Letter to the Editor

Curry spice curcumin and prostate cancer

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Prostate cancer (CaP), the sixth most common cancer overall and the third most common cause of cancer deaths, is the second most common cancer diagnosed in men [1]. Evidence from epidemiological studies indicates that diet has a role in CaP. The special issue on diet and prostate cancer very handsomely reflects this point. Carbohydrates and grains showed significant negative correlations while proteins and fats showed significant positive correlations with CaP [2]. A Mediterranean diet rich in bioactive nutrients, especially foods containing lycopene [3], selenium, vitamin E, pulses, and soy foods were shown to be protective while foods or supplements containing high calcium are thought to cause CaP [4]. A traditional Japanese diet rich in soybean products, fish and low in red meat [5], and tea as a healthier alternative than coffee [6] has been touted to reduce the risk while there is evidence to suggest that CaP incidence is positively linearly associated with heavier alcohol use [7]. The use of diet to modulate CaP lends credence to Hippocrates' statement, "Let food be thy medicine and medicine be thy food" [8].

It would be useful to add information regarding the use of curcumin (CU) in CaP, which has not been addressed in this issue. CU is a natural phytochemical occurring as the most active component in the Indian curry spice turmeric (TU), isolated from the perennial herb *Curcuma longa.* Recently CU has emerged as a "nutraceutical" capable of interacting with multiple targets to regress diseases safely and inexpensively.

Even though the cause of CaP is largely unknown, androgen and the androgen receptor (AR) are postulated to be closely involved in the development of CaP. CaP is currently treated with a combination of surgery, radiation and chemotherapy. The therapeutic agents used include steroidal and non-steroidal anti-androgens with severe side effects. These agents are unable to kill CaP cells and the cancer usually develops into an androgen refractory stage [9]

Studies have shown that inhibition of constitutive NFκB activation by curcumin can lead to inhibition of CaP proliferation and that CU can downregulate the inflammatory biomarker prostate specific antigen (PSA), which is a molecular target of CU [10]. Many groups have shown that CU can also inhibit the PI3K/Akt signaling pathway and thereby induce apoptosis of cancerous cells. One group has shown that CU inhibits the expression of the two subunits of PI3K, p110 and p85, the phosphorylation of Akt and upregulates the expression of p53 in CaP cells [11]. CU has been shown to prevent CaP progression using CaP cancer cells (DU-145), at the metastasis initial phase at least, by inhibiting matrix metalloproteinases 2 and 9 (responsible for degrading extracellular matrix required for metastases) as well as regression in size of tumor in a human CaP tumour xenograft animal model [12]. Yet another group has shown that combined treatment of CU and the naturally occurring phenylethylisothiocyanate (PEITC) (from broccoli, watercress, cabbage *etc.*) can suppress human CaP cell growth *in vitro* as well as in immunodeficient (Nu/Nu) mice carrying xenografts of androgen-independent human CaP cells. [13] These authors also showed that CU and PEITC either alone or in combination were able to significantly reduce the incidence of CaP formation using the transgenic adenocarcinoma of the mouse prostate (TRAMP) animal model [13]. CU was also shown to downregulate AR and AR-related cofactors (activator protein-1, NFκB) in LNCap and PC-3 CaP cell lines to reduce their proliferation ability [14].

Several CU analogues have been used, showing significant *in vitro* cytotoxicity in LNCaP and PC-3 human CaP cell lines [9]. 4-Hydroxy-3-methoxybenzoic acid methyl ester, derived from CU has been shown to have potential for CaP management by targeting Akt/NFκB cell survival signaling pathway [15]. Other curcumin analogues have been developed as well to control AR mediated CaP growth.

An important limitation of CU is its very limited aqueous solubility and bioavailability. We have demonstrated a 12-fold increase in CU's and a 3-fold increase in turmeric's solubility in water by heat treatment. We also showed that

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the heat-solubilized or mild alkali-solubilized CU was able to significantly inhibit 4-hydroxy-2-nonenal mediated oxidation of a peptide substrate [16–19]. We hypothesize that heat-solubilized or mild alkali-solubilized CU will achieve a greater efficacy in the management of CaP using cell lines, animal models of CaP and possibly in human trials.

It would be important to consider in what way CU could be selectively toxic to tumour cells. The cellular uptake of CU by cancer cells has been shown to be higher than in normal cells, using absorption and fluorescence spectroscopic methods. Also, CU has been shown to interact with thioredoxin reductase and convert it to NADPH oxidase, consequently resulting in elevated production of hydrogen peroxide. In addition, glutathione levels are lower in tumour cells compared to normal cells and thus the tumour cells are more sensitive to CU. Lastly, constitutively active NFκB are expressed in most tumour cells and not in normal cells, thus mediating their survival. By suppressing NFκB regulated gene products CU can reduce the survival and proliferation of cancerous cells [10].

