

Enhanced Absorption of Glutathione with Liposomal Delivery: A Randomised Double-Blind Crossover Absorption Study

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Abstract

Background: Glutathione is an intracellular antioxidant with critical roles in redox regulation, detoxification, and immune function. However, oral glutathione supplementation typically has poor bioavailability. Liposomal delivery systems have been developed to address these limitations by enhancing compound stability and facilitating absorption. **Methods:** The present study aimed to compare the absorption profile of a liposomal glutathione formulation (Cymbiotika) with a standard oral comparator in healthy adults. In this randomised, double-blind, crossover trial, participants received single doses of both formulations in random order, separated by a washout period of at least 14 days. Blood samples were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. Plasma total glutathione exposure was evaluated using baseline-corrected incremental area under the concentration-time curve from 0 to 24 hours (iAUC_{0-24h}), with negative values set to zero to isolate net exposure above baseline. Secondary outcomes included maximum concentration (C_{max}) and time to maximum concentration (T_{max}). **Results:** Fourteen participants completed the study. The liposomal formulation resulted in increased absorption, with an approximately three-fold higher iAUC_{0-24h} compared to the comparator (16.3 vs 5.6 µM·h). Peak concentration was also higher for the liposomal formulation (0.83 vs 0.35 µM), with both formulations reaching peak concentrations at approximately 8 hours post-dose. The liposomal formulation exhibited a broader and more sustained absorption profile. **Conclusion:** These findings demonstrate that liposomal delivery significantly enhances absorption of orally administered total glutathione. This supports the use of lipid-based delivery technologies to increase relative plasma exposure of compounds with otherwise limited oral absorption.

Keywords

Glutathione, GSH, Absorption, Plasma Exposure, Liposomal Delivery

1. Introduction

Glutathione is widely recognised as one of the most important endogenous antioxidants, playing a central role in maintaining cellular redox balance, supporting detoxification pathways, and modulating immune function [1]–[3]. Reduced glutathione (GSH) is particularly critical in protecting cells from oxidative damage through direct scavenging of reactive oxygen species and as a cofactor for enzymatic antioxidant systems, including glutathione peroxidases [3] [4]. Given its broad physiological relevance, there has been substantial interest in glutathione supplementation as a strategy to support health and mitigate oxidative stress-related conditions [2] [4].

Despite this interest, the effectiveness of glutathione supplementation has been shown to be variable. Early investigations have suggested that glutathione is poorly absorbed when administered orally, primarily due to degradation within the gastrointestinal tract and extensive first-pass metabolism [5]. Enzymatic breakdown by γ -glutamyltransferase in the intestinal epithelium further limits the availability of glutathione for systemic uptake [6] [7]. As a result, conventional formulations have often demonstrated minimal or inconsistent increases in circulating glutathione concentrations [5].

To overcome the absorption limitations, a range of alternative delivery strategies have been developed. Among these, liposomal formulations have gained attention due to their ability to encapsulate bioactive compounds within phospholipid bilayer vesicles. This formulation is proposed to protect glutathione from enzymatic degradation, improve solubility within the intestinal environment, and enhance transport across biological membranes [8] [9]. Liposomal delivery systems have been shown to improve the bioavailability of several compounds with similar physicochemical challenges, although data specific to glutathione are limited [8] [9].

The present study was designed to evaluate whether a liposomal glutathione formulation (Cymbiotika) provides higher plasma exposure compared to a standard formulation. Using a randomised, double-blind crossover design, this study assessed absorption parameters following single-dose administration, with a specific focus on absorption above baseline levels.

2. Methods

2.1. Study Design

This study was conducted as a randomised, double-blind, crossover absorption trial designed to evaluate the absorption characteristics of two glutathione formu-

lations in healthy adult participants. The study was conducted in January and February 2026, at RDC Clinical (Fortitude Valley, Brisbane, Australia) in accordance with the principles of Good Clinical Practice and national ethical guidelines. This study was registered with ISRCTN (registration number ISRCTN39055102).

Participants were randomised in a 1:1 ratio to receive the liposomal formulation followed by the comparator formulation or the comparator followed by the liposomal formulation. Each participant received both investigational products and therefore served as their own control. The two dosing periods were separated by a washout of at least 14 days.

