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Do Liposomal Vitamin C Formulations Have Improved Bioavailability? A Scoping Review Identifying Future Research Directions

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ABSTRACT

Due to the essential requirement of vitamin C (ascorbate) by humans, formulation of the vitamin to increase its bioavailability is of relevance, particularly for those with higher requirements for the vitamin. In this scoping review, studies assessing the bioavailability of liposomal versus non-liposomal ascorbate were identified through database and manual searching and relevant pharmacokinetic data were extracted. Of the 321 studies identified, 10 were included in the final review. Seven of the trials used randomised crossover designs, one used parallel groups and two were non-randomised. Vastly different liposomal formulations, ascorbate doses (0.15–10 g) and sample collection durations (4–24 h) were used, thereby making it difficult to directly compare the studies. Nevertheless, nine of the studies showed higher bioavailability of liposomal versus non-liposomal ascorbate: 1.2–5.4-fold higher Cmax and 1.3–7.2-fold higher AUC. However, none of the studies assessed ascorbate elimination; therefore, it is uncertain whether the ratios of liposomal to non-liposomal ascorbate in urine are equivalent to those observed in plasma. Furthermore, only two of the studies assessed in vivo cellular uptake and only two assessed potential biological effects. Thus, future studies should include urinary elimination and cellular uptake kinetics, assess participants with low baseline status and investigate potential biological effects.

Summary

- Due to the essential requirement of vitamin C by humans, formulations to increase its uptake into the body are of relevance, particularly in those with higher requirements for the vitamin.
- In this review, studies assessing the uptake of liposomal versus non-liposomal vitamin C were investigated; liposomal vitamin C comprising the vitamin encapsulated within lipids.
- Ten studies were identified, which administered different liposomal formulations, vitamin C doses (0.15-10 g) and sample collection durations (4–24 h).
- Nine of the studies showed higher uptake of liposomal vitamin C. Future studies should assess urinary excretion, cellular uptake and biological effects of liposomal vitamin C.

1 | Introduction

Vitamin C (ascorbate) is an essential nutrient for humans due to evolutionary loss of function of L-gulonolactone oxidase, the terminal enzyme in the biosynthetic pathway [1]. Thus, unlike most other animal species, which can synthesise ascorbate in their livers or kidneys [2], humans and other ascorbate-requiring animals must obtain the vitamin through dietary intake, with fresh fruit and vegetables being the primary dietary source of the vitamin [3]. As a result of the inability to synthesise the vitamin endogenously, ascorbate requiring animals express intestinal sodium-dependent ascorbate transporters (SVCT1) to actively uptake the vitamin from the diet [4]. This transporter is also expressed in renal tubules to reuptake ascorbate that has passed through glomerular filtration; this helps to conserve the vitamin during times of low dietary intake. Another transporter isoform, SVCT2, is responsible for the uptake of the vitamin into cells and tissues of the body [5]. The vitamin accumulates at variable concentrations in different tissues based on enzyme cofactor requirements [4].

The active transporter mechanisms help to maintain ascorbate homeostasis in the body and result in sigmoidal saturation kinetics in plasma [4]. In general, dietary intakes of 100 to 200 mg/day of ascorbate provide adequate to saturating circulating concentrations of 50 to 70 μmol/L in healthy individuals [6, 7]. It should be noted, however, that certain demographic, lifestyle and health factors affect ascorbate status and intake requirements [8]. For example, ascorbate status is closely associated with weight, with people living with obesity having higher intake requirements for the vitamin [8]. People with various health conditions, such as diabetes and those undergoing cancer therapy, also have lower ascorbate status and a higher intake requirement to reach adequate circulating concentrations [9, 10].

It can be challenging for some people to acquire an optimal dietary intake of ascorbate, particularly in those with factors that increase requirements; therefore, people with health concerns often resort to supplementation. In general, there is little difference in the bioavailability of ascorbate obtained from the diet versus synthetic sources [11]. However, recent research has indicated that liposomal ascorbate may have enhanced bioavailability [12]. Ascorbate is encapsulated within lipid vesicles, comprising natural or synthetic phospholipids with or without other components, using a variety of conventional and innovative encapsulation methods [13, 14]. The vesicles can vary in size from 20 nm to > 1 μm and are absorbed via SVCT-independent mechanisms, for example, endocytosis [15]. In this scoping review, the in vivo pharmacokinetics of liposomal versus non-liposomal ascorbate is assessed in published trials to determine if, and to what extent, liposomal ascorbate provides improved bioavailability relative to non-liposomal ascorbate. Knowledge gaps are also identified for future research.

2 | Methods

A scoping review of published literature was carried out using the National Library of Medicine PubMed database (up to 24 March 2025). The following Boolean search string was used to identify potential papers for inclusion: liposom* AND (vitamin C[title/abstract] OR ascorbic acid[title/abstract]). No limits were applied regarding date of publication. This search strategy resulted in the identification of 310 publications and a further 11 were identified through manual searching (Figure 1). Following removal of 26 reviews and non-English articles, title screening identified 245 records not within topic scope. Forty-nine reports were assessed for eligibility via abstract or full text screening. Of these, 39 studies were excluded due to absence of a non-liposomal comparator group, co-encapsulation with other compounds, use of ascorbate conjugates or derivatives, cell culture studies, skin studies and animal studies, the latter of which differ in oral vitamin C uptake relative to humans as most animals can synthesise their own vitamin C endogenously [16]. Ten papers were included in the final review; these comprised predominantly randomised crossover trials but also included a parallel group trial and two non-randomised trials. Data extracted from the full texts was tabulated and included: author and year, study design, participants, ascorbate (liposomal and non-liposomal control) doses, sample types (plasma or leukocyte), sample collection duration, baseline ascorbate concentrations, Cmax, area under the curve (AUC), ascorbate elimination and biological effects. Ascorbate conversions: μmol/L = mg/dL × 56.8; or mg/L × 5.68; or μg/mL × 5.68; or ng/ml × 5.68 × 10^{-3}. The corresponding authors of the publications were contacted by email to obtain additional information if required. The findings of the studies were summarised in the table below with a narrative synthesis of the findings.

3 | Results

The bioavailability of liposomal ascorbate relative to non-liposomal ascorbate control was assessed in seven randomised crossover trials [17–21], one parallel group trial [22] and two non-randomised trials [23, 24], published between 2016 and 2024. Relevant data from these studies is shown in Table 1. All 10 studies assessed plasma ascorbate concentrations before and after intervention, and two also assessed leukocyte ascorbate concentrations [17, 23]. Only two studies assessed potential biological effects of the interventions [21, 25]. The pharmacokinetic studies varied in ascorbate doses administered (from 0.15 to 10 g) and duration of sample collection (from 4 to 24 h); nevertheless, all but one [23] showed higher plasma bioavailability (1.2–5.4-fold higher Cmax and 1.3–7.2-fold higher AUC) of liposomal vitamin C relative to non-liposomal vitamin C. All of the studies had industry funding and/or authors who were employed by companies.

