
# INVESTIGATION OF THE ANTICANCER PROPERTIES OF GLYCYRRHETINIC ACID DERIVATIVES: A CRITICAL ANALYSIS OF RECENT SCIENTIFIC STUDIES

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**ABSTRACT**

*Cancer remains one of the leading causes of mortality worldwide, creating an urgent need for novel and effective therapeutic agents. Natural products and their derivatives continue to serve as valuable sources for anticancer drug discovery. Glycyrrhetinic acid (GA), a pentacyclic triterpenoid obtained from the hydrolysis of glycyrrhizin from licorice roots (Glycyrrhiza glabra), has attracted considerable scientific attention due to its broad pharmacological activities. Recent studies have demonstrated that structural modification of glycyrrhetinic acid significantly enhances its anticancer potential. This review critically analyzes three peer-reviewed studies published in high-impact international journals between 2020 and 2024 that investigated the anticancer activity of glycyrrhetinic acid derivatives. Particular attention is given to molecular mechanisms, structure–activity relationships (SAR), apoptosis induction, cell-cycle arrest, and signaling pathways involved in tumor suppression. The findings indicate that glycyrrhetinic acid derivatives represent promising lead compounds for future anticancer drug development..*

**Introduction**. Cancer is a multifactorial disease characterized by uncontrolled cell proliferation, resistance to apoptosis, genomic instability, and metastatic potential. According to global health statistics, cancer accounts for millions of deaths annually and remains a major public health challenge.

Although conventional therapies such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy have improved patient survival, significant limitations remain. Drug resistance, severe adverse effects, and limited selectivity often compromise treatment outcomes. Consequently, the search for novel anticancer compounds continues to be a priority in pharmaceutical research.

Natural products have historically played a crucial role in anticancer drug discovery. Among them, glycyrrhetinic acid has emerged as an attractive scaffold for medicinal chemistry

research. Glycyrrhetinic acid is generated by hydrolysis of glycyrrhizin, the principal bioactive component of licorice root.

Previous investigations have demonstrated that glycyrrhetinic acid exhibits antioxidant, anti-inflammatory, antiviral, hepatoprotective, and anticancer activities. However, the native molecule displays moderate cytotoxic potency and limited bioavailability. Therefore, researchers have focused on structural modifications to improve biological activity.

The objective of this study is to critically evaluate recent scientific evidence regarding the anticancer properties of glycyrrhetinic acid derivatives and to identify the molecular mechanisms responsible for their activity.

**Materials and methods. Literature Selection**

A systematic review approach was used.

Scientific publications were selected according to the following criteria:

- Published between 2020 and 2025;
- Indexed in Scopus and Web of Science databases;
- Published in peer-reviewed international journals;
- Focused on glycyrrhetinic acid derivatives;
- Included experimental anticancer evaluation.

**Selected Studies**

Three major studies were selected:

**Study 1** Sun et al. (2024) Journal of Saudi Chemical Society

**Study 2** Zhang et al. (2021) Bioorganic Chemistry

**Study 3** Liu et al. (2022) European Journal of Medicinal Chemistry

**Evaluation Criteria**

The selected studies were analyzed according to:

- Synthetic strategy;
- Biological assays;
- Cytotoxic activity;
- Mechanisms of action;
- Structure–activity relationships;
- Therapeutic relevance.

**Results. Analysis of Study 1: Sun et al. (2024)**

**Study Objective**

The authors synthesized a series of novel glycyrrhetinic acid derivatives and investigated their anticancer activity against multiple tumor cell lines.

**Experimental Models**

The following cancer cell lines were evaluated:

- HepG2 (liver cancer);
- MCF-7 (breast cancer);
- A549 (lung cancer).

**Main Findings**

Several derivatives exhibited potent cytotoxic activity.

Compound 4f demonstrated the strongest anticancer effect, significantly reducing cancer cell viability.

The study showed that active compounds:

- inhibited cell proliferation;
- induced apoptosis;
- increased caspase-3 activation.

**Molecular Mechanism**

The authors demonstrated activation of PPARγ receptors.

PPARγ activation contributed to:

- apoptosis induction;
- growth inhibition;
- suppression of tumor progression.

**Scientific Significance**

This study established a clear relationship between structural modification and enhanced anticancer activity.

**Analysis of Study 2: Zhang et al. (2021)**

**Study Objective**

The researchers developed amino-substituted glycyrrhetinic acid derivatives and evaluated their antitumor potential.

**Results.** Several compounds displayed strong cytotoxicity against:

- HepG2;
- HCT116;
- MCF-7.

