IN VIVO PHARMACODYNAMIC EVALUATION OF GLYCYRRHETINIC ACID DERIVATIVES: AN IMRAD-BASED COMPARATIVE ANALYSIS OF SIX ORIGINAL STUDIES FROM HIGH-IMPACT JOURNALS

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Historically, a large portion of the glycyrrhetinic acid literature has focused on synthesis and in vitro screening.

ABSTRACT

While many publications emphasize in vitro cytotoxicity, the translational value of GA derivatives depends heavily on their in vivo pharmacodynamic behavior, including the ability to suppress tumor growth, reduce inflammatory edema, modulate cytokine networks, inhibit metastasis, and improve histopathological outcomes in animal models. The aim of the present IMRAD-based review article was to analyze the in vivo pharmacodynamic direction of glycyrrhetinic acid derivative research through six original experimental studies published in reputable journals with real and verifiable DOI numbers. The selected papers covered several pharmacodynamic domains: antitumor activity in xenograft and ascites models, anti-inflammatory activity in topical and systemic inflammation models, anti-metastatic action, and dual anti-inflammatory/antimicrobial or antitumor properties. The six studies included: Huang et al. (Bioorganic Chemistry, 2020; DOI: 10.1016/j.bioorg.2020.104187), Yang et al. (Bioorganic Chemistry, 2020; DOI: 10.1016/j.bioorg.2020.103985), Markov et al. (Molecular Biology, 2018; DOI: 10.7868/S0026898418020143), Tu et al. (Bioorganic Chemistry, 2022; DOI: 10.1016/j.bioorg.2022.105714), Salomatina et al. (International Journal of Molecular Sciences, 2022; DOI: 10.3390/ijms23116214), and Markov et al. (Pharmaceuticals, 2022; DOI: 10.3390/ph15050603). Across these studies, the most recurrent in vivo pharmacodynamic endpoints were inhibition of ear edema or peritonitis, reduction of tumor volume or ascitic tumor burden, suppression of metastatic spread, and downregulation of inflammatory mediators such as TNF-α, IL-1β, IL-6, MCP-1, MIP-1α,

p65/NF-κB, and related signaling nodes. Several derivatives also showed mechanistic signatures that strengthen their translational relevance: apoptosis induction, ROS-associated mitochondrial dysfunction, modulation of HDAC3/Noxa/c-Flip signaling, normalization of tumor vasculature, and favorable microsomal or pharmacokinetic properties. The analysis indicates that GA derivatives can no longer be regarded as merely cytotoxic triterpenoid analogues; rather, they represent a pharmacodynamically diverse platform capable of exerting anti-inflammatory, antitumor, anti-metastatic, and microenvironment-modulating effects in vivo..

Introduction. Natural triterpenoids remain one of the most productive sources of lead structures in modern medicinal chemistry because they combine structural complexity with modifiable pharmacophores. Among them, glycyrrhetinic acid (GA), the aglycone of glycyrrhizin derived from licorice, has attracted persistent attention owing to its anti-inflammatory, hepatoprotective, antiviral, antimicrobial, and antitumor properties. However, the parent compound itself usually exhibits only moderate potency and limited pharmacokinetic performance, which has stimulated extensive efforts to create semisynthetic GA derivatives with improved pharmacological profiles.

Historically, a large portion of the glycyrrhetinic acid literature has focused on synthesis and in vitro screening. Yet from the perspective of drug discovery, in vitro activity alone is not sufficient. A derivative with low micromolar cytotoxicity or anti-inflammatory activity becomes genuinely relevant only when it demonstrates in vivo pharmacodynamic efficacy under conditions that reflect disease-associated physiology, tissue exposure, immune signaling, and whole-organism tolerability.

For glycyrrhetinic acid derivatives, the in vivo pharmacodynamic direction is especially important because the scaffold is intrinsically pleiotropic. Depending on the nature of chemical modification, GA derivatives may act not only as direct cytotoxic agents but also as regulators of inflammatory cascades, oxidative stress, mitochondrial signaling, epithelial–mesenchymal transition, tumor angiogenesis, and tumor microenvironment remodeling. Therefore, the value of a given derivative cannot be judged solely by its in vitro IC50 value; it must also be assessed by how effectively it changes biologically meaningful endpoints in animals.

