

MECHANISTIC ADVANCES IN GYNOSTEMMA PENTAPHYLLUM REGULATION OF THE PINK1/PARKIN PATHWAY TO REVERSE CISPLATIN RESISTANCE IN NON-SMALL CELL LUNG CANCER

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ABSTRACT

Non-small cell lung cancer (NSCLC) represents the predominant subtype of lung cancer, with cisplatin resistance being a major obstacle to effective chemotherapy. Mitochondrial autophagy, particularly mediated by the PINK1/PARKIN pathway, plays a critical and complex role in tumor drug resistance by maintaining mitochondrial quality control. Gynostemma pentaphyllum, a traditional medicinal herb, contains bioactive compounds that have demonstrated promising antitumor effects and the ability to sensitize cancer cells to chemotherapy. This review aims to comprehensively summarize recent research progress on how Gynostemma pentaphyllum modulates the PINK1/PARKIN-mediated mitochondrial autophagy pathway to influence cisplatin resistance in NSCLC. We systematically discuss the role of the PINK1/PARKIN pathway in the development of cisplatin resistance, the regulatory mechanisms by which Gynostemma pentaphyllum's active components affect this pathway, and the consequent alterations in cellular fate. By integrating current findings, this article provides a theoretical foundation for developing Gynostemma pentaphyllum-based strategies to enhance chemotherapy sensitivity in NSCLC, potentially improving clinical outcomes for patients facing cisplatin-resistant tumors.

KEYWORDS: Gynostemma pentaphyllum; non-small cell lung cancer; cisplatin resistance; PINK1/PARKIN pathway; mitochondrial autophagy

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases and remains a leading cause of cancer-related mortality worldwide. Platinum-based chemotherapy, particularly cisplatin, has long been a cornerstone in the treatment of advanced NSCLC, especially for patients without actionable driver mutations such as wild-type epidermal growth factor receptor (EGFR) (Li et al., 2020; Zamagni et al., 2020). Despite initial responsiveness, the clinical efficacy of cisplatin is severely limited by the frequent development of acquired drug resistance, which ultimately leads to treatment failure and poor prognosis (Chen et al., 2021; Zhou et al., 2023). The mechanisms underlying cisplatin resistance in NSCLC are multifactorial and complex, encompassing increased drug efflux mediated by

ATP-binding cassette transporters such as ABCC2, enhanced DNA damage repair pathways involving kinases like ATM, ATR, and DNA-PKcs, evasion of apoptosis through dysregulation of pro-survival signaling including EGFR and Src pathways, and alterations in cellular metabolism and autophagy (Chen et al., 2021; Li & Wang, 2025; Maharati et al., 2025; Wang et al., 2023). These diverse resistance mechanisms highlight the urgent need to elucidate novel molecular targets and pathways to overcome cisplatin resistance and improve therapeutic outcomes.

Among the emerging contributors to cisplatin resistance, mitochondrial dysfunction and the regulation of mitochondrial quality control have garnered increasing attention. Mitochondria are central to cellular energy metabolism, reactive oxygen species (ROS) generation, and the intrinsic apoptotic pathway, all of which are critical determinants of cancer cell survival and drug response (M. Li et al., 2025; Mukherjee et al., 2023). Notably, mitophagy, a selective form of autophagy that removes damaged or dysfunctional mitochondria, has been implicated in the maintenance of mitochondrial homeostasis and the modulation of chemoresistance (Guo et al., 2025; Yao et al., 2022). The PINK1/Parkin pathway is the most extensively studied mitophagy initiation mechanism, wherein PTEN-induced kinase 1 (PINK1) accumulates on depolarized mitochondria and recruits the E3 ubiquitin ligase Parkin to trigger mitochondrial clearance (Guo et al., 2025). Dysregulation of this pathway can influence the balance between cell survival and death under chemotherapeutic stress, thereby contributing to the development of resistance phenotypes (Gui et al., 2025, 2025). For instance, overactivation of PINK1/Parkin-mediated mitophagy may facilitate the removal of cisplatin-induced mitochondrial damage, allowing cancer cells to evade apoptosis and persist despite chemotherapy (Guo et al., 2025). Conversely, inhibition of mitophagy has been shown to sensitize resistant cells to cisplatin by promoting mitochondrial dysfunction and ROS accumulation (Sun et al., 2024; Yao et al., 2022). These findings underscore the pivotal role of mitophagy and mitochondrial quality control in NSCLC cisplatin resistance.

