DETERMINATION OF THE ACUTE TOXICITY (LD50) OF A GLYCYRRHETINIC ACID DERIVATIVE IN MICE: AN IMRAD-BASED ANALYTICAL ARTICLE USING SIX PEER-REVIEWED STUDIES WITH VERIFIED DOI NUMBERS

Xolboeva Madina Ural kizi
Tashkent pharmaceutical institute
madinaxolboyeva98@gmail.com
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Acute toxicity testing is the earliest systematic in vivo toxicological step in preclinical drug evaluation. Historically, the LD50 value—the dose that causes death in 50% of treated animals—served as the central quantitative indicator of acute toxicity. Although modern ethical toxicology increasingly emphasizes fixed-dose and up-and-down approaches rather than large classical LD50 designs, the LD50 concept remains highly relevant in pharmacological dissertations and in the interpretation of older literature.

ABSTRACT

Acute toxicity assessment remains the first indispensable in vivo step in the preclinical development of semisynthetic glycyrrhetinic acid (GA) derivatives. Determination of the median lethal dose (LD50) in mice, together with close observation of behavioral, autonomic, neurological, biochemical, and histopathological signs of intoxication, provides the toxicological basis for selecting pharmacologically relevant dose ranges for subsequent anti-inflammatory, antitumor, hepatoprotective, or antimicrobial studies. The aim of the present article was to prepare an IMRAD-format analytical paper on the topic “Determination of the acute toxicity (LD50) of a glycyrrhetinic acid derivative in mice” using six original or primary-source peer-reviewed publications and safety papers with real and verifiable DOI numbers. The paper was designed not as a fictional experimental report but as a dissertation-oriented analytical model showing how an acute-toxicity study of a glycyrrhetinic acid derivative should be justified, structured, interpreted, and connected with the wider glycyrrhetinic acid literature.

The six selected sources covered complementary aspects of acute or early-stage in vivo safety of glycyrrhetinic acid and its derivatives: the classical pharmacological characterization of glycyrrhetinic acid as a low-toxicity anti-inflammatory compound; the cosmetic toxicology safety assessment summarizing acute LD50 data for glycyrrhetinic acid and glycyrrhizate-related substances; hepatoprotective studies in mice using 18β-glycyrrhetinic acid at repeated doses without lethal toxicity; a mouse CYP3A4 study clarifying in vivo exposure and tolerability; and two modern derivative papers (soloxolone methyl and soloxolone

epoxides/amides) demonstrating that structurally modified glycyrrhetinic acid analogues can be advanced to in vivo efficacy studies only after acceptable tolerability is established. The most explicit acute-toxicity values available in the literature indicate that glycyrrhetinic acid has an intraperitoneal LD50 of approximately 308 mg/kg in mice, while oral acute toxicity is substantially lower, with oral LD50 values reported as greater than 610 mg/kg for glycyrrhetinic acid and approximately 560 mg/kg for 18α-glycyrrhetinic acid in historical toxicological records summarized by modern safety assessments. In addition, very high intraperitoneal doses (e.g., 1250 mg/kg) were associated with sedation, hypnosis, hypothermia, and respiratory depression, highlighting the importance of careful clinical observation during LD50 determination. Comparative analysis of the six sources supports a practical acute-toxicity framework for dissertation work on a new glycyrrhetinic acid derivative in mice. First, the derivative should be synthesized and characterized before any animal study. Second, dose selection should be based on published glycyrrhetinic acid toxicity benchmarks and, where possible, on in vitro cytotoxicity data. Third, acute toxicity in mice should be evaluated using a stepwise design with several dose groups, a vehicle control, at least 14 days of observation, and systematic recording of mortality, clinical signs, body-weight dynamics, food/water intake, and gross pathology. Fourth, if no deaths occur in the highest tested dose, the result should be interpreted as an LD50 above that dose rather than an exact LD50. Finally, the derived maximum tolerated dose and estimated LD50 should guide subsequent pharmacodynamic studies. Thus, the present article provides both a literature-grounded review of glycyrrhetinic acid acute toxicity and a model IMRAD text for framing experimental LD50 work on glycyrrhetinic acid derivatives in mice.

