailabilty, extensive metabolism, variability between P. lobata preparations, potential herb-drug interactions and uncertainty regarding clinically achievable concentrations are important translational barriers. Crucially, the present evidence is mainly preclinical and no clinical trial has demonstrated the efficacy of P. lobata or puerarin in the management of lung cancer. Future studies should be focused on standardized preparations, pharmacokinetics and toxicity evaluation, mechanistic studies, biomarker-guided approaches, systematic combination studies and well-designed clinical trials. P. lobata and puerarin are thus candidates for further investigation as anticancer agents rather than established therapeutic alternatives for lung cancer.

Keywords: Pueraria lobata; Puerarin; Lung cancer; Non-small cell lung cancer; Phytochemicals.

Introduction

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. According to global cancer estimates, approximately 2.5 million new cases of lung cancer and 1.8 million lung cancer-related deaths occurred in 2022, making lung cancer one of the most commonly diagnosed cancers and a leading cause of cancer mortality worldwide [1,2]. Recent epidemiological studies have again shown considerable regional, gender and socioeconomic inequality in lung cancer incidence and mortality rates [3]. The major risk factor is tobacco smoking, although environmental and occupational exposures, air pollution, radon, asbestos, and genetic susceptibility also contribute to disease development [4].

Lung cancer is histologically divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is the most common form and consists of adenocarcinoma, squamous cell carcinoma and other less frequent types. SCLC is less common but more aggressive with more rapid proliferation, early dissemination of metastases, and higher rates of treatment resistance [5,6]. Molecular characterization of NSCLC has advanced substantially, leading to major changes in disease management. In suitable patients, mutations or alterations of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, BRAF, MET, RET, KRAS and HER2 can guide the selection of specific treatments [7,8]. Immune checkpoint inhibitors have also emerged as an important part of therapy, especially in the case of advanced disease where there is no actionable driver alteration [9]. Despite these advances, significant

therapeutic challenges remain in lung cancer management. Tumours may develop resistance to targeted therapies and immune checkpoint inhibitors, while chemotherapy can cause adverse effects, and chemotherapy can cause side effects that affect their quality of life and restrict their treatment choices. Relapse is also a frequent occurrence, especially after chemotherapy and radiotherapy in SCLC [6]. These limitations have prompted investigation of therapeutic approaches capable of modulating multiple biological pathways. Medicinal plants and natural sources are among the sources of pharmacologically active compounds. They have potential use in cancer medicine, and some phytochemicals have been found to affect multiple cancer pathways such as the pathways of apoptosis, oxidative stress, inflammation, angiogenesis, cell-cycle control and cellular migration. However, preclinical biological activity should not be interpreted as evidence of proven clinical efficacy. Pueraria lobata (Willd.) (Figure 1), commonly known as kudzu, is an important medicinal and food plant traditionally used in East Asian medicine. Its root, known as Radix Puerariae or Gegen contains a variety of phytochemicals, including isoflavonoids. The characteristic and widely studied component is puerarin, which is followed by daidzin, daidzein, genistein and related components in relation to its biological properties [10,11,12]. The antioxidant, anti-inflammatory, metabolic, cardiovascular, hepatoprotective and anticancer properties have been reported in P. lobata and puerarin in contemporary pharmacologic studies [10,13].



Figure 1: Image of Pueraria lobata (Willd.) [Source: Ohwi, J. (1947) Bulletin of the Tokyo Science Museum : 16(1947).]

Experimental studies have shown that puerarin affects apoptosis, cell-cycle progression, PI3K/Akt/mTOR, MAPK/ERK pathway, NF-κB pathway, oxidative stress, autophagy, and other molecular pathways, which has fueled the interest in this compound as a potential anticancer agent [14]. Importantly, lung cancer-specific studies have shown inhibition of NSCLC proliferation, migration, and invasion, and induction of apoptosis, with animal experiments providing preliminary evidence of tumour growth inhibition [15,16]. Hence, this narrative review aims to explore the potential efficacy of P. lobata, with particular emphasis on puerarin, in the context of lung cancer management. It examines its botanical features, phytochemistry, molecular mechanisms that are important in lung cancer, experimental evidence, combination with conventional treatment, safety profile and pharmacokinetics, as well as the clinical applications that are hindered by the current status of translation.

