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DETERMINATION OF *IN-VITRO* METABOLIC STABILITY OF OLEANOLIC ACID DERIVED FROM *LANTANA CAMARA* ROOTS USING MOUSE, RAT, AND MONKEY LIVER MICROSOMES

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Keywords:

Drug metabolism, Metabolic stability, Cytochrome P450, ADME, Oleanolic acid

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ABSTRACT: The objective of the present study was to assess the *in-vitro* metabolic stability of oleanolic acid isolated from *Lantana camara* roots using liver microsomes from mouse, rat, and monkey, and to investigate interspecies differences in metabolic behaviour. Oleanolic acid was incubated with pooled liver microsomes in the presence of NADPH at 37 °C, and the depletion of the parent compound over time was quantified using an automated LC–MS/MS platform. Metabolic half-life (t½) and intrinsic clearance (CLint) were calculated based on the rate of disappearance of oleanolic acid during incubation. The results demonstrated clear species-dependent differences in metabolic stability. Oleanolic acid showed the longest half-life and lowest intrinsic clearance in monkey liver microsomes, indicating higher metabolic stability, followed by moderate stability in rat microsomes. In contrast, mouse liver microsomes exhibited a shorter half-life and higher intrinsic clearance, suggesting faster metabolic turnover. These findings reflect significant interspecies variability in microsomal metabolism of oleanolic acid. In conclusion, oleanolic acid exhibited moderate to good *in-vitro* metabolic stability, particularly in higher species, supporting its potential for further pharmacokinetic evaluation.

INTRODUCTION: The drug development process involves multiple sequential stages, progressing from target identification to hit discovery, hit-to-lead selection, lead optimization, and candidate identification, followed by product development. This process is supported by the systematic conduct of preclinical and clinical studies, including comprehensive toxicity and safety evaluations of new chemical entities (NCEs).

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Among the early discovery assessments, metabolic stability evaluation is a critical component, as it provides essential insights into the pharmacokinetic behaviour, safety profile, and overall viability of NCEs.

Early evaluation of drug metabolism helps to identify compounds with unfavourable clearance, potential drug–drug interactions, and species-specific metabolic liabilities, thereby reducing late-stage attrition during drug development. Drug metabolism is primarily mediated by hepatic enzymes and is broadly classified into Phase I and Phase II reactions. Among these, the cytochrome P450 (CYP) enzyme super family plays a dominant role in Phase I metabolism and is responsible for

the biotransformation of a large proportion of clinically used drugs. Consequently, assessment of CYP-mediated metabolism is an important step in understanding the metabolic fate of candidate molecules. Liver microsomes are widely used *in-vitro* systems for evaluating metabolic stability, as they are enriched with key drug-metabolizing enzymes, including CYPs, flavin monooxygenases, carboxylesterases, and epoxide hydrolases. Microsomal assays offer a rapid, reproducible, and cost-effective approach for estimating metabolic half-life and intrinsic clearance, enabling early comparison of metabolic behaviour across species.

Oleanolic acid, a naturally occurring triterpenoid isolated from *Lantana camara*, has attracted considerable interest due to its reported pharmacological activities. However, limited information is available regarding its metabolic stability and interspecies metabolic differences. Therefore, the present study was undertaken to evaluate the *in-vitro* metabolic stability of oleanolic acid using liver microsomes from mouse, rat, and monkey. These species were selected to represent commonly used preclinical models and a higher species with closer metabolic relevance to humans, thereby providing translational insight to support further pharmacokinetic and preclinical development.

MATERIAL INSTRUMENT AND METHOD: Oleanolic acid was isolated from *Lantana camara* roots. Liver microsomes from mouse, rat, and monkey were procured commercially and stored at –80 °C. NADPH and standard reagents were used for metabolic assays. All solvents were of HPLC or analytical grade.

Microsomal Incubation: Metabolic stability of oleanolic acid was evaluated using liver microsomes as the *in-vitro* test system. Microsomes were incubated with oleanolic acid at 37 °C in the presence of NADPH to initiate metabolism. Samples were collected at predetermined time points, and reactions were terminated by protein precipitation using ice-cold organic solvent, followed by centrifugation to remove precipitated proteins.

Sample Analysis: The remaining oleanolic acid was quantified using LC–MS/MS under standard chromatographic and mass spectrometric conditions. Peak areas were used to calculate the concentration of the parent compound at each time point.

Data Analysis: Metabolic half-life (t½) was determined from the decline in parent compound concentration over time. Intrinsic clearance (CLint) was calculated based on microsomal protein concentration and incubation parameters. Experiments were performed in triplicate, and results are expressed as mean ± standard deviation.

