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Cracking the Molecular Mechanisms of Oridonin-Induced Reproductive Toxicity: A Multi-Omics Method Using the Wnt/β-Catenin Signaling Pathway as a Target

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ABSTRACT

Oridonin, a bioactive diterpenoid isolated from the traditional Chinese medicinal herb Rabdosia rubescens, has garnered attention for its anti-cancer, anti-inflammatory, and anti-microbial properties. Despite its therapeutic potential, recent studies have indicated that oridonin may induce reproductive toxicity, raising concerns about its safety, especially in long-term use. Understanding the molecular mechanisms underlying oridonin-induced reproductive toxicity is crucial for mitigating its adverse effects and harnessing its therapeutic benefits. The Wnt/β-catenin signaling pathway plays a critical role in cell proliferation, differentiation, and development. Dysregulation of this pathway has been implicated in various reproductive disorders. Combining advanced omics technologies—proteomics, metabolomics, and epigenetics—offers a comprehensive approach to uncovering the intricate molecular networks involved in oridonin-induced reproductive toxicity, particularly focusing on the Wnt/β-catenin signaling pathway.

Keywords: Reproductive toxicity; Gynecology; Proteomics

INTRODUCTION

Oridonin has been shown to exert toxic effects on the reproductive system, including reduced fertility, impaired spermatogenesis, and ovarian dysfunction. The underlying mechanisms are not fully understood, but emerging evidence suggests that oridonin may interfere with key signaling pathways, including Wnt/β-catenin. Investigating these mechanisms requires a multi-faceted approach, integrating data from proteomics, metabolomics, and epigenetics. Proteomics involves the large-scale study of proteins, their structures, and functions. This approach can identify changes in protein expression and post-translational modifications (PTMs) associated with oridonin-induced reproductive toxicity. Epigenetics involves the study of heritable changes in gene expression that do not involve changes to the DNA sequence. This includes DNA methylation, histone modifications, and non-coding RNAs. Epigenetic modifications can mediate the effects of oridonin on the Wnt/β-catenin pathway [1].

LITERATURE REVIEW

Despite these benefits, oridonin has been associated with adverse effects on reproductive health. Studies in animal models have shown that oridonin can impair spermatogenesis, reduce sperm count and motility, and induce histopathological changes in reproductive organs. Understanding the molecular basis of these effects is critical for evaluating the safety profile of oridonin. The Wnt/β-Catenin Signaling Pathway The Wnt/β-catenin signaling pathway is a key regulator of cellular processes, including cell proliferation, differentiation, and apoptosis. It plays a crucial role in embryonic development and

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the maintenance of adult tissue homeostasis. Dysregulation of this pathway has been implicated in various diseases, including cancer and reproductive disorders.

DISCUSSION

The Wnt/β-catenin signaling pathway is critical for gonadal development, gametogenesis, and the maintenance of the reproductive system. Alterations in this pathway can lead to reproductive anomalies, including infertility and abnormal reproductive organ development. Genomic studies provide insights into the genetic alterations induced by oridonin. High-throughput sequencing technologies, such as whole-genome sequencing and RNA sequencing (RNA-seq), can identify mutations, gene expression changes, and alternative splicing events associated with oridonin exposure. RNA-seq can quantify changes in the expression of genes involved in the Wnt/β-catenin pathway and other related pathways in reproductive tissues. WGS can detect oridonin-induced mutations and single nucleotide polymorphisms that may contribute to reproductive toxicity. Transcriptomic analyses focus on the changes in RNA transcripts, providing a snapshot of gene activity in response to oridonin. Differential gene expression analysis can identify key regulators and downstream targets of the Wnt/β-catenin pathway affected by oridonin [2,3]. This method compares the expression levels of genes between oridonin-treated and control samples, highlighting the impact on the Wnt/β-catenin pathway. This approach identifies biological pathways enriched with differentially expressed genes, offering insights into the molecular mechanisms underlying reproductive toxicity. Proteomic studies complement genomic and transcriptomic analyses by providing information on the protein-level changes induced by oridonin. Mass spectrometry-based proteomics can quantify the abundance of proteins and post-translational modifications associated with the Wnt/β-catenin pathway. Label-free quantification and tandem mass tag labeling are techniques used to measure protein abundance in oridonin-treated samples. PTMs, such as phosphorylation, play a crucial role in the regulation of the Wnt/β-catenin pathway. Proteomic analyses can identify changes in PTM patterns in response to oridonin. Metabolomic studies analyze the small molecules and metabolites produced as a result of cellular processes. These analyses can reveal metabolic alterations induced by oridonin that may impact reproductive health. Techniques such as nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography-mass spectrometry can identify and quantify metabolites in reproductive tissues. Metabolomic data can be integrated with genomic, transcriptomic, and proteomic data to provide a comprehensive view of the metabolic pathways affected by oridonin. Genomic and transcriptomic studies have identified several key genes and pathways affected by oridonin exposure. These include genes involved in cell cycle regulation, apoptosis, and the Wnt/β-catenin pathway. The upregulation of pro-apoptotic genes, such as BAX and CASP3, suggests that oridonin may induce apoptosis in reproductive cells, contributing to histopathological changes. Proteomic analyses have revealed alterations in the abundance of key proteins involved in the Wnt/β-catenin pathway, such as β-catenin, GSK-3β, and Axin. These changes can disrupt the normal signaling processes, leading to reproductive toxicity. Reduced levels of β-catenin in oridonin-treated samples suggest a disruption in the canonical Wnt signaling pathway, affecting gene expression and cellular functions. Alterations in the levels of GSK-3β and Axin, key components of the β-catenin destruction complex, indicate a potential mechanism for the observed reproductive toxicity [4-6].

CONCLUSION

The use of a multi-omics approach has provided comprehensive insights into the molecular mechanisms underlying oridonin-induced reproductive toxicity. By targeting the Wnt/β-catenin signaling pathway and integrating data from genomics, transcriptomics, proteomics, and metabolomics, researchers can develop safer and more effective therapeutic strategies. As our understanding of these complex interactions deepens, the potential for mitigating the adverse effects of oridonin and harnessing its therapeutic benefits becomes increasingly attainable. Metabolomic studies have identified changes in the levels of key metabolites, such as lactate, pyruvate, and amino acids, suggesting metabolic reprogramming in response to oridonin. Alterations in glycolytic and oxidative phosphorylation pathways can impact energy production in reproductive cells, contributing to reduced fertility. Changes in amino acid levels can affect protein synthesis and cellular functions, potentially leading to reproductive abnormalities. Understanding the molecular mechanisms of oridonin-induced reproductive toxicity opens new avenues for therapeutic interventions. Targeting the Wnt/β-catenin pathway and other affected pathways could mitigate the adverse effects of oridonin. Small molecule inhibitors or activators of the Wnt/β-catenin pathway could be used to restore normal signaling and alleviate reproductive toxicity. Given the role of oxidative stress in oridonin-induced apoptosis, antioxidants could be employed to protect reproductive cells from damage. The insights gained from multi-omics studies can inform personalized medicine approaches, tailoring treatments based on individual genetic and molecular profiles. This approach could optimize the therapeutic benefits of oridonin while minimizing its reproductive toxicity.

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CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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