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CURCUMIN AS A DIETARY MODULATOR OF INFLAMMATION

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AN EPIDEMIC OF CHRONIC DISEASES

World Health organization estimates that 46 % of global disease burden and 59 % of global mortality is due to chronic diseases; 35 million individuals die each year from chronic diseases, and the numbers are steadily increasing (*World Health Organisation*, 2003). Accumulating evidence supports the association of chronic diseases to modern life style, stress, lack of exercise, abuse of tobacco and alcohol, and to the transition from natural unprocessed foods to processed, calorie-condensed and heat-treated foods. There is a strong association between chronic disease and reduced intake of plant fibres, plant antioxidants and increased consumption of industrially produced and processed dairy products, refined sugars and starch products. The per capita consumption of refined sugar has increased from about 0.5 kg per person and year in 1850 to almost 50 kg/person/year in the year 2000 and the per cow milk production from 2 to 50 litres/day. Dairy products, especially milk (mostly from pregnant cows) are rich in pro-inflammatory molecules: Hormones such as estrogens and growth factors such as IGF-1. Consumption of bovine milk has also been shown to release inflammatory mediators, increase intestinal permeability and induce leakage of larger molecules such as albumin and hyaluronan into the body. Heating up milk (pasteurization), and especially production of and storage of milk powder, produces large amounts of advanced glycation products (AGEs) and advanced lipoxidation products (ALEs) (*Baptista* and *Carvalho*, 2004), known as potent inducers of inflammation. This information is especially important as many foods such as ice cream, enteral nutrition solutions and baby formulas are based on milk powder. Bread, especially from gluten-containing grains, is also rich in molecules with documented pro-inflammatory effects, and bread crusts often used experimentally to induce inflammation. See further *Bengmark* (2004, 2005, 2006).

Despite some breath-taking advances in medico-pharmaceutical and surgical treatment medical and surgical emergencies, as well as advanced medical and surgical treatments, are still affected by an by unacceptably high morbidity and mortality. Sepsis is the most common medical and surgical complication, estimated only in the US to annually affect as many as 751,000 (*Arias* and *Smith*, 2003; *Angus* et al., 2001), and cause death of approximately 215,000 patients (29%) (*Angus* et a., 2001), which makes sepsis the tenth most common cause of death in the country. It is especially alarming that both morbidity and mortality in critical illness, especially when septic, is fast increasing and has done so for several decades. With a documented 1.5 % rate of increase per year it might double within the coming 50 to 60 years.

PLANT-DERIVED PROTECTION

Common to those suffering from chronic disease as well as critical illness is that they suffer an increased degree of inflammation, most likely due to their Western lifestyle. We are increasingly aware that plant-derived substances, often referred to as chemo-preventive agents, have an important role to play in control of inflammation. These substances are not only inexpensive, they are also easy available, and have no or limited toxicity. Among these numerous chemo-preventive agents are a whole series of phenolic and other compounds believed to reduced speed of aging and prevent degenerative malfunctions of organs, among them various curcumenoids found in turmeric curry foods and, thousands more of hitherto less or unexplored substances. However, this review will mainly focus on curcumin and its effects.

Polyphenols have in recent few years received an increasing attention for their strong chemo-preventive ability. Curcumin and many other plant-derived substances are increasingly regarded as shields against disease. Curcumin is the most explored of the so-called curmenoids, a family of chemo-preventive substances present in the spice turmeric. Although the substance has been known for some time, it is in the most recent years that the interest has exploded, much in parallel with increasing concern for severe side effects of synthetic COX-2 inhibitors, marketed by pharmaceutical industry. Most of the reported curcumin studies in the literature are experimental and few clinical studies are this far presented.