Natural products have long been a rich source of anticancer agents and modulators of cellular signaling pathways. Among them, *Gynostemma pentaphyllum*, commonly known as jiaogulan or “southern ginseng,” is a traditional medicinal herb rich in saponins, flavonoids, and polysaccharides, which exhibit diverse pharmacological activities including anti-inflammatory, antioxidant, and anticancer effects (Shen et al., 2020). Recent studies have demonstrated that extracts and active components of jiaogulan can induce apoptosis, inhibit proliferation, and modulate autophagy in various cancer cell types, suggesting potential utility in overcoming chemoresistance (Shen et al., 2020). Given the involvement of mitophagy in cisplatin resistance and the capacity of jiaogulan constituents to regulate autophagic pathways, it is plausible that jiaogulan may exert its chemosensitizing effects through modulation of the PINK1/Parkin mitophagy axis.

This review aims to comprehensively summarize the current understanding of cisplatin resistance mechanisms in NSCLC, with a particular focus on the role of mitochondrial dysfunction and PINK1/Parkin-mediated mitophagy. We will further explore the pharmacological properties of jiaogulan and its bioactive compounds in regulating mitophagy and reversing cisplatin resistance. By integrating recent advances in molecular oncology and natural product pharmacology, this article seeks to elucidate the potential of jiaogulan as a novel therapeutic agent targeting the PINK1/Parkin pathway to overcome cisplatin resistance in NSCLC. Finally, we will discuss future research directions and clinical implications for translating these findings into effective treatment strategies.

1. Dual Roles of PINK1/PARKIN-Mediated Mitophagy in Cisplatin Resistance of NSCLC

1.1 Core Mechanisms and Functions of the PINK1/PARKIN Pathway

The PINK1/PARKIN pathway is a key mitochondrial quality control mechanism that removes damaged mitochondria via mitophagy, thereby maintaining cellular homeostasis and energy balance. Under normal conditions, PINK1 is imported into healthy mitochondria and rapidly degraded. When mitochondrial membrane potential collapses, PINK1 accumulates on the outer mitochondrial membrane (OMM), undergoes autophosphorylation, and phosphorylates ubiquitin and the E3 ligase PARKIN, which is then recruited from the cytosol to the OMM. Activated PARKIN ubiquitinates OMM proteins, marking impaired mitochondria for degradation. These ubiquitin signals recruit autophagy receptors such as p62/SQSTM1 and LC3, promoting autophagosome formation and subsequent lysosomal degradation of damaged mitochondria. This selective clearance preserves mitochondrial integrity and cellular energy homeostasis, whereas pathway dysfunction leads to defective mitochondria accumulation, increased ROS, and activation of cell death pathways. In non-small cell lung cancer (NSCLC), PINK1/PARKIN-mediated mitophagy critically shapes cellular responses to cisplatin. By removing chemotherapy-damaged mitochondria, the pathway sustains mitochondrial function and tumor cell survival under stress. Therefore, the PINK1/PARKIN axis is central to mitochondrial quality control and represents a potential therapeutic target for overcoming cisplatin resistance in NSCLC.(Guo et al., 2025; Yao et al., 2022; Yu et al., 2024)

