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Could Antitumor Activity of Curcumin in Patients Be due to Its Metabolites? A Response

In Response: We thank Drs. Liang Shen and Hong-Fang Ji for their thoughtful comments on our article by Dhillon et al. (1) published in *Clinical Cancer Research*. The authors commented that biological activities of curcumin observed by us in pancreatic cancer patients are perhaps less likely to be due to curcumin, as the serum levels observed are only in low nanogram range (22-41 ng/mL). For several reasons, we feel that serum levels of curcumin observed *in vivo* in cancer patients cannot be directly compared with that in cell culture medium *in vitro*. First, exposure of cells to curcumin in cell culture experiments is usually only short-term (24-72 hours), whereas it is long-term (up to 6 months) in patients. Second, it is the cell/tissue levels of the drug (such as curcumin) that are more relevant rather than serum/cell culture levels.

Further, the authors go on to suggest that the activity of curcumin observed by us could be due to curcumin metabolites such as ferulic acid and vanillin, which are produced on exposure of curcumin to phosphate buffer and serum-free medium at pH 7.2 at 37°C. In addition, they state that these breakdown products are known to inhibit cyclooxygenase-1 and cyclooxygenase-2 and suppress NF-κB activation. These possibilities are highly unlikely for several reasons. First, curcumin was not exposed to phosphate buffer (pH 7.2) in our studies. Curcumin was given orally as capsules and then its levels were monitored in the plasma. Second, curcumin has been reported to be highly stable in human blood (2); even after 8 hours, more than 50% of the curcumin is still intact in the serum. Third, in phosphate buffer, curcumin is degraded into vanillin, ferulic acid, and feruroyl methane. None of these metabolites are known to have significant activity. For instance, vanillin suppressed cyclooxygenase-2 activity with an IC_{50} of 27.40 mmol/L and suppressed NF-κB reporter activity at 250 μmol/L (3). In comparison, curcumin is severalfold more potent. Moreover, vanillin is unlikely to reach these concentrations *in vivo*. Fourth, in contrast to the statement by the authors, ferulic acids, especially those with low chain length, were reported not to inhibit cyclooxygenase enzyme (see Fig. 3A in ref. 4). Suppression of NF-κB by dietary ferulates occurred only at ~200 μmol/L (5) compared with ~10 μmol/L with curcumin. Fifth, we found that vanillin and ferulic acid had no effect on suppression of tumor necrosis factor–induced NF-κB activation even at 200 μmol/L, whereas curcumin inhibited NF-κB even at 10 μmol/L (see Fig. 1). Thus, overall it is unlikely that curcumin is degraded in the plasma as described by the authors, and even if it does degrade, it is unlikely that the activity observed in our studies is due to curcumin metabolites for the reasons stated above.

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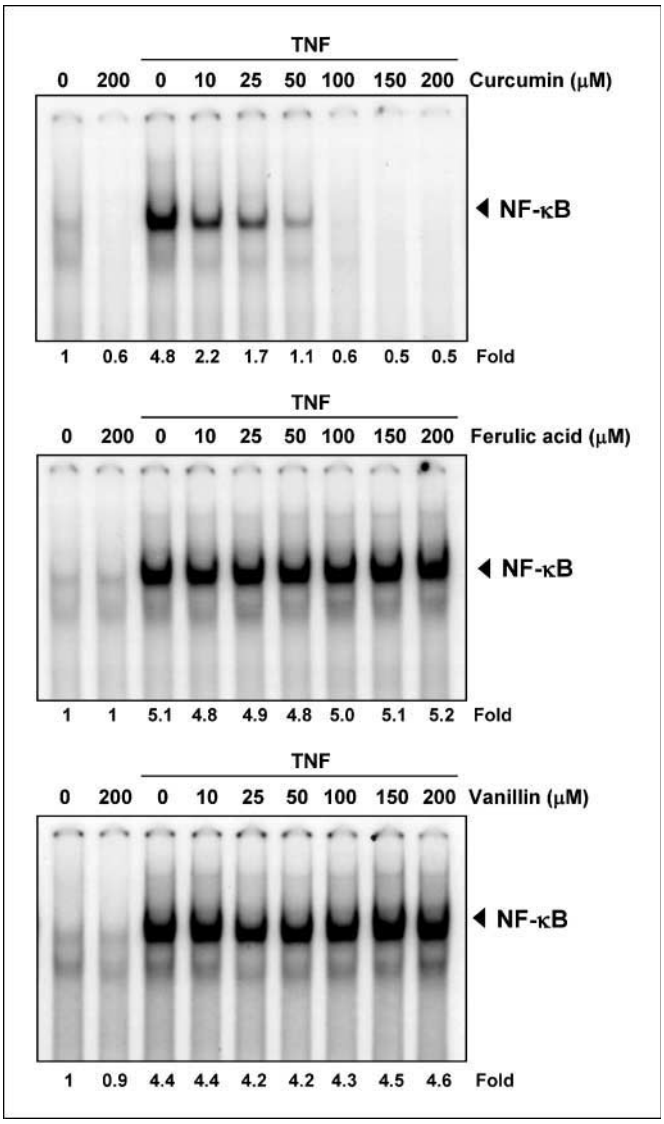

Fig. 1. Human myeloid (KBM-5) cells were incubated with the indicated concentrations of curcumin, ferulic acid, and vanillin for 4 h and then activated for NF-κB by treatment with 0.1 nmol/L tumor necrosis factor (*TNF*) for 30 min. The nuclear extracts were assayed for NF-κB activation by electrophoretic mobility shift assay.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res 2008;14:4491–9.
2. Wang YJ, Pan MH, Cheng AL, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharm Biomed Anal 1997;15:1867–76.

3. Murakami Y, Hirata A, Ito S, et al. Re-evaluation of cyclooxygenase-2-inhibiting activity of vanillin and guaiacol in macrophages stimulated with lipopolysaccharide. Anticancer Res 2007;27:801–7.
4. Jayaprakasam B, Vanisree M, Zhang Y, Dewitt DL, Nair MG. Impact of alkyl esters of caffeic and ferulic acids on tumor cell proliferation, cyclooxygenase enzyme, and lipid peroxidation. J Agric Food Chem 2006;54:5375–81.
5. Jung KJ, Go EK, Kim JY, Yu BP, Chung HY. Suppression of age-related renal changes in NF-κB and its target gene expression by dietary ferulate. J Nutr Biochem 2009;20:378–88.

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