Journal of Natural Health Product Research
2021, Vol. 3, Iss. 2, pp. 1–8.
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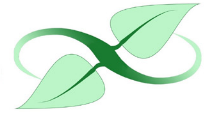

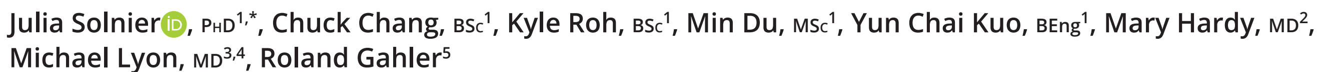

ORIGINAL RESEARCH OPEN ACCESS

Quercetin LipoMicel—A Novel Delivery System to Enhance Bioavailability of Quercetin

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ABSTRACT

BACKGROUND: Quercetin, a flavonoid found in plant-based foods, has a range of biological activities that may be beneficial for human health. The pharmacokinetic profile of quercetin remains, however, a limiting factor for its use as a nutritional supplement. Quercetin LipoMicel®—a novel delivery system encapsulating quercetin into a liquid micelle matrix—has been designed to address the low bioavailability issue associated with non-conjugated forms by improving the absorption of quercetin.

OBJECTIVE: The purpose of this study was to evaluate the solubility and gastrointestinal absorption of quercetin in a novel Quercetin LipoMicel delivery system in healthy adult volunteers by comparing it with free quercetin and another commercial quercetin product. Several pharmacokinetic parameters were compared between these three formulations.

METHODS: Twelve healthy adult male and female volunteers aged between 21 and 65, with BMIs under 30, participated in a non-blinded, crossover bioavailability study conducted with three quercetin products. Each treatment contained a total dose of 500 mg quercetin. Capillary whole blood samples from participants were collected serially at intervals from 0–24 hours. Quercetin concentrations were detected and measured by ultra-performance liquid chromatography (UHPLC) coupled to a Thermo QExactive Orbitrap Mass Spectrometer. Solubility of quercetin in water and simulated gastrointestinal media was determined by UHPLC.

RESULTS: Oral absorption of quercetin was significantly enhanced with the LipoMicel delivery system compared to free quercetin. Improvements in *in vitro* gastric stability and intestinal solubility were observed with LipoMicel, leading to significantly higher blood concentration and enhanced duration of a stable concentration of quercetin in the body. Compared to free quercetin, 8- and 9-fold increases in AUC and Cmax were attained with the LipoMicel delivery system, and 10-fold higher quercetin plasma concentrations detected at 12 hours after administration.

CONCLUSIONS: Quercetin LipoMicel represents an efficient delivery system for augmenting the bioavailability of quercetin *in vivo*. Significantly higher blood concentrations and a sustained release of quercetin over the study period was achieved following the administration of quercetin via the LipoMicel technology. Optimization in the *in vivo* bioavailability of quercetin may promote its salutary effects.

KEYWORDS: Anti-inflammation; antioxidative; antiviral; bioavailability; flavonoids; LipoMicel®; quercetin

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Introduction

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one or 3,3′,4′,5,7-pentahydroxyflavone) is one of the most abundant dietary flavonoids and is widely distributed throughout the plant kingdom including fruits and vegetables such as apples, berries, capers, cilantro, onions, kale, green tea, and red wine [1]. It is present in several plants and foods including *Ginkgo biloba*, St. John's wort, American elder, and buckwheat tea. In its natural food matrix, quercetin exists in a bound form, e.g., attached to sugars, ethers, or phenolic acids, thus limiting its bioavailability (Wang et al., 2016). Purified quercetin appears as a yellow powder that is soluble in alcohol and lipophilic solvents but is poorly soluble in water [2].

