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Inhibition of p300 and nuclear factor-κB by curcumin and its role in diabetic nephropathy

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Keywords

Curcumin; diabetes; DMSO; ethanol; solubility; anti-oxidant

Sir,

The effect of curcumin in ameliorating diabetes-induced abnormalities in the kidneys, like increased oxidative damage and increased expression of vasoactive factors eNOS and TGF-β1, through the suppression of p300 (a histone acetyl transferase) and nuclear factor-κB, as shown by Chiu et al. [1] is interesting and an important finding for further research work.

With reference to this paper, couple of points comes to mind regarding the use of dimethylsulfoxide (DMSO) and ethanol as a vehicle to deliver curcumin for the *in vivo* studies.

First, the authors do not specify the final concentration of DMSO or ethanol used in the *in vivo* administration of curcumin. Instead they direct the reader to three papers given in the reference section (reference # 20, 25 and 26). When reference #20 was accessed for this information, it further directs the reader to two other papers which are none other than reference # 25 and 26 given in this paper [1] which are both from the 1970's and are not available online. Therefore, it would be of interest to know the final concentration of DMSO and ethanol used is this study. Also, it would have been useful to have a fourth group of animals that were diabetic and treated with just DMSO/ethanol to see whether the vehicle exacerbated or ameliorated the diabetic complications. If DMSO/ethanol did ameliorate disease, then the observed effect of curcumin would be a synergistic effect of curcumin and DMSO/ethanol. If DMSO/ethanol did induce any harmful effect, it has been suppressed by curcumin as the authors have shown amelioration of diabetes related complications in the kidneys of the experimental animals.

Secondly, the concern is that both DMSO and ethanol are not the ideal vehicle for *in vivo* studies (a fifth control group of rats that was not treated with streptozotocin but with just

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DMSO/ethanol would have shown if DMSO/ethanol had any adverse effect at the levels used by the authors), especially since curcumin was administered for one month (on a daily basis, probably). Here we suggest that curcumin or turmeric heat-solubilized in water should be considered for *in vivo* and *in vitro* studies [2,3]. It is a well known fact that curcumin is practically insoluble in water. We have demonstrated heat-mediated increase in solubility of turmeric or curcumin (a 3-fold or 12-fold increase respectively) [2]. We have also shown, using matrix assisted laser desorption ionization time of flight mass spectrometry analysis and spectrophotometric profiling (400–700 nm) that there was no curcumin disintegration as a result of the heat treatment [2]. In addition, the curcumin solubilized by heat was found to maintain its bioactivity with respect to its ability to inhibit 4-hydroxy-2-nonenal (HNE) mediated oxidative modification [2]of a multiple antigenic peptide [4] substrate by 80% carried out by an ELISA [5] that employed HNE-modification of a solid phase antigen. Mild alkali-solubilized (pH 7.6; 130 μM) curcumin was also shown to significantly inhibit oxidative modification by HNE [6].

DMSO has been shown to induce both favorable and adverse effects. DMSA has anti-inflammatory properties and has therefore been used as a solvent for chemotherapeutic drugs to treat rheumatic, pulmonary, gastrointestinal, neurological, urinary and dermatological disorders. DMSO effects on the outcomes of such studies are not completely clear yet [7]. DMSO levels, considered safe for *in vivo* use differs considerably. Clinically, DMSO is beneficial in certain situations, but has been shown to have systemic side effects such as vomiting, diarrhea, hypertension, bronchospasm and pulmonary edema that are dose-dependent [8]. One *in vitro* study showed that DMSO (1% vol/vol) decreased cell viability, increased cellular apoptosis, and upregulated Bax in human lens epithelial cells [9]. In another study, the effects of very low amounts of DMSO on the brain metabolism of [3-^{13}C]pyruvate and D-[1-^{13}C]glucose was studied with ^{1}H/^{13}C NMR spectroscopy and a guinea pig cortical brain slice model. In this study DMSO was shown to accumulate in brain slices and was shown to increase the metabolic rate, at all concentrations [0.000025%–0.25% (v/v)] [10]. The adverse effects of ethanol are well known, but may be tolerated in small amounts. However, it would be interesting to know the effect of DMSO and ethanol, administered daily for one month to experimental rats

We suggest oral feeding of heat-solubilized curcumin (or given in drinking water) for animal *in vivo* experiments as a better alternative compared to delivery of curcumin solubilized in DMSO/ethanol. It would be interesting to see the effect of heat-solubilized curcumin in future *in vivo* and *in vitro* experiments [11].

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