Botanical Characteristics, Phytochemistry, and Traditional Uses of Pueraria lobata

Pueraria lobata is a perennial climbing herb in the family Fabaceae, widely distributed across East and Southeast Asia. The plant has traditionally been used medicinally for various ailments and as a food source. The root is especially significant in traditional medicine and is used in the preparation of Radix Puerariae. Recent literature indicates that Pueraria species contain a diverse range of phytochemical constituents, including isoflavonoids, triterpenoids, coumarins, polysaccharides, and other compounds [10,11]. The chemistry of P. lobata is highly dependent on the geographic origin, cultivation conditions, plant part, maturity, processing and extraction methods. This variability is worth considering when contemplating pharmacological studies, since aqueous extracts, alcoholic extracts, standardized preparations, and purified puerarin cannot be assumed to have equivalent biological activity. Puerarin is an isoflavone C-glycoside and is considered the characteristic bioactive compound of P. lobata. Other important isoflavonoids include daidzin, daidzein, and genistein. Recent studies on the biosynthesis of P. lobata have focused on the role of glycosylation and methylation in the biosynthesis and accumulation of typical isoflavonoids in the root [12]. Therefore, the compound puerarin and its derivatives are an important chemical basis for the research of medicinal properties of the plant. Recent reviews have summarized the antioxidant, anti-inflammatory, cardiovascular, metabolic, neuroprotective, and hepatoprotective effects [13,17]. The widespread biological effects have implications for cancer research due to the close links between oxidative stress, chronic inflammation, metabolic dysregulation, and tumour development and progression. P. lobata is used traditionally for the treatment of fever, intestinal symptoms, and other ailments. These traditional uses reflect the historical applications of the plant but should not be interpreted as evidence of anticancer efficacy. But traditional use should not be interpreted to mean that P. lobata can be used to treat lung cancer alone; rather, it should be taken as a basis for further studies of its pharmacological activities. Another important distinction is between whole-plant preparations and purified puerarin. Most recent research has focused upon purified puerarin, rather than on standardized P. lobata extracts. Therefore, evidence obtained from purified puerarin cannot be assumed to apply to all P. lobata preparations. On the other hand, more than one compound could exist in whole plant preparations that interact. Thus, it is crucial to conduct standardized phytochemical characterization for future clinical research [10,11].

Table 1 summarizes the botanical characteristics, phytochemical composition, traditional applications, and pharmacological relevance of Pueraria lobata. The plant is a perennial Fabaceae herb, with its medicinally important root containing several bioactive compounds, particularly puerarin, daidzin, daidzein, and genistein. Its reported antioxidant, anti-inflammatory, metabolic, neuroprotective, and hepatoprotective activities provide a rationale for further investigation in cancer research. However, evidence derived from purified puerarin should not be directly extrapolated to whole-plant preparations, highlighting the need for standardized phytochemical characterization and further mechanistic and clinical studies.

Table 1: Botanical Characteristics, Phytochemistry, and Traditional Uses of Pueraria lobata

Category	Key Characteristics	Major Constituents / Activities	Research Significance
Botanical characteristics	Perennial climbing herb belonging to the Fabaceae family; widely distributed in East and Southeast Asia. The root is particularly important medicinally and is used to prepare Radix Puerariae.	—	Provides the botanical and ethnomedicinal basis for investigation of *P. lobata* as a medicinal plant.
Phytochemical composition	Contains diverse phytochemical constituents, with composition influenced by geographical origin, cultivation conditions, plant	Isoflavonoids, triterpenoids, coumarins, polysaccharides,	Standardized phytochemical characterization is necessary because different preparations may exhibit different biological activities.

	part, maturity, processing, and extraction method.	and other bioactive compounds.	
Characteristic isoflavonoids	Puerarin is considered the characteristic bioactive compound of *P. lobata*; biosynthesis involves processes such as glycosylation and methylation.	Puerarin, daidzin, daidzein, and genistein.	Puerarin and related isoflavonoids represent important chemical targets for pharmacological and mechanistic research.
Pharmacological and traditional relevance	Traditionally used for fever, intestinal symptoms, and other ailments. Modern studies have investigated several biological activities.	Antioxidant, anti-inflammatory, cardiovascular, metabolic, neuroprotective, and hepatoprotective effects.	These activities may provide a rationale for investigating potential relevance to cancer biology, particularly pathways involving oxidative stress, inflammation, and metabolic dysregulation.
Cancer research and limitations	Traditional medicinal use should not be interpreted as evidence that *P. lobata* can treat lung cancer. Research has frequently focused on purified puerarin rather than standardized whole-plant extracts.	Purified puerarin and whole-plant preparations may differ in composition and biological effects; interactions among multiple constituents may also occur.	Future studies should distinguish purified compounds from plant extracts and incorporate standardized extraction, phytochemical characterization, mechanistic studies, and clinical evaluation.