Rationale: Liver microsomes are enriched with drug-metabolizing enzymes, primarily cytochrome P450s, and provide a rapid, reproducible model for assessing species-specific metabolic differences. Mouse, rat, and monkey microsomes were selected to represent commonly used preclinical species and a higher species with closer metabolic relevance to humans.

Description of the Test Procedure:

Preparation of Solutions:

Oleanolic Acid Stock Solution: A 40 µM stock solution of oleanolic acid was prepared in methanol and further diluted to achieve the desired working concentration.

Microsomal Working Solution: Liver microsomes (mouse, rat, and monkey) were diluted in 50 mM potassium phosphate buffer (pH 7.4) to obtain a working concentration of 0.4 mg/mL.

NADPH Solution: A 5 mM NADPH solution was prepared in 50 mM phosphate buffer for initiating metabolic reactions.

Positive Control Stock: Testosterone was used as a positive control for microsomal metabolism at a stock concentration of 10 mM, providing a final concentration of 1 µM in all species.

Internal Standard / Stop Solution: Carbamazepine was prepared as a 100 ng/mL stock in methanol and used as an internal standard to terminate the reaction and monitor analytical performance.

50 mM Potassium Phosphate Buffer (pH 7.4): Prepared by mixing appropriate ratios of 1 M KH_2PO_4 and 1 M K_2HPO_4 solutions and adjusting

the pH to 7.4. The buffer was diluted with deionized water to achieve the final working concentration.

Experimental Procedure: Dispensed 150 µL oleanolic acid stock solution (40 µM) and 330 µL of respective species (Rat, Mouse and Monkey) microsomal working solution into tubes. Pre-incubated at 37°C for 10 min. Aliquoted 80 µL of the reaction mixture into respective tubes labelled for specific time points. Final DMSO concentration ≤ 1% were made.

Reaction was initiated by the addition of 20 µL NADPH working solutions. (final concentration: 1 mM) and incubated at 37°C.Sampling was done at specific time points (0, 1, 5, 30, 60 and 120 min) and immediately added quenching solution by adding a150 µL of stop solution at respective time points (0,1 ,5, 30, 60 and 120 min). Removal of the precipitated protein was done by centrifugation at 14000 rpm for 5 min. Supernatant was collected and transferred to vials for LCMS/MS analysis [13, 14, 15, 16].

Bioanalytical Methodology: The bioanalytical method selected for this study is designed to be fit-for-purpose, ensuring that it is scientifically sound and appropriate for the intended application.

The primary objective of this study is exploration in nature, focusing on trend analysis and hypothesis generation rather than supporting pivotal regulatory submissions. Therefore, a fully validated method, as required for confirmatory studies, is not necessary at this stage.

The chosen method has been evaluated to demonstrate adequate quantitative estimation of oleanolic acid with positive control testosterone within the context of its intended use. These performance characteristics are sufficient to ensure reliable data for decision-making in early-phase development.

This approach aligns with current regulatory guidance and industry best practices, which allow for fit-for-purpose methodologies in exploratory or non-critical studies, provided that the method is scientifically justified and documented. This strategy, we optimize for resource utilization while maintaining data integrity and scientific rigor.