In the first randomised placebo-controlled crossover study, by Davis and colleagues [21], 11 fasting men and women were administered either placebo, non-liposomal ascorbate or liposomal ascorbate at a dose of 4 g (Figure 2). The mean baseline ascorbate status in the participants was nearly 50 μmol/L, which is considered adequate. Blood samples were collected over a short 4-h duration, which is a limitation as the time course was truncated before plasma ascorbate had returned to baseline, thus limiting the AUC findings. Nevertheless, the liposomal ascorbate provided a 1.4-fold increase in plasma AUC relative to non-liposomal ascorbate (Table 1). Antioxidant

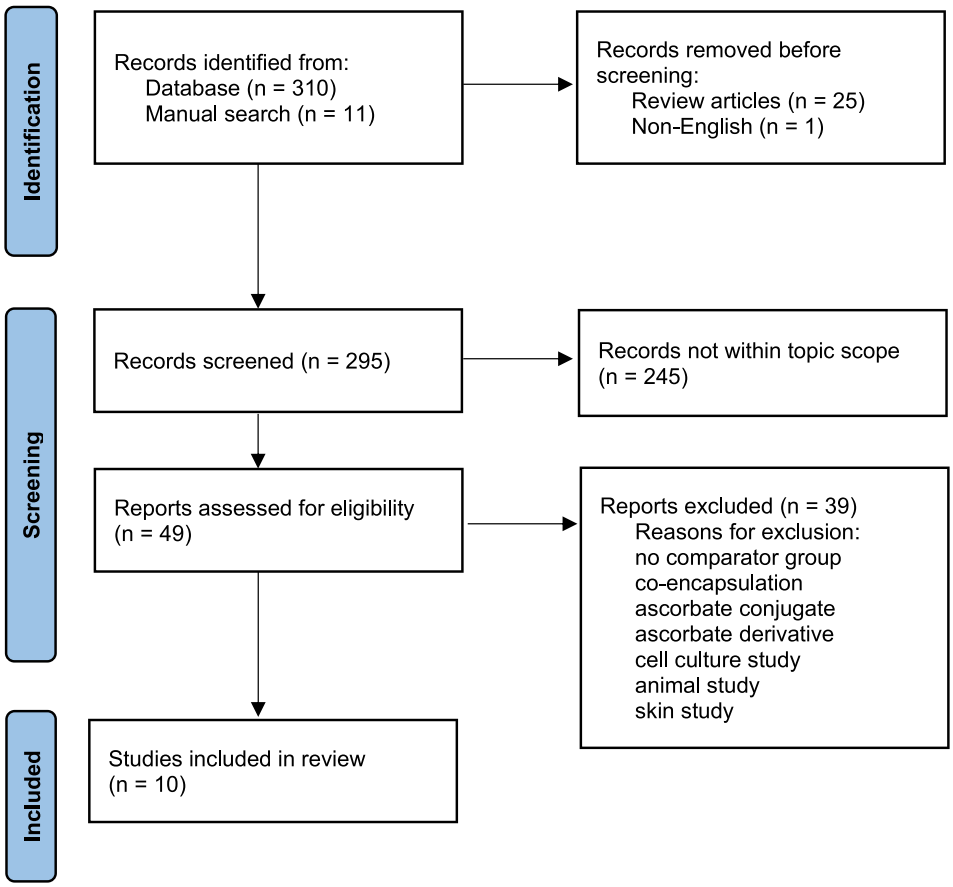

FIGURE 1 | Flow diagram of study selection.

effects were investigated using an ischemia–reperfusion injury test. Both liposomal and non-liposomal ascorbate provided equivalent protection against lipid oxidation following forearm ischemia [21].

A small non-randomised study was carried out by Mikirova and colleagues [23] in five adults (fasting status unknown) who were administered 5 g of non-liposomal sodium ascorbate followed by an equivalent dose of liposomal sodium ascorbate after a 6-day washout period (Table 1). Blood samples were collected over a short 6-h duration for extraction of plasma and leukocytes. The researchers observed a correlation between baseline plasma ascorbate concentrations and maximum concentrations achieved following intervention, therefore, all subsequent data was reported as a ratio relative to baseline concentrations. No significant difference was observed in the AUC of liposomal relative to non-liposomal sodium ascorbate (Figure 3A). The AUC values for leukocytes were not reported, but were stated as being 50% larger for liposomal ascorbate relative to non-encapsulated ascorbate (Figure 3B), with the amount of uptake depending on initial intracellular concentrations.

Lukawski and colleagues [22] subsequently carried out a parallel group trial (randomisation and blinding unknown) in which 20 fasting men and women were administered either liposomal or non-liposomal ascorbate at a dose of 10 g (Table 1). Blood samples were collected over a short 6-h duration, however, baseline ascorbate values were not reported. Liposomal ascorbate was reported to provide nearly two-fold higher plasma Cmax and AUC (Table 1; the figure is not shown due to journal copyright).

In an open-label randomised crossover trial by Gopi and Balakrishnan [20], 24 fasting adults were administered liposomal or non-liposomal sodium ascorbate at a dose of 1 g. Blood samples were collected over 24 h, however, baseline ascorbate values were not reported. Liposomal ascorbate provided approximately two-fold higher plasma Cmax and AUC (Table 1; the figure is not shown due to journal copyright).

In a double-blind randomised crossover trial, Jacob and colleagues [19] administered a lower dose of 150 mg liposomal or non-liposomal ascorbic acid to eight fasting adults and collected plasma samples over 24 h (Table 1). The reported baseline ascorbate concentrations were very low, that is, equivalent to only 2 μmol/L. The liposomal product provided nearly six-fold higher plasma Cmax and AUC than the non-liposomal ascorbic acid (Figure 4).

Joseph and colleagues [18] supplemented 14 fasting adult males and females with liposomal or non-liposomal calcium ascorbate at a dose of approximately 400 mg and collected plasma samples over 12 h in a double-blind randomised crossover study (Table 1). Baseline plasma ascorbate concentrations were not reported. Liposomal calcium ascorbate provided 5.6-fold higher Cmax and 7.2-fold higher AUC than the non-liposomal product (Figure 5). There was no difference between administering the liposomal product in the form of a tablet or capsule.

TABLE 1 | Bioavailability studies comparing liposomal with non-liposomal vitamin C.