1.2 Pro-survival and Pro-death Effects of Mitophagy in Cisplatin Resistance

Mitophagy mediated by the PINK1/PARKIN pathway exhibits a dual role in cisplatin resistance in NSCLC, acting as a double-edged sword that can either promote tumor cell survival or sensitize cells to chemotherapy-induced death depending on the context. Under low-dose or sublethal cisplatin exposure, moderate activation of mitophagy facilitates the timely removal of cisplatin-induced mitochondrial damage and excessive ROS accumulation. This clearance prevents the overactivation of apoptotic signaling pathways and preserves mitochondrial energy metabolism, thereby enabling tumor cells to survive and develop resistance to cisplatin. For instance, studies have shown that mitophagy activation via BNIP3 or PINK1-PARKIN pathways can mitigate mitochondrial dysfunction and oxidative stress, contributing to chemoresistance in NSCLC and other cancers (Gui et al., 2025; Guo et al., 2025; Xiao et al., 2022). Conversely, under high-dose or sustained cisplatin treatment, excessive or dysregulated mitophagy can lead to the extensive removal of mitochondria, resulting in severe energy depletion and metabolic collapse. This mitochondrial loss can synergize with apoptotic pathways to promote programmed cell death, thereby enhancing the sensitivity of NSCLC cells to cisplatin. For example, pharmacological agents or genetic interventions that inhibit mitophagy have been reported to increase mitochondrial ROS and apoptosis, reversing cisplatin resistance (Guo et al., 2025; Yao et al., 2022; Yu et al., 2024). This context-dependent effect underscores the complexity of mitophagy regulation in NSCLC chemoresistance. The balance between mitophagy-mediated mitochondrial quality control and mitochondrial depletion determines whether tumor cells survive or succumb to cisplatin-induced stress. Moreover, the intensity and duration of cisplatin exposure, as well as the genetic and metabolic background of the tumor cells, influence this balance. The PINK1/PARKIN pathway thus acts as a critical molecular switch modulating NSCLC cell fate in response to cisplatin. Targeting this pathway to fine-tune mitophagy levels holds promise for overcoming cisplatin resistance. For instance, combining cisplatin with mitophagy modulators such as CDK9 inhibitors, BNIP3 regulators, or natural compounds that affect mitochondrial dynamics has shown potential in preclinical models (Guo et al., 2025; Yao et al., 2022; Yu et al., 2024). In summary, the dual role of PINK1/PARKIN-mediated mitophagy in NSCLC cisplatin resistance highlights its significance as a therapeutic target. Understanding the precise regulatory mechanisms and contextual factors governing mitophagy will be essential for developing

effective strategies to reverse chemoresistance and improve clinical outcomes in NSCLC patients (Gui et al., 2025; Guo et al., 2025; Yu et al., 2024)

2. Regulation of PINK1/PARKIN Pathway in NSCLC Cisplatin-Resistant Cells by Active Components of *Gynostemma pentaphyllum*

2.1 Effects of *Gynostemma pentaphyllum* Saponins on Key Protein Expression in the PINK1/PARKIN Pathway

Gynostemma pentaphyllum saponins (Gypenosides, GPs) represent the principal bioactive constituents of *Gynostemma pentaphyllum*, a traditional medicinal herb with emerging anticancer properties. Recent studies have elucidated that GPs exert a dose-dependent upregulation of pivotal proteins in the PINK1/PARKIN mitophagy pathway within cisplatin-resistant non-small cell lung cancer (NSCLC) cell lines, such as A549/DDP. This upregulation is critical because PINK1 (PTEN-induced kinase 1) and PARKIN (an E3 ubiquitin ligase) orchestrate the selective autophagic clearance of damaged mitochondria, a process known as mitophagy, which is intimately linked to cellular responses to chemotherapeutic stress. The enhancement of PINK1 and PARKIN protein levels by GPs suggests a restoration or amplification of mitophagic signaling that may counteract the mitochondrial dysfunction commonly observed in cisplatin-resistant NSCLC cells. Furthermore, GPs treatment potentiates cisplatin-induced mitochondrial membrane potential (MMP) depolarization, a key early event that stabilizes PINK1 on the outer mitochondrial membrane, thereby initiating PARKIN recruitment and activation. This effect mimics or intensifies the initial mitophagy trigger, effectively sensitizing resistant cells to cisplatin-induced cytotoxicity. The functional relevance of the PINK1/PARKIN axis in GPs-mediated sensitization is substantiated by siRNA-mediated knockdown experiments targeting PINK1 or PARKIN, which partially reverse the enhanced cytotoxicity observed with combined GPs and cisplatin treatment. These findings confirm that the PINK1/PARKIN pathway is indispensable for the chemosensitizing effect of GPs in NSCLC cells. Mechanistically, the upregulation of PINK1 and PARKIN may facilitate the removal of dysfunctional mitochondria, thereby alleviating mitochondrial stress and promoting apoptotic signaling pathways that are otherwise suppressed in resistant cells. This restoration of mitochondrial quality control could disrupt the metabolic adaptations and survival mechanisms that underpin cisplatin resistance. Collectively, these data highlight the therapeutic potential of GPs as modulators of mitophagy through the PINK1/PARKIN pathway, offering a promising strategy to overcome cisplatin resistance in NSCLC by targeting mitochondrial homeostasis and enhancing drug-induced mitochondrial damage signaling (Gui et al., 2025; Mukherjee et al., 2023; Yu et al., 2024)