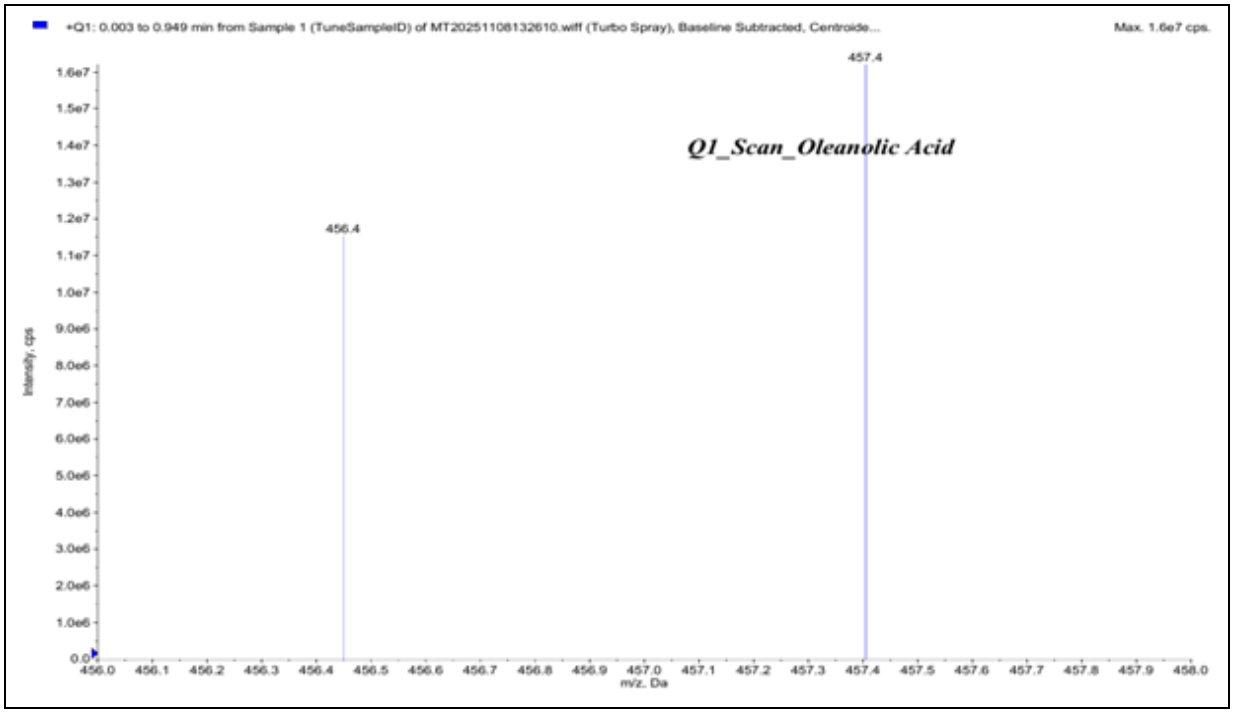


FIG. 1: USING Q1 MASS SCAN, PARENT ION SCANNING WAS PERFORMED IN POSITIVE POLARITY WITH ESI MODE OF IONISATION

Mass Spectrometric Screening of Oleanolic Acid Fig. 1: Fig. 1 shows a Q1 scan (single quadrupole scan) of oleanolic acid obtained using a mass spectrometer with Turbo Spray ionization, the

horizontal axis represents the mass-to-charge ratio (m/z) in Daltons and The vertical axis represents signal intensity in counts per second (cps) [10].

A Q1 scan was performed using electrospray ionization in positive mode to confirm the presence of oleanolic acid. The spectrum exhibited a dominant peak at m/z 457.4, corresponding to the protonated molecular ion $[M+H]^+$ of oleanolic acid (theoretical MW ≈ 456.7 Da). A minor peak at m/z 456.4 was observed, likely attributable to isotopic contribution or adduct formation.

The high signal intensity (≈1.6 × 10^7 cps) and absence of significant interfering peaks indicate good selectivity and confirm compound identity. This scan supports the suitability of the method**.** Oleanolic acid mass spectral tunning was performed with 100 ng/mL solution [10].

