ANTI-INFLAMMATORY EFFECTS OF GLYCYRRHETINIC ACID DERIVATIVES: A CRITICAL ANALYSIS OF RECENT STUDIES

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ABSTRACT

Inflammation is a fundamental biological response involved in the pathogenesis of numerous chronic diseases, including cancer, cardiovascular disorders, autoimmune diseases, and metabolic syndromes. Glycyrrhetinic acid (GA), a pentacyclic triterpenoid derived from glycyrrhizin, has attracted considerable scientific attention due to its anti-inflammatory potential. Recent advances in medicinal chemistry have led to the development of novel glycyrrhetinic acid derivatives with improved pharmacological properties. The present study critically analyzes three high-impact investigations published in Bioorganic Chemistry between 2020 and 2022. The selected studies explored the anti-inflammatory activity of structurally modified glycyrrhetinic acid derivatives through in vitro and in vivo models. The analysis focuses on pharmacological efficacy, molecular mechanisms, structure–activity relationships, and future therapeutic perspectives. The findings indicate that specific structural modifications significantly enhance anti-inflammatory activity through suppression of NF-κB, MAPK, PI3K/Akt, and oxidative stress-related pathways.

Introduction. Inflammation is a highly coordinated physiological response that protects tissues from infection and injury. However, chronic inflammation contributes to the development and progression of numerous pathological conditions. Persistent activation of inflammatory pathways promotes excessive production of cytokines, chemokines, and reactive oxygen species, ultimately leading to tissue damage.

Natural products have historically played a crucial role in the discovery of anti-inflammatory agents. Among them, glycyrrhetinic acid, the aglycone metabolite of glycyrrhizin obtained from Glycyrrhiza glabra, has emerged as a promising bioactive compound. Numerous studies have demonstrated that glycyrrhetinic acid possesses anti-inflammatory, antioxidant, antimicrobial, antiviral, and hepatoprotective activities.

Despite these promising properties, the pharmacological efficacy of native glycyrrhetinic acid remains limited by moderate potency and unfavorable physicochemical characteristics. Consequently, extensive efforts have been devoted to the synthesis of novel derivatives aimed at improving biological activity and therapeutic effectiveness.

The objective of the present study is to critically evaluate recent scientific evidence regarding the anti-inflammatory effects of glycyrrhetinic acid derivatives and to identify molecular mechanisms responsible for their pharmacological actions.

Materials and methods. A systematic literature analysis was performed using publications indexed in PubMed, Scopus, and Web of Science databases.

Selection criteria included:

- Publication between 2020 and 2025;
- Experimental investigation of glycyrrhetinic acid derivatives;
- Evaluation of anti-inflammatory activity;
- Publication in peer-reviewed international journals;
- Availability of mechanistic data.

Three studies fulfilled the inclusion criteria and were selected for detailed evaluation.

The following parameters were analyzed:

- Chemical modification strategy;
- Experimental models;
- Anti-inflammatory efficacy;
- Molecular targets;
- Structure–activity relationships;
- Therapeutic relevance.

Results. Analysis of Yang et al. (2020)

Yang and colleagues synthesized thirteen novel glycyrrhetinic acid derivatives through modifications at the C-2, C-3, and C-11 positions. The biological evaluation included antimicrobial and anti-inflammatory experiments. Compound 10 demonstrated the strongest pharmacological activity. In a TPA-induced mouse ear edema model, compound 10 reduced inflammatory swelling by approximately 59.69%, significantly outperforming the parent compound. Immunohistochemical analysis revealed substantial reductions in TNF-α and IL-1β expression. Furthermore, suppression of p65 activation suggested inhibition of the NF-κB signaling pathway. These findings indicate that structural modification substantially enhances anti-inflammatory potency. The study also demonstrated that optimized derivatives can simultaneously exhibit antimicrobial and anti-inflammatory activities. This dual functionality may provide significant therapeutic advantages in inflammatory conditions associated with infection.

