GLYCYRRHETINIC ACID IN MODERN DRUG DISCOVERY AND CANCER THERAPY

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ABSTRACT

Glycyrrhetinic acid (GA), a bioactive triterpenoid derived from licorice, has attracted considerable attention due to its anti-inflammatory, antioxidant, and anticancer properties. Recent advances in network pharmacology, molecular biology, and medicinal chemistry have enabled researchers to better understand the complex mechanisms of GA and its derivatives. This review summarizes the major findings from three representative publications and discusses the role of network pharmacology in traditional medicine drug development, the antitumor mechanisms of glycyrrhetinic acid, and the therapeutic potential of GA derivatives in cancer treatment.

Introduction. Natural products remain a major source of novel therapeutic agents. Traditional Chinese Medicine (TCM) has contributed significantly to modern drug discovery through the identification of bioactive compounds with multi-target activities. Glycyrrhetinic acid, obtained from glycyrrhizin found in licorice roots, is one such compound. Modern research has demonstrated its effectiveness against inflammation, oxidative stress, fibrosis, and multiple cancers. Simultaneously, network pharmacology has emerged as an important tool for understanding multi-component and multi-target interactions typical of traditional medicines.

Network Pharmacology and Modern Drug Discovery. The expert consensus article highlights the growing importance of network pharmacology in TCM research. Unlike conventional pharmacology that focuses on a single target, network pharmacology evaluates interactions among genes, proteins, signaling pathways, and diseases. The approach integrates bioinformatics, systems biology, molecular docking, and experimental validation. Researchers can identify active ingredients, predict therapeutic targets, construct interaction networks, and clarify mechanisms of action. This strategy is particularly useful for complex herbal medicines that contain multiple bioactive compounds.

Applications of Network Pharmacology to Glycyrrhetinic Acid Research. Network pharmacology provides a framework for identifying molecular targets of glycyrrhetinic acid. Through computational analyses, investigators have linked GA to signaling pathways involved in apoptosis, inflammation, angiogenesis, immune regulation, and tumor progression. Protein interaction networks suggest that GA influences numerous molecular targets simultaneously, supporting its role as a multi-functional therapeutic agent. Such findings help guide experimental validation and accelerate drug development. Chemical Structure and Pharmacological Properties of Glycyrrhetinic Acid.

Glycyrrhetinic acid is a pentacyclic triterpenoid characterized by a rigid hydrophobic structure and multiple functional groups capable of chemical modification. The compound exhibits anti-inflammatory, hepatoprotective, antiviral, antimicrobial, antioxidant, and anticancer effects. Structural modification of GA has generated numerous derivatives with improved solubility, bioavailability, and biological activity.

Antitumor Mechanisms of Glycyrrhetinic Acid. The reviewed literature demonstrates that GA exerts anticancer effects through several complementary mechanisms. It induces apoptosis by activating caspases and regulating Bcl-2 family proteins. GA can arrest the cell cycle at different phases, thereby inhibiting uncontrolled proliferation. Additionally, it suppresses angiogenesis, limits metastatic potential, and modulates the tumor microenvironment. These mechanisms collectively contribute to its broad-spectrum antitumor activity.

Regulation of Apoptosis. Apoptosis is a critical mechanism for eliminating malignant cells. Glycyrrhetinic acid enhances pro-apoptotic signaling while suppressing anti-apoptotic pathways. Studies indicate increased expression of Bax, activation of caspase-3 and caspase-9, and decreased expression of Bcl-2. Mitochondrial membrane disruption further promotes programmed cell death. These effects have been observed in liver, lung, breast, colorectal, and gastric cancer models.

Effects on Cell Cycle Progression. Cancer cells depend on dysregulated cell cycle control for continuous proliferation. Glycyrrhetinic acid interferes with cyclins and cyclin-dependent kinases, resulting in growth arrest. By preventing progression through critical checkpoints, GA reduces DNA replication and cellular expansion. This contributes significantly to tumor suppression.

Modulation of Inflammatory Microenvironment. One of the most important findings reported in the derivative-focused study is the ability of GA derivatives to inhibit the inflammatory microenvironment surrounding tumors. Chronic inflammation supports tumor initiation, progression, angiogenesis, and metastasis. GA derivatives suppress inflammatory mediators including TNF-alpha, IL-6, and NF-kB signaling. Reduction of inflammation weakens tumor-supportive conditions and enhances therapeutic outcomes.

Glycyrrhetinic acid affects multiple signaling pathways implicated in cancer development. These include PI3K/Akt, MAPK, JAK/STAT, NF-kB, Wnt/beta-catenin, and TGF-beta pathways. Simultaneous modulation of several pathways may explain the broad activity of GA across different cancer types and reduce the likelihood of resistance associated with single-target therapies.

Antioxidant and Immunomodulatory Activities. Oxidative stress contributes to carcinogenesis and tumor progression. GA exhibits antioxidant properties by scavenging reactive oxygen species and enhancing endogenous antioxidant defenses. Furthermore, immunomodulatory effects may improve antitumor immunity by influencing macrophage activation, cytokine production, and immune surveillance mechanisms.

Development of Glycyrrhetinic Acid Derivatives. Medicinal chemistry efforts have produced numerous derivatives with enhanced pharmacological characteristics. Structural modifications include esterification, amidation, and conjugation with other bioactive moieties.

Many derivatives demonstrate stronger cytotoxic activity against tumor cells than the parent compound. Improved pharmacokinetic properties may further increase their clinical potential.

Cancer Types Investigated. Research has evaluated GA and its derivatives in hepatocellular carcinoma, breast cancer, lung cancer, colorectal cancer, gastric cancer, pancreatic cancer, leukemia, and melanoma. Although efficacy varies among models, the overall evidence supports broad-spectrum antitumor activity. Some studies also report synergistic effects when GA is combined with conventional chemotherapeutic agents.

Advantages and Limitations. The major advantages of glycyrrhetinic acid include multi-target activity, natural origin, anti-inflammatory effects, and relatively favorable safety profiles. However, limitations remain. Poor water solubility and bioavailability restrict clinical applications. Many findings are based on in vitro and animal studies, while high-quality clinical evidence remains limited. Standardization of formulations and dosing strategies is also necessary.

Future Perspectives. Future research should combine network pharmacology, artificial intelligence, systems biology, and advanced medicinal chemistry to accelerate development of GA-based therapeutics. Improved delivery systems such as nanoparticles, liposomes, and targeted carriers may enhance bioavailability. Comprehensive clinical trials are needed to validate efficacy and safety in cancer patients. Integration of omics technologies will further clarify molecular mechanisms and identify predictive biomarkers.

General Conclusions. The three reviewed articles collectively demonstrate that glycyrrhetinic acid represents a promising natural compound for cancer therapy and drug development. Network pharmacology provides a powerful methodological framework for understanding the multi-target actions of traditional medicines and compounds such as GA. Glycyrrhetinic acid exerts anticancer effects through apoptosis induction, cell cycle arrest, suppression of inflammatory microenvironments, modulation of signaling pathways, antioxidant activity, and immune regulation. Structural derivatives often show enhanced efficacy and may overcome limitations of the parent molecule. Despite encouraging preclinical evidence, additional clinical studies are essential before widespread therapeutic application. Overall, GA and its derivatives constitute an important research direction in modern oncology and natural-product-based drug discovery.

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