2.2. Participants

Healthy adult males and females aged between 18 and 50 years were eligible for inclusion if they had a body mass index (BMI) between 18.5 and 30 kg/m², were generally healthy as determined by medical history and investigator assessment, and were able to comply with all study procedures, including fasting requirements and clinic visits. Participants were required to be non-smokers or to have abstained from smoking for at least six months prior to enrolment. Female participants of childbearing potential were required to have a negative pregnancy test at baseline and to use an acceptable method of contraception throughout the study period. All participants were required to provide written informed consent prior to participation.

Participants were excluded if they had any condition that could affect the absorption, metabolism, or distribution of nutrients, including gastrointestinal disorders such as inflammatory bowel disease (including Crohn's disease), irritable bowel syndrome, and coeliac disease, a history of gastrointestinal surgery, or suspected small intestinal bacterial overgrowth. Individuals with a history of cardiovascular disease, type 2 diabetes, neurodegenerative disease, renal disease, metabolic syndrome, muscular dystrophy, or other significant acute or chronic illnesses were excluded. Additional exclusions included individuals with unstable medical conditions, current malignancy or recent cancer treatment, and those with significant alcohol consumption or substance abuse.

Participants were also excluded if they were taking medications known to affect nutrient absorption or metabolism, including lipid absorption inhibitors, corticosteroids, anticoagulants, or medications indicative of chronic disease. The use of glutathione, pyrroloquinoline quinone (PQQ), or related supplements within 14 days prior to screening was not permitted. Individuals following dietary patterns likely to influence absorption, such as very low-fat diets or vegan diets (which may influence lipid-dependent absorption), were excluded due to the formulation characteristics of the investigational products. Participants engaged in high levels of structured physical activity (>10 hours per week) were also excluded to minimise metabolic variability. Finally, individuals who had participated in another clinical trial within the previous month or who were unable to adhere to the study protocol were excluded.

2.3. Interventions

The investigational product was a Cymbiotika liposomal glutathione and pyrroloquinoline quinone formulation supplied as a phospholipid-based liquid gel with an aqueous vehicle consisting predominantly of water and glycerin (40% to 50%). Each administered dose contained 250 mg glutathione (as L-glutathione, reduced form) and 20 mg PQQ (as PQQ disodium salt). During manufacture, glutathione, PQQ, and coenzyme Q10 are dispersed with sunflower lecithin-derived phosphatidylcholine and incorporated into the water-glycerin vehicle, followed by homogenization to form the final liposomal formulation. Once the base liposomal formulation was formed, flavor oils and other ingredients required for the gel delivery format were added, including organic medium-chain triglyceride oil, organic tapioca syrup, organic vanilla extract, organic orange peel oil, organic tangerine oil, vitamin B2, and mixed tocopherols. The product was manufactured to Good Manufacturing Practice standards and stored under cool, dry conditions below 25°C. The formulation was supplied in individual 5 mL premeasured sachets, with each sachet containing a single fixed dose as predetermined by the manufacturer, and participants consumed the entire contents of one sachet at each dosing occasion.

The comparator consisted of two commercially available, non-liposomal dietary supplement products administered at matched doses of 250 mg glutathione and 20 mg PQQ. The glutathione product was supplied as a gelatin capsule containing 250 mg of reduced L-glutathione, with dibasic calcium phosphate, colloidal silicon dioxide, and magnesium stearate as excipients; one capsule was taken at each dosing occasion. The PQQ product was supplied as a vegetarian (hypromellose) capsule containing 20 mg PQQ with rice flour as a filler; one capsule was taken at each dosing occasion. Commercial PQQ ingredients of this type are typically supplied as the disodium salt, although this was not independently confirmed for the specific product used. Both products were stored at room temperature in a cool, dry place, consistent with manufacturer labelling.

Participants attended after an overnight fast of at least 10 hours and consumed the assigned study product with approximately 250 mL of water. A standardised breakfast containing approximately 30% fat, 40% carbohydrate, and 30% protein was provided approximately 30 minutes after dosing. Participants remained in the clinic for serial blood sampling during the absorption assessment period.

