6 Appiah-Opong, R. *et al.* (2007) Inhibition of human recombinant cytochrome P450 s by curcumin and curcumin decomposition products. *Toxicology* 235, 83–91
7 Volak, L.P. *et al.* (2008) Curcuminoids inhibit multiple human cytochromes P450, UDP-glucuronosyltransferase, and sulfotransferase enzymes, whereas piperine is a relatively selective CYP3A4 inhibitor. *Drug Metab. Dispos.* 36, 1594–1605
8 Correia, M.A. (2007) Drug biotransformation. In *Basic and Clinical Pharmacology* (10th edn) (Katzung, B.G., ed.), pp. 50–63, The McGraw-Hill Companies
9 Zhou, S. *et al.* (2005) Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs. *Clin. Pharmacokinet.* 44, 279–304
10 Baum, L. *et al.* (2008) Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J. Clin. Psychopharmacol.* 28, 110–113
11 Baum, L. *et al.* (2007) Curcumin effects on blood lipid profile in a 6-month human study. *Pharmacol. Res.* 56, 509–514
12 Chainani-Wu, N. *et al.* (2007) A randomized, placebo-controlled, double-blind clinical trial of curcuminoids in oral lichen planus. *Phytomedicine* 14, 437–446
13 Hanai, H. *et al.* (2006) Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin. Gastroenterol. Hepatol.* 4, 1502–1506

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Letters

Increasing aqueous solubility of curcumin for improving bioavailability

Biji T. Kurien[1] and R. Hal Scofield[1,2,3]

[1] Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, OK 73104, USA
[2] Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, OK 73104, USA
[3] Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma, OK 73104, USA

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 after administration of 440–2200 mg of curcuma extract per day (containing 36–180 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 feces by Sharma *et al.* [2]. Cheng *et al.* [3] demonstrated that the peak concentration of curcumin in the serum after 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 subjects administered 10 and 12 g of curcumin, respectively. In another study, Dhillon *et al.* [5] showed that only ~22–41 ng/ml were detectable in plasma even when 8 g curcumin/day was given orally in 1 g caplet form. 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 threefold by heating a solution of curcumin or turmeric in water to boiling for 10 min. However, even though there is an increase in solubility by the use of heat the bulk of the curcumin or turmeric is still insoluble. 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 might 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 or turmeric should be

Corresponding author: Kurien, B.T. (biji-kurien@omrf.org).

considered for oral administration to patients in clinical trials because curcumin's full pharmacological potential is limited owing to its extremely limited solubility in water [10].

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References

1 Aggarwal, B.B. *et al.* (2009) Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol. Sci.* 30, 85–94
2 Sharma, R.A. *et al.* (2001) Pharmacodynamic and pharmacokinetic study of oral *Curcuma* extract in patients with colorectal cancer. *Clin. Cancer Res.* 7, 1894–1900
3 Cheng, A.L. *et al.* (2001) Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 21, 2895–2900
4 Lao, C.D. *et al.* (2006) Dose escalation of a curcuminoid formulation. BMC Complement. *Altern. Med.* 6, 10–13
5 Dhillon, N. *et al.* (2008) Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin. Cancer Res.* 14, 4491–4499
6 Kurien, B.T. *et al.* (2007) Improving the solubility and pharmacological efficacy of curcumin by heat treatment. *Assay Drug Dev. Technol.* 5, 567–576
7 Kurien, B.T. *et al.* (2009) Increasing the solubility of the nutraceutical curcumin by heat and inhibition of oxidative modification. *Mol. Nutr. Food Res.* 53, 308
8 Kurien, B.T. *et al.* (2005) *In vitro* modification of solid phase multiple antigenic peptides/autoantigens with 4-hydroxy-2-nonenal (HNE) provide ideal substrates for detection of anti-HNE antibodies and peptide antioxidants. *J. Immunol. Methods* 303, 66–75
9 Kurien, B.T. *et al.* (2007) Curcumin/turmeric solubilized in sodium hydroxide inhibits HNE protein modification–an *in vitro* study. *J. Ethnopharmacol.* 110, 368–373
10 Kurien, B.T. *et al.* (2009) Heat-solubilized curcumin should be considered in clinical trials for increasing bioavailability. *Clin. Cancer Res.* 15, 747

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Letters Response

Response to Kurien and Scofield: Solubility and bioavailability of curcumin

Bharat B. Aggarwal

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA

We would like to thank Kurien and Scofield for useful comments on our review. The authors acknowledge that the potential of curcumin in various diseases is limited owing to its poor bioavailability *in vivo*. They suggest that the limited bioavailability of curcumin *in vivo* is due to its lack of solubility in aqueous solvents. They have demonstrated that the solubility of curcumin can be enhanced 12-fold and that of turmeric threefold by boiling for 10 min in water [1]. They found that heat had no effect on the activity of curcumin. However, 98.5% curcumin and 94.7% turmeric is still water insoluble even after heating. Maximum in solution is only 7.4 μg/ml. Authors also suggest enhancement of solubility of curcumin in aqueous solvents by mild alkali treatment. However, this treatment has been shown to destabilize curcumin [2]. Additionally, there is no data yet provided by Kurien *et al.* or anybody else to suggest that heat-solubilized or alkaline-solubilized curcumin in aqueous solvent has any affect on its bioavailability in animals or human. Solubilization of curcumin in turmeric oil, however, has been shown to enhance its bioavailability in rat and in human [3]. Also, administration of liposome-encapsulated curcumin has been shown to provide higher serum levels in rodents [4]. Thus, whether heat solubilization or alkali solubilization of curcumin is a solution to the problem of bioavailability remains to be seen.

References

1 Kurien, B.T. *et al.* (2007) Improving the solubility and pharmacological efficacy of curcumin by heat treatment. *Assay Drug Dev. Technol.* 5, 567–576
2 Wang, Y.J. *et al.* (1997) Stability of curcumin in buffer solutions and characterization of its degradation products. *J. Pharm. Biomed. Anal.* 15, 1867–1876
3 Antony, B. *et al.* (2008) A pilot cross-over study to evaluate human oral bioavailability of BCM-95®CG (biocurcumax™), a novel bioenhanced preparation of curcumin. *Indian J. Pharmaceutical Sci.* 70, 445–450
4 Wang, D. *et al.* (2008) Liposome-encapsulated curcumin suppresses growth of head and neck squamous cell carcinoma in vitro and in xenografts through the inhibition of nuclear factor kappaB by an AKT-independent pathway. *Clin. Cancer Res.* 14, 6228–6236

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Corresponding author: Aggarwal, B.B. (aggarwal@mdanderson.org).