COMPARATIVE ANALYSIS OF GLYCYRRHETINIC ACID DERIVATIVES BASED ON THEIR ACTIVITY INDICATORS: A CROSS-STUDY EVALUATION OF CYTOTOXICITY IN STANDARD CANCER CELL LINES

Xolboeva Madina Ural kizi
Tashkent pharmaceutical institute
madinaxolboyeva98@gmail.com
https://doi.org/10.5281/zenodo.20962745

ARTICLE INFO

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

KEYWORDS

This work was designed as an analytical comparative review based exclusively on original experimental publications.

ABSTRACT

Glycyrrhetinic acid (GA, 18 β-glycyrrhetinic acid) is a pentacyclic triterpenoid scaffold of considerable interest in anticancer drug discovery because chemical modification of its hydroxyl, carboxyl, and ring A functionalities can markedly alter cytotoxic potency, selectivity, and mechanism of action. The aim of the present article was to conduct a comparative analysis of glycyrrhetinic acid derivatives on the basis of activity indicators reported in original experimental studies and to identify the most promising structural series across different standard cancer cell lines. Five peer-reviewed papers with real and verifiable DOI numbers were selected: Molecules (2016), Bioorganic Chemistry (2019), Biological and Pharmaceutical Bulletin (2020), Bioorganic Chemistry (2020), and Molecules (2023). The comparison focused on derivative class, cancer cell-line spectrum, IC50 values, selectivity toward normal cells, apoptosis-related findings, oxidative stress markers, and preliminary structure–activity relationship (SAR) trends. Across the selected studies, the strongest activity was generally observed after targeted modification at C-3, C-30, or ring A. Low-micromolar cytotoxicity was reported in breast cancer (MCF-7, MDA-MB-231), cervical cancer (HeLa), and colorectal cancer (HCT-116) models. Particularly notable were compound 42 from the 2016 series, cinnamic-acid hybrid derivative 3o from the 2019 study, apoptosis-inducing derivative 6g from the 2020 Biological and Pharmaceutical Bulletin study, ring A–modified compounds 5c and 5l from the 2020 Bioorganic Chemistry study, and derivative 3a from the 2023 HeLa-focused mechanistic study. Collectively, the evidence indicates that GA derivatives can achieve meaningful cytotoxic enhancement relative to the parent scaffold

and may act through apoptosis induction, ROS accumulation, mitochondrial dysfunction, autophagy modulation, and cell-cycle arrest. The comparative review also shows that direct cross-study ranking requires caution because experimental designs differ across papers; nevertheless, several reproducible trends emerge and may guide future derivative design and dissertation research.

Introduction. Natural-product-derived scaffolds remain a major source of inspiration in anticancer drug discovery, especially when the parent structure can be chemically diversified to improve potency and selectivity. Pentacyclic triterpenoids are among the most productive natural scaffolds in this regard, and glycyrrhetinic acid (GA), the aglycone metabolite of glycyrrhizin from licorice, occupies a prominent place in this class. GA itself exhibits anti-inflammatory, hepatoprotective, antiviral, antioxidant, and moderate antitumor effects. However, its native anticancer activity is often insufficient for direct therapeutic development, which has driven medicinal chemists to design semisynthetic GA derivatives with improved cytotoxic performance.

The structural plasticity of GA is one of its greatest advantages. The hydroxyl group at C-3, the carboxyl group at C-30, and functional elements within ring A provide chemically accessible positions for esterification, amidation, hybridization with aromatic pharmacophores, introduction of amino substituents, and installation of electrophilic motifs. Such modifications may alter membrane permeability, target affinity, redox activity, apoptosis induction, and the capacity to disturb cancer-cell metabolism. As a result, a growing body of literature has emerged in which GA derivatives are screened against standard cancer cell lines such as MCF-7, MDA-MB-231, HeLa, A549, HCT-116, SGC-7901, BEL-7402, and others.