Randomisation was performed using a computer-generated sequence through Sealed Envelope, with a 1:1 allocation ratio and block size of four. An independent person not involved in study conduct generated the allocation sequence and retained the randomisation list and seed in a sealed envelope stored in a locked cabinet. Participants were assigned to receive the products in an AB or BA sequence. Participants, investigators, laboratory personnel, and the statistician were blinded to treatment allocation, and the statistician remained blinded until the prespecified statistical analysis was complete. Because the investigational and comparator products differed in dosage form (liquid gel and capsule), an independent, unblinded

staff member prepared and administered the treatments according to the randomisation schedule. Treatment allocation otherwise remained concealed until database lock. The comparator products were prospectively selected as commercially available, non-liposomal forms of oral glutathione and PQQ that provided matched active-ingredient doses; they were therefore intended to provide a pragmatic reference against which to evaluate the complete investigational formulation, rather than a dosage-form-matched control. Beyond matching the active-ingredient doses, the two formulations could not be matched for all formulation characteristics, as the study was designed to compare commercially available products in their marketed forms. Consequently, the formulations differed in several characteristics, including dosage form (gel versus capsule), excipient composition, and the presence of a phospholipid carrier in the investigational product. The potential influence of dosage form was therefore not experimentally isolated or negated. Rather, the study was designed to compare the overall absorption performance of the complete formulations, and any observed differences may reflect the combined effects of dosage form, carrier system, excipient composition, and other compositional differences between the products.

2.4. Blood Sampling and Processing

Baseline blood samples were collected immediately before administration of the study product. Subsequent blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. Samples through 8 hours were collected during the clinic visit using an indwelling cannula placed in the antecubital vein. Participants returned to the clinic for a single venous blood sample at 24 hours. Samples collected during the initial clinic visit were obtained within ± 5 minutes of the scheduled time, and the 24-hour sample was obtained within ± 1 hour. Collected blood was immediately transferred to EDTA vacutainers and stored at 4°C prior to centrifugation.

Blood samples were centrifuged at $1600 \times g$ for 10 minutes at 4°C to separate plasma. To minimise ex vivo oxidation and degradation of glutathione, all samples were processed immediately following collection under controlled temperature conditions, with plasma separation performed promptly and samples stored at -80°C until analysis. Plasma was separated, stabilised, and frozen within 30 minutes of collection.

2.5. Analytical Methods

Plasma total glutathione was measured in EDTA plasma using the Invitrogen Glutathione Colorimetric Detection Kit (catalogue number EIAGSHC; Thermo Fisher Scientific, Victoria, Australia), a commercially available colorimetric assay for which EDTA plasma is a manufacturer-specified sample type. This assay uses a substrate that reacts with the free thiol group of reduced glutathione, with absorbance measured at 405 nm. The manufacturer reports an analytical sensitivity of 0.634 μM and a standard curve range of 0.78 - 25 μM . Total glutathione was

measured in deproteinized plasma extracts and is reported as total glutathione equivalents. Plasma was mixed with an equal volume of cold 5% sulfosalicylic acid, incubated for 10 minutes at 4°C, and centrifuged at 14,000 rpm for 10 minutes at 4°C; the resulting supernatant was collected and diluted with assay buffer to 1% sulfosalicylic acid according to the manufacturer's instructions before analysis. Plasma samples were analysed in duplicate in accordance with the manufacturer's instructions. Samples were stabilised and frozen within 30 minutes of collection. Absorbance was read on a BioTek 800TS microplate reader. Manufacturer-reported precision for this kit is an intra-assay coefficient of variation (CV) of 2.1% - 5.0% and an inter-assay CV of 7.5% - 13.3%; in-house plate CVs for this study were <5%.

2.6. Absorption and Statistical Analysis

The sample-size calculation assumed a two-period crossover design, a within-participant coefficient of variation of approximately 12%, 80% power, and a significance level of 0.05. Under these assumptions, 12 participants completing both treatment periods were estimated to be sufficient to detect a 15% difference in $iAUC_{0-24h}$ between formulations. To allow for withdrawals or non-evaluable participants, the enrolment target for the glutathione study was 16 participants in total. Fifteen participants were enrolled and 14 completed both periods and were included in the absorption analysis. Calculations were based on standard bioequivalence methods (log-transformed $iAUC_{0-24h}$ with baseline correction).