Author, year	Study design	Participants	Ascorbate doses	Samples (timing)	Baseline ascorbate	Cmax (fold)	AUC (fold)
Purpura et al., 2024 [17]	Randomised crossover trial	27 adults (19 males, 8 females)	500 mg AA 500 mg lipoAA[a]	Plasma AA Leukocyte AA (0–24 h)	Not reported	Plasma (1.4-fold) AA 6.3 μg/mL LipoAA 8.6 μg/mL Leukocytes (1.3-fold) AA 5.1 μg/mL LipoAA 6.4 μg/mL	Plasma (1.3-fold) AA 57 LipoAA 72 Leukocytes (1.1-fold) AA 49 LipoAA 53
McGarry et al., 2024 [25]	Randomised crossover trial	12 adults (7 males, 5 females)	1 g AA 1 g lipoAA[b]	Plasma AA (0–6 h)	AA 39 or 44 μmol/L	Not reported See Figure 6	Not reported
Zmuda et al., 2024 [26]	Randomised crossover trial	10 adults	1 g AA 1 g lipoAA[c]	Plasma AA (0–24 h)	Not reported	AA 23 mg/L LipoAA 28 mg/L (1.2-fold)	AA 342 LipoAA 445 (1.3-fold)
Wen et al., 2022 [24]	Non-randomised trial	11 adults	1 g AA 1 g lipoAA[b]	Plasma AA (0–8 h)	Reported as: AA 0 LipoAA 0	AA 2.2 μg/mL LipoAA[b] 7.3 μg/mL (3.3-fold)	AA 37 LipoAA[b] 86 (2.3-fold)
Joseph et al., 2021 [18]	Randomised crossover trial	14 adults (10 males, 4 females)	400 mg CaA 400 mg lipoCaA[c]	Plasma AA (0–12 h)	Not reported	CaAsc 52 μmol/L LipoCaAsc 282 μmol/L (5.4-fold)	CaAsc 311 LipoCaAsc 2232 (7.2-fold)
Jacob et al., 2021 [19]	Randomised crossover trial	8 adult males	150 mg AA 150 mg lipoAA[d]	Plasma AA (0–24 h)	AA 0.03 mg/dL LipoAA 0.04 mg/dL	AA 1.2 mg/dL LipoAA 6.7 mg/dL (5.6-fold)	AA 9.4 LipoAA 55 (5.9-fold)
Gopi and Balakrishnan, 2021 [20]	Randomised crossover trial	24 adults	1 g NaA 1 g lipoNaA[e]	Plasma AA (0–24 h)	Not reported	AA 2.2 mg/dL LipoAA 5.2 mg/dL (2.4-fold)	AA 32 LipoAA 56 (1.8-fold)
Lukawski et al., 2020 [22]	Parallel group trial	20 adults (10 males, 10 females)	10 g NaA 10 g lipoNaA[f]	Plasma AA (0–6 h)	Not reported	AA 180 μmol/L LipoAA 303 μmol/L (1.7-fold)	AA 776 LipoAA 1360 (1.8-fold)

(Continues)

TABLE 1 | (Continued)

Author, year	Study design	Participants	Ascorbate doses	Samples (timing)	Baseline ascorbate	Cmax (fold)	AUC (fold)
Mikirova et al., 2019 [23]	Non-randomised trial	5 adults	5 g NaA 5 g lipoNaA[g]	Plasma AA Leukocyte AA (0–6 h)	Ratio of baseline: 1	Plasma Not reported Leukocytes Not reported	Plasma (1.03-fold) NaA 773 LipoNaA 799 Leukocytes Not reported
Davis et al., 2016 [21]	Randomised crossover trial	11 adults	4 g NaA 4 g lipoNaA[h]	Plasma AA (0–4 h)	AA 0.84 mg/dL	Not reported See Figure 2	NaA 7.6 LipoNaA 10.3 (1.4-fold)

Abbreviations: AA, ascorbic acid; AUC, area under the curve (mass * hour/volume); CaA, calcium ascorbate; Cmax, maximum concentration; NaA, sodium ascorbate.
Conversions: 1 μg/mL = 5.68 μmol/L; 1 mg/dL = 56.8 μmol/L; 1 mg/L = 5.68 μmol/L.
[a]LipoVantage: AA, sunflower lecithin with a proprietary ratio of phospholipids, gum arabic and alginate polysaccharides.
[b]LivOn Labs Lypo-Spheric/Altrient Vitamin C consisting of cold-processed liposome-encapsulated vitamin C.
[c]Ascorbic acid with glycerol, sunflower phosphatidylcholine and maltodextrin.
[d]Double Nutri: vitamin C, acacia gum, xanthan gum, citric acid and lecithin (with high-pressure homogenisation).
[d]Hybrid-FENUMAT: lipidated CaAsc, lecithin, fenugreek galactomannan and CaA.
[d]Zeal-AA: fibre-reinforced-phospholipid (FRP) matrix-based vehicle and AA.
[e]Phospholipids and NaA.
[f]Soybean phosphatidylcholine, rapeseed lecithin and NaA.
[g]LivOn Lab Lypo-Spheric Vitamin C.
[h]Mixed natural phospholipids and NaA.

FIGURE 2 | Plasma bioavailability of liposomal versus non-liposomal sodium ascorbate. A randomised placebo-controlled cross-over trial in 11 fasting adults administered doses of 4 g sodium ascorbate either un-encapsulated or encapsulated and compared to placebo. Intravenous administration of an equivalent dose provided a Cmax of approximately 28 mg/dL (not shown). #$p < 0.01$ versus unencapsulated and placebo; ^$p < 0.001$ versus placebo. Data represent mean and SE. To convert mg/dL to μmol/L multiply by 56.8. From Davis et al [21], Creative Commons CC-BY-NC 3.0 Licence.

Wen and colleagues [24] carried out a non-randomised single-blind trial in which 11 fasting adults were administered 1 g non-liposomal ascorbic acid then liposomal ascorbic acid formulated by two different methods with 14 day washout periods between the interventions (Table 1). Blood samples were collected over 8 h, and baseline plasma ascorbate values were reported as zero. In subsequent personal communications with the authors, plasma ascorbate concentrations were reported as 8.1 to 8.6 μg/mL for the two groups, equating to 46 to 49 μmol/L, which is close to adequate. The liposomal product provided a 3.3-fold higher Cmax and a 2.3-fold higher AUC (Table 1). There were minimal differences between the two liposomal formulation methods (the figure is not shown due to journal copyright).

A double-blind randomised crossover trial was recently carried out by Zmuda and colleagues [26] to evaluate the pharmacokinetics of powdered liposomal ascorbic acid created by a method devoid of organic solvents. The trial was carried out in 10 fasting volunteers administered 1 g doses of liposomal and non-liposomal ascorbic acid (Table 1). Blood samples were collected over 24 h, although the baseline vitamin C concentrations were not reported. The liposomal form provided a 1.2-fold higher Cmax and a 1.3-fold higher AUC than the non-liposomal form (Figure 6).

