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Oridonin: Potential in Combating Cancer and Overcoming Drug Resistance

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ABSTRACT

Cancer remains a leading cause of morbidity and mortality worldwide. Oridonin, a tetracyclic diterpenoid from *Rabdosia rubescens*, has gained significant research interest due to its neuroprotective, anti-inflammatory, and anticancer properties. Structural modifications have led to derivatives with enhanced pharmacological activity. While drug resistance remains a major challenge in chemotherapy, oridonin has demonstrated the ability to overcome resistance through multiple mechanisms, making it a promising candidate for cancer treatment.

Keywords: *Diterpenoid compound, carcinoma, cytotoxic effects, chemo resistance, multi-drug resistance.*

1. INTRODUCTION

Rabdosia rubescens, a traditional herb in Chinese medicine, contains oridonin (Fig. 1), an active diterpenoid compound. For centuries, it has been valued for its antitumor, antimicrobial, anti-inflammatory, and antioxidant effects. This medicinal plant has been used to alleviate ailments such as stomach pain, pharyngitis, coughs, and sports injuries. Additionally, it has shown potential in treating various cancers, including esophageal, breast, liver, and prostate cancer.[1-2] Oridonin has gained increasing attention from cancer biologists for its potent anti-tumor properties. Recent studies suggest that oridonin can slow tumor progression, reduce tumor burden, and alleviate cancer-related symptoms, potentially enhancing patient survival rates.[3]

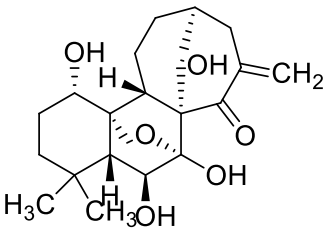

Fig. 1: Oridonine

2. THERAPEUTIC POTENTIAL OF ORIDONINE

Oridonin ($C_{20}H_{28}O_6$) is a kaurene-type diterpenoid derived from *Rabdosia rubescens*, commonly known as "Donglingcao" in Chinese and "Hara" in Japanese. First identified by Fujita et al. in 1967, it was later successfully synthesized in 1973. This bioactive compound exhibits a wide range of pharmacological and physiological properties.[4]

Anti-Inflammatory Activity: Research indicates that oridonin effectively inhibits experimental autoimmune neuritis (EAN) by reducing inflammation and promoting immune-regulating macrophages, likely via the Notch signaling pathway. This suggests its potential in treating Guillain-Barré syndrome (GBS) and other neuropathies. Additionally, oridonin alleviates carrageenan-induced pleurisy in BALB/c mice by activating the KEAP-1/Nrf2 pathway while suppressing TXNIP/NLRP3 and NF-κB pathways, reducing lung injury, cytokine release, and oxidative stress. It also mitigates LPS-induced inflammation through ROS accumulation, JNK activation, and NF-κB nuclear translocation. Furthermore, oridonin inhibits autophagy in rheumatoid arthritis synoviocytes and demonstrates anti-inflammatory effects in gingival fibroblasts, osteoarthritis chondrocytes, and endometrial cells, highlighting its therapeutic potential for inflammatory diseases.[5-6]

Hepatorenal Protective Activity: Oridonin has shown therapeutic potential in liver and kidney diseases. In LPS/D-galactosamine-induced acute liver injury, it improved survival, reduced histopathological damage, and lowered aminotransferase levels by suppressing TNF-α and JNK-associated apoptosis.[7] It also mitigated carbon tetrachloride-induced liver fibrosis by inhibiting the NLRP3 inflammasome.[8] In JS1 stellate cells, oridonin (5–15 μM) hindered IRAK4 modifications within the TLR4 pathway.[9] Additionally, in renal studies, oridonin (2.5–20 μM) reduced albuminuria, improved kidney function, and suppressed inflammation by downregulating TLR4 and inhibiting NF-κB and p38-MAPK activation in a dose-dependent manner.[10]