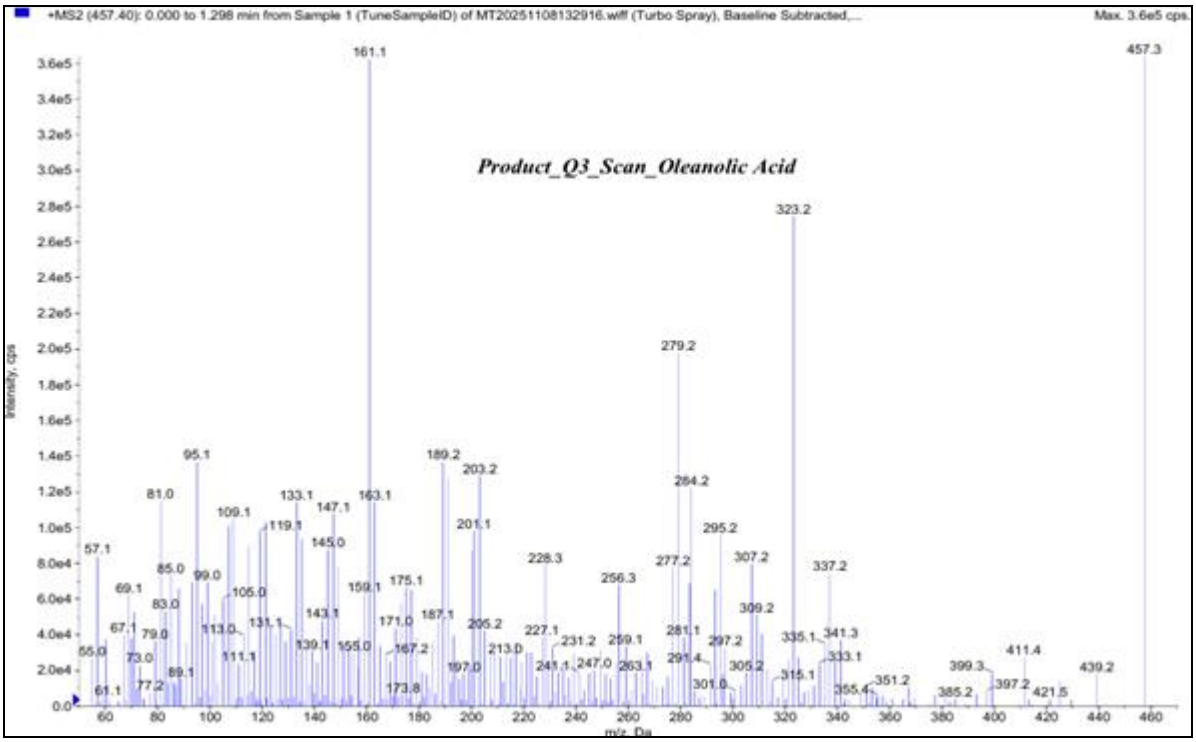


FIG. 2: THIS IS AN MS/MS SPECTRUM WHERE THE PRECURSOR ION SELECTED WAS M/Z 457.4 ($[M+H]^+$ OF OLEANOLIC ACID). THE SCAN SHOWS THE FRAGMENTATION PATTERN OF OLEANOLIC ACID AFTER COLLISION-INDUCED DISSOCIATION (CID), THE HORIZONTAL AXIS REPRESENTS THE MASS-TO-CHARGE RATIO OF FRAGMENT IONS [10]

Product Ion Scan of Oleanolic Acid Fig. 2: A product ion scan was performed on the precursor ion at m/z 457.4 ($[M+H]^+$) using collision-induced dissociation in positive mode. The fragmentation spectrum revealed a dominant base peak at m/z 161.1, along with other characteristic fragments at 95.1, 109.1, 133.1, 145.0, 163.1, 189.2, 203.2, 279.2, 323.2, and 337.2 Da.

These ions represent sequential cleavages of the triterpenoid backbone and functional groups, confirming the structural identity of oleanolic acid. The fragmentation profile provides essential transitions for targeted MS/MS analysis and supports method development for qualitative and quantitative application.

Optimisation of Mass Parameters: Once the scanning parts were optimised [19], various compound specific parameters like CE (collision energy), CXP (Collision exit potential), EP (Entrance potential) and DP (Declustering potential) were ramp during tunning and best prominent and stable values were selected for oleanolic acid [20].

Also, Ion source related parameters like curtain gas, CAD (Collision associated dissociation), Ion source temperature and GS1 and GS2 were optimized for prominent and stable response **Table 1** [10].

TABLE 1: LCMSMS PARAMETER OF OLEANOLIC ACID AND CARBAMAZEPINE (IS)

MRM	457.3/161.1 for OA	CAD	Medium
	237.5/192.9 for CBZ	Ions source Temp	550 ˚C
Ion Source	ESI Turbo spray	IS Volt	5500
Polarity	Positive	GS1	60
Curtain gas	35	GS2	60
CE	40 for OA	CXP	20
	45 for CBZ	EP	10
Dwell Time	50 mcs	DP	100

Chromatographic Conditions:

TABLE 2: CHROMATOGRAPHIC CONDITIONS USING SCIEX QTRAP-5500 LC-MS/MS SYSTEM

Instrument	:	SCIEX QTRAP-5500 LC-MS/MS System		
Column	:	Synergi F5 Fusion 50 x 2 mm 4µ		
Mobile Phase	:	MP A-0.1% Formic acid in water		
		MP-B-0.1% Formic acid in Acetonitrile		
Mobile Phase composition		Time (min)	% A (Buffer)	% B (Organic)
		0.00	95	05
		0.50	95	05
		1.50	10	95
		2.20	10	95
		2.21	95	5
		2.50	95	5
Flow rate	:	0.400 mL/min		
Column oven	:	40°C		
Injection volume	:	1.0 µL		
Run time	:	2.5 min		
Auto sampler Temperature	:	10°C		

