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Original Research Article

Comprehensive Review of *Fritillaria*: Medicinal History, Botanical Sources, Geographical Distribution, Extraction and Isolation Methods, and Anti-lung Cancer Activity

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Abstract

Background: The *Fritillaria* genus has been widely employed in traditional Chinese medicine (TCM) for thousands of years as an expectorant and cough suppressant. The primary active components in **Fritillaria** are alkaloids, yet their low content, complex composition, and high extraction costs significantly limit their commercial application. *Fritillaria* spp. exhibits notable therapeutic effects on lung diseases, especially lung cancer.
Objectives: This review addresses the limitations of previous studies by clearly defining the research gaps and employing a comprehensive methodology. It aims to summarize the medicinal history of the *Fritillaria* genus, the extraction and isolation methods of active components, and toxicological findings, and to elucidate the role of *Fritillaria* in lung cancer treatment.
Materials and Methods: Literature was systematically retrieved from databases including CNKI, PubMed, Web of Science, and SciFinder, using the keywords "*Fritillaria*" and "lung cancer".
Results: Findings indicate that the *Fritillaria* genus has a long medicinal history and is primarily distributed in western China. Existing extraction and isolation methods fail to efficiently and cost-effectively produce *Fritillaria* alkaloids. Toxicity studies have demonstrated that *Fritillaria* spp. are generally safe at recommended dosages, although dose-dependent genotoxicity at higher concentrations has been observed. Various bioactive compounds of **Fritillaria** spp. can modulate the occurrence and progression of lung cancer through apoptosis, cell cycle regulation, and inflammatory signaling pathways.
Conclusion: *Fritillaria* spp. have considerable potential for lung cancer treatment and drug development, but further improvements in extraction methodologies are necessary to facilitate clinical translation.

Keywords

Fritillaria, medicinal history, extraction, isolation methods, anti-lung cancer

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Introduction

Traditional Chinese medicine (TCM) has a long-standing historical record of using species of the genus *Fritillaria*, perennial plants belonging to the Liliaceae family, for therapeutic purposes. The Shen Nong Ben Cao Jing contains the earliest documented reference to *Fritillaria*, classifying it as an herb of moderate medicinal value. It has been recognized for its efficacy in treating ailments such as fever, phlegm retention, and sore throats (Che, 2023). Recent studies have revealed approximately 165 distinct species of *Fritillaria* spp. distributed worldwide (Paudel et al., 2021). These species are primarily distributed across the temperate regions of the Northern Hemisphere, especially the Mediterranean, Central Asia, and North America. Recent findings have greatly expanded knowledge regarding the diversity of *Fritillaria* spp. in China, with the identification of 80 species, 52 variations, and 6 forms (Li et al., 2022).

For thousands of years, TCM has highly valued *Fritillaria* spp. for its therapeutic effects on various conditions, particularly respiratory disorders such as lung abscesses and chronic coughs. Traditional preparations frequently involve combining *Fritillaria* spp. with other medicinal herbs. Recent studies have highlighted the biological activity of alkaloids found in

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Fritillaria spp., prompting extensive research into improved methods for their extraction, purification, and concentration (Hao et al., 2013). Phytochemical investigations have revealed that *Fritillaria* spp. contains a diverse array of chemical constituents, including alkaloids, organic acids and their esters, nucleosides, sterols and their glycosides, polysaccharides, volatile oils, saponins, terpenes, and trace elements (Duan et al., 2022; Liu et al., 2020; Liu, Chen, et al., 2023; Liu, Ming, et al., 2023). Alkaloids, in particular, are the most bioactive natural products of *Fritillaria* spp., serving as key bioactive and potentially toxic components. To date, over 120 alkaloids and more than 30 non-alkaloid compounds have been isolated from this genus, totaling more than 150 identified chemical constituents. Pharmacological studies have demonstrated that ethanol extracts and isolated alkaloids from *Fritillaria* spp. exhibits diverse biological activities, including anti-tussive, anti-asthmatic, anti-inflammatory, antioxidant, anti-bacterial, and anti-tumor effects (An et al., 2022).

Historical texts and pharmaceutical standards consistently document the efficacy of *Fritillaria cirrhosa* D. Don and *Fritillaria thunbergii* Miq. in relieving cough and resolving phlegm. Despite the extensive application of *Fritillaria* spp. in lung cancer treatment, research on its anti-cancer constituents remains limited. Existing studies primarily focus on its extracts, with specific alkaloids such as peimine and peiminine showing anti-cancer activities (Ruan et al., 2016). However, the molecular mechanisms underlying these effects are not well understood. This highlights the need for a comprehensive review that not only summarizes existing knowledge but also critically evaluates and synthesizes recent advancements in understanding the anti-lung cancer properties of *Fritillaria* sp. There is considerable scope for further exploration of the anti-lung cancer properties of *Fritillaria* sp., including identifying the active alkaloids, assessing their bioactivity, and elucidating the mechanisms of action (Liu et al., 2020).