Throughout the history of traditional or indigenous medicine, extracts from herbs and plants have been used to manage a variety of illnesses. The putative health promoting effects of quercetin have been reported as ranging across anti-allergic, anticancer, anti-inflammatory, antiviral, and cardiovascular protective activities [3, 4]. For example, the flavonol was found to reduce the release of inflammatory cytokines (e.g., IL-8) which may alleviate infection-related symptoms and possibly suppress inflammatory responses that are often associated with viral infections [5–7]. In the case of rheumatoid arthritis, quercetin has been reported to inhibit neutrophil activity, and reduce the plasma levels of inflammatory cytokines [8]. Kinker (2014) has suggested that the antioxidative potential of quercetin might prevent tissue damage by scavenging free radicals.

Even though quercetin may exert a broad range of biological activities, its poor pharmacokinetic profile strongly limits its clinical use.

Quercetin, orally administered, is subject to numerous degradation steps within the gastrointestinal system including: aggregate formation with salivary gland proteins in the mouth [9]; degradation to phenolic acids and limited absorption in the stomach at low pH; glucuronidation, sulfation, and methylation at intestinal and hepatic level; and formation of an aglycone by enzymes of the microbiota [10, 11].

Moreover, the intake of quercetin from food may not be sufficient to achieve clinically significant blood concentrations because of the effects noted above. In addition, the intake of quercetin from the diet can be compromised by non-host related factors which may contribute to poor bioavailability of dietary flavonoids. For example, environmental factors such as storage, sun exposure, food processing factors like cooking or freezing, chemical structure (glycosylated or polymeric structure vs aglycone form) and the concentration in the dietary substrate [12] all have an impact on bioavailability. However, oxidation during food production and storage appeared to be the main cause of changes and degradation of quercetin [3].

Encapsulating bioactive compounds into water or liquid based matrices, may improve their chemical and gastrointestinal solubility. These carrier designs may further allow for better monitoring of the rate and site of action within the gastrointestinal tract by increasing the compound's absorption and subsequent metabolism. Enhanced delivery systems such as polymeric nanoparticles, structural modifications (glycosylation), liposomes, phytosomes, micelles, and emulsions have been suggested as strategies to improve gastrointestinal solubility and absorption [13]. A liquid micelle matrix composed of natural food grade ingredients was developed to potentially increase the bioavailability of quercetin.

The Quercetin LipoMicel formula represents an improved delivery solution to manage insufficient bio-accessibility of quercetin and enhance the bioavailability of the compound. For the Quercetin LipoMicel formulation, a liquid micelle matrix composed of natural food-grade ingredients was developed to facilitate bioavailability. The purpose of the present study, then, was to evaluate solubility and gastrointestinal absorption of quercetin in this novel delivery system in healthy adults.

Material & Methods

Formulation AO (free Quercetin); AP (Quercetin Phytosome); AW (Quercetin LipoMicel)

Three different preparations of quercetin were procured from commercial sources. Each product provided in this study was intended to provide 500 mg of "free" quercetin. Quercetin LipoMicel® (batch no.: 869911) was prepared and provided by Natural Factors (Coquitlam, BC, Canada). Quercetin Phytosome® hard capsules (lot no.: 404996) were manufactured and purchased from Thorne Research Inc. (Thorne, USA). Free quercetin formulated in hard capsules (lot no.: IAY-20022B01) were manufactured and purchased from Amazing Nutrition (New Jersey, USA).

Quality control of the quercetin products used in this study was performed before testing—such as appearance, average mass, uniformity of mass, HPLC-measured content of quercetin, and microbiological quality was tested.

The first formula is provided as a single hard capsule containing quercetin dihydrate, cellulose, magnesium stearate, and silicon dioxide. For the second product, Quercetin Phytosome two hard capsules containing 250 mg each of Quercetin Phytosome including

leucine, microcrystalline cellulose, hypromellose capsule, silicon dioxide were tested. The third formulation, Quercetin LipoMicel formula, is composed of quercetin encapsulated with medium chain triglycerides. Its micellular membrane contained food-grade excipients (patent pending). 250 mg of Quercetin LipoMicel was formulated into soft-gel capsules containing gelatin, glycerin, purified water, carob powder, medium chain triglycerides, *Stevia rebaudiana* leaf, peppermint essence, and phosphatidylcholine (lecithin). Soft gels deliver drugs in solution, suspension or paste form and yet offer solid dosage form [14]. The hydrophobic active ingredient is dissolved in a hydrophilic solvent, and, when crushed or chewed, the solution is directly released into gastric juice. This facilitates a faster absorption from the gastrointestinal tract into the blood stream—resulting in higher bioavailability and rapid onset of desired therapeutic effects. Also, soft gels have been reported to improve the extent of absorption as well as to significantly reduce plasma variability. Preparations of liquid-filled soft gel have further proven beneficial to oxidative or hydrolytic degradable drugs [14, 15].