As glutathione is an endogenous compound, the pharmacokinetic analysis was conducted in accordance with the principles outlined in the ICH M13A guideline. Concentrations were corrected using the period-specific pre-dose concentration, and the baseline-corrected incremental area under the concentration-time curve from 0 to 24 hours ($iAUC_{0-24h}$) was calculated using the linear trapezoidal method. Negative baseline-corrected concentrations were set to zero before calculation of positive $iAUC_{0-24h}$ and baseline-corrected C_{max} , thereby determining net exposure above baseline and reducing the influence of physiological fluctuations unrelated to supplementation. A sensitivity analysis was also performed in which negative baseline-corrected concentrations were retained, to evaluate the robustness of the findings to the baseline-correction approach.

A linear mixed-effects model was fitted with treatment, period, and sequence as fixed effects and participant as a random effect. The model was used to estimate the treatment effect while accounting for the within-participant correlation arising from the crossover design. Potential period and sequence effects were evaluated from the model. This model was prespecified in a statistical analysis plan that superseded the original protocol.

2.7. Analysis Population

The primary analysis population comprised participants who completed both treatment periods and had sufficient concentration data for calculation of the

pharmacokinetic endpoints. Participants were analysed according to the treatment received in each period.

Missing concentration values were imputed using linear interpolation between adjacent observed timepoints for the intention-to-treat analysis.

Secondary absorption parameters included maximum observed concentration (C_{max}) and time to maximum concentration (T_{max}). Statistical analyses were performed using the prespecified linear mixed-effects model described above, with results presented as mean $\pm$ standard deviation and corresponding 95% confidence intervals. Analyses were performed using GraphPad Prism (version 11.0.0).

AEs were assessed systematically at each study visit through participant questioning, clinical observations, and monitoring of vital signs and laboratory parameters.

3. Results

3.1. Participant Characteristics

Fifteen participants were enrolled into the study, with fourteen included in the absorption analysis across the study periods (**Figure 1**). One participant was excluded due to non-compliance with the study requirements. The study population had a mean age of approximately 38 years and a mean body mass index within the normal range, with an equal distribution of male and female participants. Baseline demographic and clinical characteristics were comparable between treatment conditions (**Table 1**).

Table 1. Participant demographics and baseline characteristics.

Characteristic	Value (N = 14)
Age (years)	38.5 $\pm$ 7.7 (range: 29 - 49)
Gender (n)	Female: 7 (50%), Male: 7 (50%)
BMI (kg/m ²)	23.6 $\pm$ 2.7 (range: 20.1 - 28.2)
Height (m)	1.73 $\pm$ 0.09
Weight (kg)	70.9 $\pm$ 12.8
Systolic BP (mmHg)	110.0 $\pm$ 17.4
Diastolic BP (mmHg)	73.4 $\pm$ 9.3
Pulse (bpm)	63.0 $\pm$ 9.6
Ethnicity (n)	Caucasian: 7 (50%), SE Asian: 3 (21.4%), E Asian: 3 (21.4%), Hispanic: 1 (7.2%)

Values are presented as mean $\pm$ standard deviation or n (%).

