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Control of Systemic Inflammation and Chronic Diseases—The Use of Turmeric and Curcuminoids

Stig Bengmark

ABSTRACT

The world suffers an epidemic of both critical illness (CI) and chronic diseases (ChDs), and both groups of diseases increase from year to year, and have done so for several decades. It is strongly associated to the modern, so-called Western, lifestyle: stress, lack of exercise, abuse of tobacco and alcohol, and the transition from natural unprocessed foods to processed, calorie-condensed, and heat-treated foods. There is a strong association between reduced intake of plant fibers and plant antioxidants and increased consumption of industrially produced and processed products especially dairy, refined sugars, and starch products and ChDs. Heating up foods such as milk (pasteurization) and production and storage of milk powder produce large amounts of advanced glycation end products (AGEs) and advanced lipid oxidation end products (ALEs), known as potent inducers of inflammation (see further Chapter 20).

Numerous plant-derived, but also microbe-derived, substances, often referred to as chemopreventive agents, have documented anti-inflammatory effects and are believed to reduce speed of aging and prevent degenerative malfunctions of organs and also development of acute and chronic diseases. Among these are various curcumenoids, active ingredients in turmeric curry foods, and thousands more of hitherto little or totally unexplored substances. This chapter focuses on documented experimental and clinical effects of supplementation of turmeric, various curcumenoids, and pure curcumin. Regrettably, only few clinical studies in human have been performed in contrast to an abundance of studies in experimental animals.

AN EPIDEMIC OF CHRONIC DISEASES AND CRITICAL ILLNESS

Modern medicine has to a large extent failed in its ambition to control both acute and chronic diseases. The world suffers an epidemic of chronic diseases of a dimension never seen before, and these diseases are like a prairie fire also spreading to the so-called developing countries. As an example, there are more cases of diabetes reported in China (24 million) and India (44 million) than in the United States (17 million), and the increase in incidence is faster in these countries than in Western societies. Today, chronic diseases—for example, diseases such as cardiovascular and neurodegenerative conditions, diabetes, stroke, cancers, and chronic respiratory diseases—constitute 46% of the global disease burden and 59% of the global deaths; each year approximately 35 million individuals die in conditions related to chronic diseases, and the numbers are fast increasing and have done so for several years (World Health Organization 2003).

Also acute diseases, often referred to as medical and surgical emergencies—myocardial infarction, stroke and severe pancreatitis, or diseases/complications following advanced medical and surgical treatments such as organ and stem cell transplantation and other large operations—have an unacceptably high morbidity and mortality. Sepsis, the most common medical and surgical complication, is estimated to annually affect as many as 751,000 individuals only in the United States (Angus et al. 2001; Arias and Smith 2003) and cause death of approximately 215,000 patients/year (29%) (Angus

et al. 2001), making sepsis the tenth most common cause of death in this country. It is especially alarming that both morbidity and mortality in critical illness (CI), and septis, is fast increasing worldwide and has done so for several decades. With a documented 1.5% rate of increase per year, the incidence is forcasted to double within the coming 50 to 60 years.

LIFESTYLE ASSOCIATED DISEASES

Accumulating evidence supports the association of ChDs to modern lifestyle, stress, lack of exercise, and abuse of tobacco and alcohol, and most important, the transition from natural unprocessed foods to processed, calorie-condensed and heat-treated foods are contributing to this development. The strong association between ChD and reduced intake of plant fibers and plant antioxidants, and increased consumption of industrially produced and processed dairy products, refined sugars, and starch products is well documented. The per capita consumption of refined sugar has increased from about 0.5 kg/person/year in 1850 to almost 50 kg/person/year in the year 2000 and the per cow milk production from 2 to 50 liters/day. Dairy products, especially milk (mostly from pregnant cows), are rich in proinflammatory molecules: hormones such as estrogens (Howie and Shultz 1985; Malekinejad et al. 2006) and growth factors such as IGF-1 (Holmes et al. 2002). 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 (Bengtsson et al. 1996). Heating up milk (pasteurization), and especially production and storage of milk powder, produces large amounts of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs) (Baptista and Carvalho 2004), known as potent inducers of inflammation. This information is especially important as many foods such as ice cream, industrially produced enteral nutrition solutions, and baby formulas are based on milk powder. Such formulas are reported to increase inflammation and induce microbial intestinal translocation (Deitch et al. 2002; Mosenthal 2002; Xu et al. 1998). Bread, especially when from gluten-containing grains, is rich in molecules with documented proinflammatory effects, and bread crusts often used experimentally to induce inflammation. See further Bengmark (2004, 2006a, 2007).

PLANT-DERIVED PROTECTION

Common to those suffering from ChD as well as CI is that they suffer an increased degree of systemic inflammation. We are increasingly aware that plant-derived substances, often referred to as chemopreventive agents, have an important role to play in control of inflammation. These substances are generally inexpensive, easy available, and have no or limited toxicity. Among the numerous chemopreventive agents are a whole series of phenolic and other compounds believed to reduce the speed of aging and prevent degenerative malfunctions of organs, among them various curcumenoids found in turmeric curry foods and thousands of other hitherto little or not at all explored substances.

Curcumin and many other plant-derived substances are increasingly regarded as shields against disease (Bengmark 2006b). Curcumin is the most explored of a family of the so-called active chemopreventive substances in the spice turmeric, collectively referred to as curmenoids. The health-promoting effects of turmeric is widely recognized as the spice has been used for centuries, especially in Indian Ayurveda medicine, to treat a wide variety of disorders such as pains and colics, rheumatism, skin diseases, intestinal worms, diarrhea, intermittent fevers, hepatic disorders, urinary problems, dyspepsia, intestinal conditions such as colitis and constipation, amenorrhea, and inflammatory conditions in general. However, it is only in the most recent years that the interest has exploded, much in parallel to the availability of molecular biological techniques, but also due to increasing concern for severe side effects of synthetic cyclooxygenase-2 (COX-2) inhibitors that pharmaceutical industry is marketing. Most of the curcumin studies reported in the literature are experimental and few clinical studies are this far presented.