Solubility Study

Individual quercetin formulations used in this study were investigated in terms of their solubility in water and simulated gastrointestinal media. 1–2 g of each of the quercetin samples was added to 10 mL of simulated media resulting in a total concentration of 500 mg quercetin. The gastrointestinal media were prepared according to the method published by the USP. Briefly, for preparing the simulated gastric fluid (pH 1.2), 2 g of sodium chloride (Sigma) and 3.2 g of purified pepsin (VWR) were dissolved in 7 mL of hydrochloric acid (Sigma) and made up to 1000 mL with distilled water.

The simulated intestinal fluid was prepared by dissolving 6.8 g of monobasic potassium phosphate (Sigma) in 250 mL distilled water, mixed and then 77 mL of 0.2 N sodium hydroxide (Sigma) and 500 mL of distilled water were added. Next, 10 g of pancreatin (porcine, Sigma) was added and the media adjusted to pH 6.8 with sodium hydroxide or hydrochloric acid and diluted to 1000 mL.

For the determination of solubility in water, samples were vortexed briefly to suspend visible particles, and then sonicated for 15 minutes at 37°C before filtering through 0.45 μm polytetrafluoroethylene (PTFE) filters (Chromatographic Specialties, Canada) into glass vials for analysis.

For solubility in simulated gastric and intestinal fluid, samples were vortexed briefly to suspend visible particles, and subsequently sonicated for 60 minutes at 37°C before filtering through 0.45 μm PTFE filters into glass vials for analysis. Filtered samples contained only particles smaller than 0.45 μm. Filtered samples were analyzed using a Thermo Ultimate 3000 RS UHPLC system with a quaternary pump delivering a binary gradient of 0.2% phosphoric acid (HPLC grade, VWR) in HPLC grade water (Fisher Scientific) and HPLC grade acetonitrile (Fisher Scientific) through an Agilent Poroshell EC-C18 100 × 2.1 mm, 2.7 μm column at 0.400 mL/min. Gradient was linearly increased from 10% acetonitrile to 100% acetonitrile over a period of 5 minutes. The column was equilibrated with the starting conditions for 3.3 minutes before next injection. Column oven was set to 40°C and data collected at 375 nm. Particle size of the different quercetin formulations in water was measured by means of a Malvern Mastersizer 3000 Laser Diffraction Particle-size analyzer.

Morphological Evaluation

Atomic force microscopy (AFM) image analysis was performed to gain topographical information of Quercetin LipoMicel. ICSPI nGauge AFM (ICSPI Corp., Canada) revealed nanoscale insights and a three-dimensional surface profile using micro-electro-mechanical systems technology (Figure 1).

Subjects and Study Design

Twelve healthy volunteers participated in an open, crossover bioavailability study performed with three different commercial quercetin products. Study participants were of both sexes and aged between 21–65 (5 male and 7 female)—with BMIs under 30. Participants were non-smokers, were not taking any prescribed