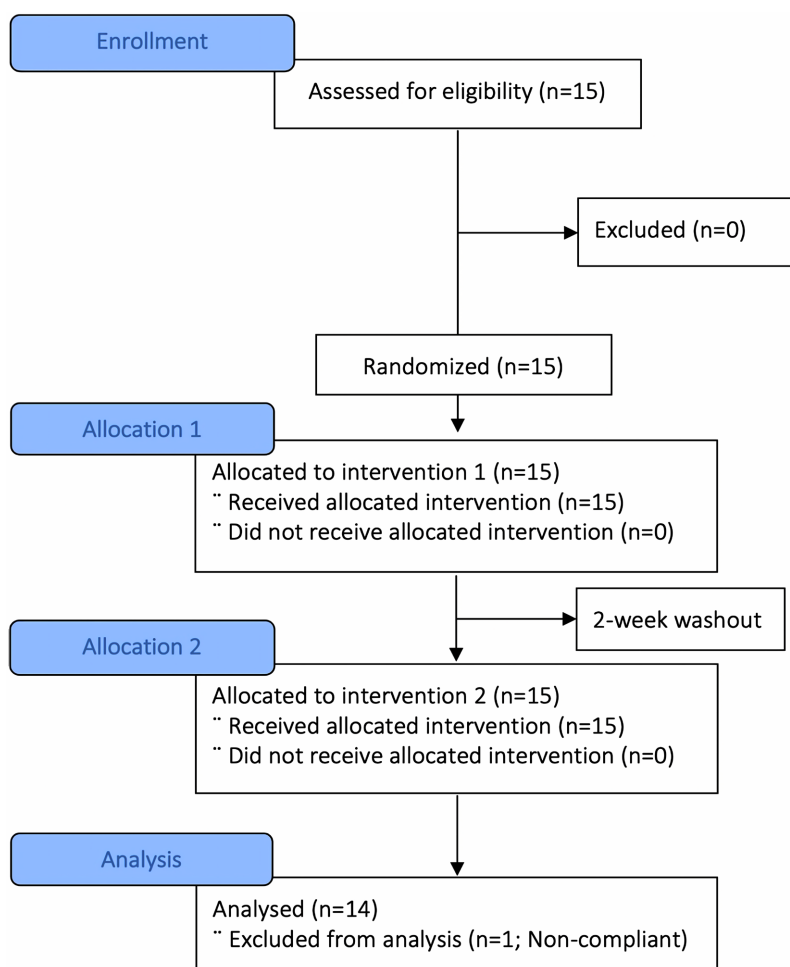


Figure 1. CONSORT flow diagram of participant progress through the trial.

3.2. Baseline Total Glutathione Concentrations

Baseline plasma total glutathione concentrations were similar between the two treatment periods, with mean values of $1.57 \pm 0.81 \mu\text{M}$ for the liposomal formulation and $1.99 \pm 1.16 \mu\text{M}$ for the comparator. These findings indicate that participants commenced each study period under comparable physiological conditions.

3.3. Absorption Outcomes

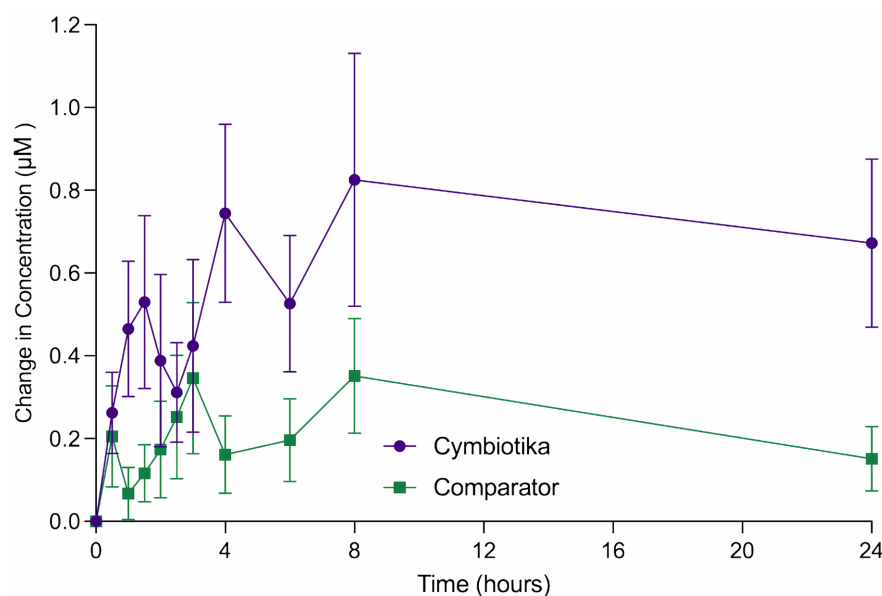
The liposomal glutathione formulation demonstrated a substantially greater increase in systemic exposure compared to the standard comparator. The incremental area under the curve ($\text{iAUC}_{0-24\text{h}}$) was approximately three-fold higher for the liposomal formulation ($16.3 \mu\text{M}\cdot\text{h}$) compared to the comparator ($5.6 \mu\text{M}\cdot\text{h}$), indicating higher baseline-corrected plasma exposure (**Table 2, Figure 2**).