Molecular and Cellular Mechanisms Relevant to Lung Cancer

The potential anticancer activity of P. lobata seems to be mediated through various molecular and cellular mechanisms. Puerarin has been extensively studied and has been shown to exert effects on apoptosis, proliferation, cell cycle control, oxidative stress, inflammatory signalling, migration, invasion, and tumour-associated pathways [14].

Evasion of apoptosis is a fundamental characteristic of malignant cells. Cancer cells frequently acquire mechanisms that allow them to evade apoptosis and survive aberrant growth signals. Experimental studies suggest that puerarin can induce apoptosis in tumour cells by two pathways: the mitochondrial pathway and the death-receptor pathway. Puerarin has been linked to alterations in Bcl-2 family proteins, activation of caspases, and mitochondrial membrane potential [14]. These mechanisms may ultimately promote programmed cell death in tumour cells. In the case of NSCLC, puerarin has been demonstrated to reduce cell viability and increase apoptosis. The findings not only show the compound's ability to slow down the proliferation of lung cancer cells but also directly demonstrate that it can impact the survival of those cells [15].

Excessive cell growth is another characteristic of cancer. Regulatory proteins called cyclins and cyclin-dependent kinases control the progression of cells through the cell cycle; their abnormalities are able to contribute to the growth of a tumour.

A representative study of NSCLC showed that puerarin suppressed tumour-cell progression via the miR-342/CCND1 pathway [16]. Puerarin could upregulate the expression of miR-342, and miR-342 could directly downregulate the expression of cyclin D1 (CCND1). Suppression of CCND1 was associated with reduced cell-cycle progression, migration and invasion, and increased apoptosis. The study also showed that in vivo [16], there was tumour growth inhibition.

The findings are significant as they contribute a molecular mechanism of action of puerarin to the specific regulatory alterations in NSCLC instead of the general cytotoxicity.

The PI3K/Akt/mTOR pathway is involved in the regulation of cell survival, proliferation, metabolism and growth and is often dysregulated in cancer. This pathway is known to be affected by puerarin in several experimental cancer models [14,18].

The proposed mechanism involves suppression of PI3K/Akt signalling which may decrease the survival signals and promote apoptosis. Modulation of PI3K/Akt signalling can also potentially affect various aspects of tumour biology, as it is also linked to metabolism, angiogenesis and treatment resistance. However, most mechanistic evidence comes from experimental models. Whether clinically attainable puerarin levels are sufficient to mimic such pathway effects in human lung tumour cells is unclear [12,13].

The p38, JNK, and ERK pathways are members of the MAPK family that control proliferation, differentiation, stress and apoptosis. Puerarin has been shown to affect the MAPK signalling pathways, such as ERK signalling [14]. In experimental models of NSCLC, puerarin was associated with alterations in MAPK/ERK1/2 signalling pathways along with apoptotic responses [15]. The results support the potential for puerarin to have a multi-target effect on the survival pathways. Cancer development and progression are closely linked with oxidative stress. Reactive oxygen species have the potential to cause DNA damage and genomic instability, as well as promoting proliferation and inflammatory signalling. Under very high concentrations, however, ROS may induce tumour cell death as well [16].

Puerarin exhibits antioxidant activities and is able to regulate redox-sensitive signalling pathways [13,14]. The relationship between the antioxidant activity of puerarin and its potential anticancer effects is complex, as high levels of antioxidants may provide tumour cells with some protection from oxidative stress, but specific modulation of ROS may promote apoptosis. Thus, the interaction between puerarin, ROS and tumour cell survival needs to be well experimentally characterized. NF-κB is an important transcriptional regulator of inflammation and cancer biology. Chronic inflammatory signals can create an environment that favors the survival of tumour cells, angiogenesis, tumour invasion, and resistance to cell death [16,17].

