The role of dietary turmeric for the low incidence of childhood leukemia in Asian Countries

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Summary

Turmeric is a spice, widely used as food ingredient reduce the mutagenic/carcinogenic burden of leukemogenic risk factors such as radiation, pollutants [benzo(a)pyrene and dimethylbenz(a)anthracene], bidi and cigarette smoke condensates and recently identified possible risk factors such as N-nitoso compounds, cured, broiled and precessed meat mutagens/carcinogens. Curcumin, the major component of turmeric, also selectively and irreversibly inhibit the proliferation of P388 drug-sensitive and drug-resistant mouse leukemia cells, human chronic myeloid leukemia cells and Jurkat T-cell leukemia cells.

Introduction

Low incidence of childhood leukemia was documented in Asian countries (India, China and Japan) compared to western countries (United States, Canada and United Kingdom). Leukemia amounts to 30% of childhood cancers in the United States (American Cancer Society 2003). The differences in diet pattern may partly contribute to these differences in leukemia incidence. Asian diet includes many spices. Turmeric is a major spice, widely used as a natural food color and that imparts specific flavor. Turmeric is also used as a food preservative, cosmetic and as an ingredient in Ayurvedic medicine, the traditional Indian system of medicine for over 6000 years (Aggarwal et al. 2003). India is the major producer of turmeric and consumes 80% of it. Curcumin, the active principle in turmeric, is a polyphenolic antioxidant and a natural yellow orange dye. Curcumin content of turmeric is in the range of 2-5%. Turmeric contains three curcumin analogues based on number of hydroxyl groups present in the parent molecule. They are Curcumin (Curcumin I), demethoxy curcumin (Curcumin II) and bis-demethoxy curcumin (Curcumin III). Minor components of turmeric are terpenes and oils that imparts turmeric-specific flavor. Turmeric and curcumins exhibit antibacterial and antifungal activity (Govindarajan 1980).

Some of the known risk factors that contribute to the high incidence of childhood leukemia are the interaction of many lifestyle and environmental factors (Zahm and Devesa, 1995; Ma 2002). These include prenatal and postnatal exposure to radiation (X-ray and gamma-rays), benzene and it metabolites through occupational and/or active and passive cigarette smoking (McBride 1998; Pogoda et al 2002; Mitacek et al. 2002), coal, wood and gasoline combustion smoke emission (Crosignani et al. 2004), environmental pollutants (Korte et al. 2000) and alkylating chemotherapeutic drugs. Some of the very recent studies suggest that processed/cured meat consumption may be the additional risk factors for childhood leukemia (Sarasua et al. 1994; Peters et al. 1994).

Results and Discussion

We have shown that some of the risk factors that contribute to the development of childhood leukemia are reduced by turmeric and curcumins in diet. With Salmonella reverse mutation assay which is used for detecting potential carcinogens as mutagens with 70-80% accuracy, we have shown that A) in 1984, for the first time that turmeric and curcumin inhibits the mutagenicity of variety of environmental mutagens. Turmeric and curcumin exhibited antimutagenic activity against cigarette smoke condensate, bidi smoke condensate (Indian version of hand rolled cigarettes), benzo(a)pyrene and dimethylbenz(a)anthracene, (Nagabhushan et al. 1984; Nagabhushan 1987, Nagabhushan et al. 1987a, 1987b). Subsequently, we have shown that turmeric and curcumin exhibit activities against: tumor growth, tumor promotion, cell proliferation, chemical and viral-induced carcinogenicity (Nagabhushan, 1987; Nagabhushan and Bhide, 1987; Bhide et al 1989; Nagabhushan and Bhide, 1992; Nagabhushan et al. 1996a).

B) Turmeric and curcumins inhibit the formation of mutagenic/carcinogenic nitroso-compounds under acidic conditions (Nagabhushan 1987, Nagabhushan et al. 1988). .Nitrite is added to improve the texture, shelf-life of meat and to prevent the spread of Boutlism. Nitrite and amines/amides are present in meat, vegetables and as

contaminants in drinking water. Under human stomach acidic pH conditions nitrite and amine/amides react to form nitroso-compounds.