This review aims to provide a comprehensive summary of the medicinal history, botanical sources, geographical distribution, extraction and isolation methods, and anti-lung cancer activities of *Fritillaria* sp., thereby offering a valuable reference for future research and development of this important genus.

Medicinal History of Fritillaria spp.

Species of the genus *Fritillaria*, well-known herbs in TCM, have been utilized medicinally for over a millennium. The earliest recorded reference to *Fritillaria* spp. appears in the *Shen Nong Ben Cao Jing*, where they are classified as medium-grade herbs, characterized by pungent, neutral properties and a non-toxic nature (Wang, Herbst, et al., 2021). Subsequent significant historical references include the *Mingyi Bielu* compiled by Tao Shi during the Wei-Jin period, the *Bencao Jing Jizhu* by Tao Hongjing in the Northern and Southern Dynasties, the *Xinxiu Bencao* by Su Jing of the Tang Dynasty, and the Tujing Bencao by Su Song in the Song Dynasty. These early texts generically referred to *Fritillaria*, without distinguishing among species (Zhijun & Xiaolong, 1995). It was not until the Ming dynasty, in Li Shizhen's Ben Cao Gang Mu, that a comprehensive description of the therapeutic properties of various *Fritillaria* species was provided. Further classification based on therapeutic efficacy and geographical origin was introduced in the Bencao Huiyan, stating that: "*Fritillaria* spp. are medicines used for relieving depression, lowering Qi, and resolving phlegm" (Zhijun & Xiaolong, 1995). They moisten the lungs, clear phlegm, relieve cough, and alleviate asthma. For treating phlegm-heat syndrome with deficiency, *Fritillaria* varieties from Sichuan are preferred, while local varieties are recommended for treating abscesses, resolving masses, and clearing substantial phlegm. The Sichuan varieties are mild and considered superior, whereas local varieties are bitter and regarded as inferior. This classification indicates that distinctions among *Fritillaria* species regarding efficacy and origin first emerged during the Ming dynasty. The 1953 edition of the Chinese Pharmacopoeia did not include detailed records for specific *Fritillaria* species. It was not until the 1963 edition that distinct categorizations for *F. cirrhosa* D. Don and *F. thunbergii* Miq. were introduced. Continued research has led to progressively refined standards for the testing and classification of *Fritillaria* spp. (Wang, Hou, et al., 2021).

In TCM, *Fritillaria* sp. is often used in combination with other medicinal herbs. For example, the Jifeng Puji Fang describes using *Fritillaria* sp. with Anemarrhena, Stemona, licorice, and ginseng to treat chronic coughs (Canton-Alvarez, 2019). The Xian Nian Ji documents its use with lotus seeds and pig lungs to treat consumptive heat and persistent cough. The Si Sheng Xin Yuan mentions its combination with Cimicifuga, Moutan, and Scrophularia to treat throat abscesses with pus (Xu et al., 2021). Despite its extensive historical use, the synergistic effects, potential interactions, and underlying mechanisms of bioactive components in *Fritillaria* sp., when used with other medicinal plants, remain largely unexplored and warrant further investigation in modern pharmacognosy.

Medicinal Plant Sources and Geographical Distribution of the Fritillaria sp.

Fritillaria spp. are perennial herbs in the Liliaceae family, comprising 160 species worldwide (Paudel et al., 2021). As shown in Tables S1 and S2 in the supplemental material, these species are widely distributed throughout temperate zones of the Northern Hemisphere, with no confirmed records from Africa. The highest species richness occurs in Turkey, the broader Mediterranean basin, and Iran. Ongoing taxonomic surveys have expanded China's inventory to >80 species, 52 varieties, and six forms of *Fritillaria* (Luo et al., 2018). Most provinces in China now report native *Fritillaria* records, with the notable exceptions of Guangdong, Guangxi, Fujian, and Taiwan. Sichuan, Xinjiang, and Gansu provinces host the

highest diversity and population abundance. This review summarizes germplasm resources and the biogeography of *Fritillaria* spp. based on recent literature (Pan et al., 2015; Z hong et al., 2019), thereby providing an ecological context for subsequent discussions on extraction strategies (Table S2 in the supplemental material).

