PHARMACOLOGICAL PROPERTIES OF GLYCYRRHETINIC ACID DERIVATIVES: A CRITICAL ANALYSIS OF RECENT SCIENTIFIC STUDIES

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https://doi.org/10.5281/zenodo.20962201

ARTICLE INFO

Qabul qilindi: 23-iyun 2026 yil
Ma'qullandi: 25- iyun 2026 yil
Nashr qilindi: 27- iyun 2026 yil

KEYWORDS

Glycyrrhetinic acid, triterpenoids, pharmacological activity, anti-inflammatory agents, antimicrobial activity, anticancer activity, structure–activity relationship.

ABSTRACT

Glycyrrhetinic acid (GA), the aglycone metabolite of glycyrrhizin derived from Glycyrrhiza glabra (licorice), has attracted significant attention due to its broad spectrum of biological activities. Recent advances in medicinal chemistry have enabled the synthesis of numerous glycyrrhetinic acid derivatives with enhanced pharmacological properties. The present study critically analyzes three recent peer-reviewed publications investigating the antimicrobial, anti-inflammatory, and antitumor activities of glycyrrhetinic acid derivatives. A systematic review approach was applied to evaluate experimental design, pharmacological efficacy, mechanisms of action, and structure–activity relationships (SAR). The findings demonstrate that chemical modifications of glycyrrhetinic acid significantly improve biological activity and therapeutic potential. The reviewed studies suggest that glycyrrhetinic acid derivatives represent promising candidates for the development of novel anti-infective, anti-inflammatory, and anticancer agents.

Introduction. Natural products continue to serve as an important source of bioactive compounds for drug discovery and development. Among these compounds, glycyrrhetinic acid (18β-glycyrrhetinic acid), a pentacyclic triterpenoid isolated from licorice roots, has gained increasing scientific interest due to its diverse pharmacological effects. Glycyrrhetinic acid is produced through the hydrolysis of glycyrrhizin, the major active constituent of licorice. Numerous studies have demonstrated that glycyrrhetinic acid exhibits anti-inflammatory, antioxidant, antiviral, hepatoprotective, antimicrobial, and anticancer activities. However, the clinical application of native glycyrrhetinic acid is often limited by its physicochemical properties and moderate biological potency. Consequently, researchers have focused on synthesizing novel derivatives to improve pharmacokinetic characteristics and therapeutic efficacy. Structural modifications of glycyrrhetinic acid mainly involve the hydroxyl group at C-3 and the carboxyl group at C-30. These modifications can significantly influence biological activity by altering molecular interactions with cellular targets. Recent investigations have

reported promising pharmacological outcomes associated with newly synthesized glycyrrhetinic acid derivatives.

The objective of this study is to critically analyze recent scientific literature concerning the pharmacological properties of glycyrrhetinic acid derivatives, focusing on antimicrobial, anti-inflammatory, and antitumor activities.

Materials and methods. Study Design. This work was conducted as a systematic literature analysis based on recent peer-reviewed publications investigating glycyrrhetinic acid derivatives.

Selection Criteria. Articles were selected according to the following criteria:

1.Published between 2020 and 2024.

2.Indexed in Scopus and Web of Science databases.

3.Published in internationally recognized journals.

4.Included experimental evaluation of glycyrrhetinic acid derivatives.

5.Reported pharmacological activity and mechanism-of-action studies.

Selected Studies. The following publications were included in the analysis:

Study 1. Yang Y. et al. (2020)

Synthesis, anti-microbial and anti-inflammatory activities of 18β-glycyrrhetinic acid derivatives. Bioorganic Chemistry.

Study 2. Li X. et al. (2022). *Novel 18β-glycyrrhetinic acid derivatives as a Two-in-One agent with potent antimicrobial and anti-inflammatory activity.*

Bioorganic Chemistry.

Study 3. Sun J. et al. (2024). *Structure–Activity Relationship of 18β-glycyrrhetinic acid derivatives on their antitumor activity through the PPARγ receptor and caspase-3 pathway.*

Journal of Saudi Chemical Society.

Evaluation Parameters

The selected studies were analyzed according to:

- Chemical synthesis strategy;
- Experimental pharmacological models;
- Biological activity;
- Mechanisms of action;
- Structure–activity relationships (SAR);
- Therapeutic implications.

Results.

Analysis of Study 1: Antimicrobial and Anti-Inflammatory Activities. Yang and colleagues synthesized a series of novel glycyrrhetinic acid derivatives through modifications of the parent triterpenoid structure. The derivatives were evaluated against several bacterial strains and inflammatory models.

Antimicrobial Activity. The synthesized compounds demonstrated significant inhibitory effects against:

- *Staphylococcus aureus*
- *Bacillus subtilis*
- *Escherichia coli*

Several derivatives exhibited stronger antibacterial activity than the parent compound, suggesting that structural modifications enhanced interactions with microbial targets.

