

Toxicokinetics

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19. In both humans and animals, curcumin when consumed as a food additive has been shown to have low oral bioavailability.

20. Approximately 75% of the administered dose was excreted unchanged in the faeces with negligible amounts appearing in the urine following oral administration of 1 g/kg bw of curcumin in rats (Wahlström and Blennow, 1978). The oral bioavailability of curcumin in the rat was < 1%, determined by comparing the Area Under the Curve (AUC) after oral and intravenous administration (Yang et al., 2007). Oral bioavailability is similarly low in humans, due to poor absorption and extensive first-pass metabolism in the intestine and liver (Ireson et al., 2002). Curcuminoids are susceptible to phase II metabolism in the gastrointestinal tract and / or the liver, with glucuronides identified as being the dominant metabolites (Wang et al., 2019).

21. Furthermore, it is also reported that the low bioavailability of curcuminoids

is due to low membrane transfer and hence low absorption. The underlying mechanisms are an active efflux by P-glycoprotein (pGP) and inter-molecular interactions (Heger et al., 2014; Jamwal, 2018; Ji et al., 2016). Curcumin is reported to act as an inhibitor of pGP, both in function and expression (at the protein and mRNA level) (Lopes-Rodrigues et al., 2016). Overall, the low bioavailability of curcuminoids can be attributed to a number of factors including rapid metabolism (Tullberg et al., 2004), efflux transport and low cellular transfer.

22. Numerous studies in animals have evaluated the systemic level of curcumin after oral administration and found that no curcumin, or only low levels, were detected in serum or tissue (Ravindranath and Chandrasekhara, 1981; Shen and Ji, 2012).

23. In supplements it is common practice to alter the curcumin product in an effort to change its metabolism and enhance its bioavailability, by reducing metabolism using metabolism inhibitors, membrane permeability or both. This can be achieved with methods such as liposomal curcumin encapsulation, nanoparticle dispersion (as part of a nano or microemulsion (Liu et al., 2020)), the use of micelles, (i.e. a curcumin phospholipid complex) and/or the use of synthetic structural analogues of curcumin that are water soluble.

24. The use of adjuvants is currently the most widely adopted modification in turmeric supplements. For example, piperine is the most widely used adjuvant. It is the major active ingredient in black pepper, and is a known inhibitor of glucuronidation in the liver and intestine (Di et al., 2015). Hence, piperine may provide a corresponding decrease in the metabolism of curcuminoids. Furthermore, it is reported that piperine may interfere with efflux mechanisms by, for example pGP, in the epithelial cells that expel compounds back into the intestine for excretion (Chen et al., 2020). This results in a change of permeation properties of the intestine (Khajuria et al., 2002) and therefore compounds with low bioavailability due to lower membrane crossing, such as curcuminoids, can subsequently be better absorbed. Piperine may also directly increase the intestinal absorptive surface due to the induction of the synthesis of proteins associated with cytoskeletal function of the epithelial cells of the intestine (Khajuria et al., 2002). However, the relevance of the findings from this last paper are highly questionable because of the use of high doses and the small changes reported.

25. In an in vitro study using Caco-2 cells, Wang et al., (2019) showed that the absorption of curcumin was significantly increased (by approximately 2.5-fold)

($p < 0.01$), when cells were exposed alongside piperine, suggesting piperine could promote the intestinal absorption of curcumin. However, this study used a co-amorphous formulation that may not be representative of 'real world' use.

26. Piperine has been shown to increase the bioavailability of curcumin by up to 154% in rats and up to 2,000% in a human study (Shoba et al., 1998). In this study, piperine was administered at 20 mg/kg concomitantly with curcumin at 2 g/kg to Wistar rats (single dose), and at 20 mg in humans with curcumin at 2 g total (also a single dose). The 'curcumin only' control group returned results $<$ LOD for curcumin in serum and the value of a 2,000% increase was based on the AUC measurement. It is not clear from this study what assumptions were made regarding the non-detects in serum when estimating AUC.

