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

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ABSTRACT

Glycyrrhetinic acid (GA) is a pentacyclic triterpenoid obtained through the hydrolysis of glycyrrhizin, the major bioactive constituent of Glycyrrhiza glabra. During the last decade, extensive efforts have been devoted to the synthesis of glycyrrhetinic acid derivatives with improved pharmacological activities. The present study critically analyzes recent investigations published between 2020 and 2025 concerning the antimicrobial, anti-inflammatory, hepatoprotective, and anticancer properties of glycyrrhetinic acid derivatives. Particular attention is given to structure–activity relationships and molecular mechanisms underlying biological effects. The reviewed evidence demonstrates that chemical modification of glycyrrhetinic acid significantly enhances therapeutic efficacy and broadens pharmacological applications. These derivatives represent promising lead compounds for the development of novel anti-inflammatory, antimicrobial, and anticancer agents.

Introduction. Natural products remain one of the most important sources of drug discovery. Among them, triterpenoids have attracted considerable scientific attention because of their diverse biological activities. Glycyrrhetinic acid is a pentacyclic triterpenoid derived from glycyrrhizin, the principal active compound of licorice roots.

Historically, licorice has been used in traditional medicine for respiratory, gastrointestinal, and inflammatory disorders. Modern pharmacological studies have confirmed that glycyrrhetinic acid possesses multiple biological activities including anti-inflammatory, antiviral, antimicrobial, hepatoprotective, antioxidant, and antitumor effects.

However, the parent molecule exhibits limitations such as low water solubility and moderate potency. Consequently, medicinal chemists have synthesized numerous derivatives aiming to improve pharmacokinetic and pharmacodynamic properties.

The purpose of this review is to critically evaluate recent scientific studies published between 2020 and 2025 investigating the pharmacological properties of glycyrrhetinic acid derivatives.

Materials and methods. Literature was collected from peer-reviewed publications indexed in Scopus, Web of Science, and PubMed databases.

Inclusion criteria:

• Publication years 2020–2025;
• Experimental studies on glycyrrhetinic acid derivatives;
• International peer-reviewed journals;
• Pharmacological evaluation supported by biological assays.

Three highly cited studies were selected for detailed critical analysis:

1. Yang et al. (Bioorganic Chemistry, 2020)
2. Li et al. (Bioorganic Chemistry, 2022)
3. Sun et al. (Journal of Saudi Chemical Society, 2024)

The studies were evaluated according to:

• Experimental design;
• Chemical synthesis approaches;
• Biological activity;
• Mechanism of action;
• Structure–activity relationship (SAR);
• Clinical relevance.

Results. 3.1 Antimicrobial Activity. Yang et al. synthesized several glycyrrhetinic acid derivatives and evaluated their antibacterial activity. The modified molecules demonstrated enhanced inhibitory effects against both Gram-positive and Gram-negative bacterial strains.

The strongest activity was observed among amide-containing derivatives. Structural modification increased lipophilicity and membrane permeability, facilitating stronger interactions with bacterial cell membranes.

Importantly, several derivatives showed greater activity than the parent glycyrrhetinic acid molecule, highlighting the importance of molecular optimization.

3.2. Anti-Inflammatory Activity. The anti-inflammatory effects were investigated using lipopolysaccharide-induced macrophage models.

The compounds significantly reduced:

• TNF-α production;
• IL-6 secretion;
• Nitric oxide synthesis.

The suppression of inflammatory mediators was associated with inhibition of NF-κB signaling pathways.

These findings indicate that glycyrrhetinic acid derivatives may be useful in chronic inflammatory diseases.

3.3. Dual Antimicrobial and Anti-Inflammatory Activity. Li et al. proposed a “two-in-one” therapeutic concept.

Their derivatives simultaneously exhibited:

• antibacterial activity;
• anti-inflammatory activity.

This dual mechanism is particularly valuable because infection and inflammation often coexist in clinical conditions.

The study demonstrated that incorporation of specific aromatic substituents significantly improved biological activity.

3.4. Antitumor Activity. Sun et al. synthesized novel derivatives containing cinnamic acid fragments and evaluated them against several cancer cell lines.

Tested cell lines included:

- HepG2;
- MCF-7;
- A549;
- SiHa.

Several derivatives demonstrated remarkable antiproliferative activity. Compound 4f showed the strongest effect with IC50 values in the low micromolar range and displayed stronger activity than several reference compounds.

3.5. Molecular Mechanisms. The antitumor effects were associated with:

- activation of PPARγ receptors;
- stimulation of caspase-3 pathways;
- induction of apoptosis;
- inhibition of tumor cell proliferation.

Molecular docking studies revealed strong interactions between active derivatives and amino acid residues within the PPARγ binding pocket.

Discussion. The reviewed studies collectively demonstrate that glycyrrhetinic acid derivatives possess broad-spectrum pharmacological properties.

One important observation is that modifications at C-3 and C-30 positions substantially alter biological activity.

Amide derivatives generally exhibit stronger antimicrobial and anti-inflammatory activity.

Introduction of aromatic fragments improves antitumor potency by increasing receptor binding affinity.

The observed pharmacological effects can be explained through multiple mechanisms:

- NF-κB inhibition;
- cytokine suppression;
- apoptosis induction;
- PPARγ activation;
- oxidative stress reduction.

4.1. Structure–Activity Relationships. SAR analysis reveals several important trends. First, incorporation of lipophilic substituents enhances membrane permeability. Second, aromatic side chains increase receptor interactions. Third, electron-donating groups often improve anticancer activity. Fourth, piperazine-containing derivatives demonstrate improved biological selectivity. These observations provide valuable guidance for future medicinal chemistry programs.

4.2. Strengths and Limitations of Current Research.

Strengths:

- Rational drug design approaches;
- Molecular docking validation;
- Broad pharmacological screening;

• Identification of lead compounds.

Limitations:

• Predominance of in vitro experiments;
• Limited in vivo evidence;
• Lack of clinical trials;
• Insufficient pharmacokinetic data.

Future perspectives.

Future investigations should focus on:

• in vivo validation;
• toxicity assessment;
• pharmacokinetic optimization;
• targeted drug delivery systems;
• clinical studies.

Nanotechnology-based formulations may further improve the therapeutic potential of glycyrrhetinic acid derivatives.

Conclusion. The evidence accumulated during 2020–2025 confirms that glycyrrhetinic acid derivatives represent a promising class of bioactive molecules.

Their pharmacological activities include:

• antimicrobial effects;
• anti-inflammatory effects;
• antioxidant activity;
• hepatoprotective properties;
• antitumor activity.

Chemical modification significantly enhances biological potency and therapeutic potential.

The available evidence strongly supports continued development of glycyrrhetinic acid derivatives as lead compounds for future pharmaceutical applications.

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