

Summary and discussion

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157. The low oral bioavailability of certain supplement compounds has led to efforts to design novel formulations to increase their absorption and reduce their first-pass metabolism. Formulations composed of food-grade surfactants and lipid excipients engineered as micellar, liposomal, emulsion-based, and lipid nanoparticle systems are emerging in the supplement market. Such systems may increase oral bioavailability by solubilising lipophilic molecules and increasing their bioaccessibility, promoting lymphatic transport, and contributing to direct

uptake via paracellular mechanisms.

158. The three case studies discussed above suggest that alternative novel formulations of vitamin C, curcuminoids, and CBD greatly alter their pharmacokinetics. An increase in oral bioavailability for novel formulations relative to standard/unformulated supplement was generally recorded, as determined by standard pharmacokinetic parameters (AUC_{0-n}, C_{max}). However, it is difficult to compare between these studies as they used different doses and reference formulations. Several of the curcumin studies administered different doses of reference and experimental formulation and used dose-normalisation to compare the relative bioavailability. The pharmacokinetics of curcumin are potentially non-linear, suggesting that this approach may misrepresent fold changes in bioavailability (Flory *et al.*, 2021).

159. EFSA (2018) also note in their 'guidance for risk assessment on nanotechnologies' that "the amounts of the shell [i.e., lipid coatings etc.; see Table 1] components derived from food materials for use in delivery systems are generally far lower than their normal intake from dietary sources or other approved uses. As such there would be little concern over the shell components, unless these were neither normal constituents of the body or approved food additives." However, given the interaction between these carrier systems and biological molecules and the formation of "new biological identities" (Giulimondi *et al.*, 2019) in these systems, the inherent toxicity of these delivery systems is an area of uncertainty, for instance, with respect to immunological interactions (Inglut *et al.*, 2020).

160. Finally, it is noted that a large proportion of the studies discussed above were potentially related to commercial interests: some studies were undertaken solely by the companies developing novel formulations, whilst others were conducted as collaborations between interested companies and academic institutions. Moreover, journals have case-by-case guidelines for declaring interests. Thus, whilst some of the presented studies did not report commercial/competing interests *per se*, declaration of funding presented in those same studies links that research to commercial interests. Based on these considerations, a likely reporting bias may be present in this literature, skewing the presented findings towards positive effects.