Similarly, peak plasma concentrations were significantly higher following administration of the liposomal formulation ($p < 0.05$), with a mean C_{max} of $0.83 \mu\text{M}$ compared to $0.35 \mu\text{M}$ for the comparator. Both formulations reached peak concentrations at approximately 8 hours post-dose, suggesting similar absorption timing but differing magnitude and extent of exposure (**Table 2, Figure 2**).

Table 2. Arithmetic mean absorption parameters following administration of a liposomal glutathione or comparator formulation.

Parameter	Liposomal (n = 14)	Comparator (n = 14)
iAUC _{0-24h} (μM·h)	16.3 ± 11.0 ^a	5.6 ± 4.9
Fold difference ^b	2.91	N/A
C _{max} (μM)	0.83 ± 1.14 ^a	0.35 ± 0.52
T _{max} (h)	8.0	8.0

^aStatistically significant difference between formulations ($p < 0.05$).

**Figure 2.** Baseline-corrected plasma total glutathione concentration-time profiles following administration of the liposomal and comparator formulations. Incremental AUC was calculated from 0 to 24 hours (iAUC_{0-24h}), which was significantly greater for the liposomal formulation compared with the comparator ($p < 0.05$).

3.4. Paired Treatment Effect and Sensitivity Analysis

Linear mixed-effects model estimated a paired treatment effect for iAUC_{0-24h} of 2.37 μM·h (two-sided 95% CI: −8.37 to 13.11; $P = 0.6373$) and for baseline-corrected C_{max} of 0.32 μM (two-sided 95% CI: −0.59 to 1.23; $P = 0.4545$), indicating that neither difference reached statistical significance. In a sensitivity analysis retaining negative baseline-corrected concentrations, the treatment effect for net iAUC_{0-24h} remained directionally in favour of the liposomal formulation (8.50 μM·h; two-sided 95% CI: −12.53 to 29.53; $P = 0.3928$). No statistically significant period or sequence effects were identified.

Inspection of the concentration-time profiles indicated that the liposomal formulation produced a broader and more sustained elevation in plasma total glutathione levels, consistent with enhanced systemic delivery and exposure sustained through the 24-hour sampling period (**Figure 2**).

3.5. Safety

Both formulations were well tolerated, with no adverse events reported during the study period.

4. Discussion

This randomised, double-blind crossover absorption study demonstrates that a liposomal glutathione formulation (Cymbiotika) resulted in substantially greater systemic exposure compared to a standard oral formulation. Using a baseline-corrected incremental AUC (iAUC_{0-24h}) approach, the study observed an approximately three-fold increase in net total glutathione exposure, accompanied by a higher peak concentration and a more sustained absorption profile.

The magnitude of this effect is notable when considered in the context of the existing literature. Early absorption investigations of oral glutathione reported minimal or no significant increases in circulating glutathione following standard oral administration [5], supporting the longstanding view that glutathione has historically shown limited bioavailability. More recent studies have started to challenge this assumption, demonstrating modest increases in plasma or whole blood glutathione with higher dosing or prolonged supplementation [10] [11], however, these effects are typically small and variable. In this context, the approximately three-fold increase in incremental exposure observed in the present study represents a comparatively large effect size for an acute, single-dose intervention.

Direct comparisons with other delivery systems are limited, as relatively few controlled absorption studies have evaluated glutathione formulations under crossover conditions. However, studies investigating alternative strategies such as liposomal, sublingual, or precursor-based approaches (e.g., N-acetylcysteine) have reported improvements in systemic glutathione status [8] [12] [13], though often assessed over longer timeframes or using indirect biomarkers. Where acute absorption data are available, increases in plasma glutathione are typically modest, and fold changes of this magnitude are uncommon. This suggests that liposomal encapsulation may provide a meaningful enhancement in early-phase absorption.