CURCUMIN – AN ANTIOXIDANT AND INHIBITOR OF NF-κB, COX-2, LOX AND INOS

NF-κB plays a critical role in several signal transduction pathways involved in chronic inflammatory diseases (*Bernes* and *Karin*, 1997) such as asthma and arthritis and various cancers (*Amit* and *Ben-Nereiah*, 2003). Activation of NF-κB is linked with apoptotic cell death; either promoting or inhibiting apoptosis, depending on cell type and condition. The expression of several genes such as cyclo-oxygenase-2 (COX-2), matrix mettaloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), tumour necrosis factor (TNF), interleukin-8 (IL-8), eotaxin, cell surface adhesion molecules and anti-apoptotic proteins are regulated by NF-κB (*Pahl*, 1999). COX-2 is inducible and barely detectable under normal physiological conditions, but is rapidly, but transiently, induced as an early response to pro-inflammatory mediators and mitogenic stimuli including cytokines, endotoxins, growth factors, oncogenes and phorbol esters. COX-2 synthesizes series-2 prostaglandins (PGE2, PGF2-α), which contribute to inflammation, swelling and pain. PGE2 promotes production of IL-10, a potent immunosuppressive cytokine produced especially by lymphocytes and macrophages, and suppression of IL-12 (*Stolina* et al., 2000). Inducible nitric oxid synthase (iNOS), activated by NF-κB is another enzyme that plays pivotal role in mediating inflammation, especially as it acts in synergy COX-2.

TURMERIC – APPROVED AS FOOD ADDITIVE

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenol) - 1,6- heptadiene - 3,5 - dione), a polyphenol rich in the dietary spice turmeric, is received from dried rhizozomes of the perennial herb *Curcuma longa* Linn, a member of the ginger family. Turmeric is mainly known for it's excellent ability preserve food and is approved as food additive in most Western countries. It is produced in several Asian and South-American countries. Only in India are about 500,000 metric tonnes produced each year, of which about half is exported. It has in addition to extensive use as food additive, for generations also been used in traditional medicine for treatment of various external or internal inflammatory conditions such as arthritis, colitis and hepatitis.

The molecule of curcumin resembles ubiquinols and other phenols known to possess strong antioxidant activities. Its bio-availability on oral supplementation is low, but can be improved by dissolution in ambivalent solvents (glycerol, ethanol, DMSO) (*Sharma* et al., 2001). It is also reported to be dramatically elevated by co-ingestion of peperine (a component of pepper), demonstrated both in experimental animals and humans (*Shoba* et al., 1998). Several studies has demonstrated that curcumin is a-toxic, also in very high doses (*Bravani Shankar* et al., 1980; *Chainani*, 2003). Treatment of humans during three months with 8000 mg curcumin per day showed no side effects (*Chainani*, 2003). It is estimated that adult Indians consume daily 80-200 mg curcumin per day (*Grant* and *Schneider*, 2000). A common therapeutic dose is 400-600 mg curcumin three times daily corresponding to up to 60 g fresh turmeric root or about 15 g turmeric powder. The content of curcumin in turmeric is usually 4-5 %.

CURCUMIN - EFFECTIVE AGAINST STRESS-INDUCED OVERINFLAMMATION

Curcumin is not only an inexpensive a-toxic and potent COX-2 and iNOS inhibitor (*Suhr* et al., 2001), it is also a potent inducer of heat shock proteins (HSPs) and potential cytoprotector (*Dunsmore* et al., 2001; *Chang*, 2001). Curcumin does not only inhibit COX-2, it also inhibits lipo-oxygenases (LOX) and leukotreines such as LBT4 and 5HETE (*Wallace*, 2002), especially when bound to phosphatidylcholine micelles (*Began* et al., 1999). It is also reported to inhibit cytochrome P450 iso-enzymes and thereby activation of carcinogens (*Thapliyal* and *Maru*, 2001). Curcumin has the ability to intercept and neutralize potent pro-oxidants and carcinogens, both ROS (superoxide, peroxyl, hydroxyl radicals) and NOS (nitric oxide, peroxynitrite) (*Jovanovic* et al., 2001). It is also a potent inhibitor of TGF-β and fibrogenesis (*Gaedeke* et al., 2004), which is one of the reasons, why it can be expected to have positive effects in diseases such as kidney fibrosis, lung fibrosis, liver cirrhosis and Crohn's disease and in prevention of formation of tissue adhesions (*Srinisan* et al., 2004). Curcumin is suggested to be especially effective in Th1-mediated immune diseases as it effectively inhibits Th1 cytokine profile in $CD4^+$ T cells by interleukin-12 production (*Kang* et al., 1999).