Extraction and Isolation Methods

Modern phytochemical studies reveal that *Fritillaria* species contain diverse compounds, with isosteroidal and steroidal alkaloids being the principal bioactive components (Duan et al., 2022; Zhou et al., 2010). According to the 2020 Chinese Pharmacopoeia, alkaloid content (0.050%–0.080%) is a key quality control index. However, low abundance and structural complexity necessitate efficient extraction and purification strategies (Figure 1, Table S3 in the supplemental material).

Traditional extraction methods such as soaking, reflux, and percolation remain widely used in *Fritillaria* alkaloid research due to their simplicity and scalability. Optimization of conditions—for example, material-to-liquid ratios (1:20–30), temperature (60°C–80°C), and alkali pretreatment improved efficiency in recent years (Minna et al., 2019). Percolation methods are preferred for thermolabile components, employing extended soaking and low-temperature flow control. However, newer techniques such as supercritical CO_2 extraction, microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), and enzyme-assisted extraction (EAE) have emerged as superior alternatives, offering higher yields, shorter extraction times, and reduced solvent use. For instance, supercritical CO_2 extraction using ethanol as an entrainer (20–30 MPa, 45°C–60°C) can increase the alkaloid yield over 10-fold compared to traditional reflux (Ruan et al., 2017). Similarly, MAE and UAE enhance mass transfer through cavitation and thermal effects, while EAE with cellulase at pH ~5 can double the extraction rate (An et al., 2022; Chen et al., 2018).

Following extraction, *Fritillaria* alkaloids require further purification due to the presence of co-extracted proteins, saponins, tannins, and other interfering compounds. A wide range of chromatographic and resin-based methods are employed for this purpose. Thin-layer chromatography (TLC) and atmospheric pressure column chromatography are widely used for the initial separation and identification of key alkaloids like peimine and verticine (Aihua et al., 2009; Xu et al., 1982). Silica gel columns, particularly with mixed mobile phases such as ethyl acetate-methanol-ammonia, have yielded purities exceeding 90% (Aihua et al., 2009). Solid-phase extraction (SPE), using C_{18} or ion-exchange columns, offers rapid and selective purification, and is often combined with liquid chromatography–mass spectrometry (LC–MS) for analytical quantification (Crews et al., 2010; Shi et al., 2022).