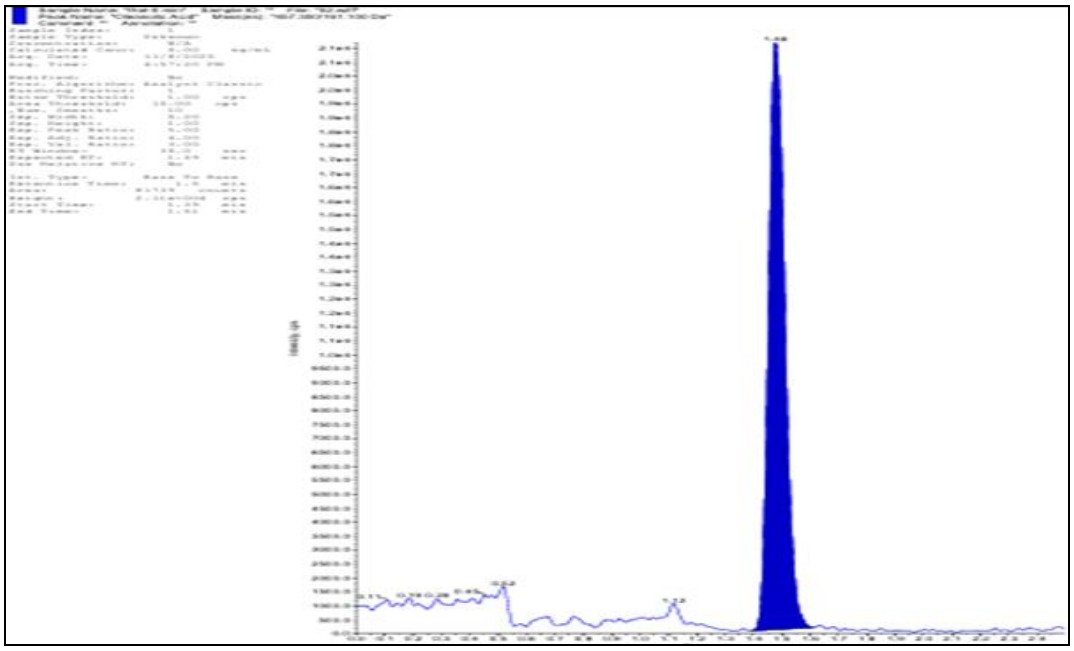


FIG. 3: CHROMATOGRAM OF OLEANOLIC ACID

Chromatographic Analysis of Oleanolic Acid: The LC-MS/MS chromatogram of oleanolic acid displayed a single, sharp peak at 1.49 min, with a maximum intensity of approximately 2.74×10^6 cps. The peak symmetry and stable baseline indicate efficient separation, minimal matrix interference, and high sensitivity. These results confirm the successful detection and retention behavior of oleanolic acid under the applied chromatographic conditions, supporting the robustness of the analytical method [10].

Preparation of Mobile Phase -A (0.1% Formic Acid in Water, v/v): Prepared 0.1% formic acid water solution by mixing appropriate amounts of formic acid in Milli-Q water using micropipette and further mixed well and sonicated to degas [10, 18].

Preparation for a Rinsing Solution: Prepared rinsing solution by mixing appropriate equal volume of Methanol, acetonitrile, Iso-propyl alcohol in Milli-Q water and further mixed well and sonicated to degas [10, 18].

RESULTS AND DISCUSSION: The present study evaluated the *in-vitro* metabolic stability of oleanolic acid using liver microsomes from mouse, rat, and monkey. The results demonstrated species-dependent differences, with the compound exhibiting the shorter half-life and faster intrinsic clearance in monkey microsomes, moderate stability in rat microsomes, and the slowest clearance in mouse microsomes. These findings are consistent with previous reports indicating that oleanolic acid and other triterpenoids undergo extensive Phase I metabolism predominantly *via* CYP-mediated oxidation [20, 22, 23]. Several studies have reported comparable metabolic trends for oleanolic acid in rat and human liver microsomes, highlighting rapid biotransformation in rodents relative to higher species, which aligns with our observations of faster clearance in monkey and rat microsomes. Structurally related compounds, such as ursolic acid and maslinic acid, have also shown similar interspecies differences, with slower metabolism in primate microsomes compared to rodents, emphasizing the influence of microsomal enzyme expression and activity on intrinsic clearance [17, 21]. The metabolic half-life and intrinsic clearance values obtained in this study provide important insight into the potential pharmacokinetic behaviour of oleanolic acid in preclinical models. The relatively higher stability in mouse microsomes suggests that higher species may better predict human metabolism, supporting the translational relevance of primate studies for dose selection and safety assessment [16, 19].