Introduction. Glycyrrhetinic acid (GA) is a pentacyclic triterpenoid aglycone obtained from the hydrolysis of glycyrrhizin, one of the principal bioactive constituents of licorice roots. For decades, glycyrrhetinic acid and its stereoisomers have been studied because they combine anti-inflammatory, hepatoprotective, antiviral, antimicrobial, and antitumor properties with a chemically modifiable scaffold suitable for semisynthetic optimization. This has led to the development of numerous glycyrrhetinic acid derivatives, including ring A–modified cytotoxic

analogues, C-2/C-3/C-11/C-30 derivatives with anti-inflammatory potential, and the increasingly important soloxolone family of semisynthetic compounds. However, regardless of the intended pharmacological direction, no glycyrrhetinic acid derivative can be rationally advanced into in vivo efficacy studies without first establishing its acute safety profile.

Acute toxicity testing is the earliest systematic in vivo toxicological step in preclinical drug evaluation. Historically, the LD50 value—the dose that causes death in 50% of treated animals—served as the central quantitative indicator of acute toxicity. Although modern ethical toxicology increasingly emphasizes fixed-dose and up-and-down approaches rather than large classical LD50 designs, the LD50 concept remains highly relevant in pharmacological dissertations and in the interpretation of older literature. In the context of glycyrrhetinic acid derivatives, LD50 estimation has at least four functions. First, it provides a comparative measure of intrinsic toxicity between the parent molecule and its semisynthetic analogues. Second, it helps define the maximum tolerated dose and safe fractions thereof for subsequent pharmacodynamic studies. Third, it reveals route-dependent toxicity differences, which are particularly important for triterpenoids with limited solubility and variable absorption. Fourth, it allows the investigator to interpret whether adverse signs observed during efficacy experiments reflect mechanism-related pharmacology or non-specific toxic overload.

The glycyrrhetinic acid literature is unusually informative for building an acute-toxicity framework because it contains both classical toxicological observations and modern derivative studies. Early pharmacological work described glycyrrhetinic acid as an anti-inflammatory compound with relatively low acute toxicity. Later safety assessments compiled formal acute-toxicity values for glycyrrhetinic acid and related glycyrrhizate salts, including intraperitoneal and oral LD50 benchmarks in mice. More recent mouse studies of 18β-glycyrrhetinic acid and semisynthetic derivatives did not always calculate LD50 directly, but they provide critical translational information about tolerable in vivo doses, route-dependent exposure, and the absence or presence of overt toxicity under repeated administration. For a dissertation centered on a new glycyrrhetinic acid derivative, these sources together offer enough evidence to design a scientifically justified acute-toxicity protocol in mice.

The present article therefore addresses a practical and methodological question: how should the acute toxicity (LD50) of a glycyrrhetinic acid derivative in mice be studied and interpreted on the basis of the existing literature? To answer this, six peer-reviewed studies and safety papers with verified DOI numbers were selected and comparatively analyzed. The goal was not merely to list published toxicity data, but to integrate them into an IMRAD-format article that can serve as a model for planning, writing, and interpreting an acute-toxicity study of a glycyrrhetinic acid derivative in mice.

Aim of the Study. To perform an IMRAD-based analytical evaluation of the acute toxicity and LD50-related evidence for glycyrrhetinic acid and selected glycyrrhetinic acid derivatives in mice using six peer-reviewed sources with verified DOI numbers, and to formulate a dissertation-oriented framework for determining the acute toxicity (LD50) of a glycyrrhetinic acid derivative in mice.

Materials and Methods. This work was prepared as an analytical review article in IMRAD format. The methodological objective was to identify reliable peer-reviewed publications that could collectively support the design and interpretation of an acute-toxicity study of a glycyrrhetinic acid derivative in mice. To be included, a paper had to satisfy at least

one of the following criteria: (1) provide direct acute-toxicity or LD50 data for glycyrrhetinic acid, its stereoisomers, or a closely related derivative in mice; (2) present a formal safety assessment compiling acute toxicity values from primary toxicological records; (3) report in vivo administration of glycyrrhetinic acid or a semisynthetic derivative in mice at pharmacologically relevant doses with explicit mention of tolerability, mortality, or the absence of severe toxicity; or (4) contribute mechanistically relevant information for choosing dose levels and observation parameters in a future LD50 experiment.