C) Turmeric and curcumins inhibit the formation of mutagenic/ carcinogenic Maillard reaction products (Usha et al. 1994; Kolpe et al. 2002). This is an important finding because during food preparation or processing with (meat broiling) or without elevated temperature and irradiation, proteins, amino acids, lipids and sugars present in the food react to form nonnutritional and harmful potent mutagenic/carcinogenic Maillard reaction products. Thus we have shown that use of turmeric and curcumins in diet may reduce mutagenic burden.

D) Turmeric when administered to volunteer bidi smokers, the urinary excretion of mutagens was decreased compared to before ingestion of tumeric. A similar decrease in urinary excretion of benzo(a)pyrene mutagens was observed when mouse fed with turmeric containing diet (Nagabhushan and Bhide, 1992; Usha et al. 1994).

In mouse bone marrow, curcumin also inhibit radiation induced chromosome damage as evidenced by decrease in micronucleus frequency (Usha et al. 1994). As discussed earlier, these mutagens/carcinogens are known to contribute to the development of childhood leukemia. Our studies indicate that turmeric in diet may lower the mutagenic/carcinogenic effects of leukemiagenic agents and may have a protective role in the prevention of development of childhood leukemia. .

Curcumin *in vitro* dose dependently inhibit the proliferation (tritiated thymidine DNA incorporation) of mouse adriamycin resistant and sensitive P388 leukemia cells, human chronic myelogenous leukemia cells and Jurkat T-cell leukemia cells. Compared to NIH3T3 cells, these cells were highly sensitive to curcumin-induced inhibition of DNA synthesis and the DNA synthesis was not reversible (Nagabhushan and Bhide, 1992; Usha et al. 1996; Nagabhushan et al. 1996b). Curcumin in diet reduced carcinogen demethylbenz(a)anthracene-induced leukemia by 50% in mouse (Huang et al. 1998).

Other beneficial health effects of turmeric and curcumin are prevention of cataract development and septic shock, promotion of wound healing in normal and diabetic patients, increase in bile flow in cyclosporine A-treated animals, anti-asthmatic, anti-colitis, anti-fibrosis, reduction of mucosal damage, prevention of UV damage to skin, inhibition of development of cancers of skin, stomach, colon, prostate, oral cavity and liver, and further more, curcumin inhibits tumor metastases, pancreatitis, drug or alcohol-induced liver fibrosis, cystic fibrosis and Alzheimer's disease (Conney, 2003; Aggarwal et al. 2003, Egan et al. 2004), promote prolonged organ preservation (Johnston et al. 1997), inhibit Epstein-Barr virus-induced human B-cell transformation (Ranjan et al. 1998a), and cyclosporine A-resistance pathways of lymphocyte proliferation (Ranjan et al. 1998b).

Turmeric and curcumins are nonmutagenic, nonteratogenic and noncarcinogenic and does not exhibit pathological changes in animals (mice, rats and dogs) administered with high doses reaching several fold higher dose than actual human consumption. In a human clinical study oral administration of curcumin at 1-2 grams per day per person for 5-10 weeks was well tolerated without any side effects Most of the curcumin is excreted through feces and minor amount through urine (Govindarajan 1980). Based on these observations WHO/FAO expert committee on food additives has approved turmeric and curcumins as the natural food colors.

More importantly, turmeric and curcumin are in clinical trials as cancer chemopreventive agents at the National Cancer Institute, Bethesda, USA. Phase I preclinical toxicological studies reveal that oral administration of curcumin and turmeric over a two year period to rats is nontoxic at hundred times above doses of human consumption. These studies confirm the non-toxicity of curcumin and turmeric reported by earlier studies.

Published reports show that the multiple effects of curcumin on cells is due to its inhibitory activity against a number of important transcription factors, such as NF kappa-B, Egr-1, C-Jun and AP-1 which regulate the secretion of a variety of cytokines, chemokines, proteases, protein kinases, tyrosine kinases and enzymes that participate in disease processes (Aggarwal et al. 2003; Duvoix et al. 2003; Han et al 2002).

Conclusions

Based on traditional safety record of turmeric in humans and based on recently obtained scientific knowledge by incorporating turmeric and curcumins in commercial foods and daily food preparations as natural food color, preservative and flavor both in adult, baby and children food may prevent childhood leukemia and other cancers. Before incorporating turmeric and curcumins in baby and children foods the appropriate beneficial doses to be determined in future scientific research.

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