McGarry and colleagues [25] carried out a double-blind randomised placebo-controlled crossover study in 12 non-fasting adults administered 1 g liposomal encapsulated ascorbic acid, 1 g ascorbic acid, phospholipids alone and placebo (Table 1). Average baseline ascorbic acid concentrations were reported to be 39–44 μmol/L, although the range of concentrations varied 10-fold (from 11 to 118 μmol/L) likely due to the participants

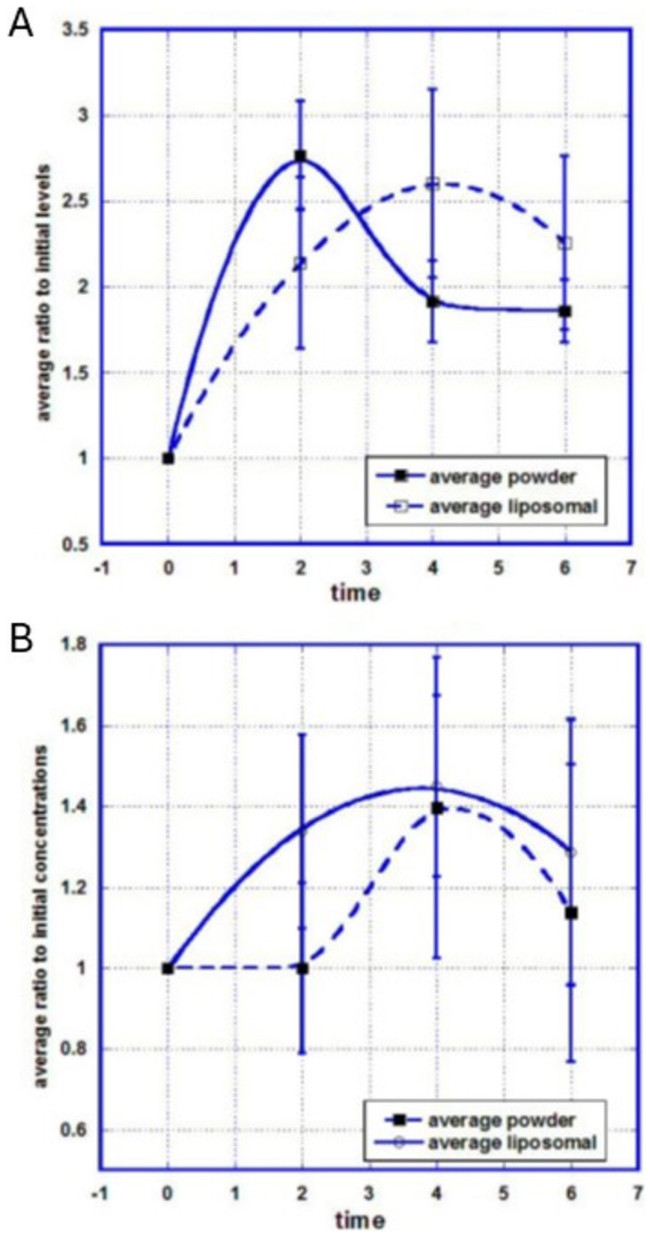

FIGURE 3 | Bioavailability of liposomal versus non-liposomal ascorbic acid in plasma (A) and leukocytes (B). A non-randomised trial in five adults administered doses of 5 g sodium ascorbate powder or the equivalent dose of liposomal product. Data are presented as ratio of ascorbate concentrations relative to initial levels. From Mikirovat e al [23], Open Access.

not fasting prior to study visits. Blood samples were collected for only 6 h. The liposomal ascorbic acid provided small, but significantly higher ($p < 0.01$) plasma concentrations over the duration of the 6-h study period (Figure 7). Potential biological effects were also assessed in this study; the liposomal encapsulated form provided about 5% more antioxidant capacity in serum than the non-liposomal form at the 2-h timepoint, but this did not translate to enhanced protection of cells and nucleic acids from oxidative damage in serum. Some serum cytokines showed differences between the liposomal and non-liposomal forms of ascorbic acid; there were small percentage decreases in interleukin-6 and macrophage inflammatory protein-1α at 2 h and a > 5% increase in interferon-γ at 6 h.

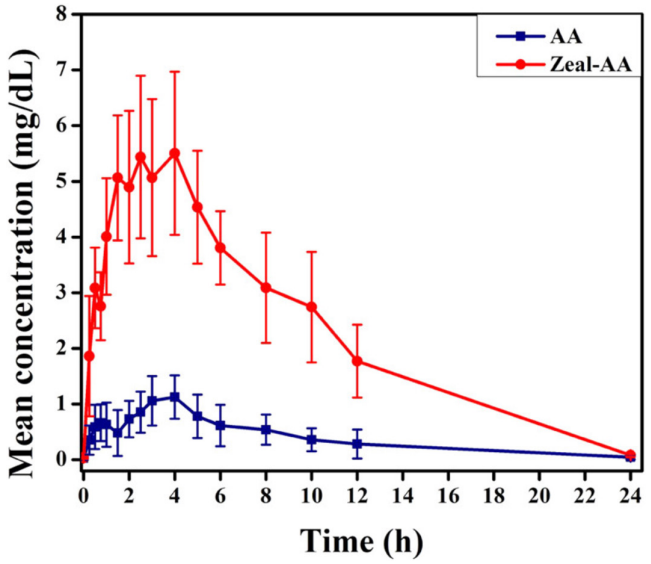

FIGURE 4 | Plasma bioavailability of liposomal versus non-liposomal ascorbic acid. A double-blind randomised crossover trial in eight fasting males administered doses of 150 mg ascorbic acid (AA) or the equivalent dose of liposomal ascorbic acid (Zeal-AA). Data represent mean and SD. To convert mg/dL to μmol/L multiply by 56.8. From Jacob et al [19], Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0).

Another recent double-blind randomised placebo-controlled crossover trial, carried out by Purpura and colleagues [17], also reported cellular ascorbate uptake. In this crossover trial, 27 fasting adults were administered liposomal or non-liposomal ascorbic acid at a dose of 500 mg and blood samples were collected over 24 h (Table 1). Baseline ascorbate values were not reported, however, in subsequent personal communications with the authors, plasma ascorbate concentrations were reported as 0.16-0.17 μg/mL for the two groups, equating to 0.9-1.0 μmol/L, which is extremely low. Liposomal ascorbic acid provided a 1.4-fold and 1.3-fold higher Cmax in plasma and leukocytes, respectively, and a 1.3-fold and 1.1-fold higher AUC in plasma and leukocytes, respectively (Figures 8A and B).