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another, and interac-

tions between herbs and drugs, even if structurally unrelated, may increase or decrease the pharmacological and toxicological effects of either component (*Fugh-Berman*, 2000; *Groten* et al., 2000). It is suggested that curcumin may increase the bioavailability of vitamins such as vitamin E and also decrease cholesterol, as curcumin in experimental studies significantly raises the concentration of α-tocopherol in lung tissues and decreases plasma cholesterol (*Kamal-Eldin* et al., 2000). Polyphenols, isothiocyanates such as curcumin and flavonoids such as resveratrol, are all made accessible for absorption into the intestinal epithelial cells and the rest of the body by digestion/fermentation in the intestine by microbial flora (*Shapiro* et al., 1998).

CURCUMIN IN ACUTE AND CHRONIC DISEASES

Atherosclerosis

Oxidation of low-density lipoproteins (LDL) is suggested to play a pivotal role in the development of arteriosclerosis, and LDL oxidation products toxic to various types of cells including endothelial cells. Curcumin has a strong capacity to prevent lipid peroxidation, stabilize cellular membranes, inhibit proliferation of vascular smooth muscle cells, and inhibit platelet aggregation; all important ingredients in the pathogenesis of arteriosclerosis. Curcumin was found to be the most effective, when the ability to inhibit the initiation and propagation phases of LDL oxidation of a defined antioxidant butylated hydroxy anisole (BHA), curcumin, quercetin, capsaisin were compared, and quercetin the least (*Naidu* and *Thippeswamy*, 2002). Supply of curcumin, but also capsaicin and garlic (allecin) to rats fed of a cholesterol-enriched diet prevented both increase in membrane cholesterol and increased fragility of the erythrocytes (*Kempaiah* and *Srinivasan*, 2002). Significant prevention of early atherosclerotic lesions in thoracic and abdominal aorta are observed in rabbits fed an atherogenic diet for thirty days, accompanied by significant increases in plasma concentrations of co-enzyme Q, retinol and α-tocopherol and reductions in LDL conjugated dienes and in TBARS (thiobarbituric acid-reactive substances, an expression of ongoing oxidation) (*Quiles* et al., 2002).

Cancer

Cancer is a group of more than 100 different diseases, which manifest itself in uncontrolled cellular reproduction, tissue invasion and distant metastases (*Levi* et al., 2001). Behind the development of these diseases are most often exposure to carcinogens, which produce genetic damage and irreversible mutations, if not repaired. During the last fifty years attempts have been made to find or produce substances that could prevent these processes, so called chemopreventive agents. Cancers are generally less frequent in the developing world, which has been associated both with less exposure to environmental carcinogens and to a richer supply of natural chemopreventive agents. The incidence per 100,000 population is in the USA considerably higher for the following diseases compared to India: prostatic cancer (23x), melanoma skin cancer (male 14x, female 9x), colorectal cancer (male 11x, female 10x), endometrial, cancer (9x), lung cancer (male 7x, female 17x), bladder cancer (male 7x, female 8x) breast cancer (5x), renal cancer (male 9x, female 12x) (*Sinha* et al., 2003). These differences are for some diseases