Overall, these results underscore the utility of species-specific microsomal assays for early metabolic profiling and highlight the importance of comparing experimental findings with published metabolic data for structurally related natural products. Such comparisons aid in identifying potential metabolic liabilities and guide the rational design of further preclinical pharmacokinetic studies [16, 18].

In the current study Oleanolic acid was incubated with liver microsomes from various species, including rat, mouse, and monkey. The metabolic reaction was initiated by the addition of NADPH, and metabolite formation was monitored over time to assess species-specific biotransformation [21-22].

The percentage of the parent compound (oleanolic acid) remaining was calculated using the formula provided below for liver microsomes from all three species

% parent compound remaining = (Area ratio of OA at specified time point) / (Area ration of OA at 0 minute) × 100

Half-life and intrinsic clearance calculation was done using below mention formula:

$$\text{Half-life } (t1/2) = 0.693 / (\text{Slope } (k))$$

$$CL_{int} = 0.693/(t1/2)$$

The detailed result for half-life and intrinsic clearance has been calculated based on the values obtained in % parent compound (OA) remaining in each species liver microsomes **Table 3** and **Fig. 4.**

TABLE 3: % PARENT COMPOUND (OA) REMAINING, HALF-LIFE AND INTRINSIC CLEARANCE

Time points	Rat liver microsome	Mouse liver microsome	Monkey liver microsome
0 min	100.0	100.0	100.0
1 min	85.71	88.89	50.00
5 min	71.43	77.78	21.43
30 min	28.57	66.67	21.43
60 min	14.29	22.22	14.29
120 min	14.29	11.11	7.14
Species	**Slope**	**Half-Life**	**CL_{int}**
Rat	-0.0322	~21.5 min	0.0322
Mouse	-0.0199	~34.8 min	0.0199
Monkey	-0.0707	~9.8 min	0.0707

Half-life for Rat Liver Microsomes: The percentage remaining of the compound was measured at multiple time points (0, 1, 5, 30, 60, and 120 minutes) during incubation with rat liver microsomes.

The observed decline in concentration followed first-order kinetics, and log-linear regression of the natural logarithm of percent remaining versus time yielded a slope of -0.0322min−1, The elimination rate constant (k) was calculated as k = 0.0322 min, from this, the half-life ($t_{1/2}$) was determined using:

Half-life (t1/2) = 0.693 / (Slope (k)

Oleanolic acid exhibits moderate metabolic stability in rat liver microsomes, with a half-life of approximately 21.5 minutes under the experimental conditions [23, 24, 26, 27].

Half-life for Mouse Liver Microsomes: The percentage remaining of the compound was measured at multiple time points (0, 1, 5, 30, 60, and 120 minutes) during incubation with mouse liver microsomes.

The observed decline in concentration followed first-order kinetics, and log-linear regression of the natural logarithm of percent remaining versus time yielded a slope of -0.0199 min^{-1}. The elimination rate constant (k) was calculated as k = 0.0199 min, from this, the half-life ($t_{1/2}$) was determined using:

Half-life (t1/2) = 0.693 / (Slope (k)

Oleanolic acid exhibits highest metabolic stability in mouse liver microsomes, with a half-life of approximately 34.8 minutes under the experimental conditions indicating slowest clearance compared to rat microsomes [23, 24, 26, 27].

Half-life for Monkey Liver Microsomes: The percentage remaining of the compound was measured at multiple time points (0, 1, 5, 30, 60, and 120 minutes) during incubation with monkey liver microsomes. The observed decline in concentration followed first-order kinetics, and log-linear regression of the natural logarithm of percent remaining versus time yielded a slope of -0.0707min^{-1}, The elimination rate constant (k) was calculated as k = 0.0707min, from this, the half-life ($t_{1/2}$) was determined using:

Half-life (t1/2) = 0.693 / (Slope (k)

Oleanolic acid exhibits slowest metabolic stability in mouse liver microsomes, with a half-life of approximately 9.8 minutes under the experimental conditions indicating faster clearance compared to rat microsomes [23, 24, 26, 27].