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References

[1] Lee, A. H., Binns, C. W., Diet and prostate cancer: evidence from epidemiological studies. *Mol. Nutr. Food Res*. 2009, *53*, 169 – 170.

[2] Moon, H. K., Kim, C. Y., Lee, S. W., Exploratory correlations of dietary nutrients with prostate cancer mortality using over two decades of observations in Korea. *Mol. Nutr. Food Res.* 2009, *53*, 185 – 190.

[3] Itsiopoulos, C., Hodge, A., Kaimakamis, M., Can the Mediterranean diet prevent prostate cancer? *Mol. Nutr. Food Res.* 2009, *53*, 227 – 239**.**

[4] Chan, R., Lok, K., Woo, J., Prostate cancer and vegetable consumption. *Mol. Nutr. Food Res.* 2009, *53*, 201 – 216.

[5] Mori, M., Masumori, N., Fukuta, F., Nagata, Y. *et al.*, Traditional Japanese diet and prostate cancer. *Mol. Nutr. Food Res*. 2009, *53*, 191 – 200.

[6] Lee, A. H., Fraser, M. L., Binns, C. W., Tea, coffee and prostate cancer. *Mol. Nutr. Food Res.* 2009, *53*, 256 – 265.

[7] Middleton Fillmore, K., Chikritzhs, T., Stockwell, T., Bostrom, A., Pascal, R., Alcohol use and prostate cancer: a meta-analysis. *Mol. Nutr. Food Res.* 2009, *53*, 240 – 255.

[8] Goel, A., Jhurani, S., Aggarwal, B. B., Multi-targeted therapy by curcumin: how spicy is it? *Mol. Nutr. Food Res.* 2008, *52*, 1010 – 1030.

[9] Itokawa, H., Shi, Q., Akiyama, T., Morris-Natschke, S. L., Lee, K. H., Recent advances in the investigation of curcuminoids. *Chin. Med.* 2008, *3*, 11 – 23.

[10] Aggarwal, B. B., Sung, B., Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol. Sci.* 2009, *30*, 85 – 94.

[11] Shankar, S., Srivastava, R. K., Involvement of Bcl-2 family members, phosphatidylinositol 3′-kinase/AKT and mitochondrial p53 in curcumin (diferulolylmethane)-induced apoptosis in prostate cancer. *Int. J. Oncol.* 2007, *30*, 905 – 918.

[12] Hong, J. H., Ahn, K. S., Bae, E., Jeon, S. S., Choi, H. Y., The effects of curcumin on the invasiveness of prostate cancer *in vitro* and *in vivo*. *Prostate Cancer Prostatic Dis.* 2006, *9*, 147 – 152.

[13] Barve, A., Khor, T. O., Hao, X., Keum, Y. S. *et al.*, Murine prostate cancer inhibition by dietary phytochemicals – curcumin and phenyethylisothiocyanate. *Pharm Res.* 2008, *25*, 2181 – 2189.

[14] Nakamura, K., Yasunaga, Y., Segawa, T., Ko, D. *et al.*, Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. *Int. J. Oncol.* 2002, *21*, 825 – 830.

[15] Kumar, A. P., Garcia, G. E., Ghosh, R., Rajnarayanan, R. V. *et al.*, 4-Hydroxy-3-methoxybenzoic acid methyl ester: a curcumin derivative targets Akt/NF kappa B cell survival signaling pathway: potential for prostate cancer management. *Neoplasia* 2003, *5*, 255 – 266.

[16] Kurien, B. T., Scofield, R. H., Increasing the solubility of the nutraceutical curcumin by heat and inhibition of oxidative modification. *Mol. Nutr. Food Res.* 2009, *53*, 308.

[17] Kurien, B. T., Scofield, R. H., Heat-solubilized curcumin should be considered in clinical trials for increasing bioavailability. *Clin. Cancer Res.* 2009, *15*, 747.

[18] Kurien, B. T., Singh, A., Matsumoto, H., Scofield, R. H., Improving the solubility and pharmacological efficacy of curcumin by heat treatment. *Assay Drug Dev. Technol.* 2007, *5*, 567 – 576.

[19] Kurien, B. T., Scofield, R. H., Curcumin/turmeric solubilized in sodium hydroxide inhibits HNE protein modification – an *in vitro* study. *J. Ethnopharmacol.* 2007, *110*, 368 – 373.