such as breast cancer and prostatic cancer even greater when compared to China. The consumption of saturated fat and sugary foods is much less in the Asian countries, but equally important, the consumption of plants with high content of chemopreventive substances is significantly higher in these countries. As an example, the consumption of curcumin has for centuries been about 100 mg/day in these Asian countries (*Choudhuri* e al., 2002). Curcumin induces *in vitro* apoptosis of various tumour cell lines: Breast cancer cells (*Choudhuri* e al., 2002; *Shao* et al., 2002), lung cancer cells (*Pillai* et al., 2004), human melanoma cells (*Zheng* et al., 2004), human myeloma cells (*Han* et al., 2002), human leukaemia cell lines (*Bharti* et al., 2004), human neuroblastoma cells (*Liontas* and *Yeger*, 2004), oral cancer cells (*Elattar* and *Virji*, 2000), and prostatic cancer cells (*Mukhopadhyay* et al., 2001; *Nakamura* et al., 2002; *Hour* et al., 2002; *Deeb* et al., 2004). Curcumin has in experimental models also demonstrated ability to inhibit intra-hepatic metastases (*Ohadshi* et al., 2003). Few *in vivo* experimental studies and no clinical controlled trials are this far concluded. However, a recent phase I study reported histologic improvement of pre-cancerous lesions in 1 out of 2 patients with recently resected bladder cancer, 2 out of 7 patients of oral leucoplakia, 1 out of 6 patients of intestinal metaplasia of the stomach, and 2 out of 6 patients with Bowen's disease (*Cheng* et al., 2001). However, the main purpose of the study was to document that curcumin is not toxic to humans when taken by mouth for 3 months in a dose of up to 8,000 mg/day.

Diabetes

Turmeric (TU, 1 g/kg body weight) or curcumin (CU, 0.08 g/kg body weight) were in a recent study supplied daily for three weeks to rats with alloxan-induced diabetes (AID) and compared to controls (CO) (*Giltay* et al., 1998). Significant improvements were observed in blood glucose (mg/dl; CO 88.3, AID 204.4, TU 142.7, CU 140.1), haemoglobin (gm/dl; CO 14.7, AID 10.8, TU 13.6, CU 13.1) and glycosylated haemoglobin (gm/dl; CO 2.8, AID 11.2, TU 9.0, CU 7.8). Significant differences were also observed in TBARS in liver tissue (nmoles/g tissue; CO 43.0, AID 54.0, TU 34.0, CU 29.0), TBARS in plasma (nmoles/ml; CO 3.8, AID 7.3, TU 5.3, CU 4.6) in glutathione in liver (μgm/mg; CO 23.4, AID 11.2, TU 16.6, CU 20.9) and glutathione in plasma (mg/dl; CO 22.4, AID 14.2, TU 18.4, CU 20.1). It was also observed that the activity of sorbitol dehydrogenase (SDH), which catalyzes the conversion of sorbitol to fructose, was significantly lowered by treatment both with turmeric and curcumin.

Gastric diseases

When the in vitro effects against 19 different *Helicobacter pylori* strains, including five cagA+ strains (cag A is the strain-specific *H. pylori* gene linked to pre-malignant and malignant lesions) were studied, both treatments were found to be equally effective as both treatments did significantly reduce growth of all the strains studied (*Mahady* et al., 2002). Subsequent studies did also demonstrate that curcumin inhibits infection and inflammation of gastric mucosal cells through the inhibition of activation of NF-κB, degradation of IκBα, NF-κB DNA binding and the activity of IκB kinases α and β. No curcumin-induced effects were observed on mitogen-activated protein kinases (MAPK), extra-cellular signal regulating kinases ½ (ERK1/2) and p38. *H. pylori*-induced mitogenic re-

sponse was completely blocked by curcumin (*Foryst-Ludwig* et al., 2004). Significant antifungal properties against various fungal, especially phytopathogenic, organisms by curcumin are also reported (*Kim* et al., 2003).