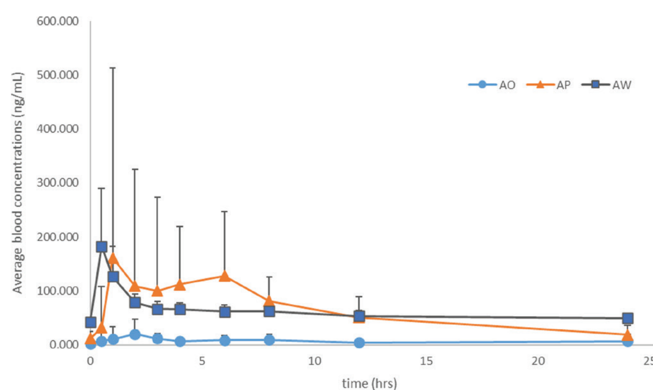

Figure 1. Pharmacokinetic profile of quercetin in study participants. Plasma concentrations after the oral administration of quercetin formulated in different treatments at a total dose of 500 mg. AO (free quercetin), AP (Quercetin Phytosome), AW (Quercetin LipoMicel). Values are means ± SD, $n = 12$ for each point. AW significantly different from AO treatment, $P < 0.005$ performed with ANOVA followed by post hoc *t* tests (Bonferroni Correction).

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medication and were not allergic to the treatment products or the provided food.

Each treatment was administered in a total dose of 500 mg quercetin to the participants. The treatments included one hard capsule of 500 mg free quercetin, two gelatin capsules of 250 mg Quercetin Phytosome Complex, or two soft-gelatin capsules of 250 mg Quercetin LipoMicel. The washout period between the treatments was one week. In contrast to hard capsules consisting of "two-pieces", a soft gel capsule represents a one-piece/unitary package containing a liquid, a suspension, or a semisolid—imbedded between gelatin outer layers [14, 15]. Such soft gel delivery systems have many advantages over other traditional dosage forms e.g., tablets and/or hard capsules, as aforementioned.

Twenty-four hours before each treatment, participants were instructed to avoid consuming quercetin-containing food such as capers, onions, green tea or fruits like apples, berries, grapes, or any supplements containing quercetin. Each participant acted as their own control. On the day of the trials, participants were asked to arrive after an overnight fast. Time zero blood samples were taken upon arrival. Next, each participant received their treatment of quercetin gelatin capsules (one of the three samples), and treatments were consumed with a glass of water along with a standardized breakfast consisting of one hardboiled egg with ham and cheese served in a commercial brioche bun. Capillary whole blood was collected at time points 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours. A standardized lunch consisting of tofu soup and rice along with an optional milk tea was served after the 4-hour blood sample. Dinners were not standardized; participants could consume any meal that does not contain foods as listed above. Coffee, juice, or water could be consumed in any volumes and at any time during the course of the study. However, other than the optional milk tea, no other tea-based beverage was consumed.

At each blood sampling time point, participants first washed their hands thoroughly with soap and warm water. A study assistant wiped the finger to be pricked for blood with a disposable alcohol wipe and lanced the participant's finger with a single-use lancet. The first drop of blood was wiped off with a sterile cotton gauze, and 50 µL of blood were collected into pre-labelled microcentrifuge tubes mixed with 5 µL of 10% w/w ascorbic acid in water. Samples that were not processed the same day were kept frozen at −20°C until further processing and analysis. Processed samples were analyzed by LC-MS within 24 hours after processing.

Ethical Considerations

In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants involved in the study. The volunteers were assured that declining to participate in the study or leaving the study at any point would not affect their relationship with ISURA.

Sample Preparation and Analysis

All samples collected during the multiple product tests were immediately frozen as whole blood. Blood samples from the same week are batched together and run as a sequence on LC-MS. For sample preparation, whole blood samples were first thawed at room temperature and then 50 µL of blood were treated with 100 µL of β-glucuronidase (from *Helix pomatia*, Millipore-Sigma, ≥100,000 IU diluted to 330 IU) in pH 5 buffer and incubated for one hour at 37°C. (-)-Epicatechin (Millipore-Sigma) was included as internal standard before sample analysis. 400 µL of ethanol (99%, Commercial Alcohol, Canada) was added to extract the samples. Samples were sonicated while maintained in a water bath at room temperature for 15 minutes. After extraction, tubes were centrifuged at 16,000 × G for 5 minutes at 25°C. The supernatant was transferred onto a microplate for LC-HRMS analysis. Processed samples were analyzed using a Thermo Vanquish UHPLC system coupled to a Thermo QExactive Orbitrap Mass Spectrometer. Briefly, liquid chromatography was carried out with a binary solvent gradient progressing from 10% A to 100% B in 5 minutes and equilibrated for 3.5 minutes before the next injection. The mobile phases were 0.5% formic acid in water in A and 0.5% formic acid in acetonitrile in B. A Phenomenex Kinetex PS C18, 100 mm × 2.1 mm, 2.6 µm column was used to perform the separation at a flow rate of 400 µL/min. LC-MS grade solvents and formic acid are obtained from Fisher Scientific (Canada).