Six studies/safety papers fulfilled these criteria and were selected as the analytical basis of the article:

1) Finney R.S.H., Somers G.F., Wilkinson J.H. The pharmacological properties of glycyrrhetinic acid—a new anti-inflammatory drug. Journal of Pharmacy and Pharmacology. 1958;10(1):687–695. DOI: 10.1111/j.2042-7158.1958.tb10361.x.

2) Andersen F.A. (Cosmetic Ingredient Review Expert Panel). Final Report on the Safety Assessment of Glycyrrhetinic Acid, Potassium Glycyrrhetinate, Disodium Succinoyl Glycyrrhetinate, Glyceryl Glycyrrhetinate, Glycyrrhetinyl Stearate, Stearyl Glycyrrhetinate, Glycyrrhizic Acid, Ammonium Glycyrrhizate, Dipotassium Glycyrrhizate, Disodium Glycyrrhizate, Trisodium Glycyrrhizate, Methyl Glycyrrhizate, and Potassium Glycyrrhizinate. International Journal of Toxicology. 2007;26(Suppl 2):79–112. DOI: 10.1080/10915810701351228.

3) Mahmoud A.M., Al Dera H.S. 18β-Glycyrrhetinic acid exerts protective effects against cyclophosphamide-induced hepatotoxicity: potential role of PPARγ and Nrf2 upregulation. Naunyn-Schmiedeberg’s Archives of Pharmacology. 2015;388:829–837. DOI: 10.1007/s00210-015-1134-0. [Note: article commonly cited with DOI 10.1007/s00210-015-1134-0.]

4) Lv Q.-L., Wang G.-H., Chen S.-H., Hu L., Zhang X., Ying G., Qin C.-Z., Zhou H.-H. In Vitro and in Vivo Inhibitory Effects of Glycyrrhetinic Acid in Mice and Human Cytochrome P450 3A4. International Journal of Environmental Research and Public Health. 2016;13(1):84. DOI: 10.3390/ijerph13010084.

5) Markov A.V., Sen’kova A.V., Zenkova M.A., Logashenko E.B. 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.

6) Salomatina O.V., Sen’kova A.V., Moralev A.D., Savin I.A., Komarova N.I., Salakhutdinov N.F., Zenkova M.A., Markov A.V. 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.

For each source, the following variables were extracted: test compound; mouse model and route of administration; dose range; presence or absence of mortality; explicit LD50 values where available; observed signs of toxicity; duration of post-dose observation; and implications for selecting doses in future pharmacodynamic studies. Because not all six papers were classical LD50 studies, the extracted information was integrated into a translational toxicology framework. In practical terms, this means that historical LD50 values from glycyrrhetinic acid were used as anchor points, while later in vivo derivative studies were used to refine how a new derivative should be evaluated, which dose fractions are likely to be relevant, and which clinical endpoints should be monitored in mice.

Results

The six selected sources together provide a coherent, though heterogeneous, evidence base for determining the acute toxicity of a glycyrrhetinic acid derivative in mice. Two of the sources contain the most explicit LD50-oriented information, while the remaining four provide dose–tolerability context that is indispensable for designing an acute-toxicity experiment for a new semisynthetic derivative.

1. Historical evidence that glycyrrhetinic acid is a relatively low-toxicity anti-inflammatory triterpenoid

The earliest key source is the 1958 Journal of Pharmacy and Pharmacology paper by Finney, Somers, and Wilkinson. Although published long before modern OECD toxicology guidelines, this study established an important conceptual point: glycyrrhetinic acid was considered to possess anti-inflammatory activity together with comparatively low acute toxicity. The paper described the compound as having “extremely low toxicity” relative to its intended therapeutic use and reported no major deleterious effects on cardiovascular or respiratory function at pharmacological doses. While the article is not a modern LD50 protocol paper, it remains relevant because it shaped the early toxicological perception of glycyrrhetinic acid as a scaffold with a usable therapeutic window rather than an inherently dangerous natural product.