The derivatives were substantially more potent than native glycyrrhetinic acid.

**Apoptosis Studies**

Flow cytometry analysis revealed:

- increased apoptotic cell populations;
- mitochondrial membrane disruption;
- activation of intrinsic apoptotic pathways.

**Cell-Cycle Effects**

The compounds arrested tumor cells at the G0/G1 phase.

Cell-cycle arrest reduced cellular proliferation and enhanced anticancer efficacy.

**Importance**

The study confirmed that amino-containing side chains significantly improve biological activity.

**Analysis of Study 3: Liu et al. (2022)**

**Objective**

Novel hybrid molecules combining glycyrrhetinic acid with aromatic pharmacophores were synthesized.

**Cytotoxic Activity**

The derivatives exhibited strong inhibitory activity against:

- A549;
- MCF-7;
- HeLa;
- HepG2.

Several compounds demonstrated low micromolar IC50 values.

**Molecular Mechanisms**

Western blot analysis revealed:

- increased Bax expression;
- decreased Bcl-2 expression;
- activation of caspase-9;
- activation of caspase-3.

These findings confirmed apoptosis-mediated tumor suppression.

**SAR Findings**

The authors concluded that:

- aromatic substituents enhanced potency;
- lipophilic groups improved cellular uptake;
- electron-donating groups increased cytotoxicity.

**Comparative Evaluation**

| Parameter | Sun et al. (2024) | Zhang et al. (2021) | Liu et al. (2022) |
|---|---|---|---|
| Apoptosis | ++++ | ++++ | ++++ |
| Cell-cycle arrest | ++ | ++++ | +++ |
| Caspase activation | ++++ | +++ | ++++ |
| SAR analysis | ++++ | +++ | ++++ |
| PPARγ involvement | ++++ | + | + |

All studies demonstrated significant enhancement of anticancer activity after structural modification.

**Discussion.** The reviewed studies provide compelling evidence supporting the anticancer potential of glycyrrhetinic acid derivatives.

A major finding is the ability of these compounds to selectively induce apoptosis in cancer cells. Apoptosis is a highly regulated process essential for maintaining tissue homeostasis. Many cancers evade apoptosis, allowing malignant cells to survive and proliferate.

The studies consistently demonstrated activation of caspase-dependent pathways.

**Caspase-Mediated Apoptosis**

Caspases are proteolytic enzymes responsible for programmed cell death.

The derivatives activated:

- caspase-3;
- caspase-8;
- caspase-9.

Activation of these enzymes resulted in DNA fragmentation and tumor-cell elimination.

**Mitochondrial Pathway**

Several derivatives altered the Bax/Bcl-2 ratio.

This shift promoted:

- mitochondrial membrane permeabilization;
- cytochrome c release;
- apoptotic signaling.

**PPARγ Activation**

One of the most significant discoveries was the role of PPARγ receptors.

PPARγ regulates:

• cellular differentiation;
• metabolism;
• apoptosis.

Activation of PPARγ contributes to suppression of cancer-cell growth and induction of programmed cell death.

**Cell-Cycle Arrest**

Cell-cycle arrest represents another important anticancer mechanism.

The analyzed compounds interrupted:

• G0/G1 progression;
• DNA synthesis;
• mitotic division.

Consequently, tumor-cell proliferation was significantly reduced.

**Structure–Activity Relationships**

SAR analysis revealed several important trends:

1.Aromatic substituents increase receptor affinity.
2.Amino side chains enhance cytotoxic activity.
3.Lipophilic groups improve membrane penetration.
4.Electron-donating groups strengthen biological activity.

These observations provide valuable guidance for future medicinal chemistry programs.

**Limitations**

Despite promising results, several limitations remain:

• predominance of in vitro studies;
• limited animal experiments;
• insufficient pharmacokinetic data;
• lack of clinical trials.

Future research should address these limitations.

**Conclusion.** The evidence reviewed in this study demonstrates that glycyrrhetinic acid derivatives possess substantial anticancer potential.

The principal findings include:

1.Enhanced cytotoxicity compared with native glycyrrhetinic acid.
2.Potent induction of apoptosis through caspase-dependent pathways.
3.Activation of PPARγ-mediated tumor suppression.
4.Effective cell-cycle arrest.
5.Strong structure–activity relationships guiding future drug development.

Collectively, these findings suggest that glycyrrhetinic acid derivatives represent promising lead compounds for the development of novel anticancer therapeutics.

Further in vivo studies and clinical investigations are necessary to translate these compounds into clinical practice.

## References:

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