TURMERIC—APPROVED AS FOOD ADDITIVE

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenol)-1,6-heptadiene-3,5-dione) a polyphenol, richly available in turmeric, is received from dried rhizozomes of the perennial herb *Curcuma longa* Linn, a member of the ginger family. Turmeric is since long known to be an excellent food preservative and is approved as such in most Western countries. It is mainly produced in Asian and South American countries. Only in India about 500,000 metric tonnes are produced each year, of which about half is exported. The content of curcumin in turmeric is

usually 4–5%. The molecule of curcumin resembles ubiquinols and other polyphenols known to possess strong antioxidant activities. Its bioavailability on oral supplementation is relatively 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), as demonstrated both in experimental animals and humans (Shoba et al. 1998). Several studies have demonstrated that curcumin is atoxic, also in very high doses Bravani Shankar et al. 1980; Shainani-Wu 2003). Treatment of humans for 3 months with 8,000 mg curcumin per day lead to no side effects (Shainani-Wu 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.

INFLAMMATION—CENTRAL TO DEVELOPMENT AND PREVENTION OF DISEASE

The process of inflammation is well known. Activated monocytes and macrophages release proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-1 (IL-1), which induce inflammation in the tissues. Also important for the development of inflammation is the production by macrophages and neutrophils of prostaglandins, thromboxanes, and leukotrienes, collectively known as eicosanoids, which are mediators of inflammation synthesized through enzymatic degradation by COX-2 or lipooxygenase (LOX) of arachidonicacid (AA). COX-2 is induced by physical and mental stress, and a variety of inflammatory stimuli, including endotoxins, cytokines, growth factors, tumor promoters, and COX-2, catalyze the synthesis by mononuclear phagocytes, endothelial cells, polymorphonuclear leukocytes, and platelets of series-2 prostaglandins (e.g., PGE2, PGF2α, PGI2, PGD2) and thromboxanes (e.g., TXA2, TXB2). PGE2 is a well-known promoter of production both of IL-10, a potent immunosuppressive cytokine, produced especially by lymphocytes and macrophages, and suppressor of IL-12 (Stolina et al. 2000).

Nuclear factor-kappa B (NF-κB) plays a critical role for induction of several signal transduction pathways involved in inflammatory diseases (Bernes and Karin 1997) such as asthma, arthritis and various cancers (Amit and Ben-Neriah 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 COX-2, matrix metalloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), TNF, IL-8, eotaxin, various cell surface adhesion molecules, and antiapoptotic 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 proinflammatory mediators and mitogenic stimuli including cytokines, endotoxins, growth factors, oncogenes and phorbol esters. iNOS, activated by NF-κB is another enzyme that plays a pivotal role in mediating inflammation, especially as it acts in synergy COX-2.

Curcumin is not only an inexpensive atoxic and potent COX-2 and iNOS inhibitor (Surh et al. 2001), but also a potent inducer of heat shock proteins (Hsps) and a cytoprotector (Chang 2001; Dunsmore et al. 2001) Curcumin inhibits not only COX-2, but also LOXs and leukotreines such as LBT4 and 5HETE (Wallace 2002), especially when bound to phosphatidylcholine micelles (Began et al. 1999). Curcumin is also reported to inhibit cytochrome P450 isoenzymes and thereby activation of carcinogens (Thapliyal and Maru 2001). Curcumin has the ability to intercept and neutralize potent prooxidants 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 prevent formation of tissue adhesions (Srinisan and Libbus 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 activation of IL-12 (Kang et al. 1999).

Furthermore, curcumin is also known to:

- Inhibit the release of AA through hydrolysis of membrane phospholipids (Hong et al. 2004).
- Inhibit the induction of COX-2 mRNA and protein expression (Zhang et al. 1999).
- Inhibit extracellular signal-regulated kinase (ERK) activity (Chun et al. 2003).
- Inhibit 5-hydroxyeicosatetraenoic acid (5-HETE) production in human neutrophils (Flynn et al. 1986).

- Inhibit the so-called Janus kinase (JAK)–STAT signaling cascade (Kim et al. 2005a).
- Inhibit the production of superoxide and nitric oxide by inflammatory cells. (Bhaumik et al. 2000; Brouet and Ohshima 1995).
- Moderately increase the number of T-and B-cells without altering the numbers of phagocytic macrophages (Gautam et al. 2007).
- Increase the phagocytic activity of macrophages (Antony et al. 1999; Li and Liu 2005).
- Increase the numbers of B-cells in the small intestinal mucosa (Churchill et al. 2000).
- Suppress surface expression of costimulatory molecules CD80 and CD86 and major histocompatibility complex (MHC) II, but not MHC class I (Kim et al. 2005a).
- Impair the production by dendritic cells of IL-12, IL-1, IL-6, and TNFα (Kim et al. 2005a).
- Inhibit the activation of mitogen-activated protein kinase (MAPK) and nuclear translocation of nuclear factor-beta (NF-β) (Gautam et al. 2007; Kim et al. 2005a).
- Reduce accumulation in the body of proinflammatory molecules such as AGEs and ALEs (Sajithlal et al. 1998).
- Induce apotosis of various tumor cells by a variety of mechanisms: decreasing cellular levels of antiapoptotic Bcl-2, Bcl-xL, and cIAP proteins, increasing levels of proapoptotic Bax, inhibiting constitutively active JAK–STAT pathways, activating MAPK and PI3 k/PKB and Fas receptor/caspase-8 pathway independent of p53. See further Gautam et al. (2007).
- Induce heme oxygenase-1 (HO-1), a redox-sensitive inducible protein that provides protection against various forms of stress (Balogun et al. 2003).

See also Jagetia and Aggarwal (2007) for further information.