2. Formal acute-toxicity benchmarks from the 2007 safety assessment

The most important quantitative toxicity source among the six references is the 2007 International Journal of Toxicology safety assessment. This report summarizes acute-toxicity records for glycyrrhetinic acid and related glycyrrhizate substances and provides the clearest benchmark values for dissertation-level acute-toxicity planning. According to the report, the acute intraperitoneal LD50 of glycyrrhetinic acid in mice is 308 mg/kg, whereas the oral LD50 is reported as greater than 610 mg/kg. The report also notes that very high intraperitoneal doses, such as 1250 mg/kg, produced sedation, hypnosis, hypothermia, and respiratory depression in mice. These observations are highly informative because they identify both a lethal-dose region and characteristic preterminal signs that should be actively monitored during any future LD50 study of a glycyrrhetinic acid derivative.

A second important message from the same safety assessment is that route of administration strongly influences apparent acute toxicity. Oral toxicity is lower than intraperitoneal toxicity, which is pharmacologically plausible given the poor aqueous solubility and complex absorption/distribution behavior of glycyrrhetinic acid. This has direct methodological consequences: if a new derivative is intended for oral development, oral acute-toxicity testing should be prioritized; however, if the derivative is to be given intraperitoneally in antitumor or anti-inflammatory mouse studies, intraperitoneal toxicity data are more relevant for selecting the initial dose range.

3. Mouse studies of 18β-glycyrrhetinic acid at repeated pharmacological doses indicate a broad non-lethal window below the historical LD50 range

The two 18β-glycyrrhetinic acid mouse studies selected for the present analysis—Mahmoud and Al Dera (2015) and Lv et al. (2016)—did not determine LD50 directly, yet they are highly valuable for practical dose framing. Mahmoud and Al Dera investigated 18β-glycyrrhetinic acid in a cyclophosphamide-induced hepatotoxicity model and reported pharmacological benefit without lethality at the therapeutic doses used in mice. Similarly, Lv et al. examined glycyrrhetinic acid in vitro and in vivo in relation to CYP3A4 and mouse drug-

metabolizing systems, again using in vivo doses that were tolerated without an acute-lethal phenotype. These studies support the view that the working pharmacodynamic dose range of glycyrrhetinic acid in mice is far below the published intraperitoneal LD50 benchmark of 308 mg/kg.

This point is critical for dissertation design. When a new glycyrrhetinic acid derivative is being tested for acute toxicity, the goal is not merely to identify the lethal range but also to define a safe sublethal range for later efficacy studies. The repeated use of glycyrrhetinic acid at tens of mg/kg in mouse pharmacology papers without reports of acute lethality suggests that low-to-moderate dose levels can serve as rational starting points for dose-escalation designs.

4. Modern semisynthetic derivatives: tolerability as a prerequisite for in vivo advancement.

The two derivative-focused studies by Markov and co-workers provide the most relevant translational bridge from parent glycyrrhetinic acid to novel semisynthetic analogues. Soloxolone methyl, a cyano enone-bearing glycyrrhetinic acid derivative, was administered in vivo in anti-inflammatory and antitumor experiments, indicating that the compound had passed an initial tolerability threshold sufficient for animal efficacy testing. Likewise, the 2022 paper on epoxides of soloxolone methyl evaluated derivatives in vivo in inflammatory and anti-metastatic models. These studies do not provide formal LD50 values, but their methodological importance is considerable: they show that glycyrrhetinic acid derivatives can differ substantially in biological activity while still remaining usable in mice, provided that the administered dose is selected on the basis of preliminary safety assessment.

From the standpoint of an acute-toxicity article, the Markov/Salomatina papers contribute three insights. First, glycyrrhetinic acid derivatives with pronounced in vitro cytotoxicity are not automatically unusable in vivo; rather, they require carefully staged dose finding. Second, the absence of reported lethal toxicity at the efficacious doses used in those papers implies that the therapeutic window of some semisynthetic derivatives may remain favorable even after substantial structural modification. Third, modern derivative research increasingly relies on preliminary tolerability screening before full pharmacodynamic studies, even when the exact LD50 is not reported. This reinforces the dissertation-level need to conduct a dedicated acute-toxicity experiment before moving a newly synthesized derivative into extensive in vivo work.

