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Increasing aqueous solubility of curcumin for improving bioavailability

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The interesting review by Aggarwal and Sung [1] provides a comprehensive description of the pharmacological basis for the role of curcumin in chronic diseases. Towards the end of the manuscript the authors list important limitations of curcumin, the prime limitation being curcumin's insolubility in aqueous solutions and consequently its poor bioavailability. Therefore, any method to improve curcumin's solubility in water would be of immense interest to investigators working to find therapeutic advances to several debilitating and terminal illnesses. Several investigators have studied the solubility and bioavailability of curcumin.

Sharma *et al*. [2] showed that there was no detectable curcumin or its metabolites in the blood or urine following administration of 440 to 2200 mg of curcuma extract per day (containing 36 to 180 mg of curcumin) for up to 29 days to patients with advanced colorectal cancer. The curcuma extract contained curcumin and desmethoxycurcumin suspended in essential oils obtained from *Curcuma* spp (*Curcuma* essential oil mixtures typically contain tumerone, atlantone, and zingiberene). However, curcumin was recovered from the faeces by Sharma *et al*. [2]. Cheng *et al*. [3] demonstrated that the peak concentration of curcumin in the serum following administration of 4, 6 and 8 g of curcumin (given in the form of tablets obtained from a commercial source, with each tablet containing 500 mg curcumin) was 0.51, 0.64 and 1.77 μM respectively. Moreover, these investigators found that doses below 4 g were barely detectable. Lao *et al*. [4] found no curcumin in the serum of volunteers given 0.5, 1.0, 2.0, 4.0, 6.0 or 8.0 g curcumin (provided in a capsule form as a standardized powder extract, obtained commercially, containing minimum 95% concentration of the three curcuminoids curcumin, bisdemethoxycurcumin, and demethoxycurcumin). However, these authors found that curcumin levels reached 50.5 and 51.2 ng/ml sera by four hours in two

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subjects administered 10 and 12 g of curcumin respectively. In another study, Dhillon *et al.* showed that only about 22-41 ng/ml were detectable in plasma even when 8 g curcumin/day was given orally in 1 g caplet form [5]. Each capsule contained 1 g of curcuminoids (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin, confirmed by high-performance liquid chromatography and tandem mass spectrometry) [5].

Studies from our laboratory have shown that it is possible to increase the solubility of curcumin 12-fold and that of turmeric 3-fold by heating a solution of curcumin/turmeric in water to boiling for 10 minutes. Profiling of the heat-extracted curcumin with matrix assisted laser desorption ionization mass spectrometry and spectrophotometry (400-700 nm) displayed no heat-mediated disintegration of curcumin [6,7]. The heat-solubilized curcumin was found to inhibit 4-hydroxy-2-nonenal (HNE)-protein modification by 80%. This inhibition experiment was carried out using an enzyme-linked immunosorbent assay that used HNE modification of a solid-phase multiple antigen peptide substrate [8]. Mild alkali (sodium hydroxide 130 μM, pH 7.6) solubilized curcumin has also been shown to inhibit HNE-protein modification significantly [9]. Thus, inhibition of HNE modification of proteins may be a mechanism by which curcumin exerts its effect in many disorders [6,9].

A solution to the problem of bioavailability would be to increase the solubility of curcumin with the use of heat. Heat-solubilized curcumin/turmeric should be considered for oral administration to patients in clinical trials since curcumin's full pharmacological potential is limited owing to its extremely limited solubility in water [10].

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