Puerarin has been shown to inhibit NF-κB-mediated inflammatory pathways and decrease NF-κB-mediated inflammatory mediator expression [14]. This might apply to lung cancer since the tumour microenvironment has inflammatory cells and cytokines that can help guide the progression of a tumour. Metastatic dissemination is a major determinant of morbidity and mortality in lung cancer. Migratory and invasive properties enable malignant cells to interact with and degrade the extracellular matrix and invade surrounding tissues.

Puerarin has been shown to inhibit migration and invasion in NSCLC models [16]. In relation to the antimetastatic effects of puerarin, changes in matrix metalloproteinases (MMP-2 and MMP-9) have been linked to the effect [14]. The lowered activity of these enzymes can hinder extracellular matrix degradation and thus invasion.

Epithelial–mesenchymal transition (EMT) is linked to the enhanced motility, invasiveness, and metastatic capabilities of tumour cells. EMT can be regulated by signalling pathways like PI3K/Akt and MAPK pathways and inflammatory pathways. The potential anti-EMT effect of puerarin may be explained by its modulation of these pathways. However, direct evidence showing puerarin-induced EMT inhibition in lung cancer is less comprehensive than that of apoptosis and proliferation. This is an area for further study [15,16].

Figure 2 shows the proposed molecular and cellular mechanisms through which puerarin may exert anticancer effects in non-small-cell lung cancer (NSCLC). It highlights modulation of apoptosis, cell-cycle progression, PI3K/Akt/mTOR and MAPK signalling, oxidative stress, NF-κB-mediated inflammation, and tumour-cell migration and invasion.

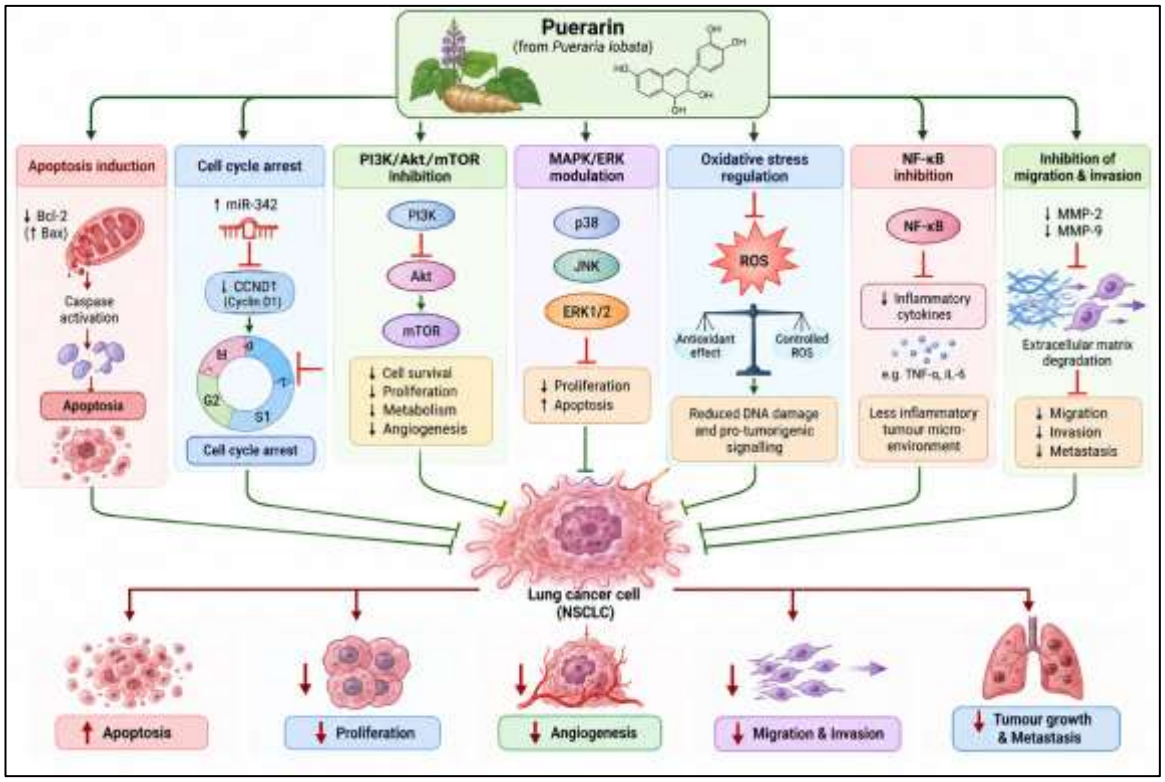


Figure 2: Molecular and Cellular Mechanisms of Puerarin-Mediated Anticancer Effects in Non-Small-Cell Lung Cancer (NSCLC)