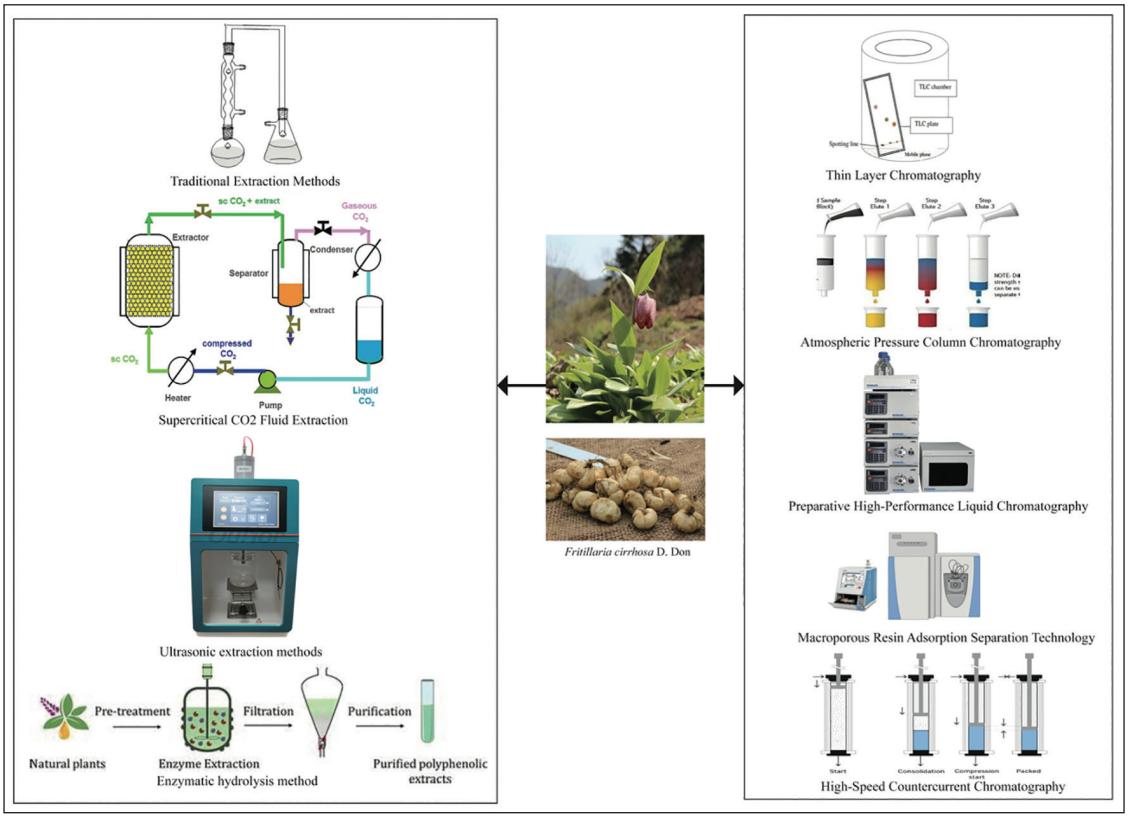


Figure 1. Extraction and Isolation Methods.

Preparative high-performance liquid chromatography (pre-HPLC) and macroporous resin adsorption are essential for large-scale separation, especially when targeting minor or structurally similar alkaloids. Pre-HPLC provides automation and high resolution but may require sample pretreatment and has limited capacity (Yun-Xia et al., 2004). Macroporous resins such as HPD-100, operated under alkaline pH and moderate ethanol concentrations, effectively remove polar impurities and concentrate total alkaloids, yielding over 50% purity and >75% recovery (Huimei & Ping, 2016). Additionally, high-speed countercurrent chromatography (HSCCC), a liquid–liquid partitioning technique that eliminates solid-phase interactions, enables high-purity (95%+) separation of alkaloids like verticine in a single step, using biphasic systems such as hexane/ethyl acetate/methanol/water (Jiang et al., 2015).

Overall, the integration of conventional and modern extraction techniques, paired with robust purification strategies, has substantially advanced the ability to isolate pharmacologically relevant alkaloids from *Fritillaria* spp., facilitating downstream research and potential drug development (Borjigin et al., 2023).

Research Progress on the Molecular Mechanisms of Fritillaria sp. Against Lung Cancer

Lung cancer currently ranks second among all malignancies worldwide, with an estimated 2.21 million new diagnoses in 2020, representing 11.4 % of the global cancer burden. It is simultaneously the leading cause of cancer-related mortality, accounting for 1.80 million deaths (18% of total cancer fatalities) in the same year. According to Siegel et al. (2022), the incidence of advanced-stage lung cancer is declining, whereas stage 0 (*in situ*) diagnoses have been rising at approximately 4.5% per year. The proportion of early detections increased from 17% (2004) to 28% (2018), with the 3-year relative survival improving from 21% to 31% (Sung et al., 2021).

Lung cancer is broadly categorized as non-small-cell lung cancer (NSCLC; ≈85%) and small-cell lung cancer (SCLC; ≈15%) (Thai et al., 2021). The World Health Organization further subdivides NSCLC into lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell lung carcinoma (LCLC). Data from Chen et al. (2016) indicate significant variation in incidence and mortality by sex, age, and geographic region. In that year, 520,300 men and 266,700 women were newly diagnosed, and age-standardized mortality was 0.40% in men versus 0.16% in women, yielding an approximate two-fold sex disparity (Chen et al., 2016; Sung et al., 2021; Zheng et al., 2022).

Surgical resection may be curative for early-stage disease but carries risks of reduced pulmonary function, pneumonia, respiratory failure, pulmonary embolism, and arrhythmia. Radiotherapy can induce acute pneumonitis, late-onset pulmonary fibrosis, pericardial disease, esophagitis, myelitis, and cutaneous desquamation or fibrosis (Zugazagoitia & Paz-Ares, 2022). Cytotoxic chemotherapy remains a cornerstone of systemic therapy, but is associated with substantial toxicities. These adverse events encompass myelosuppression (neutropenia, thrombocytopenia, anemia), gastrointestinal distress, nephrotoxicity, peripheral neuropathy, and chemotherapy-induced pneumonitis or fibrosis, each of which can compromise survival. Targeted agents and immune checkpoint inhibitors generally produce fewer depressive symptoms and milder chronic inflammation in long-term survivors than conventional chemotherapy (Bolaki & Antoniou, 2020). Nevertheless, both primary and acquired resistance frequently emerge, culminating in disease progression (Wang, Herbst, et al., 2021; Wang, Hou, et al., 2021). Consequently, early integration of palliative care is recommended to optimize quality of life in parallel with anti-cancer therapy (Herbst et al., 2018).