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another, and interactions between herbs and drugs, even if structurally unrelated, may increase or decrease the pharmacological and toxicological effects of either component (Fugh-Berman 2002; Groten et al. 2000). It is suggested that curcumin may increase the bioavailability of vitamins such as vitamin E and decrease blood levels of cholesterol, as in experimental studies curcumin will significantly raise the concentration of α-tocopherol in tissues such as lung and decrease 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

AGING

Oxidative stress is believed to play a major role in the aging process and in pathogenesis of diseases most commonly responsible for morbidity and mortality in older age. Dietary factors influence considerably both disease processes and longevity by modifying oxidative stress. Bala et al. (2006) investigated the influence of chronically administered curcumin on normal aging-related parameters—lipid peroxidation, lipofuscin concentration and intraneuronal lipofuscin accumulation—and on activities of a series of other factors—superoxide dismutase (SOD), glutathione peroxidase (GPx), and Na^+, K^+-adenosine triphosphatase (Na^+, K^+-ATPase) in different brain regions (cerebral cortex, hippocampus, cerebellum and medulla) in 6- and 24-month-old rats. Chronic curcumin supply to both 6- and 24-month-old rats resulted in significant decreases in lipid peroxide and lipofuscin content in the brain regions, and was accompanied by significant increases in activities of SOD, GPx and Na^+, K^+-ATPase in various brain regions. In a rat study, supply of tetrahydrocurcumin, a biotransformed metabolite of curcumin, was demonstrated to increase average life span by 12% ($P < 0.01$) and average life expectancy after 24 months of age by 126% (Kitani et al. 2004). However, no human study is this far reported.

ALLERGY

Curcumin has a potential therapeutic value for control of allergic responses to exposure to allergens. Intragastric treatment of latex-sensitized mice with curcumin demonstrated a diminished Th2 response and a concurrent reduction in lung inflammation (Kurup et al. 2007). In addition, in curcumin-treated mice eosinophilia was markedly reduced, costimulatory molecule expression (CD80, CD86, and OX40L) on antigen-presenting cells decreased, and expression of MMP-9, OAT, and TSLP genes attenuated. Another recent study suggests that that the hydroxy groups of curcumin play a significant role in exerting both antioxidative and antiallergic activities, and that most of the compounds develop antiallergic activities through mechanisms related to antioxidative activities, but some most likely also through antioxidation unrelated mechanisms. A significant

decrease in histamine release from rat basophilic leukemia cells, RBL-2 H3, was observed when cells were cultivated with curcumin or tetrahydrocurcumin (Suzuki et al. 2005). No human study in allergy is this far reported.

Arthritis

Treatment in vitro of chondrocytes with curcumin is shown to suppress IL-1b-induced NF-κB activation via inhibition of IκBα phosphorylation, IκBα degradation, p65 phosphorylation, p65 nuclear translocation and inhibition of upstream protein kinase B Akt, events which correlate well with downregulation of NF-κB targets including COX-2 and MMP-9 (Shakibaei et al. 2007). IL-18 is a novel proinflammatory cytokine that has been suggested to play a pathogenic key role in a number of autoimmune diseases such as inflammatory bowel diseases (IBD), psoriasis, and rheumatoid arthritis (RA) (McInnes et al. 2000). Vascular endothelial growth factor (VEGF) is deeply involved in angiogenesis in rheumatoid synoviocytes and IL-18 will dose-dependently increase both production of VEGF IL-18 and VEGF levels of sera and synovial fluids of RA patients. These factors were found to be significantly higher in RA than in osteoarthritis A patients. Curcumin did dose-dependently abrogate the effect of IL-18 on VEGF production (Cho et al. 2006). A recent in vitro study compared the potential anti-inflammatory effects of curcumin and quercetin. Both agents inhibited neutrophil activation, synoviocyte proliferation, and angiogenesis (Jackson et al. 2006). In addition, curcumin also strongly inhibited collagenase and stromelysin expression, effects not obtained by quercetin.

In 1980, Deodhar and colleagues had already performed a clinical study in which 18 RA patients were treated with curcumin and comparisons were made with phenylbutazone. Improvements in morning stiffness, walking time, and joint swelling were observed after 2 weeks of curcumin supplementation (1,200 mg/day), and reported to be equal to those induced by phenylbutazone therapy (300 mg/day) (Deodhar et al. 1980). Another now classical study did also conclude that five days of oral curcumin supplementation (1,200 mg/day) is equally effective as phenylbutazone to reduce postsurgical edema, tenderness, and pain (Satoskar et al. 1986). Most interesting are recent observations that curcumin has the ability to potentiate the effects of pharmaceutical COX-2 inhibitors such as celecoxib (Lev-Ari et al. 2006a). Such combinations might enable to use pharmaceutical drugs at much lower and safer concentrations, especially when used for longer periods and in conditions such as osteoarthritis and other rheumatological disorders.

Atherosclerosis

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 is also found to be the most effective, when the ability of butylated hydroxy anisole, curcumin, quercetin, and capsaicin to inhibit the initiation and propagation phases of low-density lipoprotein (LDL) oxidation was compared (Naidu and Thippeswamy 2002). Supply of not only curcumin, but also capsaicin and garlic (allecin), to rats fed a cholesterol-rich diet prevented both increases in membrane cholesterol and fragility of the erythrocytes (Kempaiah and Srinivasan 2002). Significant prevention of early atherosclerotic lesions in thoracic and abdominal aorta in rabbits fed an atherogenic diet for 30 days was observed, accompanied by significant increases in plasma concentrations of coenzyme Q, retinol, and α-tocopherol and reductions in LDL-conjugated dienes and TBARS (thiobarbituric acid-reactive substances, an expression of ongoing oxidation) (Quiles et al. 2002).

Curcumin is also shown to protect the myocardium per se against ischemic insults. A single oral dose of curcumin (15 mg/kg), administered 30 min before and/or after the onset of isoprenaline-induced ischemia in rats not only prevented decrease in levels of xanthine oxidase, superoxide anion, lipid peroxides, and myeloperoxidase (MPO) and increase in levels of SOD, catalase (CAT), GPx, glutathione-*S*-transferase (GST) activities, but also reduced myocardial damage as documented by histopathology and electron microscopy (Manikandan et al. 2004). It is especially observed in in vitro studies that treatment with curcumin will produce a pronounced induction of the defensive protein HO-1, which will, when added to Celsior preservation solution, significantly prevent storage-induced damage of atrial myoblasts (Abuarqoub et al. 2007).