Despite the expanding literature, researchers often face a practical problem: individual papers report promising compounds, but the results are difficult to compare across studies because the derivatives belong to different structural families and are tested in partially overlapping cell-line panels. For dissertation work and laboratory planning, it is therefore not enough to know that GA derivatives can be cytotoxic; it is more important to determine which derivative classes perform best, in which cell lines, and by what mechanistic patterns. A comparative activity-based analysis can provide that missing synthesis.

Aim of the Study. To conduct a comparative analysis of glycyrrhetinic acid derivatives based on reported activity indicators in five original studies with verified DOI numbers, and to identify the most active derivative classes, their cell-line-specific cytotoxic profiles, mechanistic signatures, and preliminary structure–activity relationships.

Materials and Methods. This work was designed as an analytical comparative review based exclusively on original experimental publications. The literature set was restricted to studies that met all of the following criteria: (1) the paper investigated glycyrrhetinic acid or 18β-glycyrrhetinic acid derivatives; (2) cytotoxicity was evaluated in vitro against one or more standard cancer cell lines; (3) the article was an original experimental study rather than a review; (4) a real, verifiable DOI number was available; and (5) the paper was published in a reputable peer-reviewed journal.

Five studies were selected for comparative analysis:

1) Li Y., Feng L., Song Z.-F., Li H.-B., Huai Q.-Y. Synthesis and Anticancer Activities of Glycyrrhetinic Acid Derivatives. Molecules. 2016;21(2):199. DOI: 10.3390/molecules21020199.

2) Wang R., Yang W., Fan Y., Dehaen W., Li Y., Li H., Wang W., Zheng Q., Huai Q. Design and synthesis of the novel oleanolic acid-cinnamic acid ester derivatives and glycyrrhetinic acid-cinnamic acid ester derivatives with cytotoxic properties. Bioorganic Chemistry. 2019; 88:102951. DOI: 10.1016/j.bioorg.2019.102951.

3) Zheng Q.-X., Wang R., Xu Y., et al. Design, Preparation and Studies Regarding Cytotoxic Properties of Glycyrrhetinic Acid Derivatives. Biological and Pharmaceutical Bulletin. 2020;43(1):102–109. DOI: 10.1248/bpb.b19-00615.

4) Huang M., Gong P., Wang Y., Xie X., Ma Z., Xu Q., Liu D., Jing Y., Zhao L. 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.

5) Chen J., Xu Y., Yang Y., et al. Evaluation of the Anticancer Activity and Mechanism Studies of Glycyhetic Acid Derivatives toward HeLa Cells. Molecules. 2023;28(7):3164. DOI: 10.3390/molecules28073164.

For each paper, the following variables were extracted and compared: derivative class and structural modification strategy; cancer and normal cell lines tested; cytotoxicity assay; most active derivatives and their IC50 values; evidence of apoptosis, autophagy, ROS accumulation, mitochondrial dysfunction, or cell-cycle arrest; and any explicit claims regarding selectivity or in vivo relevance.

Results. The five selected studies reveal that glycyrrhetinic acid derivatives can be grouped into several functionally distinct design strategies: broad C-3/C-30 diversification aimed at improving baseline cytotoxicity; hybridization with cinnamic-acid fragments to enhance selectivity and apoptosis/autophagy-inducing capacity; optimization of cytotoxicity through compact derivative libraries with direct comparison to commercial drugs; ring A engineering to generate electrophilic analogues with strong antitumor activity and improved pharmacological behavior; and ester derivative series subjected to deeper mechanistic investigation in HeLa cells. The 2016 Molecules study by Li et al. synthesized 40 GA derivatives and tested them against MCF-7 and MDA-MB-231 breast cancer cells. Among the derivatives, compound 42 showed the most impressive activity, with IC50 values of 1.88 ± 0.20 μM in MCF-7 cells and 1.37 ± 0.18 μM in MDA-MB-231 cells.

The 2019 Bioorganic Chemistry study by Wang et al. introduced a hybrid strategy in which glycyrrhetinic acid was linked to cinnamic-acid motifs. The derivatives were evaluated in HeLa, MCF-7, and L-O2 cells. The most striking result was the strong selective cytotoxicity of compound 3o against HeLa cells (IC50 = 1.35 μM), while compound 2d also displayed strong HeLa-selective inhibition (IC50 = 1.55 μM). Compound 3e showed the strongest activity against MCF-7 cells (IC50 = 1.79 μM).