Beyond its traditional anti-tussive use, *F. cirrhosa* displays documented anti-inflammatory and anti-tumor activities (Wu et al., 2022). Alkaloids isolated from *F. cirrhosa* exert anti-proliferative and pro-apoptotic effects across multiple tumor cell lines and have been shown to reverse multidrug resistance in breast, leukemia, lung, and gastric cancer models. However, the molecular mechanisms underpinning the anti-lung cancer activity of *Fritillaria* spp. remain insufficiently reviewed.

Molecular Mechanisms of Fritillaria sp. Against Lung Cancer

Over the last decade, pharmacological investigations have shifted from symptomatic endpoints, such as anti-tussive or anti-asthmatic activity, to mechanistic oncology research that interrogates tumor-driving pathways. Table S3 in the supplemental material summarizes six convergent anti-tumor mechanisms: (a) apoptosis induction, (b) cell-cycle arrest, (c) anti-angiogenesis, (d) immune modulation, (e) multipathway regulation, and (f) inhibition of migration and invasion (Table S4 in the supplemental material, Figure 2). Notably, the iso-steroidal alkaloid peimine inhibits A549 proliferation by blocking canonical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling: it diminishes IκBα phosphorylation, prevents p65 nuclear import, and downregulates matrix metalloproteinase-9 (MMP-9), thereby reducing migration ($IC_{50} \approx 12$ μM, 48 h). Collectively, these data identify NF-κB, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), and signal transducer and activator of transcription 1/4 (STAT1/4) as principal signaling axes modulated by *Fritillaria* alkaloids, supporting their use in combination with pathway-selective inhibitors.

Currently, lung cancer, the most prevalent type of cancer, is garnering increased attention. Previous studies have demonstrated that *F. cirrhosa* and its active components significantly inhibit lung cancer progression. The water extract of *F. cirrhosa* aqueous extract (FC-AE) exhibits anti-tumor effects comparable to those of the total alkaloids of *F. cirrhosa* (Li,

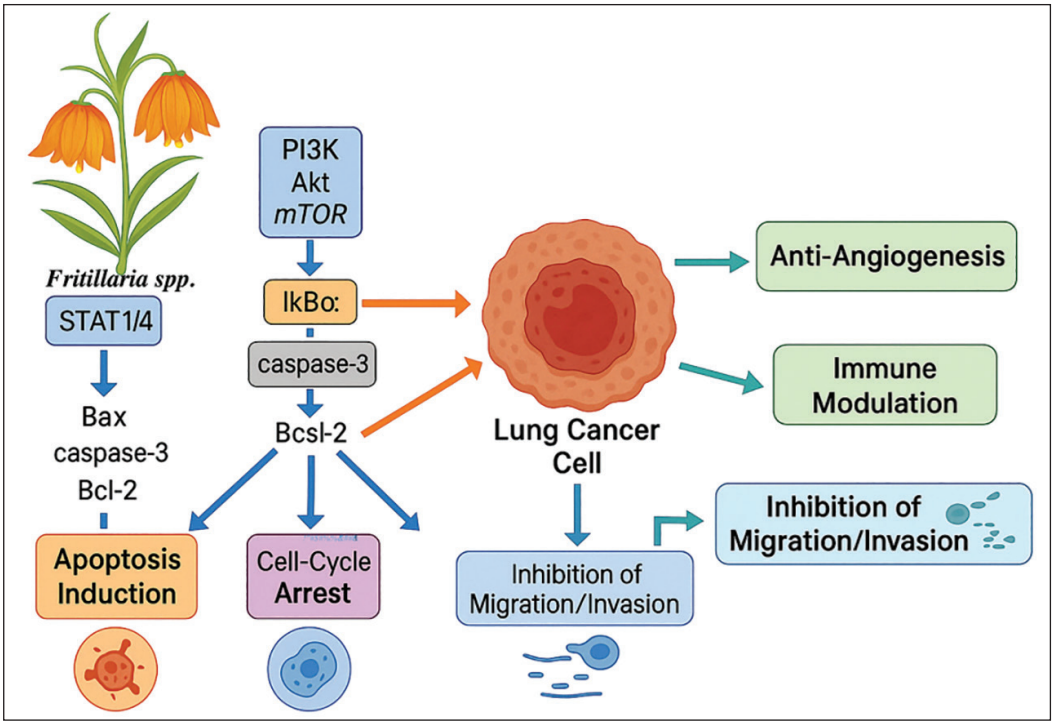


Figure 2. Mechanistic Insights into the Anti-tumor Effects of *Fritillaria* sp. on Lung Cancer Cells.