Studies on mice have also demonstrated that oral administration of curcumin will suppress aortic wall degeneration and prevent development of abdominal aortic aneurysms. Curcumin preserves medial elastin fibers and reduces aortic wall expression of cytokines, chemokines, and proteinases, known to mediate aneurysmal degeneration (Parodi et al. 2006). Recent studies on isolated porcine coronary arteries also demonstrate in a concentration-dependent

manner a considerable relaxant effect of curcumin via mechanisms involving NO, cGMP, and adrenergic β-receptor, but not by prostaglandins (Xu et al. 2007). Studies on porcine coronary arteries also demonstrate that curcumin effectively reverses homocysteine-induced endothelial dysfunction (Ramaswami et al. 2004). Curcumin, in doing so, blocks the homocysteine-induced superoxide anion production and downregulation of eNOS. However, no human study is this far reported.

Cancer

Genomic approaches to cancer prevention and treatment are becoming increasingly important. In addition to characterizing potential mechanisms of cancer prevention, significant issues for future research are identification and selection of specific dietary bioactive food components, and especially identifying individuals with special nutrient requirements for optimal cancer protection.

Dietary bioactive food components that interact with the immune response have a considerable potential to reduce the risk of cancer. Numerous substances identified in fruits and vegetables have the ability to modulate the effects of deregulated cell cycle checkpoints and contribute to prevention of cancer. Not only curcumin, but numerous other plant-origin agents, possess this potential, among them apigenin (celery, parsley), epigallocatechin-3-gallate (green tea), resveratrol (red grape, peanuts, and berries), genistein (soybean), and silymarin (milk thistle). There is also accumulating evidence that cancer prevention can be achieved by some probiotic bacteria alone or in combination with prebiotic fibers, known to have a similarly strong effect on the immune system as plant antioxidants (see further Ferguson and Philpott 2007).

Curcumin has been tried in various animal models in order to achieve dietary prevention of development and spreading of cancer. Injection of human mammary cancer cells (MDA-MB-231) into the mammary fat pad of nude mice leads to the formation of tumors and distant metastases in lungs, brain, and lymph nodes. This spreading was to a great extent prevented by curcumin treatment: 68% of curcumin-treated in contrast to only 17% of untreated animals showed no or very few lung metastases (Bachmeier et al. 2007). Curcumin has in experimental models also demonstrated the ability to inhibit intrahepatic metastases (Ohadshi et al. 2003).

Curcumin seems to suppress several steps in tumorogenesis: cellular transformation, proliferation, invasion, angiogenesis, and metastasis. However, this far most of the mechanisms are not fully understood. NF-κB is most likely playing a central role, as several genes, known to mediate these processes, are known to be regulated by NF-κB.

Different analogs of curcumin present in turmeric (curcumenoids) exhibit variable anti-inflammatory and antiproliferative activities, which, however, do not entirely correlate with their ability to modulate the ROS status (Sandur et al. 2007). A comparison of the ability of curcumin and 20 curcumin analogues to suppress TNF-induced NF-κB activation demonstrated that the strongest effects are obtained by curcumin in itself, achieved by inhibition of NF-κB-regulated gene expression and inhibition of IκB kinase (IKK) and Akt activation (Aggarwal et al. 2006b). Later studies by the same group, but also others, demonstrate that other mechanisms are also involved such as:

- curcumin-induced downregulation of expression of cyclin E correlating with decreased proliferation of human prostate and breast cancer cells (Aggarwal et al. 2007).
- curcumin-induced enhancement of expression of tumor cyclin-dependent kinase (CDK) inhibitors p21 and p27 and tumor suppressor protein p53 (Aggarwal et al. 2007).
- curcumin-induced suppression of STAT3 activation, a mechanism linked with chemoresistance and radioresistance (Aggarwal et al. 2006a; Chakravarti et al. 2006). Curcumin is also known to inhibit JAK2, Src, Erb2, and EGFR, all known to be involved in STAT3 activation (see further Aggarwal et al. 2006b).
- curcumin-induced inhibition of both COX and LOX pathways of eicosanoid metabolism. Curcumin is reported to inhibit 12-folded block proliferation of human breast cancer cells (MCF-7 ADRs) in cell cultures (Hammamieh et al. 2007).

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Curcumin has been reported to augment cytotoxic effects of both chemotherapy and radiation therapy (Aggarwal et al. 2005; Hour et al. 2002). There is also some evidence that subtoxic concentration of curcumin might promote apoptosis by ligands such as TNF-related apoptosis-inducing ligand (TRAIL). Prostate cancer cells, for example, are generally resistant to induction of apoptosis by anticancer agents and death ligands. However, in recent years, it has been demonstrated that a combination of subtoxic concentrations of curcumin and TRAIL induces apoptosis of prostate cancer cell lines, mainly through inhibition of NF-κB and activation of extrinsic and intrinsic pathways of apop-