The 2020 Biological and Pharmaceutical Bulletin study by Zheng et al. examined 18 GA derivatives against MDA-MB-231 and HeLa cells. Several compounds exhibited cytotoxicity comparable to or stronger than gefitinib and doxorubicin. Compound 6g was highlighted for its

ability to induce concentration-dependent apoptosis in MDA-MB-231 cells.

The 2020 Bioorganic Chemistry study by Huang et al. generated ring A–modified GA derivatives featuring an exocyclic α,β-unsaturated carbonyl moiety. Compounds 5c and 5l emerged as lead structures and showed stronger cytotoxicity than other analogues and the previously reported GA analogue CDODA-Me. Compound 5l also displayed improved stability, favorable pharmacokinetic properties, and in vivo tumor-growth inhibition.

The 2023 Molecules study by Chen et al. evaluated six esterified GA derivatives (3a–3f) in SGC-7901, BEL-7402, A549, HeLa, B16, and normal LO2 cells. Compound 3a was identified as the most active derivative against HeLa cells, with an IC50 value of 11.4 ± 0.2 μM. Although this potency is weaker than that of the best compounds in the earlier studies, the 2023 paper provides unusually rich mechanistic evidence, including ROS increase, GSH depletion, mitochondrial dysfunction, caspase activation, PARP cleavage, and S-phase arrest.

Discussion. The comparative evaluation of the five selected studies demonstrates that glycyrrhetinic acid is a highly adaptable scaffold whose biological performance depends heavily on the type and position of chemical modification. Across the literature analyzed here, three structural regions repeatedly emerge as critical for activity optimization: the C-3 hydroxyl group, the C-30 carboxyl group, and ring A. Modifications at these sites appear to influence not only potency but also cell-line preference, selectivity against normal cells, and the dominant mechanism of cell death.

The 2016 study established a foundational medicinal-chemistry principle for GA derivatives: broad diversification can reveal unexpectedly potent leads. Compound 42 showed sub-2 μM activity in both MCF-7 and MDA-MB-231 cells, which is notable because MDA-MB-231 represents a triple-negative breast cancer model associated with therapeutic difficulty.

The 2019 hybridization study illustrates a second important design principle: linking GA to another bioactive pharmacophore can yield both potency and selectivity. The cinnamic-acid hybrids did not simply increase activity uniformly; rather, they redistributed activity across cell lines. Compound 3o was highly active in HeLa but inactive in MCF-7 and L-O2 under the reported conditions, while 3e was stronger in MCF-7.

The 2020 Biological and Pharmaceutical Bulletin paper adds a clinically relevant comparative layer because the derivatives were assessed relative to standard anticancer drugs. The apoptosis data for 6g show that the cytotoxicity of GA derivatives can be biologically meaningful rather than nonspecific.

The 2020 Bioorganic Chemistry study by Huang et al. arguably represents the most advanced lead-optimization step among the five papers because it integrates cytotoxicity with apoptosis biomarkers, signaling effects, metabolic stability, pharmacokinetics, and in vivo tumor inhibition. By contrast, the 2023 mechanistic study contributes exceptional depth of mechanism, mapping oxidative stress, mitochondrial injury, apoptosis, cell-cycle arrest, clonogenicity, and migration.

Taken together, the five studies support several tentative SAR conclusions. First, incorporation of aromatic or hybrid pharmacophoric fragments can improve potency and, in some cases, confer selectivity. Second, ring A modifications capable of creating electrophilic or signaling-active motifs may enhance apoptosis-inducing capacity and even improve in vivo performance. Third, derivatives that disturb ROS balance and mitochondrial function repeatedly emerge as active compounds, suggesting that

oxidative-stress-related vulnerability may be one of the central exploitable mechanisms in GA-based anticancer design.

