



NAMEY/BURNETT PREVENTIVE MEDICINE WRITING AWARD 2009

Natural Chemopreventive Therapy: Curcumin

Owen D. Vincent, OMS-IV

From Lincoln Memorial University-DeBusk College of Osteopathic Medicine, Harrogate, TN.

KEYWORDS:

Natural;
Chemo;
Preventive;
Chemopreventive;
Therapy;
Curcumin

Curcumin is a therapeutically active, natural biomolecule found in the spice turmeric. The antitumor, antioxidant, antiarthritic, and antiinflammatory effects on the body highlight the medicinal versatility of the compound. Turmeric has been used in traditional Ayurvedic medicine in India for millennia, and recent analytical assessments have calculated the chemical profile of curcumin and its related compounds, curcuminoids. The bioavailability of curcumin and other curcuminoids is considerably limited, and optimal absorption may be achieved with the concomitant ingestion of piperine, the pungent compound from black pepper, which preferentially binds curcumin metabolic enzymes to increase curcumin blood plasma levels. Once in circulation, the medicinal effects of curcumin are best realized: inhibiting intravascular lipid peroxidation, preventing transcriptional induction of viral DNA synthesis, and increasing neuronal activity to heighten a sense of mental wellness. These properties note only a few of the known medical uses for curcumin and curcuminoids, as novel therapy applications are explored for their medicinal quotient and scope of therapeutic efficacy. Curcumin, a naturally therapeutic compound found in turmeric, is available, inexpensive, and efficacious for multiple medical conditions. Perhaps future pharmacotherapy will include turmeric from the local grocery.

© 2011 Elsevier Inc. All rights reserved.

Natural medicinal therapies were the essential origins of modern medicine. Whether it was willow bark tea for pain relief (analgesia from aspirin) or cinchona bark extracts for fever reduction (antipyrexia from quinine), most early pharmacotherapies were derived from plant origins. Ironically, many botanical remedies contained potentially toxic compounds as well, such that excessive treatment occasionally resulted in fatal outcomes. Consequent interests to purify and isolate solely the medicinal compounds in natural medicines burgeoned into the advent of modern pharmacology and pharmacy. Thereafter, synthetic versions of natural drugs were developed for well over a century and continue to be developed today. However, the increasing demand for new therapies and chemopreventive agents has redirected current research back to natural sources for medicinal com-

pounds, notably specific molecules found in common herbs and spices.

Herbs and spices have been revered throughout human history for their flavorful and healthful qualities in the culinary and medical arts, respectively. Specific curative and preventive medicinal properties have been associated with dozens of spices. One spice in particular has been revered for its pronounced antitumor, antioxidant, antiarthritic, and antiinflammatory effects on the body: turmeric. Turmeric has a rich history in Ayurvedic medicine, an ancient medicinal approach in India, for more than 4000 years; yet only in the last 50 years has modern research shown the majority of medicinal and biological activity in turmeric is predominantly a result of one molecule: curcumin.¹ Numerous studies—*in vitro* (in laboratory preparations) and *in vivo* (in living organisms), in animals and humans—have shown an extensive scope of potential therapeutic and preventive effects using curcumin. Current clinical trials with curcumin range from myelodysplastic syndromes to colon cancer as its myriad medicinal applications continue to expand.²

Corresponding author: Owen D. Vincent, OMS-IV, Lincoln Memorial University-DeBusk College of Osteopathic Medicine, 6965 Cumberland Gap Parkway, Harrogate, TN 37752.

E-mail address: owen.vincent@lmunet.edu.

Chemopreventive therapy

Curcumin has been shown to have numerous beneficial medicinal effects, both qualified in observation and quantified in calculation, in treating and preventing numerous disease pathologies. It exhibits considerable antitumor properties, insofar as inhibiting inducible factors in tumor-forming genes as well as down-regulating several oncogenes and positive feedback inflammatory mechanisms.³ A recent study demonstrates how a curcumin supplement diet mitigates diabetic retinopathy by suppressing the oxidative stressors and inflammatory chemokines that promote the resultant microvascular damage.⁴ Another study *in situ* (in functional context) found that 50% and 100% inhibition of mammosphere development (mammary cell tumorigenesis) with concentrations at 5 mcM (0.1842 mg/dL) and 10 mcM (0.3684 mg/dL), respectively, outline its concentration-dependent activity and remarkable efficacy at low concentrations.⁵ This is to say that which could induce or augment tumor formation or propagation, respectively, will be markedly less with curcumin present.⁶ Curcumin is also considered a strong intravascular antioxidant because of its intrinsic polyphenolic chemical structure, which is analogous to similar structures in green tea and berry pigments. Within the vascular lumen, current research has shown curcumin to have strong antioxidant properties, inhibiting lipid and cholesterol oxidation as a buffer for free radical oxidation, and inducing glutathione S-transferase activation to yield higher output of the reduced enzymatic product for greater antioxidant potential.⁷ These are both potent antioxidant properties that protect the intimal lining of blood vessels from damage, thereby preserving vascular compliance and attenuating atherosclerosis.⁷