Evidence of anticancer activity in lung cancer

The evidence available on lung cancer is mostly from experimental models of NSCLC. It has been reported that puerarin could decrease cell viability and cell proliferation, and induce apoptosis [15,16]. Huang et al. showed that puerarin suppressed cell viability, migration, invasion, and cell cycle progression of NSCLC, and induced apoptosis [16,17]. Mechanistically, puerarin increased miR-342 expression, which subsequently reduced CCND1 expression. The authors also showed that modulation of this pathway had an impact on tumour growth in vivo [16]. The results have implications because migration and invasion are important clinically for aggressive lung cancer. These findings suggest that puerarin may affect not only tumour-cell proliferation but also processes associated with metastatic progression. Animal studies should be viewed as an intermediate level of evidence between cell culture and clinical studies. In experimental NSCLC xenograft models, puerarin has been shown to inhibit tumour growth [15,16]. These findings extend the evidence of biological activity from cell culture models to an in vivo setting. There are limitations to xenograft models, however, as there are differences in the immune system, metabolism and tumour microenvironment compared to humans. Based on the current evidence, The findings support further investigation but do not establish clinical efficacy in humans. The tumour microenvironment includes immune cells, fibroblasts, endothelial cells, extracellular matrix and tumoural signalling molecules, which affect the behavior of the tumour. Recent research has increased interest in the potential effects of natural compounds on the tumour microenvironment. The pharmacology of puerarin has been reviewed, and its immunomodulatory and anti-inflammatory effects are described which may theoretically affect the tumour microenvironment [13,14]. Experimental studies have reported alterations in pathways and inflammatory mediators associated with macrophages. However, evidence specific to lung cancer remains limited compared with studies focused on tumour-cell proliferation. Further and more complex models involving tumour-associated macrophages, fibroblasts, endothelial cells and immune cells are needed. One of the main drawbacks of the current evidence is the absence of comprehensive clinical trials that target a specific anticancer effect of P. lobata or puerarin in the case of lung cancer. The clinical studies of puerarin in cardiovascular, cerebrovascular, and other non-oncological diseases fail to provide evidence of lung cancer efficacy [13,17]. Likewise, multiple herb formulations used traditionally do not provide specific

evidence regarding the effect(s) of P. lobata, as several components of these formulations may contribute to the effects observed.

The current evidence should therefore be viewed as hypothesis-generating rather than as evidence supporting replacement of established lung cancer therapies.

Possible Combinations of Pueraria lobata with the conventional treatment of lung cancer

Lung cancer treatment has become increasingly complex, often using a combination of chemotherapy, radiotherapy, targeted therapy and immunotherapy. Treatment of molecularly targeted NSCLC has been revolutionized and for advanced disease, immune checkpoint inhibitors have significantly broadened treatment options [7, 8, 9,19]. This therapeutic setting raises an interesting question for further research: This raises the possibility that puerarin or standardized P. lobata preparations could enhance the efficacy of conventional treatments. There is a theoretical basis for this because puerarin affects multiple pathways that are involved in the survival of tumour cells and resistance to drugs. There are some recent reviews that mention the possible interactions between puerarin and conventional anticancer drugs, such as increased activity in experimental models when combined with some chemotherapeutic drugs [20]. But there is a lack of specific evidence for clinically significant synergy in lung cancer.