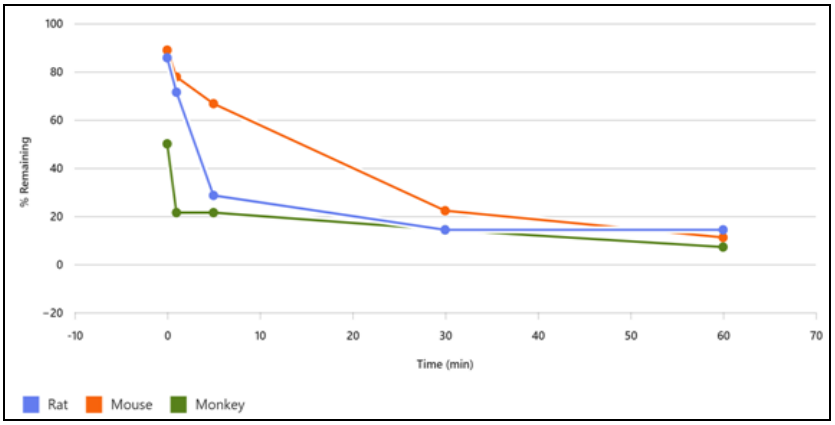


FIG. 4: GRAPHICAL REPRESENTATION OF % PARENT COMPOUND (OA) REMAINING

Species Comparison [23]: Microsomal stability was assessed in rat, mouse, and monkey liver microsomes using log-linear regression of in (% remaining) vs time. Reported slopes (min^{-1}) are negative by convention; the elimination rate constant is, k = -slope and half-life is T1/2 = 0.693 / k. CLint is presented as relative intrinsic clearance (≈ k min^{-1}) for cross-species comparison [23, 24, 26, 27].

TABLE 4: SPECIES COMPARISON FOR METABOLIC STABILITY OF OLEANOLIC ACID

Species	Observation	Implications	Results
Monkey Liver Microsomes	OA shows the fastest depletion, with only ~50% remaining at 1	Indicates highest metabolic activity, likely due to higher	Shortest half-life (~9.8 min) and highest intrinsic clearance

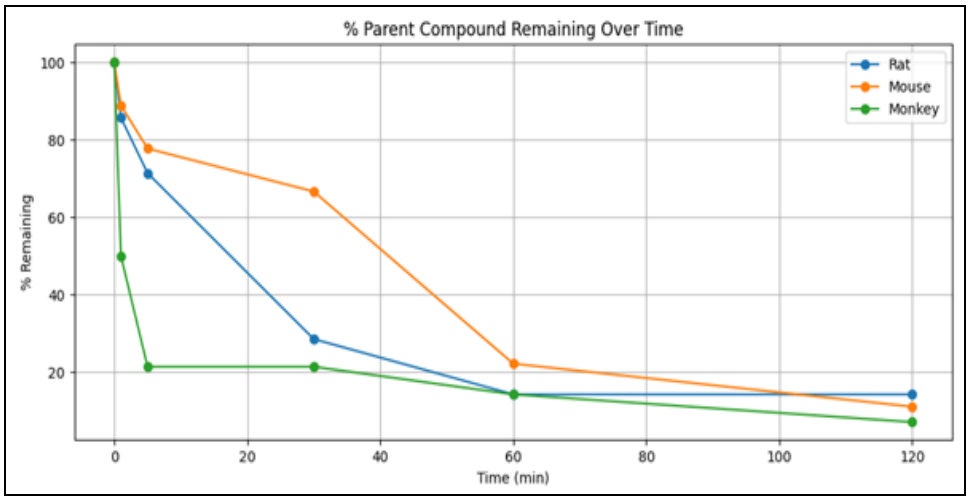
	min and ~7% at 120 min.	expression or activity of oxidative enzymes (e.g., CYP450 isoforms).	(CLint ≈ 0.0707).
Mouse Liver Microsomes	OA remains relatively stable, with ~66% still present at 30 min and ~11% at 120 min.	Suggests lowest metabolic activity, possibly due to lower enzyme affinity or abundance.	Longest half-life (~34.8 min) and lowest intrinsic clearance (CLint ≈ 0.0199).
Rat Liver Microsomes	OA metabolism is intermediate, with ~28% remaining at 30 min and ~14% at 120 min.	Rat microsomes exhibit metabolic capacity between monkey and mouse	Half-life (~21.5 min) and clearance (CLint ≈ 0.0322) fall between the other two species.