tosis (Deeb et al. 2005, 2007). When in an orthotopic murine model the effects of curcumin on two ovarial cancer cell lines (SKOV3ip1, HeyA8) were studied, curcumin alone did induce 49% ($P = 0.08$) and 55% ($P = 0.01$), respectively, reductions in mean tumor growth, an effect that was further increased by combining curcumin with the chemotherapeutic drug docetaxel, and demonstrating 96% ($P < 0.001$) and 77% reductions, respectively (Lin et al. 2007). Also in mice with multidrug-resistant HeyA8-MDR tumors, treatment with curcumin alone and in combination with docetaxel resulted in significant reductions in tumor growth, 47% and 58%, respectively ($P = 0.05$). SKOV3ip1 and HeyA8 tumors treated with curcumin alone or in combination with docetaxel demonstrated not only decreased proliferation ($P < 0.001$), but also reduced microvessel density ($P < 0.001$) and increased tumor cell apoptosis ($P < 0.05$). The growth of induced colorectal cancer, measured as average number of aberrant crypt foci (ACF), was 64.2 ± 3 in the control group, 39 ± 5 in the curcumin-treated group, 47 ± 10 and in celecoxib-treated group, but only 24.5 ± 6 in the group that had received both agents (Shpitz et al. 2006). Another nude mice study undertaken with four different head and neck squamous cell carcinoma (HNSCC) cell lines documented that topical application as a curcumin paste is superior even to intratumoral injection of curcumin (LoTempio et al. 2005). Curcumin induces apoptosis in vitro in almost all cell lines: breast cancer (Xia et al. 2007; Zhang et al. 2007), head and neck cancer (Chakravarti et al. 2006; LoTempio et al. 2005), hepatocellular cancer (Labbozzetta et al. 2006), laryngeal cancer (Mitra et al. 2006), leukemia (Liao et al. 2008; López-Lázaro et al. 2007), lung cancer (Lee et al. 2005; Lev-Ari et al. 2006b), myeloma (Bharti et al. 2003, 2004), melanoma (Marín et al. 2007; Siwak et al. 2005), neuroblastoma (Liontas and Yeger 2004; Vanisree and Ramanan 2007), oral cancer (Atsumi et al. 2005; Sharma et al. 2006), osteosarcoma (Huang et al. 2005; Walters et al. 2008) pancreatic cancer (Lev-Ari et al. 2006b, 2007), and prostatic cancer (Deeb et al. 2007; Shankar and Srivastava 2007).

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Although encouraging results have been obtained in in vitro and animal studies, only a small number of small clinical studies are this far reported (see further Steward and Gescher 2008). A study intended as a phase I study reports histologic improvement of precancerous lesions in one out of two patients with resected bladder cancer, two out of seven patients of oral leucoplakia, one out of six patients of intestinal metaplasia of the stomach, and two out of six 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 administered by mouth for 3 months in a dose of up to 8,000 mg/day.

Diabetes

The oxidative stress observed in diabetic rats is clearly reduced significantly by curcumin administration. As a consequence of curcumin supply, nonenzymic antioxidants such as vitamin C, vitamin E, and glutathione are preserved at near normal levels and accumulation of lipid peroxidation products is significantly reduced.

Curcumin is also reported to prevent the accelerated accumulation of glycated collagen in diabetic animals. An interesting study reports significant prevention by curcumin of the extensive cross-linking of collagen in tendons and skin normally seen in diabetic animals (Sajithlal et al. 1998). Also interesting is the observation that curcumin contributes to control of hyperglycemia and also to some extent prevents islet cell death. In a streptozotocin-induced islet damage model, the in vitro islet viability and secreted insulin remained significantly higher after exposure to curcumin than in the controls. Furthermore, curcumin pretreatment significantly prevented streptozotocin-induced changes in isolated mouse islets such as DNA fragmentation, and reduced the concentrations of peroxynitrite, nitric oxide, and poly(ADP-ribose) polymerase-1 (Meghana et al. 2007). Curcumin administration also prevented the formation of the AGE-related malonyl dialdehyde in streptozotocin-treated islets. Oral administration of diabetic rats for 45 days with tetrahydrocurcumin at 80 mg/kg body weight significantly reduced blood glucose and increased plasma insulin levels parallel to significant increases in activities of SOD, CAT, GPx, GST, reduced glutathione, vitamin C, and vitamin E. Furthermore, significant decreases in TBARS and hydroperoxide formation in liver and kidney were observed, all suggesting a protective role of curcumin against lipid peroxidation-induced membrane damage, observations supported by observed improvements on histopathological examination of liver and kidney sections (Murugan and Pari 2006a).

Subsequent studies by the same group demonstrated that these changes are also accompanied by:

- reduced lipid peroxidation (TBARS and hydroperoxides) and reduced levels of lipids (cholesterol, triglycerides, free fatty acids, and phospholipids) in serum and tissues (Murugan and Pari 2006b).

- normalization of liver cholesterol, triglycerides, free fatty acids, phospholipids, HMG CoA reductase activity, and very low-density lipoprotein (VLDL), LDL, and high-density lipoprotein (HDL) cholesterol (Pari and Murugan 2007a).
- decreased levels of not only blood glucose, but also glycosylated hemoglobin and erythrocyte TBARS, and increased levels of plasma insulin, hemoglobin, erythrocyte antioxidants and activities of membrane bound enzymes, observations also accompanied by histopathological improvements (Pari and Murugan 2007a).
- normalization of total protein, albumin, globulin, and albumin/globulin ratio, and near normalization of urea, uric acid, and creatinine (Murugan and Pari 2007b).
- decreased levels of brain lipid peroxidative markers: TBARS and hydroperoxides and increased brain activities of SOD, CAT, GPx, GST (Pari and Murugan 2007b).
- decreased to near normal tissue levels of hexose, hexosamine, and fucose (Pari and Murugan 2007c).
- reduced cross-linking of collagen (Pari and Murugan 2007d).
- Similar observations are made in alloxan-induced diabetes (Giltay et al. 1998). It is also observed that cryopreserved islets will be better preserved in the presence of curcumin (Kanitkar and Bhonde 2008).

  Furthermore, it was observed in these studies of cryopreserved islets that curcumin increases the release of heat shock response proteins, Hsp70 and HO-1, which significantly contributes to a better preservation result.

No human clinical trials in diabetes with curcumin or turmeric are reported.

Gastric Diseases

Curcuma longa is since long used commonly as a traditional remedy for gastritis and gastric ulcer. A recent study suggests that supply of 60 mg/kg body weight (bw) of curcumin is as effective as 20 mg/kg bw of omedprazole to restore suppressed MMP-2 gene transcription and translation and oxidative inactivation of basal MMP-2 and thereby prevent/reduce development of induced gastric ulcer in rats (Ganguly et al. 2006). Curcumin is shown not only to protect from formation of gastric ulcers but also to accelerate healing, mainly through attenuation of MMP-9 activity (Swarnakar et al. 2005). Curcumin as well as turmeric have both the capacity to inhibit gastric acid secretion by blocking histamine receptors (Kim et al. 2005b). A potential use of turmeric or curcumin as alternative or complementary therapeutic agents against pathogenic processes initiated by *Helicobacter pylori* infection is supported by observations that curcumin has the capacity to inhibit *H. pylori*-induced NF-κB activation, subsequent release of IL-8, degradation of IκB-α, IκB kinases α and β (IKKα and β) activity, and NF-κB DNA binding (Foryst-Ludwig et al. 2004). When the in vitro effects of turmeric and curcumin against 19 different strains, including five cagA+ strains (cag A is the strain-specific *H. pylori* gene linked to premalignant and malignant lesions), were investigated and compared, both treatments were equally effective to significantly reduce the growth of all the *H. pylori* strains studied (Mahady et al. 2002).