The present article addresses this need by analyzing six original experimental papers from reputable journals that specifically include in vivo pharmacodynamic evaluation of glycyrrhetinic acid derivatives. Rather than reviewing the entire GA literature, the article concentrates on studies in which semisynthetic derivatives were actually tested in animal models and where pharmacodynamic outcomes—such as tumor suppression, edema inhibition, anti-metastatic effects, or cytokine modulation—were reported.

Aim of the Study. To perform an IMRAD-based comparative analysis of the in vivo pharmacodynamic activity of glycyrrhetinic acid derivatives using six original peer-reviewed studies with verified DOI numbers, and to identify the major pharmacodynamic directions,

effective animal models, leading compounds, mechanistic biomarkers, and translational strengths of these derivatives.

Materials and Methods. This work was designed as an analytical review in IMRAD format based exclusively on original experimental publications. The central inclusion criterion was the presence of in vivo pharmacodynamic evaluation of a glycyrrhetinic acid derivative or a clearly defined semisynthetic derivative class built on the 18β-glycyrrhetinic acid scaffold. Six original studies fulfilled the selection criteria and were chosen as the analytical basis of this review:

1) Huang M. et al. Synthesis and antitumor effects of novel 18β-glycyrrhetinic acid derivatives featuring an exocyclic α,β-unsaturated carbonyl moiety in ring A. Bioorganic Chemistry. 2020;103:104187. DOI: 10.1016/j.bioorg.2020.104187.

2) Yang Y. et al. Synthesis, anti-microbial and anti-inflammatory activities of 18β-glycyrrhetinic acid derivatives. Bioorganic Chemistry. 2020;101:103985. DOI: 10.1016/j.bioorg.2020.103985.

3) Markov A.V. et al. Novel Glycyrrhetinic Acid Derivative Soloxolone Methyl Inhibits the Inflammatory Response and Tumor Growth in vivo. Molecular Biology. 2018;52(2):306–313. DOI: 10.7868/S0026898418020143.

4) Tu B. et al. Novel 18β-glycyrrhetinic acid derivatives as a Two-in-One agent with potent antimicrobial and anti-inflammatory activity. Bioorganic Chemistry. 2022;122:105714. DOI: 10.1016/j.bioorg.2022.105714.

5) Salomatina O.V. et al. Novel Epoxides of Soloxolone Methyl: An Effect of the Formation of Oxirane Ring and Stereoisomerism on Cytotoxic Profile, Anti-Metastatic and Anti-Inflammatory Activities In Vitro and In Vivo. International Journal of Molecular Sciences. 2022;23(11):6214. DOI: 10.3390/ijms23116214.

6) Markov A.V. et al. Novel Soloxolone Amides as Potent Anti-Glioblastoma Candidates: Design, Synthesis, In Silico Analysis and Biological Activities In Vitro and In Vivo. Pharmaceuticals. 2022;15(5):603. DOI: 10.3390/ph15050603.

For each article, the following variables were extracted: derivative class and structural modification strategy; disease model and animal species; route of administration and dose when reported; primary pharmacodynamic endpoint; molecular or histological biomarkers; and the authors’ claims regarding preclinical relevance, selectivity, or pharmacokinetic advantages.

Results. The six selected studies collectively demonstrate that glycyrrhetinic acid derivatives have already entered a meaningful preclinical stage in which in vivo pharmacodynamic efficacy can be documented across multiple disease domains. Two major therapeutic directions dominate the dataset: anti-inflammatory activity and antitumor activity. However, several studies bridge these categories by showing that one derivative can simultaneously suppress inflammation and inhibit tumor progression or metastatic spread.

Yang et al. (2020) synthesized thirteen 18β-glycyrrhetinic acid derivatives and evaluated their anti-inflammatory effect in a TPA-induced mouse ear edema model. Compound 10 reduced ear edema by approximately 59.69% and decreased TNF-α,

IL-1β, and p65 expression, indicating suppression of NF-κB-linked inflammatory signaling.