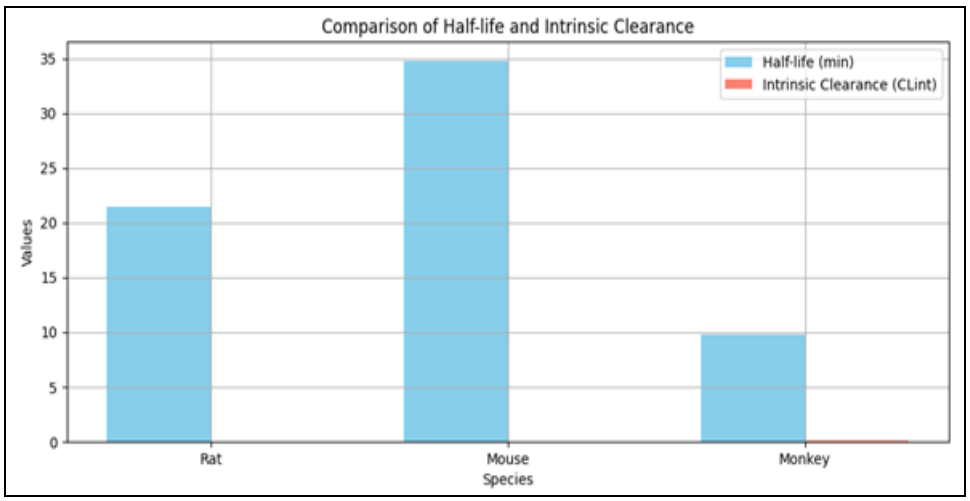
The inverse relationship between half-life and CLint is consistent with first-order microsomal kinetics: higher k (and CLint) yields shorter t1/2. Species differences imply that mouse may demonstrate higher *in-vitro* metabolic capacity for this compound, potentially translating to greater *in-vivo* clearance if other ADME processes are comparable. Monkey data suggest lower metabolic turnover, which could correspond to longer systemic exposure *in-vivo*, subject to absorption, distribution, and extrahepatic pathways [23, 24, 26, 27]. The decline in OA concentration is proportional to the remaining amount, confirming first-order behaviour.

Species Variability: Differences in metabolic rate may arise from CYP450 in inform composition and activity, Microsomal protein binding or Cofactor regeneration efficiency **Fig. 5.**

Monkey data may over predict human clearance, while mouse may underpredict. Rat provides intermediate scaling.

Potential Pathways: OA metabolism likely involves oxidation and hydroxylation (Phase I), possibly followed by conjugation (Phase II *in-vivo*).





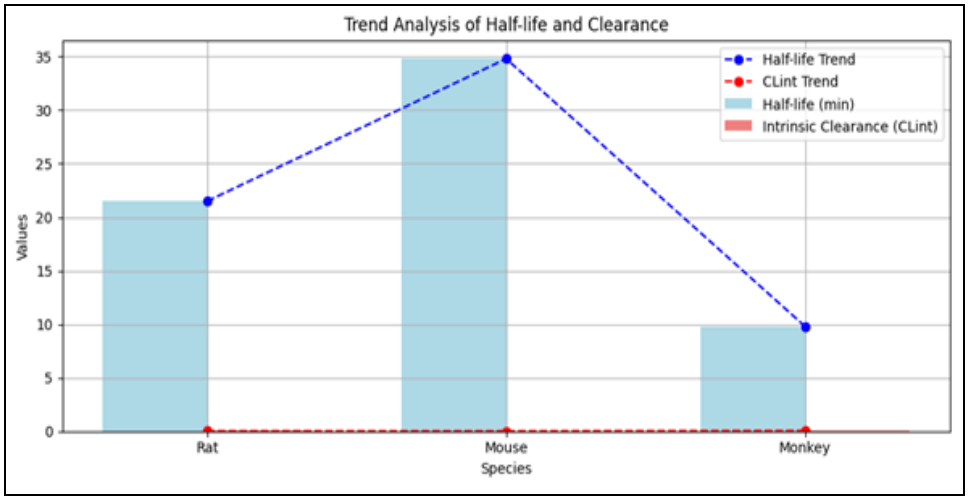


FIG. 5: METABOLIC STABILITY OF OLEANOLIC ACID ACROSS SPECIES LIVER MICROSOMES

CONCLUSION: This study demonstrates that oleanolic acid exhibits species-dependent *in-vitro* metabolic stability. Mouse liver microsomes showed the highest metabolic activity, with shorter half-life and higher intrinsic clearance, while monkey microsomes displayed the lowest activity, resulting in longer half-life and lower clearance. Rat liver microsomes exhibited intermediate metabolism. These results highlight clear interspecies differences and provide critical insight for selecting appropriate preclinical models. The findings offer valuable preliminary data to support early drug discovery, guiding pharmacokinetic evaluation, safety assessment, and rational progression of oleanolic acid in preclinical development [27].

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CONFLICT OF INTERESTS: The authors declare that there is no conflict of interest regarding the publication of this article.

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