Analysis of Bian et al. (2021)

Bian and coworkers synthesized thirty-four structurally modified glycyrrhetinic acid derivatives using four distinct synthetic strategies. Anti-inflammatory activity was evaluated in LPS-stimulated RAW264.7 macrophages. Among the synthesized compounds, derivative 5b exhibited the strongest activity. Treatment with compound 5b significantly reduced the production of TNF-α, IL-6, nitric oxide, iNOS, and COX-2. Mechanistic investigations revealed that the anti-inflammatory effects were mediated through inhibition of both NF-κB and MAPK signaling pathways. Compared with the parent glycyrrhetinic acid molecule, compound 5b

demonstrated superior efficacy and stronger suppression of inflammatory mediators. The study provided valuable evidence that targeted structural optimization can substantially improve anti-inflammatory performance.

Analysis of Tu et al. (2022)

Tu and colleagues designed a series of novel C-2 phenyl-substituted glycyrrhetinic acid derivatives. The compounds were developed according to a “Two-in-One” strategy, aiming to simultaneously provide antimicrobial and anti-inflammatory activities. Biological evaluation demonstrated that compounds GA-O-02 and GA-O-06 exhibited potent anti-inflammatory effects. The derivatives significantly suppressed nitric oxide production and reduced the secretion of multiple pro-inflammatory cytokines and chemokines. Mechanistic studies demonstrated inhibition of NF-κB, MAPK, and PI3K/Akt signaling pathways. Moreover, activation of the Nrf2/HO-1 antioxidant pathway contributed to the anti-inflammatory response. These findings indicate that modulation of multiple signaling networks may account for the superior efficacy of these compounds.

Comparative Analysis

A comparison of the three studies demonstrates several consistent findings.

First, all investigations identified NF-κB inhibition as a central mechanism responsible for anti-inflammatory activity.

Second, all studies reported significant reductions in major inflammatory mediators, including TNF-α, IL-6, IL-1β, and nitric oxide.

Third, structural modification consistently improved biological activity relative to native glycyrrhetinic acid.

Finally, multifunctional derivatives exhibited broader pharmacological profiles than the parent molecule.

Discussion. The reviewed studies collectively provide strong evidence supporting the anti-inflammatory potential of glycyrrhetinic acid derivatives.

The suppression of NF-κB signaling appears to represent the primary mechanism underlying their activity. NF-κB regulates numerous genes involved in inflammatory responses, and its inhibition results in reduced cytokine production and decreased tissue injury.

An additional important finding is the involvement of MAPK signaling pathways. MAPKs regulate inflammatory gene expression and cellular responses to stress. Simultaneous inhibition of NF-κB and MAPK pathways may explain the enhanced efficacy observed in several derivatives.

The study by Tu et al. further demonstrated participation of PI3K/Akt and Nrf2/HO-1 pathways. Nrf2 activation contributes to antioxidant defense and reduction of oxidative stress, which frequently accompanies chronic inflammation.

Structure–activity relationship analysis revealed several important trends. Modifications at C-2, C-3, and C-11 positions significantly influence biological activity. Aromatic substituents generally improve receptor interactions and cellular uptake. Increased lipophilicity may facilitate membrane permeability and intracellular target engagement.

Although the available evidence is highly encouraging, most investigations remain limited to in vitro models and animal studies. Clinical validation remains necessary before therapeutic application can be considered.

Conclusion. The present analysis demonstrates that glycyrrhetinic acid derivatives possess remarkable anti-inflammatory properties. Structural modification significantly enhances biological activity compared with native glycyrrhetinic acid.

The principal mechanisms include:

- inhibition of NF-κB signaling;
- suppression of MAPK pathways;
- modulation of PI3K/Akt signaling;
- activation of Nrf2/HO-1 antioxidant responses;
- reduction of pro-inflammatory cytokine production.

Among the reviewed studies, compounds developed by Yang et al., Bian et al., and Tu et al. demonstrated particularly promising pharmacological profiles. These findings support the continued development of glycyrrhetinic acid derivatives as potential anti-inflammatory drug candidates.

Future research should focus on pharmacokinetic optimization, toxicity assessment, and clinical evaluation to facilitate translation into therapeutic applications.

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