4 | Discussion

One of the first studies to assess the bioavailability of liposomal versus non-liposomal ascorbate was by Hickey and colleagues in 2008 [27]. This study, however, reported data from only two cases and was not included in this scoping review. Nine of the 10 studies included in this review reported higher plasma bioavailability of liposomal ascorbate relative to non-liposomal ascorbate [17–22, 24–26]. Reported values ranged from 1.2- to 5.4-fold higher Cmax and 1.3- to 7.2-fold higher AUC for the liposomal preparations. The highly variable ratios are perhaps not surprising based on the vastly different liposomal formulations, doses administered (ranging from 0.15 to 10 g of ascorbate), sample collection durations (ranging from 4 to 24 h) and baseline ascorbate concentrations (means ranging from approximately 1 to 50 μmol/L, with up to 10-fold variability within studies). Only two studies investigated cellular uptake [17, 23], which appeared to be comparable to plasma bioavailability [17]. Overall, there did not appear to be any clear dose-concentration relationship. For example, the seven-fold

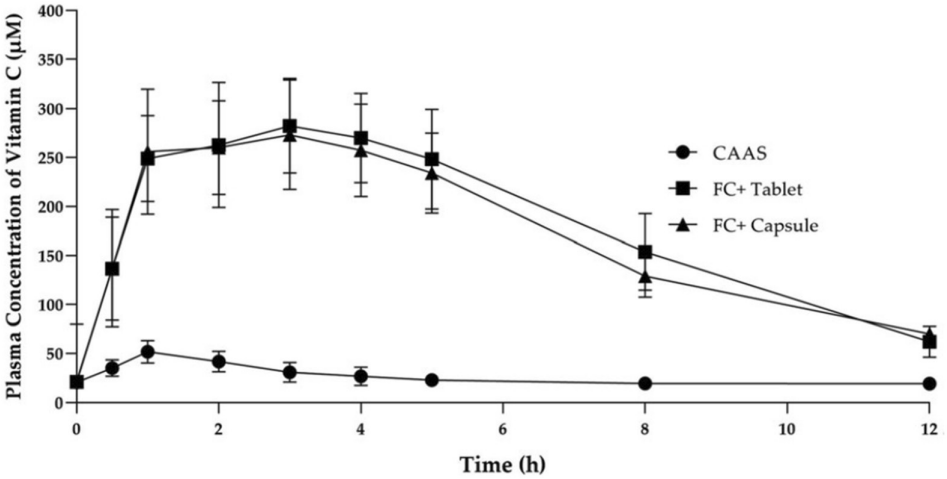

FIGURE 5 | Plasma bioavailability of liposomal versus non-liposomal calcium ascorbate. A double-blind randomised crossover trial in 14 adults administered doses of 400 mg calcium ascorbate tablets (CAAS) or the equivalent dose of liposomal product formulated into tablets or capsules. Data represent mean and SD. From Joseph et al [18], Creative Commons Attribution-NonCommercial 3.0 Unported Licence (CC BY-NC 3.0).

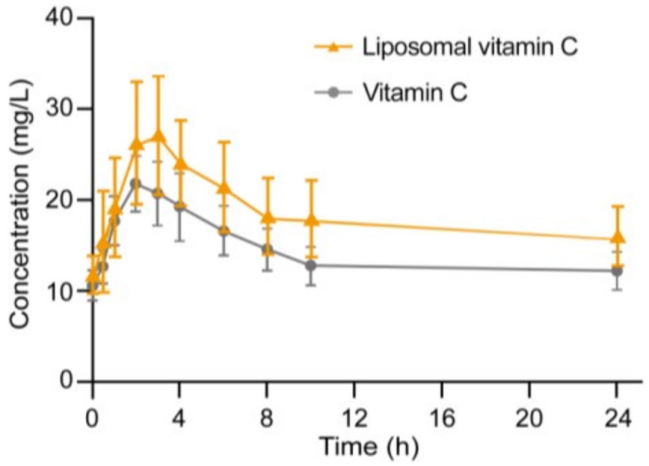

FIGURE 6 | Plasma bioavailability of liposomal versus non-liposomal ascorbic acid. A double-blind randomised crossover trial in 10 fasting adults administered doses of 1 g vitamin C or the equivalent dose of liposomal vitamin C. To convert mg/L to µmol/L multiply by 5.68. From Zmuda et al, 2024 [26], Creative Commons Attribution (CC BY) licence (https://creativecommons.org/licenses/by/4.0/).

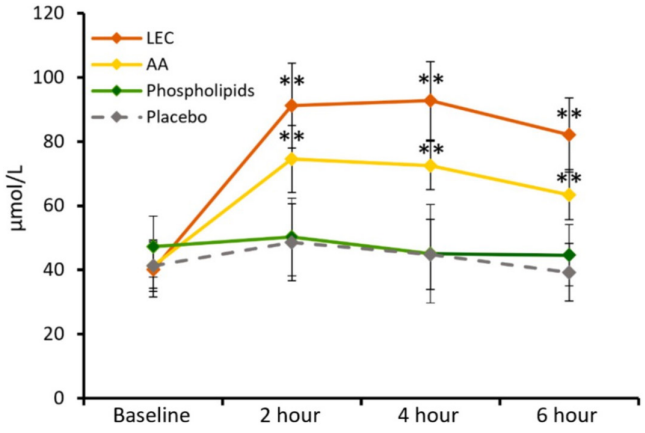

FIGURE 7 | Plasma bioavailability of liposomal versus non-liposomal ascorbic acid. A double-blind randomised crossover trial in 12 non-fasting adults administered doses of 1 g ascorbic acid (AA) or the equivalent dose of liposomal encapsulated vitamin C (LEC) and compared to phospholipids alone and placebo. Data represent mean and SE. $^{**}p < 0.01$. From McGarry et al, 2024 [25], Creative Commons Attribution (CC BY) licence (https://creativecommons.org/licenses/by/4.0/).

difference in liposomal ascorbate doses provided between the Jacob et al [19] and Gopi et al [20] studies (i.e., 0.15 vs 1 g) provided comparable Cmax and AUC values.

Differences in bioavailability between liposomal and non-liposomal forms of vitamin C would ideally translate to differences in biological effects. To date, only two studies have investigated potential biological effects [21, 25]. In the earlier study, which had a 1.4-fold difference in AUC between liposomal and non-liposomal ascorbate, both provided comparable protection against in vivo lipid oxidation following forearm ischemia [21]. In the more recent study, although an approximately 50% higher plasma uptake of liposomal vitamin C was indicated, only a small percentage increase in serum antioxidant potential at 2 h was observed in those administered the liposomal form, and this did not translate into improved protection against cellular or nucleic acid oxidation, although small differences in some cytokines were observed at the 2- or 6-h time points between the liposomal and non-liposomal forms [25]. The clinical significance of these small percentage differences is uncertain and likely to be minimal.