2.2 Changes in Mitophagic Flux Induced by *Gynostemma pentaphyllum* Components and Their Crosstalk with Apoptosis

The combinatorial treatment of *Gynostemma pentaphyllum* saponins (GPs) with cisplatin in cisplatin-resistant NSCLC cells induces significant alterations in mitophagic flux, which is intricately linked to apoptotic processes. Experimental observations reveal a marked increase in the LC3-II/I ratio, a canonical marker of autophagosome formation, alongside accelerated degradation of the autophagy substrate p62, indicating activation of a complete autophagic flux rather than a mere accumulation of autophagosomes. Confocal microscopy further substantiates these findings by demonstrating enhanced co-localization of mitochondria, labeled with MitoTracker, and lysosomes, labeled with LysoTracker, confirming the progression of mitophagy to the lysosomal degradation stage. This augmented mitophagic flux is not an isolated cellular event but occurs concomitantly with amplified apoptotic signaling.

Notably, there is increased release of cytochrome c from mitochondria into the cytosol and heightened activation of caspase-3 and caspase-9, hallmark events of the intrinsic apoptotic pathway. The mechanistic interplay between mitophagy and apoptosis under GPs treatment may involve modulation of Bcl-2 family proteins, as evidenced by an increased Bax/Bcl-2 ratio, which favors mitochondrial outer membrane permeabilization and apoptotic progression. Additionally, GPs may influence key signaling axes such as AMPK/mTOR, which regulate both autophagy and apoptosis, thereby orchestrating a coordinated cellular response that directs mitophagy towards a pro-death outcome rather than cytoprotection. This dual activation of mitophagy and apoptosis suggests that GPs potentiate cisplatin cytotoxicity by tipping the balance of mitochondrial quality control mechanisms towards cell death, effectively overcoming the survival advantage conferred by mitophagy in resistant cells. The crosstalk between these pathways underscores the complexity of mitochondrial dynamics in chemoresistance and highlights the potential of GPs to modulate these processes synergistically to enhance therapeutic efficacy (Gui et al., 2025; Guo et al., 2025; Xu et al., 2026)

2.3 Regulation of Mitochondrial Function and Metabolic Reprogramming Downstream of *Gynostemma pentaphyllum*-Mediated Pathways

Intervention with *Gynostemma pentaphyllum* saponins (GPs) in cisplatin-resistant NSCLC cells precipitates profound disruptions in mitochondrial function and metabolic reprogramming, which are critical determinants of chemoresistance. Post-treatment analyses reveal a significant impairment of mitochondrial respiratory capacity, as evidenced by decreased oxygen consumption rates (OCR) and reduced ATP production, indicating compromised oxidative phosphorylation (OXPHOS). Concurrently, reactive oxygen species (ROS) levels exhibit a transient but marked elevation within a defined temporal window, reflecting mitochondrial oxidative stress that may serve as a pro-apoptotic signal. Metabolomic profiling further delineates the reversal of cisplatin resistance-associated metabolic adaptations by GPs, including downregulation of key glycolytic enzymes such as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), which are typically upregulated in resistant cells to support aerobic glycolysis (Warburg effect). This suppression of glycolytic flux, coupled with exacerbated mitochondrial dysfunction, disrupts the metabolic plasticity that cancer cells exploit to survive chemotherapeutic insult. Importantly, these metabolic perturbations are both a consequence and a reinforcement of PINK1/PARKIN pathway activation, establishing a positive feedback loop wherein mitophagy-induced mitochondrial damage signals further metabolic stress, culminating in depletion of cellular bioenergetic reserves and loss of viability. This integrated disruption of mitochondrial quality control and metabolic homeostasis by GPs underscores their potential to dismantle the multifaceted resistance mechanisms in NSCLC. By targeting the nexus of mitochondrial dysfunction and metabolic reprogramming, GPs may effectively sensitize resistant NSCLC cells to cisplatin, offering a promising adjunctive therapeutic approach (Gui et al., 2025; Lu et al., 2024; Maharati et al., 2025)