The cytotoxic effect of chemotherapeutic drugs including platinum compounds is mediated by DNA damage and subsequent mechanisms. Puerarin induces apoptosis or blocks survival signals, which could make tumours more vulnerable to chemotherapy. Importantly, synergistic effects observed in experimental models cannot be assumed to translate into clinically meaningful synergy. Human plasma and tumour concentrations of the compounds used in cell experiments may not be attainable. Therefore, prior to clinical testing, formal combination-index studies followed by animal pharmacokinetic and toxicity studies are needed. Targeted therapies are becoming more and more relevant in the molecularly defined NSCLC. Targeted therapies against EGFR, ALK, KRAS and others are still a significant clinical challenge [7,8]. Puerarin has the potential to modulate pathways, including PI3K/Akt, MAPK and inflammatory pathways, which may also mean that it could have an impact on bypass signalling that is linked to resistance. But no evidence is available yet to recommend puerarin as resistance-reversing agent in patients undergoing molecular targeted therapy. Radiotherapy primarily exerts its effects through DNA damage and oxidative stress. The antioxidant and redox-modulating activity of puerarin presents an interesting scenario: protection of the normal tissues as well as improvement of the radiosensitivity of tumours or, depending on the situation, reduction of the radiation-induced oxidative damage in tumour cells. This question remains difficult to resolve, as a compound that would protect both normal and malignant tissue would not give any net therapeutic benefit. Newly introduced immune checkpoint inhibitors targeting PD-1, PD-L1 and related pathways are important in the management of NSCLC [9,19]. The anti-inflammatory and immunomodulatory effects of puerarin are biologically plausible in terms of interactions with immune-based treatment. However, an appropriate immune response is essential for the efficacy of immunotherapy. Theoretically, an unknown immunomodulatory effect may be beneficial or detrimental to treatment. Thus, the combination with immune checkpoint inhibitors should continue to be investigated until there is pharmacodynamic and clinical evidence.

Figure 3 summarizes experimental evidence demonstrating the potential anticancer effects of puerarin in lung cancer models, including inhibition of proliferation, migration, invasion, and tumour growth. It also illustrates potential interactions with chemotherapy, targeted therapy, radiotherapy, and immunotherapy, while emphasizing that clinical efficacy in humans remains unestablished.