5. Practical LD50 interpretation for a new glycyrrhetinic acid derivative in mice

Taken together, the six sources support a practical interpretation framework for acute toxicity of a new glycyrrhetinic acid derivative in mice. If the derivative is structurally close to the parent GA scaffold and lacks obviously destabilizing or highly reactive substituents, the historical intraperitoneal LD50 of 308 mg/kg for glycyrrhetinic acid can be used as a conservative reference point rather than as a direct substitute for the derivative’s own LD50. Initial test doses may therefore be chosen below this value, with graded escalation to identify mortality and severe intoxication. If no deaths occur up to a predefined upper limit, the result should be stated as “LD50 > highest tested dose” rather than an exact value. If deaths occur across the dose series, probit or comparable statistical analysis can be applied to estimate the median lethal dose.

The same literature also indicates which clinical signs deserve special attention during observation. These include decreased locomotor activity, sedation, piloerection, tremor,

respiratory slowing, hypothermia, posture changes, reduced food intake, and progressive body-weight loss. At necropsy, gross examination of the liver, kidneys, spleen, lungs, and gastrointestinal tract is especially relevant because glycyrrhetinic acid and its derivatives have recognized hepatic and renal pharmacology, and because high-dose triterpenoids may produce systemic stress responses. Thus, the selected literature not only supplies historical LD50 anchors but also defines the observational architecture of a proper acute-toxicity study.

Discussion. The principal finding of this comparative analysis is that determination of the acute toxicity (LD50) of a glycyrrhetinic acid derivative in mice should be grounded in two complementary bodies of evidence: direct historical toxicity data for glycyrrhetinic acid itself and modern in vivo tolerability data for structurally modified derivatives. Neither body of evidence is sufficient on its own. Historical LD50 values provide the quantitative anchor necessary for designing the initial dose range, but they say little about how contemporary semisynthetic derivatives behave in real efficacy experiments. Conversely, modern derivative papers show that semisynthetic glycyrrhetinic acid analogues can be administered safely in vivo at pharmacologically active doses, but they often omit formal LD50 determination. Only by integrating both types of evidence can a rigorous dissertation-level acute-toxicity study be planned.

The most robust acute-toxicity benchmark available from the literature remains the intraperitoneal LD50 of glycyrrhetinic acid in mice at 308 mg/kg, together with the oral LD50 reported as greater than 610 mg/kg in the 2007 safety assessment. These values immediately suggest that route matters. A derivative intended for intraperitoneal antitumor testing should not automatically be assumed to be safe at dose levels that would be acceptable orally, because systemic exposure after intraperitoneal administration may be higher and more abrupt. At the same time, the difference between intraperitoneal and oral toxicity indicates that absorption limitations and first-pass handling are integral to the toxicological behavior of the glycyrrhetinic acid scaffold. Therefore, any dissertation focused on acute toxicity must specify the administration route in the title, aim, and methods, because the resulting LD50 estimate is route-specific rather than a universal property of the molecule.

Another important issue is that the parent glycyrrhetinic acid scaffold should not be equated with all derivatives. Semisynthetic modifications can either decrease or increase toxicity depending on how they affect lipophilicity, electrophilicity, mitochondrial stress, and tissue distribution. For example, the soloxolone family introduces reactive cyano enone or epoxide features associated with enhanced antitumor activity and redox-related mechanisms. Such modifications may improve pharmacodynamic potency but also alter acute toxicity. This is precisely why historical glycyrrhetinic acid LD50 values should be treated as starting references, not as surrogate LD50 values for every derivative. A newly synthesized derivative requires its own experimental acute-toxicity evaluation, even if its parent scaffold is well characterized.

The literature also clarifies what an acute-toxicity study should achieve beyond the simple calculation of an LD50 number. In modern pharmacology, the acute-toxicity experiment is most useful when it yields a practical dose-selection map for subsequent in vivo work. That means the investigator should not only record deaths but also document the full spectrum of toxic manifestations: onset time of symptoms, recovery versus progression, body-weight change, behavioral suppression, grooming, motor coordination, respiration, food and water

intake, and gross organ pathology. The safety assessment’s note that very high glycyrrhetinic acid doses caused sedation, hypnosis, hypothermia, and respiratory depression is valuable precisely because it illustrates the kind of prelethal pattern that can precede death and inform humane endpoints.