Tu et al. (2022) extended this anti-inflammatory direction by developing new GA derivatives functionalized mainly at the C-2 position. Two lead compounds, GA-O-02 and GA-O-06, showed potent anti-inflammatory activity in the TPA-induced mouse ear inflammation model. Mechanistic experiments demonstrated downregulation of NO and multiple pro-inflammatory cytokines and chemokines, including IL-1β, IL-6, IL-12, TNF-α, MCP-1, and MIP-1α, along with upregulation of

IL-10. The authors further implicated inhibition of NF-κB, MAPKs, and PI3K/Akt signaling and activation of the Nrf2/HO-1 pathway.

Markov et al. (2018) investigated soloxolone methyl (SM), a cyano enone-bearing derivative of 18βH-glycyrrhetinic acid, in mouse models of carrageenan- and histamine-induced acute inflammation. SM efficiently suppressed edema development in vivo. The same paper also showed that SM inhibited tumor growth in mice bearing Krebs-2 ascites carcinoma and reduced tumor-cell counts in ascitic fluid, demonstrating a dual anti-inflammatory and antitumor pharmacodynamic profile.

Huang et al. (2020) synthesized ring A–modified GA derivatives containing an exocyclic α,β-unsaturated carbonyl moiety and identified compounds 5c and 5l as lead antitumor candidates. Compound 5l inhibited tumor growth in mice and displayed favorable microsomal and plasma stability together with improved pharmacokinetic behavior. Mechanistically, 5c and 5l induced apoptosis and were associated with c-Flip downregulation, Noxa induction, decreased HDAC3 expression, and increased histone H3 acetylation.

Salomatina et al. (2022) prepared α- and β-epoxides of soloxolone methyl and evaluated not only their cytotoxicity but also their anti-metastatic and anti-inflammatory effects in vivo. The epoxide derivatives preserved strong antitumor properties, inhibited metastasis of B16 melanoma in mice, and suppressed carrageenan-induced peritonitis. This combination of anti-metastatic and anti-inflammatory activity is highly relevant because metastasis is deeply intertwined with inflammation and immune-cell behavior.

The most specialized antitumor pharmacodynamic study among the six papers is the 2022 Pharmaceuticals article by Markov et al., which focused on novel soloxolone amides as anti-glioblastoma candidates. Compound 12 (soloxolone tryptamide) significantly inhibited the growth of U87 glioblastoma xenografts after intraperitoneal administration. Beyond tumor volume reduction, the study reported decreased proliferative potential of the tumor, depletion of collagen content, and normalization of blood vessels within tumor tissue.

Discussion. The central conclusion emerging from this comparative review is that glycyrrhetinic acid derivatives have progressed beyond the stage of isolated in vitro curiosities and now constitute a pharmacodynamically meaningful class of semisynthetic triterpenoids. The selected studies show that chemical modification of the GA scaffold can generate compounds capable of suppressing acute inflammation, reducing tumor burden, blocking metastatic progression, and modulating the tumor microenvironment in vivo.

From a structural perspective, the pharmacodynamic diversification of GA derivatives appears to be closely linked to rational scaffold engineering. The anti-inflammatory derivatives described by Yang et al. and Tu et al. emphasize modifications around the C-2, C-3, C-11, and C-30 regions, generating compounds that interfere with inflammatory mediator production and edema formation. In contrast, the most advanced antitumor derivatives—such as 5l and the soloxolone family—feature more aggressive pharmacophoric

redesign, including α,β-unsaturated carbonyl systems, cyano enone motifs, epoxide formation, or amide-bearing side chains.

A particularly instructive theme is the convergence of anti-inflammatory and antitumor pharmacodynamics. Markov et al. (2018) showed that soloxolone methyl can suppress both inflammatory edema and tumor growth. Salomatina et al. (2022) demonstrated that epoxidized soloxolone derivatives retain anti-inflammatory properties while inhibiting metastatic behavior. These findings are consistent with the broader biological reality that inflammation is deeply integrated into cancer progression through cytokine signaling, immune-cell recruitment, angiogenesis, matrix remodeling, and metastatic niche formation.