An additional consideration is the inclusion of PQQ in both study formulations. PQQ has been investigated for its potential effects on mitochondrial function and redox biology; however, it was not a variable of interest in the present study and was not measured as part of the absorption analysis. Importantly, both the liposomal and comparator formulations contained equivalent doses of PQQ, and therefore any potential effects of PQQ would be expected to be consistent across treatment conditions. As such, the observed differences in systemic total glutathione exposure are most appropriately attributed to the delivery system rather than the presence of PQQ.

A related consideration is that the investigational and comparator products differed in dosage form (liquid gel and capsule) as well as in broader formulation composition. The comparator capsules contained excipients typical of solid oral dosage forms that are not present in the liposomal gel, and the two products fur-

ther differed in excipient composition and in the presence of a phospholipid carrier in the investigational formulation. As the comparator was evaluated in its complete, commercially marketed capsule form rather than as a dosage-form-matched control, the influence of dosage form on absorption was not the primary focus of this study. The observed differences in systemic total glutathione exposure should therefore be interpreted as reflecting the combined effects of dosage form, carrier system, excipient composition, and other compositional differences between the complete formulations, rather than the liposomal carrier in isolation.

The observed C_{max} difference (0.83 vs 0.35 μ M) further supports higher observed plasma exposure, indicating that the liposomal formulation not only increases total exposure but also produces a higher baseline-corrected peak concentration. The similar T_{max} observed for both formulations (~8 hours) suggests that the timing of absorption is not substantially altered, but rather that the magnitude of observed plasma exposure was higher. The relatively delayed T_{max} compared to many small molecules may reflect the complex handling of glutathione, including digestion, transport, and potential redistribution processes.

An important consideration in interpreting glutathione absorption is the biological matrix used for measurement. In the present study, plasma total glutathione concentrations were assessed, which reflect the circulating extracellular pool. Plasma measurements are sensitive to acute changes and are therefore appropriate for absorption studies focused on short-term absorption. However, plasma total glutathione concentrations are typically low, and can be influenced by rapid turnover, oxidative processes, and methodological variability [14]. In the present study, sample handling procedures were designed to minimise these effects, with immediate processing, temperature-controlled handling, and rapid storage at -80°C . These precautions are consistent with established methodological recommendations and support the reliability of the observed absorption differences.

In contrast, whole blood or red blood cell (RBC) total glutathione measurements provide an alternative representation of intracellular total glutathione status, as erythrocytes contain high concentrations of glutathione and serve as a major reservoir [15] [16]. RBC total glutathione is considered a marker of longer-term total glutathione status and is less susceptible to short-term fluctuations. However, changes in RBC total glutathione occur more slowly and may not accurately reflect acute absorption following a single dose. For this reason, plasma total glutathione is more appropriate for absorption studies assessing immediate post-dose exposure, whereas RBC or whole blood measurements may be more informative in chronic supplementation studies evaluating steady-state effects.

The analytical approach used in this study—baseline-corrected incremental AUC with negative values set to zero—was selected to isolate the contribution of supplementation to systemic exposure. This approach is particularly relevant for endogenous compounds such as glutathione, where physiological fluctuations can obscure treatment effects. By focusing on incremental increases above baseline, the analysis provides a more precise estimate of absorption attributable to the in-

tervention. This method is consistent with analytical approaches used in nutritional and metabolic research, particularly in the context of postprandial responses.

Mean $iAUC_{0-24h}$ remained numerically higher following the liposomal formulation than the comparator. Setting negative baseline-corrected concentrations to zero, consistent with the principles outlined in ICH M13A for endogenous compounds, estimates positive incremental exposure attributable to supplementation, whereas retaining negative values estimates net change over the sampling period. The consistent direction of the treatment effect across both approaches provides some support for greater exposure following the liposomal formulation.