Hepatic diseases

Dietary supply of curcuminoids is also reported to increase hepatic acyl-CoA and prevent high-fat diet-induced accumulation in the liver and adipose tissues in rats (*Asai* and *Miyazawa*, 2001). Ethanol-induced steatosis is known to be further aggravated by supply of PUFA-rich vegetable oils, which has been thermally oxidized. Rats gavaged for 45 days with a diet containing 20 % ethanol and 15 % sunflower oil, heated to 180° C for 30 min (AO), showed extensive histo-pathological changes with focal and feathery degeneration, micro-necroses and extensive steatosis in the liver and extensive inflammation vessel congestion and fatty infiltration in the kidneys, changes, which largely could be prevented by simultaneous supply of curcumin (CU) or particularly photo-irradiated curcumin (PCU) e.g. curcumin kept in bright sunshine for five hours (*Rukkumani* et al., 2002). Both products were supplied in a dose of 80 mg/kg body weight. Both products did significantly inhibit elevations in alkaline phosphatases (ALP): controls (CO) 85.88, PCU 239.56, CU 177.41 and PCU 149.15 and γ-glutamyl transferase (GGT): CO 0.60, PCU 2.51, CU 1.43, PCU 1.15. Similar beneficial effects were observed on histology in various tissues and in hepatic content of cholesterol, triglycerides free fatty acids and phospholipids. Rats were in another study for four weeks fed with fish oil and ethanol (FE), which resulted in hepatic lesions consisting in fatty liver, necrosis and inflammation. Supply of curcumin in a daily dose of 75 mg/kg body weight to these rats prevented the histological lesions (*Nanji* et al., 2003). Curcumin was observed to in part to suppress NF-κB-dependent genes, to block endotoxin-mediated activation of NF-κB and to suppress the expression of cytokines, chemokines, COX-2 and iNOS in Kupffer cells. Similar effects were also observed in carbon tetrachloride-induced injuries. Pre-treatment for four days with curcumin (100 mg/kg body weight) before intraperitoneal injection of CCl_4 prevented significantly subsequent increases in TBARS: CO 274, CCl_4 556, CU 374, alanine aminotransferase (ALT): CO 46, CCL_4 182, CU 97 and aspertate aminotransferase (AST): CO 97, CCl_4 330, CU 211 and in hydroxyproline (µg/g liver tissue): CO 281, CCl_4 777, CU 373 (*Park* et al., 2000).

Intestinal diseases

Pre-treatment during 10 days with curcumin in a daily dose of 50 mg/kg body weight before induction of trinitrobenzene sulphonic acid (TNBS) colitis resulted in a significant reduction in degree of histological tissue injury, neutrophil infiltration (measured as decrease in myelo-peroxidase activity) and lipid peroxidation (measured as decrease in malondialdehyde activity) in the inflamed colon and in a decreased serine protease activity (*Ukil* et al., 2003). A significant reduction in NF-κB activation and reduced levels of NO and a marked suppression of Th1 functions: IFNγ and IL-12p40 mRNA, was also observed. Curcumin was in another similarly designed study added to the diet during five days before induction of TNBS colitis, which resulted in a significant reduction in myelo-peroxidase, and attenuation of the TNBS-induced message for IL-1β on semi-quantitative RT-PCR (*van 't Land* et al., 2004). Western blotting revealed a significant attenuation of the

activation of p38 MAPK. Curcumin was also supplied in combination with caffeic acid phenethyl ester (CAPE) to animals treated with cytostatic drugs (arabinose cytosine, Ara-C, and methotrexate, MTX) (*van 't Land* et al., 2004). The treatment did not only inhibit the NF-κB induced mucosal barrier injury but was also shown to increase the *in vitro* susceptibility of the non-transformed small intestinal rat epithelial cell, IEC-6, to the cytostatic agents.