Ma, et al., 2020; Wang et al., 2014). In a nude mouse model, FC-AE (0.5 mg/mL every 2 days for 20 days) inhibited the growth of A549 tumors by enhancing the levels of STAT1, STAT4, interferon-gamma (IFNγ), interleukin-12 (IL-12), caspase-3, and B-cell lymphoma-2 (Bcl-2) associated Bcl-2-associated X protein (Bax) protein, while reducing Bcl-2 production. Additionally, FC-AE (0–100 μg/mL, 48 h) exhibited significant anti-proliferative effects on A549 cells, attributed to G2 phase cell accumulation, increased Bax, STAT1, and STAT4 activities, and downregulated Bcl-2 protein levels (Cui et al., 2021; Li, Zhang et al., 2020).

F. thunbergii (FTF), historically prescribed for bronchitis, has emerged as a candidate adjuvant in lung cancer therapy, yet its molecular basis remains elusive. A recent investigation unified ligand profiling, target prediction, network pharmacology, and murine validation to elucidate FTF's anti-lung cancer mechanism. The resulting network comprised 114 nodes—44 candidate compounds and 70 predicted targets—interconnected by 361 edges that influence inflammation, angiogenesis, apoptosis, and proliferative signaling. In Lewis lung carcinoma (LLC)-bearing mice, ethanol-extracted FTF markedly slowed tumor growth and prolonged survival. Mechanistically, FTF downregulated PIK3CG, Bcl-2, iNOS, VEGF, p-STAT3, and total STAT3 in tumor tissue (Cui et al., 2021), highlighting its multi-target capacity to modulate oncogenic pathways that drive lung cancer progression coordinately.

Cumulative evidence shows that the total-alkaloid fraction of *F. cirrhosa* (total *F. cirrhosa* bulb alkaloids (TFCB); 10–40 mg kg^{-1} day^{-1} for 10 days) markedly attenuates transplantable LLC growth in mice via anti-angiogenic and pro-apoptotic effects, evidenced by decreased CD31 and activated caspase-3 (Wang, Li, et al., 2016; Wang, Yang, et al., 2016). *In vitro*, TFCB (30 μg mL^{-1}) suppressed LLC proliferation through S-phase arrest and apoptosis. Wang et al. further evaluated several *F. cirrhosa* extracts across A2780, HepG2, and A549 lines. They corroborated their activity in xenograft models: extracts induced G_0/G_1 arrest, upregulated caspase-3, and reduced tumor microvessel density, thereby restricting tumor expansion (Lin et al., 2020). Together, these data underscore the pathway pleiotropy of *F. cirrhosa* extracts in oncological models.

Wang et al. further studied the anti-tumor activity of *F. cirrhosa* extracts on Lewis lung cancer cells *in vitro* and *in vivo*. The results indicated that the chloroform extract and total alkaloids had stronger inhibitory effects on lung cancer cell proliferation than other extracts (Wang, Herbst, et al., 2021; Wang, Hou, et al., 2021). Total alkaloids induced cell cycle arrest and apoptosis, with *in vitro* studies revealing that total alkaloids significantly inhibited tumor angiogenesis and induced cell apoptosis by activating caspase-3. The combination of *F. thunbergii* and licorice root has drawn attention due to its significant anti-cancer efficacy. Recent *in vivo* experiments demonstrated that administering the combination (equivalent to 15 g of *F. thunbergii* and 6 g of licorice root per 50 kg body weight) for 4 weeks significantly inhibited tumor cell proliferation and promoted apoptosis. This anti-cancer effect is mainly achieved by suppressing the expression of

NF-κB signaling pathway-related proteins, including toll-like receptor 4 (TLR-4), NF-κB, and RelA. The study suggests that the combination may serve as an effective natural anti-cancer therapy (Wang et al., 2014).

Beyond total extracts, some individual chemical components, such as peimine and imperialine, show significant potential in lung cancer treatment. For example, peimine (5–15 μg/mL, 48 h) significantly reduces the viability of LLC cells by causing S-phase cell accumulation and reducing G_0/G_1 phase cells, leading to increased apoptosis (Li et al., 2016). *In vivo* studies showed that peimine (10–40 mg/kg/day for 10 days) significantly inhibited the growth of transplantable LLC tumors in mice by deactivating CD31-mediated tumor angiogenesis and promoting caspase-3-mediated apoptosis. Extensive research has demonstrated the anti-tumor effects of imperialine (Li et al., 2016). A recent study indicated that imperialine (200 ng/mL, 24 h) inhibited the proliferation of the human LUAD cell line A549 by downregulating key regulators in the NF-κB pathway, including PI3K III, Akt, p-Akt, NIK, IKKα and β, and IκBα, while reducing Ki67 expression (a clinical biomarker of tumor progression), and increasing caspase-3 levels (Lin et al., 2020). Moreover, imperialine (10 mg/kg, 18 days) significantly blocked the progression of NSCLC in mice, involving decreased levels of inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and reduced Ki67 expression (Lin et al., 2020). Imperialine, known for its anti-inflammatory effects, was shown in this study to have anti-cancer properties against NSCLC by inhibiting NF-κB activity. Additionally, the development of a liposomal drug delivery system for imperialine improved its accumulation at tumor sites, enhancing anti-tumor efficacy and ensuring systemic safety. In summary, imperialine is a promising anti-cancer compound, and its targeted delivery system significantly improves therapeutic outcomes and reduces side effects.