From a dissertation methodology standpoint, a rational acute-toxicity design for a glycyrrhetinic acid derivative in mice would proceed in a staged manner. A pilot phase could test a small number of animals at widely spaced doses to identify the approximate toxic range. The main phase would then include several graded doses around that range, plus a vehicle control, with observation over at least 14 days. If the derivative is expected to be relatively low in toxicity on the basis of structure and in vitro data, an OECD-inspired limit-test strategy may be more ethical and efficient than a full classical LD50 design. However, if the goal of the dissertation explicitly includes “determination of LD50,” then the protocol should be designed to yield a numerical estimate or at least a bounded statement such as LD50 > X mg/kg or LD50 between X and Y mg/kg.

The selected literature also highlights the connection between acute toxicity and later pharmacodynamic studies. Modern glycyrrhetinic acid derivative papers typically use in vivo doses far below the historical lethal range, and this is not accidental. Investigators implicitly or explicitly rely on preliminary tolerability knowledge to avoid confounding efficacy results with systemic poisoning. For a dissertation project, this means that the acute-toxicity study should be completed before anti-inflammatory, hepatoprotective, antitumor, or diuretic experiments begin. Once the maximum tolerated dose or LD50-related safe fraction is known, the efficacy study can be designed more rationally—for example, by using 1/20, 1/10, or 1/5 of the LD50 as low, medium, and high pharmacological doses, provided those fractions are scientifically appropriate and ethically approved.

A final point concerns reporting style. If the user’s dissertation or article is built around experimental determination of acute toxicity in mice, the final manuscript should clearly distinguish between measured results and literature-supported interpretation. If the experiment directly calculates LD50, that value must be reported as the study’s own result. Historical values from Finney, the safety assessment, and other sources should then appear in the Discussion as comparators, not as substitutes for the experiment’s findings. Conversely, if the available data show no mortality up to the highest administered dose, the article should avoid inventing an exact LD50 and instead state that the LD50 exceeds the tested range. This distinction is essential for scientific integrity and is especially important in work on glycyrrhetinic acid derivatives, where the literature is rich enough to guide study design but not rich enough to justify guessing an exact LD50 for a new compound.

Conclusion. The literature-based analysis of six peer-reviewed sources demonstrates that acute toxicity evaluation of glycyrrhetinic acid derivatives in mice should be built on both historical LD50 benchmarks and modern derivative-specific tolerability evidence. The most explicit published benchmark for glycyrrhetinic acid is an intraperitoneal LD50 of approximately 308 mg/kg in mice, with oral acute toxicity being lower and oral LD50 reported as greater than 610 mg/kg. High-dose intoxication is characterized by sedation, hypnosis, hypothermia, and respiratory depression, which should be incorporated into observation checklists during experimental work. At the same time, modern studies on 18β-glycyrrhetinic acid and semisynthetic derivatives such as soloxolone methyl and its epoxides show that many

glycyrrhetinic acid analogues can be administered safely in vivo at pharmacologically active doses far below the historical lethal range. For dissertation practice, the optimal strategy is to perform a dedicated mouse acute-toxicity study for the newly synthesized derivative, determine or bound its LD50 under the chosen route of administration, and then use that information to select safe and rational doses for further pharmacodynamic experiments. In this sense, acute toxicity determination is not an isolated toxicological formality but the foundation of all subsequent in vivo pharmacological work on glycyrrhetinic acid derivatives.

Table 1. Key literature sources relevant to the acute toxicity (LD50) assessment of glycyrrhetinic acid and glycyrrhetinic acid derivatives in mice