The Orbitrap mass spectrometer was calibrated at 70,000 resolution with an accepted range for mass deviation of +/− 5.0 ppm using Thermo Pierce LTQ Velos ESI Positive Ion Calibration Solution and Thermo Pierce ESI Negative Ion Calibration Solution. To reduce interference with sample matrix, the mass spectrometer was operated in Parallel Reaction Monitoring (PRM) Mode with heated electrospray at a resolution of 35,000 and isolation window of 1.0 m/z. Epicatechin (internal standard) was detected as a hydrogen adduct with a product ion of 139.0388. Quercetin was detected as a hydrogen adduct with product ions of 153.0182, 229.0495, 257.0442, 165.0183, and 137.0235.

Data were collected using Thermo Xcalibur 5.0 and analyzed with Thermo TraceFinder 5.0 software with default mass tolerance set to 5.00 ppm. Concentrations of quercetin in capillary whole blood were determined based on internal standard calibration with a 6-point calibration curve using quercetin dihydrate as the chemical standard (Millipore Sigma).

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https://doi.org/10.33211/jnhpr.17

Statistical Analysis

Calculated concentrations were recorded with Microsoft Excel and calculated on a per individual basis using each participant as his/her own control, using aggregated averages. Results of the pharmacokinetic study are reported as difference of means ± SD ($n = 12$) as a method of converting all variance of the individual values to a similar scale. Statistical data analysis was performed by ANOVA followed by post hoc t tests (Bonferroni Correction). Data were considered significant at $P < 0.05$.

Results

Solubility

Results of the *in-vitro* solubility studies performed with different formulations of quercetin are summarized in Table 1. Considering the solubility in gastric conditions (pH 1.2), LipoMicel had the highest stability—protecting quercetin against the premature degradation in the stomach. Intestinal solubility of quercetin (pH 6.8) could be substantially improved by using new technologies such as LipoMicel or Phytosome formulations. This may correlate with a smaller particle size of quercetin aggregates when encapsulated into carriers as compared to free quercetin. Conversely, free quercetin's poor solubility in water and gastric media seemed to be associated with its large aggregate particle size as demonstrated in Table 1.

Pharmacokinetic Properties

Three commercially available quercetin products were evaluated pharmacokinetically *in vivo*. The efficacy of the LipoMicel delivery form on the bioavailability of quercetin in the body was compared to that of free quercetin and the phytosome formulation. Plasma concentrations after the oral administration of a total dose of 500 mg quercetin formulated in the three different products were measured.

No withdrawal by any subject occurred during the course of the trial.

The quercetin plasma concentrations plotted against time are displayed in Figure 1 for each of the individual preparations. As illustrated, a significantly higher blood concentration (ng/mL) of quercetin was achieved when administered by the LipoMicel formulation as compared to free quercetin. The LipoMicel formulation attained a peak blood concentration of quercetin (C_{max}: 182.85 ng/mL) within the shortest period of time (T_{max}: 0.5 h). Table 2 presents the individual pharmacokinetic parameters—such as C_{max}, T_{max} and $t_{½}$—obtained with the different dosage forms. 8- and 9-fold increases in AUC and C_{max} were attained with LipoMicel in contrast to free quercetin; 10-fold higher quercetin blood concentrations were still measured after 12 hours. The LipoMicel formulation achieved an increase of roughly 18% in C_{max} including a 2-fold reduction in T_{max}—when compared to Quercetin Phytosome. The AUC for Quercetin Phytosome was slightly higher than for Quercetin LipoMicel (1536.00 +/− 115.66 ng h/mL vs 1477.27 +/− 25.57), but longer steady state levels of quercetin were provided by LipoMicel.