Several considerations should be noted when interpreting these findings. The study employed a single-dose design, providing an initial assessment of acute absorption. While repeated-dosing and steady-state effects represent an important area for future research. The sample size, while consistent with typical crossover absorption study designs, means these findings would benefit from confirmation in larger populations. Additionally, the study focused on plasma exposure rather than intracellular total glutathione or functional outcomes, which represent valuable directions for future research.

Overall, the findings provide clear evidence that liposomal delivery enhances the systemic exposure of orally administered total glutathione. Future studies should evaluate whether these acute absorption advantages translate into meaningful improvements in cellular total glutathione status and clinical outcomes during longer-term supplementation.

5. Conclusion

In conclusion, this study demonstrates that liposomal delivery significantly enhances the systemic exposure of orally administered total glutathione compared to a standard formulation. The approximately three-fold increase in incremental AUC ($iAUC_{0-24h}$) observed with the liposomal formulation indicates higher baseline-corrected plasma exposure. These findings indicate that the tested liposomal formulation produced higher baseline-corrected plasma total glutathione exposure over 24 hours than the tested non-liposomal comparator. Further studies are required to determine whether this difference translates into changes in intracellular total glutathione status or clinical outcomes.

Author Contributions

Conceptualization, David B. and Amanda R.; Methodology, David B., Sandra R. and Amanda R.; Software, David B., Sandra R. and Amanda R.; Validation, David B., Sandra R. and Amanda R.; Formal Analysis, Amanda R.; Investigation, David B., Sandra R. and Amanda R.; Resources, David B., Shilpa R., Chervin J. and Amanda R.; Data Curation, David B. and Amanda R.; Writing-Original Draft Preparation, David B.; Writing-Review & Editing, David B., Sandra R., Shilpa R., Chervin J. and Amanda R.; Visualization, David B. and Amanda R.; Supervision,

David B., Sandra R and Amanda R; Project Administration, Amanda R.; Funding Acquisition, Shilpa R., Chervin J. and Amanda R.

Ethics

This study involving human participants was reviewed and approved by The University of Queensland Human Ethics Committee A on 24th November 2025 (Approval No. 2025/HE001712). All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to participation in the study.

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Conflicts of Interest

David Briskey, Sandra Rahman, and Amanda Rao declare that the research was conducted in the absence of commercial or financial relationships that could be construed as a potential conflict of interest. Shilpa Raut and Chervin Jafarieh are employees of the study sponsor, Cymbiotika LLC. They contributed to the provision of study resources, funding acquisition, and manuscript review but had no involvement in study methodology, participant recruitment, data collection, laboratory analysis, statistical analysis, or interpretation of the results.

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Supplementary CONSORT 2025 Checklist of Information to Include When Reporting a Randomised Trial

Section/Topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomised trial	1
	1b	Structured summary of the trial design, methods, results, and conclusions	2
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	4
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	15
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	15
Funding and conflicts of interest	5a	Sources of funding and other support (e.g., supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	15
	5b	Financial and other conflicts of interest of the manuscript authors	14
Introduction			
Background and rationale	6	Scientific background and rationale	3
Objectives	7	Specific objectives related to benefits and harms	3
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	N/A
Trial design	9	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	4
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	N/A
Trial setting	11	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial was conducted	4
Eligibility criteria	12a	Eligibility criteria for participants	4, 5
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (e.g., surgeons, physiotherapists)	N/A
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	5, 6

Continued

Outcomes	14	Pre-specified primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	2, 6, 7
Harms	15	How harms were defined and assessed (e.g., systematically, non-systematically)	7
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	6
	16b	Explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	17a	Who generated the random allocation sequence and the method used	6
	17b	Type of randomisation and details of any restriction (e.g., stratification, blocking and block size)	6
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	6
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	6
Blinding	20a	Who was blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	6
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	6
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	6, 7
	21b	Definition of who is included in each analysis (e.g., all randomised participants), and in which group	7, 8
	21c	How missing data were handled in the analysis	N/A
	21d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses), distinguishing prespecified from post-hoc	N/A
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	7, 8
	22b	For each group, losses and exclusions after randomisation, together with reasons	7, 8
Recruitment	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	4
	23b	If relevant, why the trial ended or was stopped	N/A
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (e.g., where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended [fidelity])	