This manuscript describes the nature, safety, and advantages of lipid-based nanocarriers in drug delivery to brain endothelial cells. Drug delivery to the CNS is particularly challenging, and this manuscript provides an interesting overview of the challenges, offering nanoparticles as a potential solution. The article is generally well-written. There were some unclear concepts, for example, in the abstract, it was unclear why the colloidal nanocarrier is important for delivery of natural substances specifically. There are also some edits recommended.

Detailed comments are included below.

- Can the author offer peer-reviewed literature in support of the claim that there was no change in the particle size distribution over time? Reference 2 appears to be a book chapter.
- Some sentences are vague or not clear, for example, the sentence in the abstract that starts with Such colloidal…searched in a holistic integrative approach was unclear. Also on page 13, "the charge neutrality greatly increases the blood-tissue compatibility" – please explain and provide a peer-reviewed reference.
- Some paragraphs are overly wordy and have too many methods inserted, for example, suggest delete that the analyses were carried out at CT Associates (pg 6). Also the mention of Particles Measuring Systems is not necessary. I would also suggest deleting the section starting (The five counters… concentrations.) as well as (The experiment was performed by preparing… final suspensions) as it does not seem relevant and detracts from the message.
- How many particles were > 0.65um.
- How many particle aggregates were <5um?
- More detail should be provided on the acute toxicity study, ie what does "gross toxicity" mean- was histology performed?
- What concentration of particles were injected IV at 4.8 ml/kg, was it 10^10 particles / ml? Please clarify.
- Suggest the Edaravone section on page 10 could be incorporated as a footnote. What pathways does it target specifically (pg 11)
- "Sizeable" on pg 13 is vague, please be more specific.