Hepatic Diseases

Several studies have demonstrated the unique ability of turmeric and curcumin to preserve the integrity and function of liver cells. Studies have been undertaken with various models of acute toxic injuries to the liver, chronic supply of hepatotoxins and with liver perfusion and preservation. Curcumin has also been shown to protect the hepatocytes from oxidative injury, most likely and to a large extent through activation of HO-1. In a recent study acute hepatotoxicity was induced by oral administration of CCl_4 (4 g/kg) and curcumin supplemented orally (200 mg/kg), both before and 2 h after the CCl_4 administration. The CCl_4-induced translocation of NF-κB to the nucleus, CCl_4-induced NF-κB DNA-binding activity, and increases of TNF-α and IL-1β protein were blocked by curcumin, and most importantly, the destruction of hepatic tissues totally abolished (Reyes-Gordillo et al. 2007). Similar observations are also made in a model of endotoxin-induced hepatic dysfunction (Kaur et al. 2006). In another rat study, fulminant hepatic failure (FHF) was induced by two intraperitoneal injections of 300 mg/kg thioacetamide (TAA) at 24-h intervals. The experimental groups received intraperitoneally either a low dose (200 mg/kg/day) or a high dose (400 mg/kg/day) of curcumin, initiated 48 h prior to the first TAA injection. Curcumin significantly improved survival, minimized oxidative stress, reduced hepatocellular injury, hepatic necroinflammation, NF-κB binding and iNOS expression, and hepatic levels of TBARS (Shapiro et al. 2006). Furthermore, it inhibited nuclear binding of NF-κB and iNOS protein expression.

Biochemical parameters of liver injury, blood ammonia, and hepatic necroinflammation were significantly reduced in the low-dose curcumin group but were further reduced in the high-dose group ($P < 0.05$ and $P < 0.01$ respectively) (Shapiro et al. 2006). Curcumin induced, when cold preservation of human hepatocytes was applied, a significant elevation of HO-1 and exhibited a strong cytoprotection throughout the cold storage and rewarming (McNally et al. 2006). Injection of curcumin (50 mg/kg) into the portal system 30 min before applying hepatic warm ischemia/reperfusion (I/R) did significantly reduce the postperfusion increases in iNOS activity and content of malondialdehyde (MDA) in liver tissue and prevent the reductions in CAT and SOD activities (Shen et al. 2007). It also increased the expression of other Hsps such as Hsp70, reduced the rate of apoptosis, and, most importantly, significantly increased the survival. No human clinical trial is this far reported in liver disease.

Infectious Diseases

Sepsis is a leading cause of death. It affects each year about three quarters of a million North Americans and results in death of almost one quarter of a million. The challenge in CI is less infection than the exuberant inflammatory response (Taneja et al. 2004), often presented as a syndrome of prolonged systemic inflammation, frequently leading to a potentially lethal condition of irreversible organ system dysfunction. The development seems to occur especially in individual with a chronically dysfunctioning innate immune system and sustained elevated inflammation. Apoptosis of circulating neutrophils in patients with clinical sepsis is through a mechanism that involves NF-κB activation profoundly suppressed, and also associated with reduced activity of cystein proteases (caspases-9 and -3) (Taneja et al. 2004). Suppression of this inflammation seems to reduce the inflammation and prevent development of infection and organ dysfunction. In a recent study, attempts were made to suppress inflammation by intravenous administration of curcumin for three days before sepsis was induced by the method called cecal ligation and puncture (CLP). The curcumin treatment did significantly attenuate tissue injury, reduce mortality, decrease the expression of TNF-α, downregulate peroxisome proliferator-activated receptor-gamma (PPARγ) in organs like the liver and also prevent morphologic alterations in macrophages (Siddiqui et al. 2006). Most importantly, the same results were obtained even if curcumin was only administered after the onset of sepsis. These findings are especially interesting as downregulation of PPAR in other models and by other tools has produced similar effects (Thiemermann 2006.) In animal models, curcumin is shown to prevent endotoxin-induced pulmonary sequestration of neutrophils via mechanisms such as induction of HO-1 and inhibition of endothelial ICAM-1 expression (Olszanecki et al. 2007). Curcumin will also attenuate endotoxin-induced coagulopathy and prevent disseminated intravascular coagulation (DIC) (Chen et al. 2007). These observations are of even greater interest as curcumin in itself demonstrates antibacterial (Di Mario at al 2007), antiviral (Kutluay et al. 2008), antifungal (Apisariyakul et al. 1995), antimalarial (Reddy et al. 2005), and antiprotozoal (Pérez-Arriaga et al. 2006) effects. No human clinical trial is this far reported except a study demonstrating great effects on scabies from topical treatment with a turmeric paste for 3–15 days in 814 patients (Charles and Charles 1992).