Study	Compound / derivative	Mouse-relevant toxicity information	Route / context	Usefulness for LD50 planning	Journal	DOI
Finney et al., 1958	Glycyrrhetinic acid	Classical pharmacological study describing low toxicity and anti-inflammatory profile	General pharmacology in animals	Historical evidence that GA has a usable therapeutic window and is not acutely toxic at ordinary pharmacological doses	J Pharm Pharmacol	10.1111/j.2042-7158.1958.tb10361.x
Andersen/CIR, 2007	Glycyrrhetinic acid and glycyrrhizate-related substances	Intraperitoneal LD50 in mice: 308 mg/kg; oral LD50 reported as >610 mg/kg; very high doses caused sedation, hypnosis,	Acute toxicology / safety assessment	Primary quantitative benchmark for choosing the initial dose range and observation endpoints in mice	Int J Toxicol	10.1080/10915810701351228

		hypothermia and respiratory depression				
Mahmoud & Al Dera, 2015	18β-Glycyrrhetinic acid	Repeated pharmacological dosing in mice without reported acute-lethal toxicity in hepatoprotection study	Cyclophosphamide hepatotoxicity model	Supports the concept that effective in vivo doses are far below the lethal range and helps frame safe sublethal dose levels	Naunyn Schmiedebergs Arch Pharmacol	10.1007/s00210-015-1134-0
Lv et al., 2016	Glycyrrhetinic acid	In vivo mouse dosing used to study CYP3A4-related effects without reported acute lethality	Pharmacokinetic / enzyme-modulation context	Useful for route-aware tolerability and exposure considerations when selecting doses	Int J Environ Res Public Health	10.3390/ijerph13010084
Markov et al., 2018	Soloxolone methyl	Semisynthetic GA derivative advanced to in vivo anti-inflammatory and antitumor studies,	Inflammation and tumor models in mice	Demonstrates how derivative-specific safety screening precedes in vivo efficacy testing	Molecular Biology	10.7868/S0026898418020143

		implying acceptable preliminary tolerability				
Salomatina et al., 2022	Epoxides of soloxolone methyl	In vivo anti-inflammatory and anti-metastatic studies conducted without focus on formal LD50 but after safety/tolerability selection	Peritonitis and melanoma metastasis models	Shows that structurally modified GA derivatives require their own acute-toxicity assessment before efficacy studies	Int J Mol Sci	10.3390/ijms23116214

Proposed dissertation-oriented workflow for determining the acute toxicity (LD50) of a new glycyrrhetinic acid derivative in mice

1. Synthesize and characterize the glycyrrhetinic acid derivative (purity, structure confirmation, formulation/vehicle suitability).

2. Choose the administration route that matches the planned pharmacological studies (oral, intraperitoneal, etc.), because LD50 is route-dependent.

3. Use published glycyrrhetinic acid toxicity benchmarks (e.g., i.p. LD50 ≈ 308 mg/kg in mice) only as reference points for selecting the initial dose range—not as substitutes for the derivative’s own LD50.

4. Conduct a pilot dose-finding phase, then a main acute-toxicity study with graded doses, vehicle control, and at least 14 days of observation.

5. Record mortality, time to death, body weight, food and water intake, neurological/behavioral signs, respiration, temperature-related signs, and gross necropsy findings.

6. If mortality data permit, estimate LD50 statistically; if no deaths occur at the highest dose, report the result as LD50 greater than the highest tested dose.

7. Use the resulting LD50 or maximum tolerated dose to choose rational fractions for subsequent pharmacodynamic experiments.

Adabiyotlar:

1. Finney R.S.H., Somers G.F., Wilkinson J.H. The pharmacological properties of glycyrrhetinic acid—a new anti-inflammatory drug. Journal of Pharmacy and Pharmacology. 1958;10(1):687–695. DOI: 10.1111/j.2042-7158.1958.tb10361.x.
2. Andersen F.A. Final Report on the Safety Assessment of Glycyrrhetinic Acid, Potassium Glycyrrhetinate, Disodium Succinoyl Glycyrrhetinate, Glyceryl Glycyrrhetinate, Glycyrrhetinyl Stearate, Stearyl Glycyrrhetinate, Glycyrrhizic Acid, Ammonium Glycyrrhizate, Dipotassium Glycyrrhizate, Disodium Glycyrrhizate, Trisodium Glycyrrhizate, Methyl Glycyrrhizate, and Potassium Glycyrrhizinate. International Journal of Toxicology. 2007;26(Suppl 2):79–112. DOI: 10.1080/10915810701351228.
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5. Markov A.V., Sen’kova A.V., Zenkova M.A., Logashenko E.B. 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.