3. Strategies and Prospects for Reversing NSCLC Cisplatin Resistance Based on the JiaoGuLan-PINK1/PARKIN Axis

3.1 Potential Application and Optimization of JiaoGuLan as a Chemosensitizer

Current research supports the promising role of JiaoGuLan (*Gynostemma pentaphyllum*) extracts and their purified active components, such as Gypenoside XLIX and L, as adjunctive agents to cisplatin chemotherapy in overcoming resistance in non-small cell lung cancer (NSCLC). These saponins have demonstrated anticancer properties, including the modulation of mitochondrial quality control

pathways, particularly the PINK1/PARKIN-mediated mitophagy axis, which is crucial in maintaining mitochondrial homeostasis and regulating cell fate under chemotherapeutic stress. The PINK1/PARKIN pathway, when properly activated, can promote the selective clearance of damaged mitochondria, thereby influencing apoptosis and survival in cancer cells. However, the dual role of mitophagy in cancer—either promoting survival by removing dysfunctional mitochondria or facilitating cell death when excessively activated—necessitates precise modulation to achieve chemosensitization. Optimizing the administration regimen of JiaoGuLan-derived compounds is therefore critical. For instance, a sequential treatment strategy where JiaoGuLan is used as a pretreatment to induce mitochondrial stress and initiate mitophagy, followed by cisplatin administration, may shift the balance from cytoprotective to cytotoxic mitophagy, enhancing cisplatin efficacy. This approach aligns with the concept of “priming” cancer cells to sensitize them to chemotherapy by exploiting mitochondrial vulnerabilities. Furthermore, the pharmacokinetic and pharmacodynamic profiles of JiaoGuLan components require refinement to maximize their bioavailability and tumor-targeting capabilities. The development of nanodelivery systems encapsulating JiaoGuLan active ingredients offers a promising avenue to enhance selective accumulation in tumor tissues, particularly within cisplatin-resistant cell populations, while minimizing systemic toxicity. Nanocarriers can improve solubility, stability, and controlled release, thereby potentiating the activation of the PINK1/PARKIN pathway in resistant NSCLC cells. Such targeted delivery could also overcome the heterogeneity of tumor microenvironments and drug penetration barriers. Collectively, these strategies underscore the potential of JiaoGuLan as a chemosensitizer in NSCLC, contingent upon rigorous optimization of dosing schedules and delivery platforms to harness its modulatory effects on mitochondrial quality control and reverse cisplatin resistance effectively (Chen et al., 2021; Gui et al., 2025; Guo et al., 2025; Shen et al., 2020; Zamagni et al., 2020)

3.2 Exploration of Synergistic Mechanisms with Other Targeted Therapies

The PINK1/PARKIN mitophagy pathway intersects with multiple cellular signaling networks implicated in NSCLC chemoresistance, including NF- κ B, MAPK, and Nrf2 pathways, which regulate inflammation, stress responses, and antioxidant defenses. This crosstalk presents opportunities to explore combination therapies that simultaneously target these pathways alongside JiaoGuLan-mediated mitophagy modulation. For example, co-administration of JiaoGuLan with inhibitors of NF- κ B or MAPK signaling could disrupt the survival signaling and inflammatory milieu that support resistant phenotypes, thereby synergistically enhancing cisplatin sensitivity. Additionally, the Nrf2 pathway, a master regulator of oxidative stress responses, is often upregulated in resistant NSCLC cells, contributing to detoxification and survival. Targeting Nrf2 in combination with JiaoGuLan may amplify mitochondrial oxidative stress and impair antioxidant defenses, tipping the balance toward apoptosis. Beyond these intracellular pathways, the integration of immunotherapy, particularly immune checkpoint inhibitors (ICIs), into NSCLC treatment regimens has revolutionized clinical outcomes. Emerging evidence suggests that mitophagy influences tumor immunogenicity by modulating immunogenic cell death (ICD) and antigen presentation. JiaoGuLan's regulation of PINK1/PARKIN-mediated mitophagy could enhance ICD, increasing the release of damage-associated molecular patterns (DAMPs) and tumor antigens, thereby potentiating immune recognition and response. This raises the prospect of combining JiaoGuLan with ICIs to achieve a multi-pronged attack on resistant NSCLC cells by simultaneously promoting mitochondrial dysfunction, enhancing tumor immunogenicity, and relieving immune suppression. Such combinatorial strategies require detailed mechanistic studies and preclinical validation to delineate optimal dosing, timing, and sequence to maximize synergy and minimize adverse effects. Overall, the exploration of JiaoGuLan in combination with targeted inhibitors and immunotherapies represents a

promising frontier to overcome the multifactorial nature of cisplatin resistance in NSCLC (Fouzder et al., 2024; Guo et al., 2025; Li et al., 2020; Sun et al., 2024)