Anti-Inflammatory Activity. The anti-inflammatory potential was assessed using lipopolysaccharide (LPS)-stimulated macrophage models. The derivatives significantly reduced the production of:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-6 (IL-6)
- Nitric oxide (NO)

These findings indicate effective suppression of inflammatory signaling pathways.

Significance. The study demonstrated that the introduction of amide and ester groups can substantially improve the pharmacological profile of glycyrrhetinic acid.

Analysis of Study 2: Dual Antimicrobial and Anti-Inflammatory Effects

Li et al. developed a novel series of glycyrrhetinic acid derivatives designed to simultaneously target microbial infection and inflammation.

Antibacterial Properties. Several compounds exhibited potent activity against Gram-positive bacteria, particularly antibiotic-resistant strains. The derivatives showed lower minimum inhibitory concentrations (MICs) compared to native glycyrrhetinic acid.

Anti-Inflammatory Properties. The compounds effectively inhibited inflammatory mediator production and suppressed activation of the NF-κB signaling pathway, a major regulator of inflammation.

Mechanistic Insights. Experimental findings suggested that the compounds:

- Reduced cytokine secretion;
- Inhibited NF-κB translocation;
- Decreased oxidative stress markers.

Scientific Importance. The development of dual-function molecules capable of simultaneously controlling infection and inflammation represents an innovative therapeutic strategy.

Analysis of Study 3: Antitumor Activity and SAR Investigation

Sun and colleagues focused on the anticancer potential of glycyrrhetinic acid derivatives.

Experimental Models. The compounds were evaluated against various human cancer cell lines:

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

Anticancer Effects. Several derivatives demonstrated potent cytotoxic activity characterized by:

- Reduced cell proliferation;
- Increased apoptosis;
- Cell cycle arrest;
- Enhanced caspase-3 activation.

Molecular Mechanisms.

The study identified two principal pathways:

PPARγ Activation

Activation of peroxisome proliferator-activated receptor gamma (PPARγ) promoted differentiation and apoptosis in tumor cells.

Caspase-3 Signaling

Upregulation of caspase-3 initiated programmed cell death, contributing to tumor suppression.

Structure–Activity Relationship Findings

The authors reported that:

1.Carboxyl group modification enhanced potency.

2.Aromatic substituents improved anticancer activity.

3.Electron-donating groups increased cytotoxic efficacy.

4.Lipophilic side chains improved cellular uptake.

These findings provide valuable guidance for future drug design.

Discussion. The reviewed studies collectively demonstrate that glycyrrhetinic acid derivatives possess substantial pharmacological potential.

One notable observation is the broad spectrum of biological activity exhibited by structurally modified derivatives. The introduction of specific functional groups resulted in significant improvements in antimicrobial, anti-inflammatory, and anticancer properties.

The antimicrobial effects observed in Studies 1 and 2 may be attributed to enhanced interactions with bacterial membranes and intracellular targets. Furthermore, suppression of inflammatory mediators suggests that these compounds can effectively regulate immune responses.

The anticancer effects reported in Study 3 are particularly promising. Activation of PPARγ and caspase-dependent apoptotic pathways indicates that glycyrrhetinic acid derivatives may serve as potential lead compounds for novel cancer therapeutics.

Structure–Activity Relationships.

The SAR analysis revealed several important trends:

- Amide derivatives generally displayed stronger biological activity.
- Aromatic substitutions enhanced antitumor effects.
- Increased lipophilicity improved membrane permeability.
- Electron-donating groups contributed to greater pharmacological potency.

These observations emphasize the importance of rational molecular design in optimizing therapeutic efficacy.

Limitations of Current Research

Despite encouraging results, several limitations remain:

1.Most studies were conducted in vitro.

2.Limited animal studies have been performed.

3.Long-term toxicity profiles remain unclear.

4.Clinical investigations are currently insufficient.

Future research should prioritize translational studies and clinical validation.

Conclusion. The present analysis demonstrates that glycyrrhetinic acid derivatives represent a highly promising class of bioactive compounds with diverse pharmacological activities.

The major conclusions are as follows:

1.Glycyrrhetinic acid derivatives exhibit significant antimicrobial activity against multiple bacterial species.

2.These compounds effectively suppress inflammatory mediators and signaling pathways.

3.Several derivatives demonstrate potent antitumor activity through PPARγ activation and caspase-3-mediated apoptosis.

4.Structural modifications substantially influence biological activity and therapeutic potential.

5.Glycyrrhetinic acid derivatives may serve as valuable lead compounds for the development of novel anti-infective, anti-inflammatory, and anticancer drugs.

Further in vivo studies and clinical trials are necessary to fully establish their safety and efficacy for therapeutic use.

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