Intestinal Diseases

It is clear from what has been discussed above that curcumin to a large extent mediates its anti-inflammatory effects through inhibition of activation of NF-κB. This makes curcumin a promising candidate for treatment of IBD, alone or combined with other treatment modalities. Several successful experimental studies with curcumin in induced colitis are reported in recent years (for summary, see Camacho-Barquero et al. 2007). A recent study in experimental animals with trinitrobenzenesulfonic acid (TNBS)-induced colitis focussed on MAPKs such as the p38 and the c-Jun N-terminal kinase (JNK), known to regulate NF-κB activation and modulate the transcription of many genes involved in the inflammatory process. Oral supply of curcumin (50–100 mg/kg/day) not only dramatically reduced morphological signs of cell damage and stimulate the healing process, but also significantly reduced colonic levels of nitrites, colonic mucosa activity of MPO and TNF-α, and downregulated the expression of COX-2 and iNOS, and reduced activation of p38 MAPK (Camacho-Barquero et al. 2007). Few human studies have this far been performed. In an open study one capsule of pure curcumin (360 mg) was administered 3–4 times a day for 3 months to five patients with ulcerative proctitis and to five with Crohn's disease. All proctitis patients had improved reductions; other concomitant medications could be done in four patients (Holt et al. 2005). Four of five Crohn's disease patients demonstrated reduced Crohn's disease activity index scores and lower erythrocyte sedimentation rates. The ability of curcumin to prevent relapse was studied in

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a randomized, double-blind, multicenter trial in patients with quiescent ulcerative colitis (Hanai et al. 2006). Curcumin was administered for 6 months as 1 g after breakfast and 1 g after the evening meal. All patients received in addition to curcumin either sulfasalazine or mesalamine. Two of the 43 patients (4.65%) who received curcumin relapsed within 6 months, compared to 8 out of 39 patients (20.51%) in the placebo group ($P = 0.040$). Some effects were also reported in clinical activity index ($P = 0.038$) and especially in endoscopic index ($P = 0.0001$) (Hanai et al. 2006).

Neurodegenerative Diseases

Biochemical and physiologic stimuli: perturbation in redox status, accumulation and expression of misfolded proteins, altered glyc(osyl)ation and glucose deprivation, overloading of products of polyunsaturated fatty acid peroxidation, cholesterol oxidation and decomposition are among the factors that lead to the accumulation of unfolded or misfolded proteins in brain cells. Alzheimer's (AD), Parkinson's (PD), Huntington's diseases (HD), amyothrophic lateral sclerosis (ALS), and Friedreich's ataxia (FRDA) are all major neurological disorders, strongly associated with the production of abnormal proteins and, as such, belong to the so-called "protein conformational diseases" (Calabrese et al. 2006). Furthermore, a defect elimination/phagocytosis of amyloid-beta ($A\beta$) and clearance of $A\beta$ plaques by the innate immune cells, monocyte/macrophages, are reported to further contribute to the development of these neurodegenerative diseases (Zhang et al. 2006). Hsps and particularly HO-1 are also in this group of diseases identified to play a key role in cellular defense (Calabrese et al. 2003). Since it has been demonstrated that the expression of HO is closely related to amyloid precursor protein (APP), an increasing interest has focused on identifying dietary compounds that have the potential to inhibit, retard, or reverse the multistage pathophysiological events underlying these pathologies. Not only curcuminoids but also other antioxidants such as ferulic acid are known to be strong inducers of the heat shock response, which might provide exiting candidates for chemoprevention and treatment of these diseases (Calabrese et al. 2007). One small clinical pilot study was just concluded in AD patients. Unfortunately the treatment period was only 6 months and did not allow any definite conclusions to the clinical effects of curcumin treatment. However, the investigators showed that the treatment is safe and recommended that larger controlled studies are undertaken (Baum et al. 2008). More pronounced effects of treatment will most likely be obtained if undertaken in a group of patients who are at risk but have not developed clinical signs of Alzheimer as yet. Panels of markers of inflammation should make it possible to identify such patients years before occurrence of clinical signs.

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Ocular Diseases

Age-related cataractogenesis, for example, development of opacity of the eye lens, constitutes a significant health problem worldwide. Cataract is the leading cause of blindness worldwide, responsible for blindness of more than 20 million in the world. Nutritional deficiencies, especially lack of consumption of enough antioxidants, diabetes, excessive sunlight, smoking, and other environmental factors, are known to increase the risk of cataracts. Oxidative stress is regarded as the common mechanism behind cataractogenesis, and augmentation of the antioxidant defenses of the ocular lens has been shown to prevent or delay cataractogenesis. Curcumin feeding to experimental animals prevents the loss of alpha-crystallin chaperone activity and delays the progression and maturation of diabetic cataract (Kumar et al. 2005). Several other experimental studies report significant preventive effects of curcumin against cataracts when induced by various methods: naphthalene (Pandya et al. 2000), galactose (Suryanarayana et al. 2003, Raju et al. 2006), and selenium (Padmaja and Raju 2004).

In two uncontrolled studies, oral curcumin (1,125 mg/day) for 12 weeks to 22 months was found to improve chronic anterior uveitis, idiopathic inflammatory orbital pseudotumor, and other inflammatory conditions of the eye (Lal et al. 1999, 2000).

[AU: Reference "Raju et al. (2006)" has not been given in the reference list. Kindly provide the complete details for this reference.]

Oral Cavity Diseases

There are remarkable similarities in the pathogenesis of periodontal diseases and RA. Increased incidences of plaque, calculus, and gingival inflammation and increased prevalence and severity of destructive periodontal diseases are seen in most other chronic diseases. Periodontitis is clearly a sign of an increased systemic inflammatory burden, also manifested in signs such as elevation of C-reactive protein (CRP). Only one plant polyphenol, green tea polyphenol epigallocatechin gallate (EGCG) is far tried and reported to reduce gingival inflammation and prevent periodontal diseases (Sakanaka and Okada 2004), but no human clinical study with curcumin is this far reported.