Cardioprotective Activity: Oridonin exhibits cardioprotective effects by reducing oxidative stress and inhibiting NLRP3 inflammasome activation in myocardial ischemia-reperfusion injury models, as confirmed by metabolomic analyses.[11-12] It also mitigates cardiac hypertrophy and fibrosis, preserves heart function, and enhances autophagy in pressure-overloaded hearts and angiotensin II-stimulated cardiomyocytes.[13] Additionally, oridonin alleviates vascular inflammation by reducing endothelial-leukocyte adhesion, inhibiting TNF-α-induced adhesion molecules, suppressing leukocyte infiltration, and blocking TNF-α-activated MAPK and NF-κB pathways.[14]

Lung Protective Activity: Oridonin protects against LPS-induced acute lung injury (ALI) through both Nrf2-independent anti-inflammatory and Nrf2-dependent antioxidant mechanisms.[15] It also shields against chemically induced pulmonary fibrosis by reducing α-SMA and COL1A1 expression in TGF-β1-induced MRC-5 cells and alleviating alveolar collapse, emphysema, and inflammatory cell infiltration in BLM-induced models. Additionally, oridonin mitigates ventilator-induced lung injury (VILI) by inhibiting the NEK7-NLRP3 interaction, preventing NLRP3 inflammasome activation.[16]

3. ORIDONIN DERIVATIVES AS PROMISING CANCER TREATMENTS

Oridonin has demonstrated anticancer potential across various cancer types.[17] Oridonin's anticancer properties have been observed in various cancer cell types, including gastric cancer, colorectal carcinoma, breast cancer, ovarian cancer, pancreatic cancer, non-small cell lung cancer, acute leukemia, glioblastoma multiforme, and human melanoma cells.[18-23] The α-methylene cyclopentanone group is recognized as the key active center responsible for oridonin's anticancer activity.[24] Its primary mechanisms of action involve inhibiting cell proliferation[25] inducing apoptosis and autophagy, suppressing migration and invasion, and overcoming drug resistance.

Oral squamous cell carcinoma (OSCC), the most prevalent form of oral cancer, accounts for 96% of all cases. Jing Yang et al. investigated oridonin's anticancer effects on OSCC cells, focusing on proliferation, apoptosis, and underlying mechanisms using the OSCC cell lines UM1 and SCC25. Their findings revealed that oridonin not only suppressed cell proliferation and colony formation but also induced G2/M cell cycle arrest and apoptosis in a dose-dependent manner. Western blot analysis showed that oridonin treatment increased the Bax/Bcl-2 ratio and activated the cleavage of caspase-3, caspase-9, and PARP-1. Furthermore, oridonin induced G2/M phase arrest by downregulating G2/M transition-related proteins such as cyclin B1 while upregulating cyclin D1, cyclin D3, P21, phosphorylated CDK1, and cyclin A2. Additionally, oridonin significantly inhibited the phosphorylation of PI3K and Akt, leading to suppressed tumor growth in OSCC xenografts in nude mice. Collectively, these results suggest that oridonin exerts anti-oral cancer effects by inhibiting the PI3K/Akt signaling pathway, inducing apoptosis, and causing G2/M-phase arrest, highlighting its potential as a therapeutic agent for oral cancer treatment.[26]

Zhou and colleagues[27] notably found that oridonin demonstrated strong antileukemic effects while providing organ protection without significant adverse effects. Their study showed that oridonin treatment limited disease spread and maintained the structural integrity of leukemia-affected liver and spleen tissues, suggesting a protective role for the liver. Moreover, additional research has reinforced oridonin's capacity to suppress inflammatory signaling in various tissues, including the renal cortex, colon, hippocampus, and cancer cells such as BxPC-3 pancreatic cancer cells and U937 human histiocytic lymphoma cells.[28] In research conducted by Kui-Kui Ren and his team, oridonin displayed significant anti-cancer properties across multiple cell types. Their findings indicated that oridonin substantially inhibited the proliferation of murine K1735M2 cells grown in vitro and induced a dose-dependent G2/M phase cell cycle arrest. These results support the potential of oridonin as a promising therapeutic option for melanoma treatment.[29]

Lili Tian's et al demonstrated that oridonin inhibits angiogenesis both in vitro and in vivo. Further investigation revealed that this anti-angiogenic effect may be linked to the downregulation of VEGFA, VEGFR2, and VEGFR3, as well as the

upregulation of the TP53 gene. Additionally, the proteins Claudin 1, Claudin 4, and Claudin 7 were identified as key contributors to oridonin's anti-tumor effects through the suppression of angiogenesis.[30]

Oridonin has been explored as part of combination treatment strategies with other chemotherapeutic drugs. For example, studies in PANC-1 pancreatic cancer cells have demonstrated that oridonin enhances gemcitabine-induced apoptosis by triggering cell cycle arrest in the G0/G1 phase.[31] The combination of oridonin and cetuximab demonstrated enhanced anticancer activity against laryngeal squamous cell carcinoma, producing a synergistic effect.[32] Collectively, these results suggest that oridonin and its derivatives hold significant, yet-to-be-fully-explored promise as treatments for various cancers, whether used alone or in combination with other therapies.