Neurodegenerative diseases

A growing body of evidence implicates free radical toxicity, radical induced mutations and oxidative enzyme impairment and mitochondrial dysfunction in neurodegenerative diseases (NDD). Significant oxidative damage is observed all NDDs, which in the case of Alzheimer disease (AD) leads to extra-cellular deposition of β-amyloid (Aβ) as senile plaques. Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen has proven effective to prevent progress of AD in animal models (*Lim* et al., 2000), but gastrointestinal and occasional liver and kidney toxicity induced by inhibition of COX-1 precludes widespread chronic use of the drug (*Björkman*, 1998). Use of antioxidants such as vitamin E (α-tocopherol) has proven rather unsuccessful even when high doses were used (*Sano* et al., 1997). Vitamin E, α-tocopherol, is in contrast to γ-tocopherol a poor scavenger of nitric oxide (NO) based free radicals. Curcumin is a several times more potent scavenger than vitamin E (*Zhao* et al., 1989), and in addition also a specific scavenger of NO-based radicals (*Sreejavan* and *Rao*, 1997). When tried in a transgenic mouse model of AD did a modest dose (24 mg/kg body weight), but not a > 30 times higher dose (750 mg/kg body weight) of curcumin significantly reduce oxidative damage and amyloid pathology (*Lim* et al., 2001). Similar observations, reductions in both Aβ deposits and in memory deficits are also made in Sprague Dawley rats (*Frautschy* et al., 2001). The age-adjusted prevalence of both AD (*Ganguli* et al., 2000) and Parkinson´s disease (PD) is in India, with its significantly higher intake of turmeric, much lower than in Western countries, especially the USA (*Muthane* et al., 1998). However, the preventive effects of consumption of turmeric can also be achieved with other polyphenol-rich fruits and vegetables if consumed in enough quantities. Blueberries, strawberries and spinach in doses of 18.6, 14.8 and 9.1 gm of dried extract/kg body weight were demonstrated effective in reversing age-related deficits in both neuronal and behavioural parameters (*Joseph* et al., 1999). A study from 1999 is of special interest: Rats on chronic ethanol supply were randomized to 80 mg/kg body weight of curcumin (CU) or control (CO) and compared to non-intoxicated normal rats (NI) (*Rajakrishnan* et al., 1999). The degree of histo-pathological changes, the levels of TBARS (NI 1.29, CU 2.41, CO 2.98), cholesterol (NI 1531.9, CU 1658.2, CO 2031.1), phospholipids (NI 1845.5, CU 2011.5, CO 2795.1), and free fatty acids (NI 26.7, CU 39.9, CO 53.1) in brain tissue were significantly improved after curcumin treatment.

Ocular diseases

Cataract, an opacity of the eye lens, is the leading cause of blindness worldwide, responsible for blindness of almost 20 million in the world (*Thylefors*, 1998). Nutritional deficiencies, especially lack of consumption of enough antioxidants, diabetes, excessive sunlight, smoking and other environmental factors are known to in-

crease the risk of cataracts (*Ughade* et al., 1998). The age-adjusted prevalence of cataract in India is, however, three times that of the United States (*Brian* and *Taylor*, 2001). Despite that have three different experimental studies reported significant preventive effects of curcumin against cataracts induced by naphthalene (*Pandya* et al., 2000), galactose (*Suryanarayana* et al., 2003), and selenium (*Padmaja* and *Raju*, 2004).

Pancreatic diseases

The effect of curcumin to reduce the damage to pancreas was studied in two different models; cerulein-induced and ethanol & CCK-induced pancreatitis (*Gukocvsky* et al., 2003). Curcumin was administered intravenously in parallel with induction of pancreatitis. A total of 200 mg/kg body weight was administered during the treatment period of six hours. Curcumin treatment reduced significantly histological injuries, the acinar cell vacuolization and neutrophil infiltration of the pancreatic tissue, the intra-pancreatic activation of trypsin, the hyper-amylasaemia and hyper-lipasaemia, and the pancreatic activation of NF-κB, IκB degradation, activation of activator protein (AP)-1and various inflammatory molecules such as IL-6, TNF-α, chemokine KC, iNOS and acidic ribosomal phosphoprotein (ARP). Curcumin did in both models also significantly stimulate pancreatic activation of caspase-3.