The anti-inflammatory branch of GA-derivative pharmacodynamics is noteworthy not only because it shows measurable efficacy, but because it reveals a coherent mechanistic pattern. Across the Yang and Tu studies, pharmacodynamic benefit correlates with suppression of TNF-α, IL-1β, IL-6, and p65/NF-κB, together with changes in NO and chemokine output. The antitumor branch is even more diverse. Huang et al. emphasized apoptosis-related and epigenetic signaling, while the glioblastoma study by Markov et al. adds another layer by demonstrating effects on collagen content and vessel normalization, implying that some GA derivatives can act on stromal and vascular elements of the tumor microenvironment.

Among the derivative families discussed in this review, the soloxolone series deserves special attention. Soloxolone methyl already has documented anti-inflammatory and antitumor efficacy in vivo. Subsequent epoxide and amide modifications did not abolish this pharmacodynamic core; instead, they expanded it into anti-metastatic and anti-glioblastoma territory. This suggests that soloxolone derivatives may represent a particularly fertile platform for future medicinal-chemistry optimization and dissertation-level experimental work.

Conclusion. The six original studies analyzed in this article demonstrate that glycyrrhetinic acid derivatives possess substantial in vivo pharmacodynamic potential across several therapeutic directions. In acute inflammatory models, derivatives such as compound 10, GA-O-02, and GA-O-06 reduced edema and suppressed major inflammatory mediators including TNF-α, IL-1β, IL-6, and p65/NF-κB. In antitumor settings, ring A–modified derivatives and soloxolone-based analogues inhibited tumor growth, reduced ascitic tumor burden, blocked metastasis, and in some cases normalized tumor vasculature or remodeled stromal architecture. Particularly important are derivatives such as 5l and soloxolone-based amides, which combine in vivo efficacy with mechanistic or pharmacokinetic advantages. Overall, the evidence supports the view that glycyrrhetinic acid derivatives represent a versatile pharmacodynamic platform rather than a single-purpose class of cytotoxic molecules.

Table 1. Comparative summary of six original studies on the in vivo pharmacodynamics of glycyrrhetinic acid derivatives

Study	Lead derivative(s)	In vivo model	Direction	Main outcome	Mechanistic notes	Journal	DOI
Huang et al., 2020	5c, 5l	Mouse tumor model	Antitumor	5l inhibited tumor growth; better stability/PK	c-Flip↓, Noxa↑, HDAC3↓, H3 acetylation↑	Bioorg Chem	10.1016/j.bioorg.2020.104187
Yang et al., 2020	Compound 10	TPA ear edema	Anti-inflammatory	Edema reduction ~59.69%	TNF-α↓, IL-1β↓, p65↓	Bioorg Chem	10.1016/j.bioorg.2020.103985
Markov et al., 2018	Soloxolone methyl	Carrageenan/histamine edema; Krebs-2 ascites	Dual anti-inflammatory + antitumor	Suppressed edema; reduced tumor burden	Cyanoenone derivative	Molecular Biology	10.7868/S0026898418020143
Tu et al., 2022	GA-O-02, GA-O-06	TPA ear inflammation	Anti-inflammatory	Potent ear anti-inflammatory activity	NO↓, TNF-α↓, IL-1β↓, IL-6↓; NF-κB/MAPK/PI3K-Akt inhibition	Bioorg Chem	10.1016/j.bioorg.2022.105714
Salomatina et al., 2022	αO-SM, βO-SM	Melanoma metastasis; peritonitis	Anti-metastatic + anti-inflammatory	Suppressed metastasis and inflammation	Mitochondrial apoptosis; macrophage NO suppression	Int J Mol Sci	10.3390/ijms23116214
Markov et al., 2022	Compound 12	U87 glioblastoma xenograft	Antitumor	Inhibited xenograft growth	ROS-dependent mitochondrial apoptosis; vessel normalization	Pharmaceuticals	10.3390/ph15050603

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1. Huang M. et al. Synthesis and antitumor effects of novel 18β-glycyrrhetinic acid derivatives featuring an exocyclic α,β-unsaturated carbonyl moiety in ring A. Bioorganic Chemistry. 2020;103:104187. DOI: 10.1016/j.bioorg.2020.104187.
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