27. A study by Khajeh et al., (2023) investigated the effects of pepper on curcumin bioavailability. Black pepper co-administration increased the average curcumin half-life from 2.2 to 4.5 hours and significantly increased urinary average excretion concentration of curcumin at 24 hours (49 vs 218 μ g). The authors concluded that the "study indicates that piperine significantly increased CCM [curcumin] oral absorption, reduced systemic clearance, and improved bioavailability." However, this study is only described as a pilot study and is based upon 3 individuals only.

28. Thanawala et al., (2023) compared the pharmacokinetics of oral curcuminoids with and without piperine co-formulation. The trial was conducted in 16 healthy fasted male volunteers and curcuminoids were detected in plasma at up to 24 hours using an LC-MS method. C_{max} and AUC 0-24h were determined, and the study concluded that "The test formulation WDTE60N [i.e., including piperine] showed improved relative absorption and equivalent exposure at a 10-fold-lower dose of actives than the reference formulation CPC." It should be noted that the authors of this research in the Journal of Alternative Therapies in Health and Medicine all work for nutraceutical companies.

29. There is evidence that piperine may have less of an effect on bioavailability as an adjuvant compound than reported in some studies. Fanca-Berthon et al., (2021) undertook a study using a cohort of 30 human volunteers assessing several different curcumin supplement delivery mechanisms. The piperine-curcuminoid dose combination included approximately 15 mg of piperine with 1,500 mg of curcuminoids. The study monitored blood plasma concentrations over a 24-hour period after a single dose and included metabolites of curcuminoids as well as the parent compounds curcumin, BDMC and DMC to provide a 'total curcuminoids' blood plasma concentration. The piperine-

curcuminoid combination did not show any significant differences to the curcuminoid only standard extract, contrary to the Shoba et al., (1998) human study (Fança-Berthon et al., 2021).

30. Fança-Berthon et al., (2021) gave several potential reasons for the differences in these findings from the Shoba et al., (1998) study:

- The Shoba study had only 8 study participants compared to 30 in the Fança-Berthon et al. study.
- Shoba et al. studied a shorter kinetic duration, sampling for only 6 hours compared to 24 hours in the Fança-Berthon study, which found a T_{max} of 6 hours for the parent curcuminoid compounds.
- Shoba et al. only measured the single compound curcumin, compared to the metabolites and other related curcuminoids analysed in the Fança-Berthon study and used for their conclusions, which state: 'Based on the individual quantification of 15 curcuminoid metabolites, this study demonstrated that unconjugated curcumin, DMC, and BDMC represented only 1% of the total plasma curcuminoids following oral administration of a variety of turmeric formulations. Curcumin plasma concentration alone only reached a maximum of 18 – 21.5 ng/mL in contrast to >400 ng/mL for all metabolites combined.'

31. Some of these criticisms apply to the most recent studies Khajeh et al, 2023; Thanawala et al, 2023), particularly with respect to the range of compounds analysed.

32. There is a lack of any further studies providing direct evidence of piperine enhancing the bioavailability of curcumin in humans. Mimica et al., (2022) recently reviewed clinical studies on curcumin, and although piperine was used in a substantial number of them, there was no comparison of its effect on bioavailability. It appears that most studies rely on the findings of Shoba et al., (1998). However, there are several examples of piperine being used to aid the bioavailability of other compounds in humans and rodents. The maximum increase in bio-availability observed was approximately 2-fold (Bano et al., 1991; Di et al., 2015; Lambert et al., 2004).

33. No other studies could be found in the literature that reported a negative or 'no effect' of piperine when used as an adjuvant compound to increase the bioavailability of curcuminoids. This may be due to the common drawbacks of assessing the peer reviewed literature for negative or 'no effect' conclusions, i.e. these studies are often unreported (Joober et al., 2012).

34. Based on the in vitro and in vivo studies above, the TK of curcuminoids, taken as a supplement alongside piperine, could be very different to the kinetics when consumed via conventional dietary exposure as a flavouring. However, based on the evidence available it is unclear whether any difference in consumers would be marked.