4.1 | Limitations of Included Studies

Most of the studies did not report baseline ascorbate concentrations [17, 18, 20, 22–24], and some reported only very low baseline values [17, 19], which could reflect issues with sample processing, storage or analysis [28], for example storage of plasma samples at −20 °C rather than -80 °C [19]. Although a majority of the studies utilised HPLC for analysis of vitamin C concentrations, two used fluorescence and colourimetric kits [23, 24], which can be less accurate than HPLC methods [29].

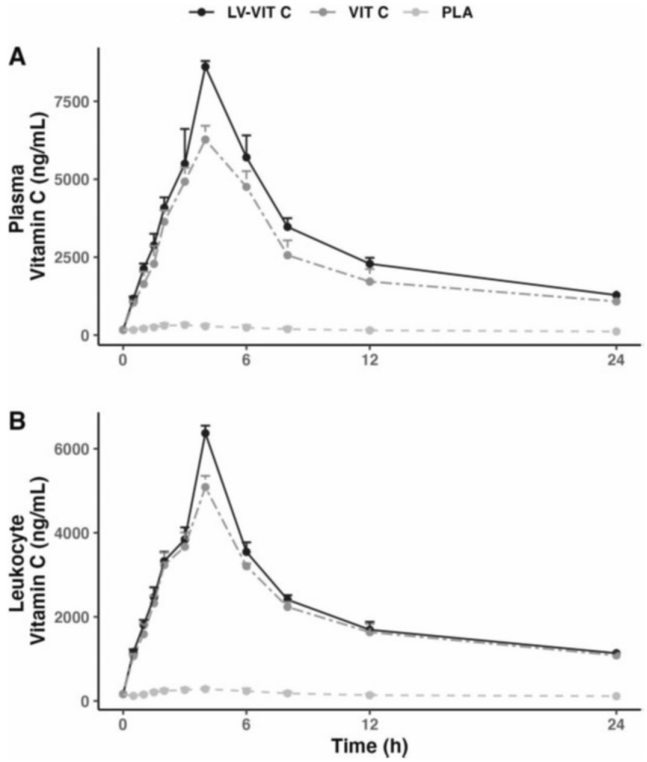

FIGURE 8 | Bioavailability of liposomal versus non-liposomal ascorbic acid in plasma (A) and leukocytes (B). A double-blind randomised placebo-controlled crossover trial in 27 fasting adults administered doses of 500 mg vitamin C (VIT C) or the equivalent dose of liposomal product (LV-VIT C) and compared to placebo (PLA). To convert ng/mL to μmol/L multiply by 5.68×10^{-3}. From Purpura et al [17], Creative Commons Attribution 4.0 International Licence (CC BY 4.0).

One study reported a 10-fold range of baseline ascorbate values in their participants, from deficient to saturating concentrations [25], which is a limitation as Cmax values correlate with baseline ascorbate concentrations [23]. In general, ascorbate peaks will only be observed in plasma following oral administration if participants already have adequate ascorbate status, i.e. around 50 μmol/L. If participants have less than adequate plasma ascorbate status at baseline, this indicates that their tissues will preferentially absorb ascorbate from the bloodstream and, thus, no clear plasma peak will be observed following administration. Whether this is also the case for liposomal ascorbate is uncertain and could explain some of the variability observed between liposomal and non-liposomal ascorbate Cmax and AUC ratios.

This premise is supported by the Joseph et al [18] and Jacob et al [19] studies, whereby participants had less than adequate vitamin C status at baseline (means < 23 μmol/L), which resulted in minimal plasma peaks in the unencapsulated ascorbate groups versus six- to seven-fold larger AUCs in the liposomal ascorbate groups in comparison. As such, the observed differences in plasma AUC between non-liposomal and liposomal ascorbate in those who are hypovitaminosis C may not be reflecting differences in uptake of oral ascorbate into the blood stream, but rather differences in tissue uptake of ascorbate from the bloodstream. In contrast, studies in which the participants had adequate vitamin C status at baseline (means approximately 50 μmol/L) had

TABLE 2 | Recommendations for future liposomal versus non-liposomal ascorbate studies.

Recommendations	Rationale
Assess urinary ascorbate elimination	To determine if urinary elimination ratios are comparable or different to plasma uptake ratios
Assess in vivo ascorbate uptake into cells and tissues	To determine if there are differences in body retention of the formulations
Assess duration of ascorbate repletion in depleted individuals using steady state study designs	This is a physiologically relevant scenario and could be carried out in people with low ascorbate intake or conditions predisposing to low ascorbate status e.g. obesity, diabetes
Assess biological effects of formulations if differences in repletion duration and/or tissue bioavailability are confirmed	This is a physiologically relevant scenario and outcomes could include oxidative stress, inflammation and immune function parameters

much smaller differences between the non-liposomal and liposomal AUCs (e.g., 1.3- to 1.4-fold) [21, 25, 26],

None of the studies reported ascorbate elimination over the sampling period. Thus, it is uncertain whether higher uptake of liposomal ascorbate may simply be reflected in greater elimination of the product. Assessment of ascorbate elimination helps determine if and how much of the administered ascorbate is retained in the body. Furthermore, some studies were only of short duration, for example, 4 to 6 h [21–23, 25], making it difficult to ascertain plasma clearance kinetics. The large disparity in types of liposomal formulations and ascorbate doses administered also make it difficult to directly compare the studies. The higher ascorbate doses administered in some of the studies, for example, 1–10 g [20–26], do not take into account the highly regulated dose-dependency of vitamin C kinetics and may influence the AUC of the non-liposomal vitamin C relative to the liposomal vitamin C, which is taken up by different mechanisms [4, 15]. Instead, longer duration steady-state study designs would provide more relevant information on comparative bioavailability than the current short-term pharmacokinetic studies.

4.2 | Future Research Directions

To determine if there are differences in elimination between liposomal and non-liposomal ascorbate, urinary excretion of ascorbate should be monitored (Table 2). If the ratio of excreted liposomal to non-liposomal ascorbate is comparable to that in plasma, then liposomal ascorbate may not have any added health benefits relative to non-liposomal ascorbate. If, however, the ratio of excreted liposomal to non-liposomal ascorbate is less than that observed in plasma, this may indicated better retention of liposomal ascorbate in the body. This could be confirmed by assessing in vivo uptake into cells and tissue to determine if more liposomal ascorbate is transported into cells (Table 2). Preliminary evidence indicates that there may be slightly higher uptake of liposomal ascorbate into leukocytes relative to non-liposomal ascorbate [17, 23], but this needs to be confirmed with additional studies and other cell types. For example, muscle biopsies could be carried out to determine uptake into skeletal muscle [30].