Ding et al. studied the effects of peiminine on the invasion and migration of human lung cancer A549 cells. The results showed that peiminine treatment significantly reduced the cell transmembrane number, scratch healing rate, MMP-9, MMP-2, FN protein expression, p-PI3K/PI3K, p-mTOR/mTOR, and p-Akt/Akt levels. This indicates that peiminine inhibits cell migration and exerts anti-tumor effects by regulating the PI3K/Akt/mTOR pathway. Peiminine (PMI) also significantly decreased A549 cell viability ($p < .05$) and increased the apoptosis rate ($p < .05$), with elevated expression levels of Bax, cleaved-caspase-3, p-p38MAPK (Thr180/Thr182), p-p53 (Ser15), p53, and PUMA proteins ($p < .05$) and reduced expression levels of Bcl-2 and MDM2 proteins ($p < .05$) (Li, Ma, et al., 2020). Compared to the 0.20 mmol L^{-1} PMI group, the combination group showed increased A549 cell viability ($p < .05$) and decreased apoptosis rate ($p < .05$), with decreased levels of Bax, cleaved-caspase-3, p-p38MAPK (Thr180/Thr182), p-p53 (Ser15), p53, and PUMA proteins ($p < .05$) and increased levels of Bcl-2 and MDM2 proteins ($p < .05$). Immunofluorescence detection indicated p53 protein translocation from the cytoplasm to the nucleus, with p53 protein expressed in both the cytoplasm and the nucleus (Ding, 2019).

Lin et al. found that solanidine inhibits NSCLC tumors and related inflammation *in vivo* and *in vitro* through an inflammation-cancer feedback loop, with its activity closely related to NF-κB expression regulation. They successfully constructed a targeted liposomal delivery system, greatly enhancing the anti-cancer activity of solanidine (Lin et al., 2020). Other studies have shown that solanidine has anti-fibrotic activity *in vitro*, though its activity strength is slightly weaker than imperialine (Lin et al., 2006). Chuanbeinone exhibited good anti-cancer activity against Lewis lung cancer cells, inducing S-phase cell cycle arrest, reducing anti-apoptotic protein Bcl-2 expression, and increasing pro-apoptotic protein Bax and caspase-3 expression, collectively inducing apoptosis in Lewis lung cancer cells (Li et al., 2016).

Toxicity Studies

Acute Toxicity

Mo et al. conducted acute oral toxicity evaluations of ethanol extracts derived from cultivated *F. cirrhosa*, *Fritillaria walujewii*, and wild *Fritillaria delavayi*. The maximum tolerated dose, administered via oral gavage, was equivalent to approximately 480-fold the recommended clinical dosage, indicating minimal acute toxicity for *F. cirrhosa* (Guo et al., 2017). Similarly, Wang et al. performed a 14-day repeated-dose toxicity test on Nin Jiom Pei Pa Koa in Sprague-Dawley rats, administering doses at 2.5×, 5×, and 10× the clinical equivalent. No adverse effects were observed (Qiong & Ying-Min, 2018). Gao et al. assessed both acute systemic toxicity and genotoxic potential of Chuanbei loquat cream, observing neither toxicity nor mutagenic activities (Ju-Mei et al., 2003). Sun et al. administered 187.53 g/kg of *F. cirrhosa* cough-relieving granules—over 200 times the clinical dose—to mice without inducing mortality or significant toxicity. In contrast, *F. walujewii* exhibited significantly higher toxicity than *F. cirrhosa*, warranting caution in its extended or high-dose use (Xu et al., 2019; Xie & Lv, 2001). These studies consistently indicate that *F. cirrhosa* exhibits low acute toxicity and is likely safe for short-term clinical application.

Genotoxicity

Guo et al. investigated the impact of *F. cirrhosa* extract on the spindle assembly checkpoint (SAC), mitotic integrity, and genomic stability in human NCM460 colon epithelial cells. Exposure to *F. cirrhosa* increased the metaphase-anaphase transition index and induced widespread chromosomal abnormalities, including misaligned chromosomes, lagging chromosomes, bridges, micronuclei, and nucleoplasmic buds. This was the first study to demonstrate that *F. cirrhosa* disrupts mitotic fidelity in normal epithelial cells via dysregulation of SAC-related genes such as MPS1, BUB1, and MAD1 (Guo et al., 2017).