Respiratory diseases

As mentioned above, curcumin is a potent inhibitor of TGF-β and fibrogenesis (*Srinisan* et al., 2004), and suggested to have positive effects in fibrotic diseases in kidneys, liver, intestine (Crohn's Disease), body cavities (prevention of fibrous adhesions) (*Chang*, 2001) and on conditions with lung fibrosis, including cystic fibrosis. The latter is of special interest as it has been especially linked to glutathione deficiency. The effect of curcumin against amiodarone-induced lung fibrosis was recently studied in rats (*Punithavatihi* et al., 2003). Significant inhibition of LDH activity, infiltration of neutrophils, eosinophils and macrophages in lung tissue, LPS-stimulated TNF-α release, phorbole myristate acetate (PMA)-stimulated superoxide generation, myeloperoxidase (MPO) activity, TGF- β1 activity, lung hydroxyproline content and expression of type I collagen and c-Jun protein were observed when curcumin was supplemented in a dosis of 200 mg/kg body weight in parallel with intra-tracheal instillation of 6.25 mg/kg body weight of amiodarone. Curcumin exhibits structural similarities to isoflavonoid compounds that seem to bind directly to the CFTR protein and alter its channel properties (*Illek* et al., 2000). *Egan* et al. (2004), who had previously observed that curcumin inhibits a calcium pump in endoplasmic reticulum, thought that that reducing the calcium levels might liberate the mutant CFTR and increase its odds of reaching the cell surface- see also *Zeitlin* (2004). The ΔF508 mutation, the most common cause of cystic fibrosis, will induce a misprocess in the endoplasmatic reticulum of a mutant cystic fibrosis trans-membrane conductance regulator (CFTR) gene. A dramatic increase in survival rate and in normal cAMP-mediated chloride transport across nasal and gastrointestinal epithelia was observed in gene-targeted mice homozygous for the ΔF508 when supplemented curcumin (*Illek* et al., 2000). No human studies are yet reported and it too early to know if this treatment will be able to halt or reverse the decline in lung function also in patients with cystic fibrosis. An eventual anti-asthmatic effect of curcumin was re-

cently tested in guinea-pigs sensitized with ovalbumin and significant reductions observed both in airway constriction and in airway hyper-reactivity to histamine (*Ram* et al., 2003).

Tobacco/cigarette smoke (CS)-induced injuries

CS is suggested to cause 20 % of all deaths and ~30 % of all deaths from cancer. CS contains thousands of compounds of which about hundred are known carcinogens, co-carcinogens, mutagens and/or tumour promoters. Each puff of smoke contains over 10 trillion free radicals. Antioxidant levels in blood are also significantly reduced in smokers. Activation of NF-κB has been implicated in chemical carcinogenesis and tumourigenesis through activation of several genes such as COX-2, iNOS, matrix metalloproteinase (MMP)-9, IL-8, cell surface adhesion molecules anti-apoptotic protein and others. A recent study reports that curcumin abrogates the activation of NF-κB, which correlates with down-regulation of COX-2, MMP-9 and cyclin D1 in human lung epithelial cells (*Shishodia* et al., 2003).