In addition, curcumin can help prevent virus-induced disease exacerbation because it interferes with replication of the virus. A recent study outlined that low concentrations of measured serum curcumin correlated with replication interference of the herpes simplex virus-1 (HSV-1) because it specifically prevents transcription factors and enzymes from synthesizing viral DNA.⁸ An earlier investigation similarly demonstrated that curcumin plays a protective role as well, preventing virus acquisition upon exposure.⁹ These data show that curcumin can play a considerable role in both mitigating HSV-1 infections, and preventing its transmission. It is possible that curcumin may prevent analogous enzymes from replicating DNA in the case of other viruses as well, such as the human papillomavirus (HPV) and the human immunodeficiency virus (HIV).

Several studies have also shown curcumin to increase neurogenesis in the hippocampus of the brain as well as increased brain-derived neurotrophic factor concentrations, both of which are associated with decreased depression, anxiety, and stress. Curcumin is one of only a few other known stimulants in this regard, along with strenuous exercise, full-spectrum light exposure, and prescription antidepressants.^{10,11} It is clear that curcumin plays a considerable role in down-regulating and abating molecular stressor

responses, such that compensatory homeostatic mechanisms may effectively re-establish a healthy balance from the point of biochemical dysfunction.

Bioavailability

The first and foremost issue regarding curcumin and its medicinal efficacy is absorption into bodily circulation. Absorbing curcumin from oral ingestion is generally poor, thus it does not enter into circulating blood easily; however, high doses of turmeric, up to 10 grams per day, showed no consumptive toxic thresholds or oral intake adverse effects.³ Once consumed, the gastric, enteric, and hepatic pass also results in considerable degradation to and metabolism of curcumin before entering systemic circulation. Curcumin is a lipid-soluble molecule, thus it dissolves better in oil than water. Therefore, any source of curcumin should be prepared in a lipid medium for increased bioavailability, such as heating turmeric in cooking oil before oral consumption. Once absorbed, the next considerable hurdle is the unaltered release of curcumin into circulation. As the majority of ingested curcumin is degraded in the liver, hepatic metabolism greatly inactivates the curcumin molecule, significantly reducing its medicinal potential.

Conversely, the addition of other culinary compounds may increase curcumin absorption into circulation relatively unaltered. Piperine, the pungent molecule of black pepper taste and smell, is well known to inhibit several metabolic enzymes in the liver.¹² Piperine is also lipid-soluble and therefore will dissolve in oil as well as curcumin. Ingesting curcumin and piperine prepared concomitantly, for example, i.e., consuming turmeric and black pepper prepared in cooking oil at a low heat to optimize lipid solubility and minimize heat-related degradation, may dramatically increase curcumin bioavailability. One notable human study shows that ingesting curcumin with a proportionally small amount of piperine, a ratio less than 100:1, will increase the circulating serum curcumin concentration by more than 2000% without adverse effects.¹³ This recent evidence shows curcumin directly modulates gene expression in a concentration-dependent manner in human cancer cells through its bound interaction with target proteins and transcriptional regulators for demonstrable phenotype effect.¹⁴

In comparing synthetic versus natural curcumin, one of many recent studies shows that laboratory formulations of curcumin with other lipid-soluble components has a notably greater bioavailability than free curcumin.¹⁵ However, these novel curcumin-related compounds (curcuminoids), whether naturally derived and modulated or chemically synthesized, are considerably expensive to create, isolate, and use medically. Although curcuminoids may allow increased absorption, their overall expense is cost-prohibitive for commonplace use as a chemopreventive therapy. Therefore, a preparation of turmeric and black pepper in cooking oil may be the most cost-effective and widespread means of increasing curcumin in bodily cir-

ulation for applicable medicinal efficacy and therapeutic value.