Morphological Evaluation

A 3-dimensional reconstruction of the surface of the LipoMicel formulation was created using nGauge AFM. AFM image analysis revealed nanoscale insights of LipoMicel showing quercetin dispersed in microdroplets with a distinct spherical shape (Figure 2).

Safety

No adverse events or GI intolerances were reported throughout the trial.

Discussion

A major factor limiting the clinical application of quercetin is its poor pharmacokinetic profile. Therefore, various galenic formulations have been designed in an effort to improve quercetin's rate of absorption.

In the present study, a formulation designed and manufactured by Natural Factors was found to significantly increase the *in vivo* bioavailability of quercetin. By encapsulating quercetin within a liquid micelle matrix, the (LipoMicel) delivery system was associated with enhanced permeability and retention effects—with elevated blood concentrations of quercetin.

It has been reported that quercetin formulated into a lecithin-based Phytosome delivery system could substantially improve its solubility and bioavailability in humans [16]. In the case of the LipoMicel technique, a

Table 1. Solubility and particle size of different quercetin formulations.

Formulation	Water (mg/mL)	Simulated gastric (mg/mL)	Simulated intestinal (mg/mL)	Particle size (μm)
Free Quercetin	1.17	0.477	0.086	217
Quercetin LipoMicel	0.034	0.001	1.768	110
Quercetin Phytosome	8.217	10.788	10.925	20.3

Note: Quercetin tested in water, simulated gastric fluid pH 1.2; and simulated intestinal fluid pH 6.8. Particle size measured in water.

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Table 2. Pharmacokinetic parameters obtained after oral administration of different quercetin formulations.

Formulation	AUC_{0-24} (ng h/mL)	C_{max} (ng/mL)	T_{max} (hours)	$t_{1/2}$ (hours)
AO (free Quercetin)	172.87 ± 12.21	19.77 ± 27.29	2 ± 0.15	11.66 ± 0.55
AW (Quercetin LipoMicel)	1477.27 ± 25.57*	182.85 ± 106.64*	0.5 ± 0.02*	8.29 ± 0.49*
AP (Quercetin Phytosome)	1536.00 ± 115.66	150.27 ± 61.43	1 ± 0.30	6.02 ± 0.52

Note: Results are expressed as the mean ± standard deviation; $n = 12$. One-way ANOVA with post hoc *t*-tests (Bonferroni Correction). *$P < 0.005$ in comparison to treatment AO.
Abbreviations: C_{max} maximum plasma concentration; AUC area under the concentration-time curve; $t_{1/2}$ elimination half-life.

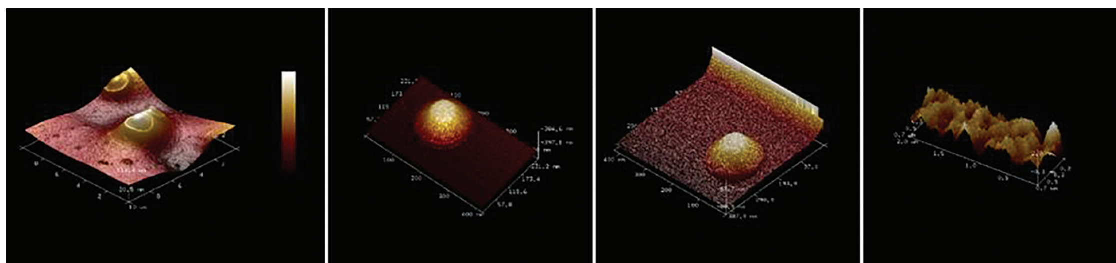

Figure 2. Topography AFM images of Quercetin LipoMicel formulation in 3-dimensional representation.