CONCLUSIONS

All chronic diseases are in a way related, they develop all as a result of a prolonged and exaggerated inflammation (*Bengmark*, 2004). Their development can most likely be prevented or at least delayed by extensive consumption of anti-oxidants such as curcumin. It is important to remember, that it is almost exclusively through microbial fermentation of the different plants that bioactive anti-oxidants are released and absorbed. Clearly flora and supplied lactic acid bacteria/probiotics play an important role. It is therefore unfortunate that both size and diversity of flora is impaired and intake of probiotic bacteria significantly reduced among Westerners. For example, reduction in total numbers and diversity of flora is also associated with certain chronic diseases such as IBD (*Ott* et al., 2004). A study from 1983 demonstrated that *Lactobacillus plantarum,* a strong fibre fermentor, is found in only 25 % of omnivorous Americans and in about 2/3 of vegetarian Americans (*Finegold* et al., 1983). Great differences in volume and diversity of flora have also been observed between different human cultures. It is reported that Scandinavian children have compared to Pakistani children a much reduced flora (*Adlerberth* et al., 1991). Astronauts, who return from space flights have during the flight lost most of their commensal flora including *lactobacillus* species such as *Lactobacillus plantarum* (lost to almost 100%), *Lactobacillus casei* (lost to almost 100%), *Lactobacillus fermentum* (reduced by 43%), *Lactobacillus acidophilus* (reduced by 27%), *Lactobacillus salivarius* (reduced by 22%) and *Lactobacillus brevis* (reduced by 12%) (*Lencner* et al., 1984), changes most likely attributed to poor eating (dried food, no fresh fruits and vegetables) and a much reduced intake of plant fibres and natural antioxidants, to the mental and physical stress and eventually also to the lack of physical exercise. Many individuals in Western Societies exhibit a type of “astronaut-like lifestyle” with unsatisfactory consumption of fresh fruits, vegetables, too much stress and no or little outdoor/sport activities. Furthermore flora seems not to tolerate exposure to chemicals including pharmaceuticals. This is also demonstrated in critically

ill, who most often have lost their entire *Lactobacillus* flora (*Knight* et al., 2004). A recent Scandinavian study suggest that fibre-fermenting LAB such as *Lactobacillus plantarum, Lactobacillus rhamnosus* and *Lactobacillus paracasei* ssp. *paracasei,* present in all humans with a rural lifestyle, are only found 52%, 26% and 17% respectively of persons with a more urban Western type lifestyle (*Ahrné* et al., 1998). These LAB are present in all with more rural lifestyle. The lack of these LAB is probably negative as these LAB are unique in their ability to ferment important fibres such as inulin and phlein, otherwise resistant to fermentation by most *Lactobacillus* species (*Müller* and *Lier*, 1994), and superior to other *Lactobacillus* in their ability to eliminate pathogenic microorganisms such as *Clostridium difficile* (*Naaber* et al., 2004).

To use medicinal plants and their active components is becoming an increasingly attractive approach for the treatment of various inflammatory disorders among patients unresponsive or unwilling to take standard medicines. Food derivates have the advantage of being relatively non-toxic. This is certainly so for turmeric and curcumin. If one chooses to supply it with the fibre e.g. as turmeric, additional supplementation with probiotic bacteria will most likely enhance the efficacy of treatment.

Increasing evidence suggest that saturated fat in the diet increases and plant fibre intake reduces the inflammatory reaction in the body (*King* et al., 2003). A high fat/low fibre diet is clearly associated with chronic diseases (*Campbell* and *Junchi*, 1994), and fruit and vegetable intake with reduction in incidence of chronic diseases (*Knekt* et al., 2002). Focus is increasingly turning from fibre per se to active ingredients in the plant fibres such as curcumin in turmeric.

Not only turmeric and curcumin, but also numerous other plants contain compounds that reduce inflammation and protects against disease. Among them are several thousands of plant-derived chemo-preventive agents, polyphenols and many other, most often unexplored, substances, which seem to have potential to reduce inflammation, speed of aging, prevent degenerative malfunctions of organs and development of chronic diseases. Among them isothiocyanates in cruciferous vegetables, anthocyanins and hydroxycinnamic acids in cherries, epigallocatechin-3-gallate (EGCG) in green tee, chlorogenic acid and caffeic acid in coffee beans and also in virgin tobacco leaves, capsaicin in hot chilli peppers, chalcones in apples, euginol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, rutin and quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine and virgin peanuts, various curcumenoids, the main yellow pigments in turmeric curry foods, and daidzein and genistein from the soy bean. These compounds have all slightly different functions and seem to complement each other well.

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