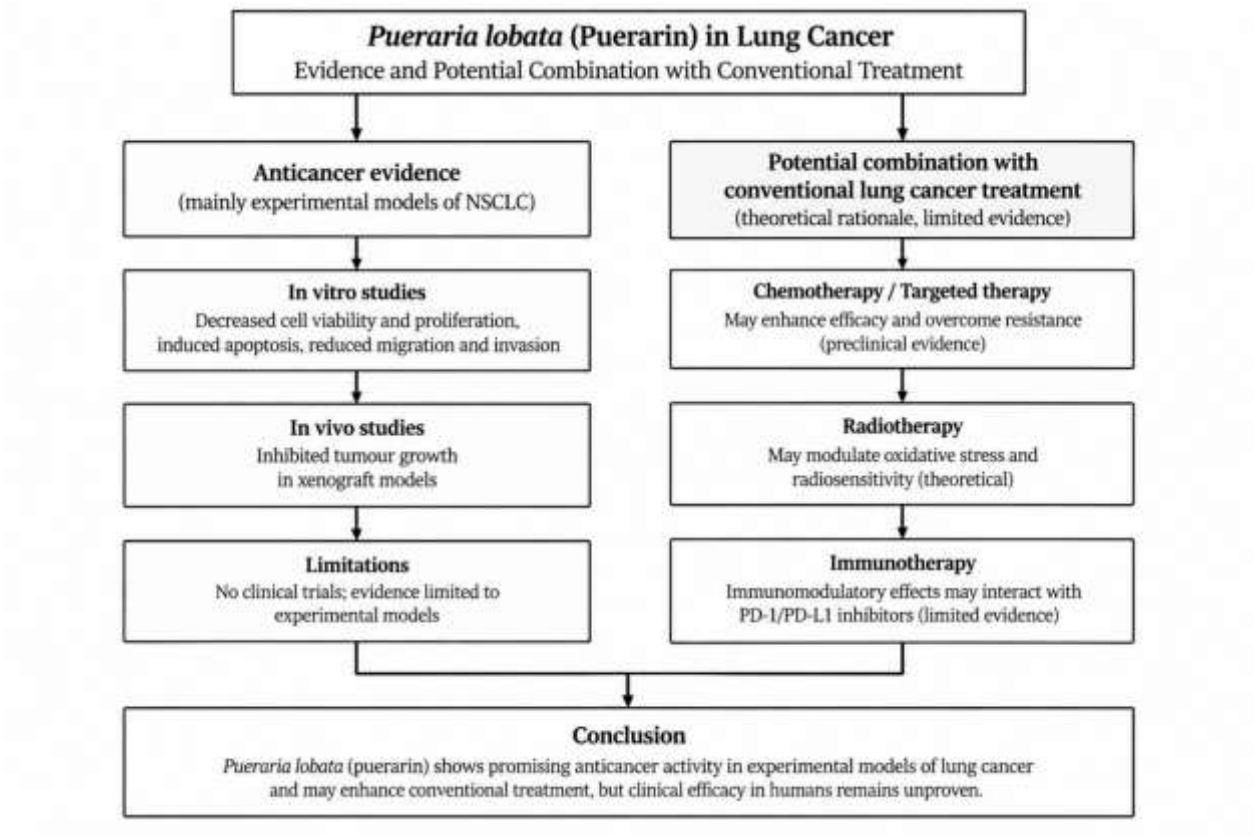


Figure 3. Preclinical Evidence and Potential Therapeutic Combinations of Pueraria lobata (Puerarin) in Lung Cancer

Safety and Pharmacokinetics, Limitations and Translational Challenges

Safety of P. lobata should be assessed independently of the safety of purified puerarin. The active ingredients, contaminants and other pharmacologically active substances in plant preparations may vary significantly. Therefore, the safety of P. lobata preparations requires independent evaluation, particularly in the context of complex oncology treatment. The poor physicochemical and pharmacokinetic properties of puerarin is one of the main challenges for its clinical translation. Puerarin has poor water solubility, low oral bioavailability, and extensive metabolism [21,22]. A 2019 review summarized that daidzein and its glucuronide conjugates are significant metabolites of puerarin and that P-glycoprotein, multidrug-resistance-associated proteins and metabolic enzymes play a role in the disposition of puerarin [21]. Due to the low solubility and bioavailability, the investigation of other types of delivery systems, such as dendrimers and microemulsions, as well as nanoparticles, has been encouraged [21]. Another review similarly highlighted limited membrane permeability, a short half-life, intestinal efflux, and extensive first-pass metabolism, all of which can reduce oral bioavailability [22]. The development of new drug delivery methods may offer the potential of enhanced systemic exposures and tissue distribution. However, increased bioavailability does not necessarily translate into improved clinical efficacy. Not necessarily, because increasing the exposure can also lead to increased toxicity or change interactions with other drugs. Herb–drug interactions are especially significant in cancer patients who often are taking multiple drugs. Puerarin may interact with drug-metabolizing enzymes and transport systems, which may result in changes in drug exposure when given in combination with other drugs [21]. This is particularly significant for medicines with a narrow therapeutic window (NTW). Therefore, the possible interaction of puerarin or P. lobata preparations with anti-cancer drugs should be investigated systematically. Another significant problem is the variability of P. lobata preparations. Biological effects can vary greatly depending on differences in the geographic origin, extraction, processing and concentrations of the constituents. One of the frequent issues in natural product research is the high concentration used in vitro. The concentration needed for the inhibition of the cancer cell line might not be reached in human plasma or tumour tissue.

Therefore, dose selection should be done in relation to the pharmacokinetic and/or the pharmacodynamic aspects of the drug action, and not solely based on extrapolation from cell culture experiments. In a clinical study, the majority of the evidence that comes from preclinical studies is used. The evidence base is currently skewed towards laboratory-based

studies. Puerarin (2025–2026) has been reported to be a potential multi-targeted anticancer agent, and standardization, selectivity, and safety are still issues to be addressed, as well as delivery and clinical translation [20,23]. The evidence is also heterogeneous with respect to cancer type, experimental system, dose and formulation. Such heterogeneity limits quantitative comparison across studies. The other drawback is that numerous studies do not focus on P. lobata itself, but rather on the plant's component puerarin. Conclusions on purified puerarin are therefore not meant to be used as conclusive proof of crude or traditional P. lobata preparations.