In order to derive pharmacokinetic parameters such as Cmax and AUC, participants generally need to have adequate ascorbate status at baseline to produce ascorbate peaks post-administration. However, in general, ascorbate does not need to be administered to healthy people who already have adequate to optimal ascorbate status at baseline as excess vitamin is readily excreted by renal filtration [4]. Thus, future studies could focus on recruiting people with low baseline ascorbate status, either due to low dietary intake or conditions, such as obesity or diabetes, which predispose to lower ascorbate status [8, 9], and use steady state study designs to determine which of liposomal or non-liposomal ascorbate is able to restore adequate to optimal plasma ascorbate status more rapidly (Table 2).

Finally, biological effects should also be assessed, particularly if liposomal formulations of ascorbate appear to restore depleted ascorbate status more rapidly and/or provide higher concentrations of ascorbate in the body relative to non-liposomal ascorbate (Table 2). Preliminary evidence indicates minimal differences between the antioxidant and cytokine modulating effects of liposomal versus non-liposomal ascorbate [21, 25], however, this needs to be confirmed with additional studies and different outcome measures. The most appropriate outcome measures to assess are not certain but could include markers of oxidative stress, inflammation and immune function [12, 31]. It should be noted, however, that intravenous ascorbate, being able to bypass the regulated intestinal uptake of the vitamin, is able to provide vastly higher Cmax and AUC than oral/liposomal ascorbate [21, 32]. As such, this is the preferred route of administration for certain patient groups with significantly enhanced requirements, for example, patients undergoing cancer therapy or critically ill patients in intensive care [10, 33].

5 | Conclusion

Overall, liposomal ascorbate does appear to provide greater plasma bioavailability than non-liposomal vitamin in short-term pharmacokinetic studies, although there is significant variability in the plasma uptake ratios between studies, likely due to the varied formulations used, doses administered, study durations and baseline ascorbate status. Because urinary elimination and cellular uptake have not been explored in great detail, it is not certain as to how much of the liposomal products are retained in the body versus simply being eliminated. Furthermore, whether there are any clinically relevant differences in biological effects between liposomal and non-liposomal ascorbate and whether any differences might translate into improved health outcomes remain to be explored.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain: - Purpura et al 2024, https://pubmed.ncbi.nlm.nih.gov/39237620/ - Wen et al 2022, https://pubmed.ncbi.nlm.nih.gov/35715901/ - Joseph et al 2021, https://pubmed.ncbi.nlm.nih.gov/35498071/ - Jacob et al 2021, https://pubmed.ncbi.nlm.nih.gov/33681596/ - Gopi et al 2021, https://pubmed.ncbi.nlm.nih.gov/32901526/ - Davis et al 2016, https://pubmed.ncbi.nlm.nih.gov/27375360/ - Lukawski et al 2020, https://pubmed.ncbi.nlm.nih.gov/31264495/ - Mikirova et al 2019, https://isom.ca/article/the-levels-of-ascorbic-acid-in-blood-and-mononuclear-blood-cells-after-oral-liposome-encapsulated-and-oral-non-encapsulated-vitamin-c-supplementation-taken-without-and-with-iv-hydrocortisone/ - Zmuda et al 2024, https://www.mdpi.com/2076-3417/14/17/7718 - McGarry et al 2024, https://www.mdpi.com/1661-3821/4/4/34.

References

1. M. Nishikimi and K. Yagi, "Molecular Basis for the Deficiency in Humans of Gulonolactone Oxidase, a Key Enzyme for Ascorbic Acid Biosynthesis," *American Journal of Clinical Nutrition* 54 (1991): 1203S–1208S.

2. I. B. Chatterjee, A. K. Majumder, B. K. Nandi, and N. Subramanian, "Synthesis and Some Major Functions of Vitamin C in Animals," *Annals of the New York Academy of Sciences* 258 (1975): 24–47.

3. A. C. Carr and S. Rowe, "Factors Affecting Vitamin C Status and Prevalence of Deficiency: A Global Health Perspective," *Nutrients* 12 (2020): 1963, https://doi.org/10.3390/nu12071963.

4. J. Lykkesfeldt, A. C. Carr, and P. Tveden-Nyborg, "The Pharmacology of Vitamin C," *Pharmacological Reviews* 77 (2025): 100043, https://doi.org/10.1016/j.pharmr.2025.100043.

5. I. Savini, A. Rossi, C. Pierro, L. Avigliano, and M. V. Catani, "SVCT1 and SVCT2: Key Proteins for Vitamin C Uptake," *Amino Acids* 34 (2008): 347–355.

6. M. Levine, C. Conry-Cantilena, Y. Wang, et al., "Vitamin C Pharmacokinetics in Healthy Volunteers: Evidence for a Recommended Dietary Allowance," *Proceedings of the National Academy of Sciences of the United States of America* 93 (1996): 3704–3709.

7. M. Levine, Y. Wang, S. J. Padayatty, and J. Morrow, "A new Recommended Dietary Allowance of Vitamin C for Healthy Young Women," *Proceedings of the National Academy of Sciences of the United States of America* 98 (2001): 9842–9846.

8. A. C. Carr and J. Lykkesfeldt, "Factors Affecting the Vitamin C Dose-Concentration Relationship: Implications for Global Vitamin C Dietary Recommendations," *Nutrients* 15 (2023): 1657.

9. A. C. Carr, H. Lunt, N. J. Wareham, and P. K. Myint, "Estimating Vitamin C Intake Requirements in Diabetes Mellitus: Analysis of NHANES 2017–2018 and EPIC-Norfolk Cohorts," *Antioxidants (Basel)* 12, no. 10 (2023): 1863, https://doi.org/10.3390/antiox12101863.

10. A. C. Carr and J. Cook, "Intravenous Vitamin C for Cancer Therapy—Identifying the Current Gaps in Our Knowledge," *Frontiers in Physiology* 9 (2018): 1182, https://doi.org/10.3389/fphys.2018.01182.

11. A. C. Carr and M. C. Vissers, "Synthetic or Food-Derived Vitamin C—Are They Equally Bioavailable?," *Nutrients* 5 (2013): 4284–4304, https://doi.org/10.3390/nu5114284.

12. P. C. Calder, R. B. Kreider, and D. L. McKay, "Enhanced Vitamin C Delivery: A Systematic Literature Review Assessing the Efficacy and Safety of Alternative Supplement Forms in Healthy Adults," *Nutrients* 17 (2025): 279, https://doi.org/10.3390/nu17020279.