Subsequent experiments showed that high concentrations of *F. cirrhosa* extract (80–160 μg/mL) exhibit genotoxicity, attributed to SAC dysfunction, cytokinesis failure, and centrosome amplification. Key alkaloids—imperialine, peimine, sipeimine, and ebeime—were identified as genotoxic contributors, with sipeimine and ebeime displaying synergistic toxicity (Guo et al., 2021). Moreover, aqueous extracts of *F. cirrhosa* bulbs induced spindle multipolarity via centrosome fragmentation in a dose- and time-dependent manner, accompanied by altered expression of p53, Rb, centrin-2, PLK4, PLK1, and aurora-A. These findings indicate that *F. cirrhosa* has the potential for genotoxic effects that merit caution in therapeutic applications.

Subchronic Toxicity

Liu et al. evaluated both acute and subchronic toxicological profiles of orally administered *F. cirrhosa* ethanol extracts. Chronic administration primarily led to tracheal and bronchial epithelial hyperplasia and increased goblet cell numbers, without additional systemic toxicity (Hu et al., 2023). In a 90-day subchronic study using cultivated *F. cirrhosa* bulb ethanol extract, Sprague-Dawley rats were orally administered doses of 0.34, 0.68, and 2.04 g/kg daily. The no-observed-adverse-effect level (NOAEL) was 0.34 g/kg, while higher doses exhibited dose-dependent toxicity in the spleen, liver, and kidneys (Liu, Ming, et al., 2023).

Additionally, Liang et al. reported no significant toxicity from *F. cirrhosa* loquat cream in rats (He et al., 2021). Wang et al. demonstrated that a *Fritillaria*-based syrup (Fahansha Luo Han Guo Chuanbei Pipa) exhibited no observable chronic toxicity following 30-day administration, based on clinical, hematological, and histopathological assessments (Hui et al., 2005). Collectively, these findings support the safety of *F. cirrhosa* in long-term oral administration within recommended therapeutic limits (Table S5 in the supplemental material).

Conclusion

This review concludes that *Fritillaria* spp. possesses well-documented ethnopharmacological applications, with specific efficacy against pulmonary diseases through apoptosis induction and inflammatory pathway modulation. While existing extraction methods show limitations in scalability and cost-efficiency, *Fritillaria* constituents exhibit dose-dependent anti-lung cancer activity via coordinated regulation of STAT1/4, PI3K/AKT/mTOR, and NF-κB pathways. These findings establish *Fritillaria* as a multi-target phytotherapeutic candidate for combination therapy with pathway-selective inhibitors. Toxicological assessments demonstrate acceptable safety profiles within established therapeutic ranges (NOAEL 0.34 g/kg), though genotoxic risks emerge at supraclinical concentrations (>80 μg/mL). This synthesis identifies key translational barriers, including poor bioavailability of active alkaloids and formulation instability, while proposing artificial intelligence (AI)-guided extraction optimization and liposomal delivery systems as priority solutions. Addressing these challenges will enable the clinical translation of *Fritillaria*-derived therapeutics, bridging traditional medicine with precision oncology paradigms.

Abbreviations

AKT: Protein kinase B; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma-2; EAE: Enzyme-assisted extraction; FC-AE: *Fritillaria cirrhosa* aqueous extract; HSCCC: High-speed countercurrent chromatography; IFN-γ: Interferon-gamma; IL-12: Interleukin-12; LCLC: Large cell lung carcinoma; LLC: Lewis lung carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MAE: Microwave-assisted extraction; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NOAEL: No-observed-adverse-effect level; NSCLC: Non-small-cell lung cancer; PI3K: Phosphatidylinositol 3-kinase; Pre-HPLC: Preparative high-performance liquid chromatography; SCLC: Small cell lung cancer; SPE: Solid-phase extraction; STAT: Signal transducer and activator of transcription; TCM: Traditional Chinese medicine; TFCB: Total *Fritillaria cirrhosa* bulb alkaloids; TLC: Thin-layer chromatography; TLR-4: Toll-like receptor 4; UAE: Ultrasound-assisted extraction.

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Authors' Contribution

CZM designed the study; JFY drafted the initial manuscript; DSH reviewed the article; JRC and SSC are the corresponding authors. All authors approved the final manuscript.

Declaration of Conflicting Interests

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Supplemental Material

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