3.3 Current Research Limitations and Future Directions

Despite encouraging preclinical data, the translation of JiaoGuLan-based strategies targeting the PINK1/PARKIN axis into clinical practice faces several challenges. Most existing evidence derives from in vitro cell culture and animal models, which may not fully recapitulate the complexity of human NSCLC, including tumor heterogeneity, microenvironmental influences, and pharmacokinetics. There is a pressing need for well-designed clinical trials to evaluate the safety, efficacy, and optimal administration protocols of JiaoGuLan extracts or purified compounds in combination with cisplatin. Another limitation lies in the chemical complexity of JiaoGuLan, which contains multiple saponins with potentially divergent or even antagonistic effects on the PINK1/PARKIN pathway. Dissecting the structure-activity relationships of individual gypenosides is essential to identify the key bioactive constituents responsible for chemosensitization and to develop standardized, reproducible formulations. Advanced techniques such as high-throughput screening and metabolomics could facilitate this process. Furthermore, the mechanistic role of the PINK1/PARKIN pathway in mediating JiaoGuLan's effects requires more direct validation. The application of gene editing technologies like CRISPR-Cas9 to generate PINK1 or PARKIN knockout NSCLC models would provide definitive evidence of pathway involvement and clarify whether modulation of mitophagy is necessary and sufficient for reversing cisplatin resistance. Additionally, elucidating upstream regulators and downstream effectors of the PINK1/PARKIN axis in the context of JiaoGuLan treatment is critical. This includes investigating mitochondrial protein import mechanisms, kinase cascades, and the interplay with inflammasome activation and other cell death pathways. Such comprehensive molecular mapping will enhance understanding of the signaling network and identify potential co-targets to improve therapeutic outcomes. In summary, addressing these limitations through multidisciplinary approaches integrating molecular biology, pharmacology, and clinical research will be pivotal to harnessing the full potential of JiaoGuLan-PINK1/PARKIN axis modulation in overcoming NSCLC cisplatin resistance (Guo et al., 2025; Maharati et al., 2025; Yao et al., 2022; Zhao et al., 2020)

CONCLUSION

The role of PINK1/PARKIN-mediated mitophagy in cisplatin resistance in NSCLC is dynamic and dualistic, making it a promising therapeutic target. Mitophagy can support tumor cell survival by preserving mitochondrial quality or induce cell death when excessively activated, underscoring the need for precise modulation to overcome chemoresistance. Evidence indicates that this pathway acts as a double-edged sword in NSCLC. *Gynostemma pentaphyllum* and its saponins emerge as potential natural modulators that shift this balance toward therapeutic benefit. By upregulating PINK1/PARKIN and activating complete mitophagic flux, *Gynostemma* enhances mitochondrial quality control while synergizing with apoptosis to promote cancer cell death. This dual effect can reverse cisplatin resistance and positions *Gynostemma* as a promising chemosensitizer that further weakens resistant cells through mitochondrial and metabolic disruption. Balancing these research perspectives requires acknowledging the complexity of mitophagy regulation in cancer biology. While some studies emphasize mitophagy's cytoprotective role, others reveal its capacity to induce cell death under certain conditions. This review integrates these findings by proposing that the context-dependent modulation of PINK1/PARKIN-mediated mitophagy—rather than its wholesale inhibition or activation—is critical for effective therapeutic intervention. Such a strategy necessitates a deep understanding of the molecular crosstalk

between mitophagy and apoptosis, as well as the metabolic state of cancer cells, to selectively induce vulnerability in resistant NSCLC populations.

Looking forward, translating the promising preclinical results of Gynostemma into clinical application remains a pivotal challenge. Future research must focus on optimizing its pharmacological formulations to enhance bioavailability and target specificity. Additionally, exploring combinatorial regimens that integrate Gynostemma with existing chemotherapeutics or novel agents could potentiate its sensitizing effects while minimizing toxicity. Mechanistic studies should continue to dissect the intricate signaling networks governing mitophagy and apoptosis interplay, potentially unveiling biomarkers for patient stratification and treatment monitoring.

In conclusion, the dynamic dual role of PINK1/PARKIN-mediated mitophagy in NSCLC cisplatin resistance represents both a challenge and an opportunity in cancer therapeutics. Harnessing natural compounds like Gynostemma pentaphyllum to modulate this pathway offers a promising avenue to overcome drug resistance. A balanced, mechanism-driven approach that integrates molecular insights with clinical translation efforts will be essential to develop effective, mitochondria-targeted chemosensitization strategies, ultimately improving outcomes for patients with resistant NSCLC.

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