liquid micelle matrix that disperses quercetin into tiny micro-droplets (Figure 1) resulted in greater bioaccessability and absorption of the compound (Table 1). Oral administration of LipoMicel allowed for better gastric stability and intestinal solubility of quercetin compared to free quercetin. The LipoMicel formulation was associated with a significant improvement of AUC, C_{max} and T_{max}—tested at a standardized dose of 500 mg non-modified quercetin. It is noteworthy that approximately, 8- and 9-fold increases in AUC and C_{max} were attained when using LipoMicel in contrast to free quercetin. 10-fold higher quercetin blood concentrations were measured after 12 hours. Comparing the two formulations—Quercetin Phytosome and Quercetin LipoMicel, an increase of roughly 18% in C_{max} including a 2-fold reduction in T_{max} was accomplished by the LipoMicel carrier design. Both products appeared to enhance bioavailability more than unmodified quercetin. Unlike the other treatments, the LipoMicel formula reached a peak blood concentration of quercetin within a minimum time of 30 mins. Over the total measurement period—significant higher, stable blood concentrations of quercetin were observed with LipoMicel in relation to free quercetin. Similarly, the use of LipoMicel resulted in improved gastric stability and intestinal solubility of quercetin compared to free quercetin when tested in simulated gastrointestinal conditions. This is supported by the early rise of quercetin *in vivo*—with peak blood concentrations at 0.5 h—as well as with sustained high concentrations throughout the 24 h study period. Delivery vehicles such as LipoMicel or Phytosome that encapsulate quercetin at an aggregate particle size of ≤110 μm were associated with greater intestinal solubility, as suggested in *in vitro* experiments. Conversely, a larger aggregate particle size such as that of free quercetin was associated with poor solubility in water and in simulated static gastrointestinal conditions.

Both delivery systems, LipoMicel and Phytosome, appeared to be proficient carriers for enhancing the *in-vivo* absorption of quercetin. While the Phytosome formulation appears to improve quercetin bioavailability by increasing its solubility in water, the LipoMicel formulation demonstrates an alternate route to increased bioavailability: one that may not be related to solubility. One possible explanation for the greater bioavailability of Quercetin LipoMicel could involve bypass of efflux by P-glycoprotein (P-gp) transport protein, which is extensively present along the intestinal tract [17, 18]. However, to evaluate this possibility, further experiments perhaps with caco-2-cell models might be helpful to gain insight into mechanisms of intestinal permeability and stability. Furthermore, long-term *in vivo* studies with quercetin on a larger sample size are required in order to obtain more comprehensive pharmacokinetic data. Also, the effect of different food substrates on quercetin absorption, including differences between fasting and various standardized meals should be studied in future investigation.

Conflict of Interest

JS, CC, KR, MD, and YCK are employees of Isura and have no conflicts. MH and ML receive consulting fees from the Factors Group of Companies. RG is the owner of the Factors Group of Companies. Isura is a not-for-profit independent organization.

Authors' Contributions

JS, CC, KR, MD, YCK: contributed equally to this work.

JS: helped to design research, analyzed and interpreted data and drafted the original manuscript.

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CC: designed and supervised research and contributed to drafting the manuscript—original draft preparation.

KR, MD, YCK: conducted experiments and contributed to drafting the manuscript—review and editing.

MH, ML, RG: contributed to drafting the manuscript—review and editing.

All authors gave final approval of the version to be published.

Funding

The study was funded by Natural Factors.

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Article Information

Managing Editor: Kieran Cooley
Peer Reviewers: Olina Dagher, Kent TJ Chen
Article Dates: Received Apr 20 21; Accepted Jun 29 21; Published Jul 26 21

Citation

Please cite this article as follows:
Solnier J, Chang C, Roh K, Du M, Kuo YC, Hardy M, Lyon M, Gahler R. Quercetin LipoMicel—A Novel Delivery System to Enhance Bioavailability of Quercetin. Journal of Natural Health Product Research. 2021 Jul 26: 3(2). https://jnhpresearch.com/index.php/jnhpr/article/view/17
DOI Link: https://doi.org/10.33211/jnhpr.17

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