4. ORIDONIN DERIVATIVES IN OVERCOMING CANCER RESISTANCE

Chemoresistance poses a significant obstacle in cancer chemotherapy, with both inherent and acquired resistance linked to poorer outcomes in patients. Additionally, multi-drug resistance (MDR) occurs when cancer cells, after developing resistance to one chemotherapeutic agent, also become resistant to other drugs through either similar or different mechanisms.[33] Recent studies indicate that oridonin, whether used alone or alongside other chemotherapy drugs, primarily combats chemoresistance by inducing apoptosis. This effect may be achieved by modulating the expression of drug resistance-related proteins, such as P-glycoprotein (P-gp) and MDR-associated protein 1 (MRP1).[34-35] Nearly all chemotherapeutic agents induce apoptosis in cancer cells. However, once these cells develop chemoresistance, they also become less susceptible to apoptosis, enabling them to evade immune surveillance. Oridonin has been shown to counteract this chemoresistance by modulating various apoptotic pathways to trigger cancer cell death, with microRNAs potentially playing a crucial role in both the onset and maintenance of chemoresistance.[36-37]

Research indicates that oridonin not only triggers apoptosis but also activates alternative programmed cell death mechanisms such as necroptosis, which can enhance the efficacy of chemotherapy and help overcome resistance to apoptosis. Moreover, the overexpression or activation of genes associated with multi-drug resistance (MDR) significantly contributes to chemoresistance in various cancers. Both published evidence and our unpublished data point to a critical role for Akt and STAT3 signaling pathways in mediating oridonin's ability to counteract chemoresistance.[38]

The BCR-ABL gene produces a tyrosine kinase that is a primary target for leukemia treatment. However, when this gene is amplified or when mutations occur in its kinase domain, resistance to imatinib often develops. Studies have shown that oridonin can counteract this resistance associated with targeted therapies against BCR-ABL, and its effect appears to be broad enough that it is not limited to any single tyrosine kinase inhibitor. Additionally oridonin was found to reduce, in a dose-dependent manner, the expression of MMP-2 and MMP-9—two enzymes crucially involved in cancer cell invasion and metastasis.[39]

Onat Kadioglu and colleagues investigated the cytotoxic effects of oridonin on a range of drug-resistant cancer cells—including those with overexpression of ABCB1, ABCG2, or EGFR, as well as cells lacking TP53. Notably, oridonin demonstrated a lower level of resistance compared to the control drug, doxorubicin. Molecular docking studies showed that oridonin binds to proteins within the Akt/EGFR pathway with binding energies and docking poses similar to those of established inhibitors, while molecular dynamics simulations confirmed a stable binding conformation on the Akt kinase domain. Furthermore, Western blot analyses revealed that oridonin treatment leads to a dose-dependent decrease in Akt and STAT3 expression. Overall, these findings suggest that oridonin can bypass key drug resistance mechanisms by targeting the Akt pathway, making it a promising candidate for treating drug-refractory tumors.[40]

5. CONCLUSION

In summary Oridonin, a naturally derived compound possesses potent pharmacological properties, including anti-tumor, anti-inflammatory, and immune-regulatory effects. Its diverse anti-proliferative mechanisms, such as modulation of the cell cycle, apoptosis, and autophagy, highlight its potential as an effective anticancer agent. Additionally, oridonin has demonstrated the ability to overcome drug resistance through various mechanisms, though its precise molecular target remains undefined. Further research is necessary to evaluate its efficacy in both standalone and combination therapies, as well as its role in combating chemoresistance, reinforcing the potential of oridonin and its derivatives as viable therapeutic candidates.

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