13. M. A. Chaves, L. S. Ferreira, L. Baldino, S. C. Pinho, and E. Reverchon, "Current Applications of Liposomes for the Delivery of Vitamins: A Systematic Review," *Nanomaterials (Basel)* 13, no. 9 (2023): 1557, https://doi.org/10.3390/nano13091557.

14. H. Nsairat, D. Khater, U. Sayed, F. Odeh, A. Al Bawab, and W. Alshaer, "Liposomes: Structure, Composition, Types, and Clinical Applications," *Heliyon* 8 (2022): e09394, https://doi.org/10.1016/j.heliyon.2022.e09394.

15. D. L. Gbian and A. Omri, "Lipid-Based Drug Delivery Systems for Diseases Managements," *Biomedicine* 10, no. 9 (2022): 2137, https://doi.org/10.3390/biomedicines10092137.

16. A. J. Michels and B. Frei, "Myths, Artifacts, and Fatal Flaws: Identifying Limitations and Opportunities in Vitamin C Research," *Nutrients* 5 (2013): 5161–5192, https://doi.org/10.3390/nu5125161.

17. M. Purpura, R. Jäger, A. Godavarthi, D. Bhaskarachar, and G. M. Tinsley, "Liposomal Delivery Enhances Absorption of Vitamin C Into Plasma and Leukocytes: A Double-Blind, Placebo-Controlled, Randomized Trial," *European Journal of Nutrition* 63 (2024): 3037–3046, https://doi.org/10.1007/s00394-024-03487-8.

18. A. Joseph, D. Kumar, A. Balakrishnan, P. Shanmughan, B. Maliakel, and K. Im, "Surface-Engineered Liposomal Particles of Calcium Ascorbate With Fenugreek Galactomannan Enhanced the Oral Bioavailability of Ascorbic Acid: A Randomized, Double-Blinded, 3-Sequence, Crossover Study," *RSC Advances* 11 (2021): 38161–38171, https://doi.org/10.1039/d1ra06483e.

19. J. Jacob, N. P. Sukumaran, and S. Jude, "Fiber-Reinforced-Phospholipid Vehicle-Based Delivery of l-Ascorbic Acid: Development, Characterization, ADMET Profiling, and Efficacy by a Randomized, Single-Dose, Crossover Oral Bioavailability Study," *ACS Omega* 6, no. 8 (2021): 5560–5568, https://doi.org/10.1021/acsomega.0c05963.

20. S. Gopi and P. Balakrishnan, "Evaluation and Clinical Comparison Studies on Liposomal and non-liposomal Ascorbic Acid (Vitamin C) and Their Enhanced Bioavailability," *Journal of Liposome Research* 31 (2021): 356–364, https://doi.org/10.1080/08982104.2020.1820521.

21. J. L. Davis, H. L. Paris, J. W. Beals, et al., "Liposomal-Encapsulated Ascorbic Acid: Influence on Vitamin C Bioavailability and Capacity to Protect Against Ischemia-Reperfusion Injury," *Nutrition and Metabolic Insights* 9 (2016): 25–30, https://doi.org/10.4137/nmi.s39764.

22. M. Lukawski, P. Dalek, T. Borowik, et al., "New Oral Liposomal Vitamin C Formulation: Properties and Bioavailability," *Journal of Liposome Research* 30 (2020): 1–8, https://doi.org/10.1080/08982104.2019.1630642.

23. N. Mikirova, T. Levy, and R. Hunninghake, "The Levels of Ascorbic Acid in Blood and Mononuclear Blood Cells After Oral Liposome-Encapsulated and Oral Non-Encapsulated Vitamin C Supplementation, Taken Without and With IV Hydrocortisone," *Journal of Orthomolecular Medicine* 34 (2019): 1–8.

24. C. J. Wen, C. F. Chiang, C. S. Lee, Y. H. Lin, and J. S. Tsai, "Double Nutri (Liposomal Encapsulation) Enhances Bioavailability of Vitamin C and Extends Its Half-Life in Plasma," *Journal of Biomedical Nanotechnology* 18 (2022): 922–927, https://doi.org/10.1166/jbn.2022.3274.

25. S. V. McGarry, D. Cruikshank, I. Iloba, and G. S. Jensen, "Enhanced Bioavailability and Immune Benefits of Liposome-Encapsulated Vitamin C: A Combination of the Effects of Ascorbic Acid and Phospholipid Membranes," *Nutraceuticals* 4 (2024): 626–642, https://doi.org/10.3390/nutraceuticals4040034.

26. P. Zmuda, B. Khaidakov, M. Krasowska, et al., "Bioavailability of Liposomal Vitamin C in Powder Form: A Randomized, Double-Blind, Cross-Over Trial," *Applied Sciences* 14 (2024): 7718, https://doi.org/10.3390/app14177718.

27. S. Hickey, H. J. Roberts, and N. J. Miller, "Pharmacokinetics of Oral Vitamin C," *Journal of Nutritional and Environmental Medicine* 17 (2008): 169–177.

28. J. M. Pullar, S. Bayer, and A. C. Carr, "Appropriate Handling, Processing and Analysis of Blood Samples Is Essential to Avoid Oxidation of Vitamin C to Dehydroascorbic Acid," *Antioxidants* 7, no. 2 (2018): 29, https://doi.org/10.3390/antiox7020029.

29. P. W. Washko, R. W. Welch, K. R. Dhariwal, Y. Wang, and M. Levine, "Ascorbic Acid and Dehydroascorbic Acid Analyses in Biological Samples," *Analytical Biochemistry* 204 (1992): 1–14.

30. A. C. Carr, S. M. Bozonet, J. M. Pullar, J. W. Simcock, and M. C. Vissers, "Human Skeletal Muscle Ascorbate Is Highly Responsive to Changes in Vitamin C Intake and Plasma Concentrations," *American Journal of Clinical Nutrition* 97, no. 4 (2013): 800–807, https://doi.org/10.3945/ajcn.112.053207.

31. T. Bedhiafi, S. Idoudi, Q. Fernandes, et al., "Nano-Vitamin C: A Promising Candidate for Therapeutic Applications," *Biomedicine & Pharmacotherapy* 158 (2023): 114093, https://doi.org/10.1016/j.biopha.2022.114093.

32. S. J. Padayatty, H. Sun, Y. Wang, et al., "Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use," *Annals of Internal Medicine* 140 (2004): 533–537.

33. A. C. Carr, "Vitamin C in Pneumonia and Sepsis," in *Vitamin C: New Biochemical and Functional Insights*, eds. Q. Chen and M. Vissers (Boca Raton, FL: CRC Press/Taylor & Francis, 2020), 115–135.