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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 indicate 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, 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] have 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]

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Studies have shown that inhibition of constitutive NF κ B activation by curcumin can lead to inhibition of CaP proliferation and that CU can down regulate the inflammatory biomarkers 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 up-regulates 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 down-regulate AR and AR-related cofactors (activator protein-1, NF κ B) 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/NF κ B 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 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 as to how CU could be toxic to tumour cells selectively. 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 NF κ B are expressed in most tumour cells and not the normal cells, thus mediating their survival. By suppressing NF κ B regulated gene products CU can reduce the survival and proliferation of cancerous cells [10].

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