Future Perspectives and Conclusion

Further studies should first focus on the standardization of preparations of P. lobata. All experimental and clinical studies should include the chemical fingerprinting and quantitative determination of puerarin, daidzin, daidzein, genistein and other relevant constituents routinely. Second, the investigations of the mechanisms should not be limited to individual signalling pathways. A combination study of transcriptomic, proteomic, metabolomic, and single-cell studies might help to elucidate the mechanism of action of puerarin in tumour cells and the microenvironment. Third, future research should account for the biological and clinical heterogeneity of lung cancer. The available experimental evidence is for NSCLC, and there is limited information available for SCLC. Dedicated studies in SCLC are clearly needed as it has a unique biology and therapeutic properties. Fourth, pharmacokinetic studies should determine whether puerarin to reach therapeutic levels in lung tumours. New delivery systems could enhance absorption and tissue distribution, but the safety and pharmacologic equivalence must be proven [21,22]. Fifth, Systematic studies of combination treatment are also warranted. In vitro pharmacological interaction studies and animal studies on the response to tumour, toxicity, and pharmacokinetics must be conducted before assuming any synergy. Then promising combinations can be tested in the early stages of clinical testing. Biomarker-guided approaches could also be useful in the identification of patients that might benefit from benefiting from puerarin-based interventions. Molecular markers associated with PI3K/Akt, MAPK, inflammatory pathways, apoptosis, or drug-resistance pathways could be considered as candidates for predictive biomarkers. Finally, for the quality of the evidence to be good, there should be well-designed randomized clinical trials. Initial studies may be used to determine the safety and tolerability of the product followed by larger efficacy studies. Standardized preparations and clinically meaningful endpoints (e.g., objective response, progression-free survival, overall survival, quality of life and treatment-related toxicity) should be used during trials.

Novelty

The novelty of this narrative review is lung cancer-specific and translational with focus on the principal isoflavonoid of Pueraria lobata, puerarin. This review goes beyond the broad pharmacological properties of P. lobata and integrates the current evidence on its phytochemical composition, molecular mechanisms relevant to lung carcinogenesis, experimental evidence in NSCLC, possible interactions with chemotherapy, targeted therapy, radiotherapy, and immunotherapy, and the main obstacles to clinical translation. Another important consideration is the distinction between purified puerarin and whole-plant P. lobata preparations, as evidence from the isolated compound cannot be directly extrapolated to traditional or crude extracts. The review also critically discusses limitations of pharmacokinetics, variability of preparation, achievable concentrations of drugs, potential interactions between herbs and drugs, and lack of clinical trials specific to lung cancer. Here, we provide a translational framework to determine whether puerarin or standardized preparations of P. lobata can be advanced from experimental anticancer agents to clinically relevant interventions in lung cancer based on the integration of preclinical molecular observations and practical considerations for pharmacokinetic, toxicity, combination, biomarker, and clinical studies.

Conclusion

Pueraria lobata and its principal isoflavonoid, puerarin, have attracted considerable scientific interest because of their widespread pharmacological activities and anticancer properties. Recent studies have shown that puerarin may modulate various biological processes important for lung cancer, such as apoptosis, cell-cycle progression, oxidative stress, inflammatory signalling, PI3K/Akt and MAPK pathways, migration and invasion [14–16,20]. The experimental models that are most directly relevant to lung cancer are those of NSCLC. Puerarin has been reported to inhibit the viability and progression of NSCLC cells, induce apoptosi and inhibit the migration and invasion of cells. One pathway that has been demonstrated to play a role is the miR-342/CCND1 pathway and other studies and reviews have indicated that

other signalling pathways, such as PI3K/Akt, MAPK/ERK, NF-κB and others may be involved [14,16]. However, these findings should be interpreted cautiously given the predominantly preclinical nature of the evidence. No clinical trials have been carried out with P. lobata or puerarin; the existing literature shows that its efficacy as a treatment for lung cancer has not been established. Evidence is largely preclinical and there are many uncertainties with translation of dosage, bioavailability, standardization, pharmacokinetics and the impact of herb–drug interactions and prolonged use. Thus, at this moment, P. lobata may be considered a candidate for further anticancer drug development, rather than a potential drug product. Lastly, the potential of standardized formulations of puerarin or puerarin combination therapy with chemotherapy could be potential areas for further investigation. This must be done along with the most thorough pharmacological research and reproducible preparations, biomarker research, and appropriately designed clinical trials.

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