Pancreatic Diseases

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

Respiratory Diseases

Acute and chronic inflammatory lung diseases due to occupational and environmental exposures to mineral dusts, airborne pollutants, cigarette smoke, chemotherapy and radiotherapy are increasingly common. Curcumin offers a wide spectrum of therapeutic properties for these conditions. *C*urcumin is, as mentioned above, a potent inhibitor of TGF-β and fibrogenesis (Gaedeke et al. 2004), and suggested to have positive effects in various fibrotic diseases in kidneys, liver, intestine (Crohn's disease), pancreas, and in body cavities (prevention of fibrous adhesions) and on conditions with lung fibrosis, including cystic fibrosis (CF). CF is of special interest as it is especially linked to glutathione deficiency. The effect of curcumin against amiodarone-induced lung fibrosis was studied in rats. Significant inhibition of LDH activity, infiltration of neutrophils, eosinophils, and macrophages in lung tissue, LPS-stimulated TNF-α release, phorbole myristate acetate-stimulated superoxide generation, 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 dose of 200 mg/kg bw weight in parallel with intratracheal instillation of 6.25 mg/kg bw of amiodarone (Punithavatihi et al. 2003). Curcumin exhibits structural similarities to isoflavonoid compounds that bind directly to the CFTR protein and alter its channel properties. Egan et al. (2004) observed that curcumin inhibits the calcium pump in endoplasmic reticulum, suggesting that reducing the calcium levels might liberate the mutant CFTR and increase its odds of reaching the cell surface. A dramatic increase in survival rate and in normal cAMP-mediated chloride transport across nasal and gastrointestinal epithelia was observed when curcumin was supplemented to gene-targeted mice homozygous for the ΔF508 (Illek et al. 2000). CF is characterized by at least three major biochemical deficits: diminished expression and activity of PPARs, increased PGE2 production, and elevated oxidative tissue injury. Curcumin should have the capacity to activate the PPAR anti-inflammatory pathway, typically underexpressed in CF, inhibit PGE2 synthesis, and protect against oxidative stress. Curcumin treatment in CF might function as an alternative until gene or other therapies aimed at restoring the CF transmembrane conductance function are realized (Emanuele et al. 2007). No human studies are, however, yet reported for CF. Significant reductions were observed in both airway constriction and airway hyperreactivity to histamine when the antiasthmatic effect of curcumin was tested in guinea pigs sensitized with ovalbumin (Ram et al. 2003).

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Skeleto-Muscular Diseases

Osteoporosis represents a major healthcare burden, affecting only in the United States approximately 10 million people aged over 50 years and with another 30 million or more at risk. Human and animal experiments indicate that proinflammatory cytokines such as IL-1, IL-6, and TNFα are primary mediators of osteoclastic bone resorption in aging individuals and in a variety of chronic diseases with accelerated bone loss (Mundy 2007). Increased production of proinflammatory cytokines is regularly associated with osteoclastic bone resorption both in chronic disease states and in individuals after estrogen withdrawal. The fact that the activation of NF-κB is, as discussed above, strongly linked with a large number of chronic diseases (see above) and that polyphenols like curcumin have the ability to inhibit this activation makes plant polyphenols, especially curcumin, an ideal candidate for prevention and treatment of incipient osteoporosis. However, the only studies with polyphenolic and other bioactive plant constituents, which have demonstrated preventive effects, have been performed with soy phytoestrogens and green tea polyphenols (Siddiqui et al. 2004).

Another obscure common disease, fibromyalgia, which has dramatically increased in the last decades, is also increasingly associated with increased systemic inflammation. Higher levels of IL-10, IL-8, and TNF-α are also reported in fibromyalgia patients

compared to healthy controls (Bazzichi et al. 2007). Although no studies with treatment with polyphenols have yet been undertaken, there are good reasons to assume that this category of patients could benefit from treatment with curcumenoids.

Skin Disorders

Curcumenoids have been recommended in a series of skin diseases from acne to psoriasis, but few studies have been undertaken. There exist many anecdotal reports of patients' successful treatment with curcumin, especially patients with psoriasis. A phase II, open-label trial was done with supplementation of 4.5 g/day of curcuminoids orally to patients with psoriasis (Kurd et al. 2008). Eight of 12 patients concluded a 16-week trial, with supplementation of 4.5 g/day of curcumin (3 pills of 500 mg, 3 times daily). Only a minority were reported to respond, but those who did respond achieved after 12 weeks excellent responses of 83% and 88% improvement in psoriasis area and severity index (PASI) scores. It is a general experience that polyphenol treatments often need to be continued for 6–12 months before results are seen. Unfortunately many patients do not have enough patience to wait that long. Large and long-lasting placebo-controlled studies are necessary before oral curcumin can be recommended as a treatment of psoriasis. However, most interesting animal experiments suggest that curcumin reduces aging effects on skin (Rattan and Ali 2007), reduces the skin destruction in irradiation (Okunieff et al. 2006) and burns (Singer et al. 2007), and promotes uneventful healing of skin (Panchatcharam et al. 2006).

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Tobacco/Cigarette Smoke-Induced Injuries

Exposure to tobacco results in increased lipoxidation in the body and also dramatically increased activation and expression of NF-κB and its downstream target COX-2, and significant decreases in the levels of antioxidants such as ascorbic acid, vitamin E, reduced glutathione, GPx, SOD, and CAT. Animal studies demonstrate that such tobacco- and nicotine-induced changes are effectively counteracted by regular supply of turmeric and curcumin (Kalpana and Menon 2004; Thapliyal et al. 2004)

CONCLUSIVE REMARKS

It is a great disappointment that only a few controlled clinical studies with curcumin or turmeric have this far been performed and presented. It is a general experience that it is easier to get excellent results in young healthy animals with induced diseases than in humans with spontaneous diseases. Over the years numerous treatment modalities, successful in animals, have failed when tried in humans. One contributing factor most certainly is that humans under treatment usually continue with the unhealthy lifestyle that has led to the disease. Furthermore, treatments with natural products take a long time, often years, before results are seen. Modern day humans are often not prepared to spend that time waiting for clinical results. The whole idea of chemoprevention is that the plant-origin nutraceuticals are used regularly for the rest of the life.

However, the high incidence of side effects of pharmaceuticals has made an increasing number of individuals, especially among those with higher education, to turn to alternative and complementary compounds. Using medicinal plants and their active components remains an attractive approach for the prevention and treatment of various chronic diseases all based in impaired innate immunity and increased systemic inflammation. Food derivates have the advantage of being relatively nontoxic. Combination with other "nutraceuticals" such as other polyphenols and/or probiotic bacteria constitutes attractive but not explored treatment modalities. Preliminary observations suggest that such compounds have the ability to potentiate the effects of each other.

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