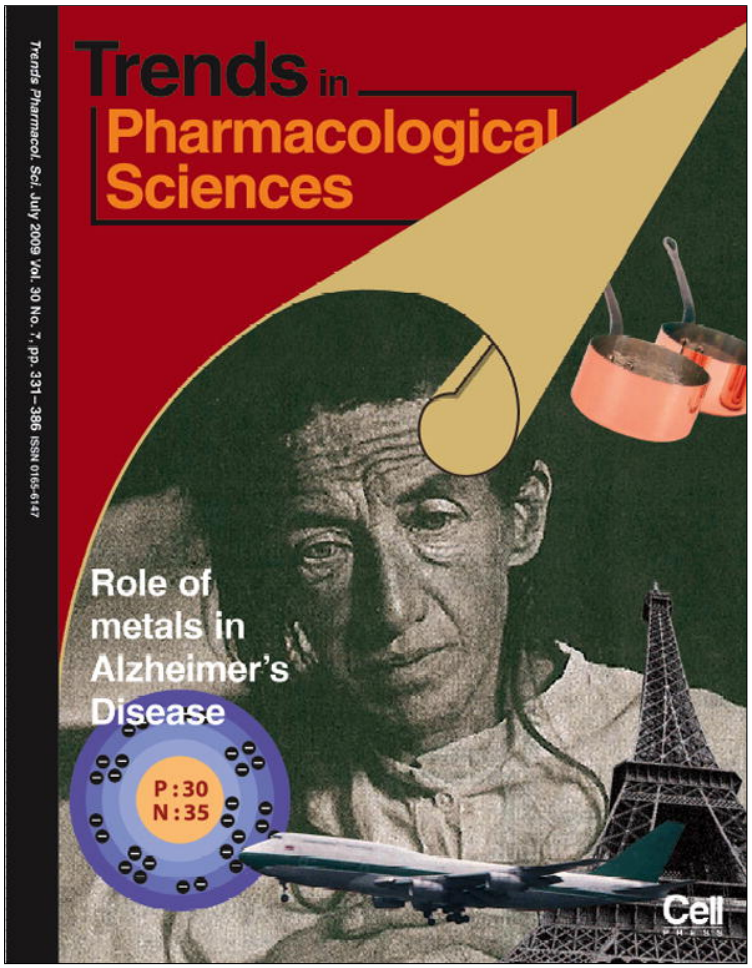

Letters

Curcumin in clinical practice: myth or reality?

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In the interesting paper 'Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets' published in the February issue of *Trends in Pharmacological Sciences* [1], Aggarwal and Sung provided an extensive overview of the main molecular targets and pharmacological effects of curcumin in animals and humans. Although the authors propose a potential use of curcumin in the therapy of free-radical-related diseases in the next future, in our opinion some crucial aspects of curcumin pharmacology deserve to be further addressed.

First of all, the poor bioavailability of curcumin, when given by oral route, must be considered to be an important clinical concern. However, worthy of mention is also the interaction of curcumin with drug-metabolizing enzymes and the possible repercussions in therapy. Curcumin and its derivatives have been shown to inhibit the activity of several isoforms of drug-metabolizing enzymes such as cytochrome P450, including CYP3A4, glutathione-*S*-transferase and UDP-glicuronosyltransferase [2–7], and this effect could be responsible for an undesired increase in plasma concentrations of drugs metabolized through these enzymes, such as digoxin, acetaminophen and morphine [8]. Furthermore, even piperine, which has been used in combination with curcumin to increase its bioavailability, has been shown to be a non-competitive inhibitor of CYP3A4 [7]. The inhibition by curcumin, alone or in combination with piperine, of CYP3A4 is potentially harmful, in particular in the case of prolonged exposure to these substances. In fact, it has been shown that CYP3A4 inhibitors could alter the metabolism of several drugs commonly used in the elderly, for example amiodarone and quinidine, thus increasing the risk to develop life-threatening ventricular arrythmias such as *torsades de pointes* [8,9].

Regarding the use of curcumin in humans, almost all the clinical studies showing some therapeutic effects of curcumin are characterized by the original sin to be non-randomized, open-label and with a small number of patients. We would like to drive the attention of the readers on the results of three recent randomized, placebo-controlled, double-blind clinical trials of curcumin and derivatives in subjects suffering from chronic diseases in which long-lasting inflammation has a pivotal role. Although promising neuroprotective effects have been shown *in vitro*, curcumin at doses of 1–4 g/day for 6 months did not reduce peripheral biomarkers of inflammation, such as serum amyloid-β-peptide and isoprostanes, in patients suffering from Alzheimer's disease (AD); more importantly, curcumin did not ameliorate cognitive performance in these patients [10]. Since curcumin has been hypothesized to have a protective role in cardiovascular diseases owing to its ability to reduce cholesterolemia, the same AD patients have been monitored also for the plasma lipid profile. The results clearly demonstrated that curcumin did not have any significant effect on plasma triglycerides or total, LDL and HDL cholesterol over 1 or 6 months; rather, a slight increase in cholesterol plasma levels was detected in AD patients when the absorbed dose of curcumin was taken into consideration [11]. Furthermore, curcuminoids at the dose of 2 g/day for 7 weeks did not improve symptoms, clinical signs and occurrence of side effects in patients affected by oral *lichen planus*, a mucocutaneous disease characterized by chronic inflammatory and immunologic response, and the trial was ended for futility after the first *ad-interim* analysis [12]. In a clinical trial of curcumin in ulcerative colitis, patients treated with curcumin 2 g/day for 6 months exhibited a reduction in the recurrence rate of the disease respect to control, but the P value of 0.049 raises some doubts about the clinical significance of this result [13] and a possible local effect of unabsorbed curcumin could be considered.

Finally, the fact that the beneficial effects of curcumin and derivatives demonstrated *in vitro* have not been adequately confirmed by randomized, double-blind, placebo-controlled clinical trials as well as the potential occurrence of harmful side-effects resulting from herb–drug interaction does not justify a wide and uncontrolled use of curcumin in therapy. It is very important and ethically relevant to not provide people with ambiguous information about the benefit coming from the use of curcumin in chronic inflammatory diseases and to focus the attention on the 'risk to benefit' ratio of supplemental therapy with curcumin, which might be shifted towards the 'risk'.

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Letters

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 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

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