Discussion

The medicinal properties of turmeric have been observed for centuries and researched for decades, because current clinical trials and molecular research continue to provide strong support for the curcumin molecule specifically. Curcumin is one of a very few natural biomolecules to have widespread preventive medicinal value. Described previously, curcumin has been shown to mitigate oxidative damage in blood vessels; reduce aberrant cell growth; prevent viral transmission; and ultimately improve anxiety, depression, and mental stress. These data show a common theme throughout: curcumin impedes biomolecular aberration. In the case of endovascular damage, curcumin may behave as a strong antioxidant to protect lipids and cholesterol from oxidation, a primary contributing cause of atherosclerosis. Both cell growth abnormalities and viral transmission share a common thread: they need active DNA enzymes for synthesis. In this instance, curcumin may inhibit enzyme activation, whether directly, indirectly, or as a combined dynamic to the two. This abnormal cell growth inhibition most specifically prevents tumor cells and virus-infected cells from proliferating. Lastly, yet not well understood, curcumin may prevent cerebral congestion, facilitating growth and maintenance of higher brain function. Although the chemopreventive benefits have been qualified and quantified repeatedly, the medicinal efficacy of curcumin still has yet to be demonstrated in randomized, double-blind, placebo-controlled, human clinical trials.¹⁶ However, with no known side effects from curcumin alone, or in combination with piperine to increase circulatory concentrations from oral ingestion, it is an excellent candidate for chemopreventive and chemomodulatory adjunctive therapy in clinical medicine.

Curcumin is apparently the great biomolecular equilibrater in its scope of medicinal application. It augments homeostasis at multiple levels of scale throughout the body and neutralizes compounding metabolic stressors. Most remarkable is its ability to interrupt exponential, positive feedback cycles in disease processes, which otherwise progressively exacerbate the disease to morbidity or fatality. The resultant equilibrium from curcumin chemopreventive therapy is most congruent with the osteopathic emphasis on holistic medicine. As an osteopathic juxtaposition, curcumin is a considerable, intracellular regulator of molecular stability and homeostatic maintenance, mitigating biochemical dysfunction from the inside out. Curcumin and turmeric extracts are an excellent adjunctive therapy, particularly in chronic disease states when the current standards of care have reached their limits in the extent of modern medicine.¹⁷ Therefore, curcumin, the principal, active biomol-

ecule of turmeric, is clearly readily available, inexpensive, and efficacious with targeted medicinal application. Perhaps in the future, visits to the local pharmacy will include a trip down the spice aisle.

References

1. Aggarwal BB, Sundaram C, Malani N, Ichikawa H: Curcumin: the Indian solid gold. *Adv Exp Med Biol* 595:1-75, 2007
2. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV: Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci* 65:1631-1652, 2008
3. Aggarwal BB, Kumar A, Bharti AC: Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res* 23:363-398, 2003
4. Kowluru RA, Kanwar M: Effects of curcumin on retinal oxidative stress and inflammation in diabetes. *Nutr Metab (Lond)* 16:4-8, 2007
5. Kakarala M, Brenner DE, Korkaya H, et al: Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. *Breast Cancer Res Treat* 122:777-785, 2010
6. Choi H, Chun YS, Kim SW, Kim MS, Park JW: Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: a mechanism of tumor growth inhibition. *Mol Pharmacol* 70:1664-1671, 2006
7. Shukla PK, Khanna VK, Khan MY, Srimal RC: Protective effect of curcumin against lead neurotoxicity in rat. *Hum Exp Toxicol* 22:653-658, 2003
8. Kutluay SB, Doroghazi J, Roemer ME, Triezenberg SJ: Curcumin inhibits herpes simplex virus immediate-early gene expression by a mechanism independent of p300/CBP histone acetyltransferase activity. *Virology* 373:239-247, 2008
9. Bourne KZ, Bourne N, Reising SF, Stanberry LR: Plant products as topical microbicide candidates: assessment of in vitro and in vivo activity against herpes simplex virus type 2. *Antivir Res* 42:219-226, 1999
10. Xu Y, Ku B, Cui L, et al: Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res* 1162:9-18, 2007
11. Wu A, Ying Z, Gomez-Pinilla F: Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. *Exp Neurol* 197:309-317, 2006
12. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF: Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther* 302:645-650, 2002
13. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS: Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med* 64:353-356, 1998
14. Puliyappadamba VT, Cheriyan VT, Thulasidas AK, et al: Nicotine-induced survival signaling in lung cancer cells is dependent on their p53 status while its down-regulation by curcumin is independent. *Mol Cancer* 9:220, 2010
15. Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ: Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. *Cancer Chemother Pharmacol* 60:171-177, 2007
16. Mancuso C, Barone E: Curcumin in clinical practice: myth or reality? *Trends Pharmacol Sci* 30:333-334, 2009
17. Aggarwal BB, Sung B: Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci* 30:85-94, 2009