Conclusion. A comparative analysis of five original studies demonstrates that glycyrrhetinic acid derivatives constitute a diverse and pharmacologically promising class of anticancer candidates. The strongest in vitro cytotoxicity was observed for compound 42 from the 2016 Molecules study and for the cinnamic-acid hybrid derivatives 3o, 2d, and 3e from the 2019 Bioorganic Chemistry study. The 2020 Biological and Pharmaceutical Bulletin study highlighted apoptosis-inducing derivative 6g and showed that some GA derivatives can rival established anticancer drugs under in vitro conditions. The 2020 Bioorganic Chemistry study identified ring A–modified derivatives 5c and 5l as especially important because they combined strong antitumor activity with mechanistic and preclinical advantages, including in vivo efficacy. Finally, the 2023 Molecules study demonstrated that even moderately potent GA derivatives such as 3a can provide major mechanistic insight through ROS-associated mitochondrial apoptosis and cell-cycle disruption. Overall, future GA-derivative development should prioritize not potency alone but the combination of low-micromolar cytotoxicity, tumor selectivity, apoptosis-promoting capacity, and acceptable pharmacokinetic behavior.

Table 1. Comparative summary of five original studies on glycyrrhetinic acid derivatives

Study	Derivative strategy	Cell lines	Lead com-pound(s)	Key activity indicator(s)	Mechanistic notes	DOI
Li et al., 2016	Broad GA diversification	MCF-7, MDA-MB-231	42	1.88±0.20 μM (MCF-7); 1.37±0.18 μM (MDA-MB-231)	Potency-focused screen	10.3390/molecules 21020199
Wang et al., 2019	GA–cinnamic acid hybrids	HeLa, MCF-7, L-O2	3o, 2d, 3e	3o HeLa 1.35 μM; 2d HeLa 1.55 μM; 3e MCF-7 1.79 μM	Apoptosis/autophagy; selectivity	10.1016/j.bioorg. 2019.102951
Zheng et al., 2020	18-derivative GA library	MDA-MB-231, HeLa	6g	Several compounds comparable to gefitinib/doxorubicin	Apoptosis in MDA-MB-231	10.1248/bpb.b19-00615
Huang et al., 2020	Ring A electrophilic derivatives	HCT-116 and others	5c, 5l	Stronger than CDODA-Me	Apoptosis; PK and in vivo data	10.1016/j.bioorg.2020.104187
Chen et al., 2023	Esterified GA derivatives	SGC-7901, BEL-7402, A549, HeLa, B16, LO2	3a	HeLa 11.4±0.2 μM	ROS, caspases, S-phase arrest	10.3390/molecules28073164

References:

1. Li Y., Feng L., Song Z.-F., Li H.-B., Huai Q.-Y. Synthesis and Anticancer Activities of Glycyrrhetinic Acid Derivatives. Molecules. 2016;21(2):199. DOI: 10.3390/molecules21020199.

2. Wang R., Yang W., Fan Y., Dehaen W., Li Y., Li H., Wang W., Zheng Q., Huai Q. Design and synthesis of the novel oleanolic acid-cinnamic acid ester derivatives and glycyrrhetinic acid-cinnamic acid ester derivatives with cytotoxic properties. Bioorganic Chemistry. 2019;88:102951. DOI: 10.1016/j.bioorg.2019.102951.

3. Zheng Q.-X., Wang R., Xu Y., He C.-X., Zhao C.-Y., Wang Z.-F., Zhang R., Dehaen W., Li H.-J., Huai Q.-Y. Design, Preparation and Studies Regarding Cytotoxic Properties of Glycyrrhetinic Acid Derivatives. Biological and Pharmaceutical Bulletin. 2020;43(1):102–109. DOI: 10.1248/bpb.b19-00615.
4. Huang M., Gong P., Wang Y., Xie X., Ma Z., Xu Q., Liu D., Jing Y., Zhao L. 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.
5. Chen J., Xu Y., Yang Y., Yao X., Fu Y., Wang Y., Liu Y., Wang X. Evaluation of the Anticancer Activity and Mechanism Studies of Glycyhetic Acid Derivatives toward HeLa Cells. Molecules. 2023;28(7):3164. DOI: 10.3390/molecules28073164.