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Revisión

Plant-derived health - the effects of turmeric and curcuminoids

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Abstract

Plants contain numerous polyphenols, which have been shown to reduce inflammation and hereby to increase resistance to disease. Examples of such polyphenols are isothiocyanates in cabbage and broccoli, epigallocatechin in green tee, capsaicin in chili peppers, chalones, rutin and naringenin in apples, resveratrol in red wine and fresh peanuts and curcumin/curcuminoids in turmeric. Most diseases are maintained by a sustained discreet but obvious increased systemic inflammation. Many studies suggest that the effect of treatment can be improved by a combination of restriction in intake of proinflammatory molecules such as advanced glycation end products (AGE), advanced lipoperoxidation end products (ALE), and rich supply of antiinflammatory molecules such as plant polyphenols. To the polyphenols with a bulk of experimental documentation belong the curcuminoid family and especially its main ingredient, curcumin. This review summarizes the present knowledge about these turmeric-derived ingredients, which have proven to be strong antioxidants and inhibitors of cyclooxigenase-2 (COX-2), lipoxygenase (LOX) and nuclear factor κ B (NF-κB) but also AGE. A plethora of clinical effects are reported in various experimental diseases, but clinical studies in humans are few. It is suggested that supply of polyphenols and particularly curcuminoids might be value as complement to pharmaceutical treatment, but also prebiotic treatment, in conditions proven to be rather therapy-resistant such as Crohn's, long-stayed patients in intensive care units, but also in conditions such as cancer, liver cirrhosis, chronic renal disease, chronic obstructive lung disease, diabetes and Alzheimer's disease.

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Key words: *Diabetes. Alzheimer's disease. Turmeric. Curcuminoids.*

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EFECTOS SALUDABLES DE LA CÚRCUMA Y DE LOS CURCUMINOIDES

Resumen

Las plantas contienen un gran número de sustancias de naturaleza polifenólica con capacidad para reducir los procesos inflamatorios y, por lo tanto, incrementar la resistencia a determinadas enfermedades. Ejemplos de algunos polifenoles son los isotiocianatos presentes en la col y el brócoli, epigalocatequinas del té verde, capsaicina de las guindillas, chalonas, rutina y naringenina de las manzanas, resveratrol del vino tinto y de los cacahuetes, y curcumina y curcuminoides de la cúrcuma. La mayoría de las enfermedades tienen un componente discreto pero obvio de inflamación sistémica. Muchos trabajos han sugerido que los efectos de estos tratamientos podrían ser mejorados tras la restricción de la ingesta de moléculas proinflamatorias, como los productos avanzados de la glicación (AGE) y lipoperoxidación (ALE), junto con la suplementación de moléculas antiinflamatorias, como algunos polifenoles obtenidos de las plantas. Concretamente, los efectos de los curcuminoides y de su principal componente, la curcumina, han sido ampliamente documentados. Esta revisión, recopila los datos actuales acerca de las principales moléculas activas derivadas de la cúrcuma, para las cuales se ha demostrado que poseen una potente actividad antioxidante, inhiben la ciclooxigenasa 1 (COX-1), la lipoperoxidasa (LPO), el factor nuclear NF-κB (NF-κB), así como los AGE. La mayoría de los efectos han sido demostrados mediante estudios experimentales; sin embargo, los estudios clínicos en humanos son escasos. Se ha sugerido que la suplementación con curcuminoides podría ser interesante como un complemento para los tratamientos farmacológicos, además de cómo tratamiento prebiótico en condiciones en las que no existe una terapia eficaz, como en el caso de la enfermedad de Crohn, en pacientes ingresados en Unidades de Cuidados Intensivos durante periodos prolongados, y también en patologías tales como el cáncer, la cirrosis hepática, la enfermedad renal crónica, la enfermedad digestiva obstructiva, la diabetes y la enfermedad de Alzheimer. (Full spanish translation in www.nutricionhospitalaria.com).

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Palabras clave: *Diabetes. Alzheimer. Cúrcuma. Curcuminoides.*

Introduction

Modern medicine has to a large extent failed in its ambition to control both acute and chronic diseases. Acute diseases have an unacceptably high morbidity and co-morbidity. Furthermore, the world suffers an epidemy of chronic diseases of a dimension never seen before, and these diseases are now like a prairie fire also spreading to so called developing countries. Chronic diseases —including diseases such as cardiovascular and neurodegenerative conditions, diabetes, stroke, cancers and respiratory diseases— constitute today 46% of the global disease burden and 59% of the global deaths; each year on earth approximately 35 million individuals will die in conditions related to chronic diseases, and the numbers are increasing and have done so for several years.[1] Similarly, the morbidity related to advanced medical and surgical treatments and emergencies, especially infectious complications, is also fast increasing; sepsis is the most common medical and surgical complication.

Accumulating evidence supports the association of chronic diseases (ChDs) 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 ChD and reduced intake of plant fibres, plant antioxidants and increased consumption of industrially produced and processed dairy products, refined sugars and starch products. 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), known as potent inducers of inflammation.[2] This information is especially important as many foods such as ice cream, enteral nutrition solutions and baby formulas are based on milk powder and its derivatives. 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.[3-5]

Plant consumption-derived protection

Common to those suffering ChD as well as critical illness (CI) 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 chemopreventive 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. For these reasons, the interest for the study of these compounds has increased in the last years. Among them, various curcuminoids found in turmeric curry foods and thousands more of hitherto less or unexplored substances have received an increasing attention for their strong chemo-preventive ability in recent few years. Curcumin is the most explored of the so called curminoids, a family of chemopreventive 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 cyclooxigenase-2 (COX-2) inhibitors, marketed by pharmaceutical industry. This review reported mainly curcumin experimental and clinical studies focus on curcumin and its effects (table I).

Table I
Curcuminoid main effects

	Main mechanisms of action
Atherosclerosis	↓ LDL oxidation[29,31]; Cell membrane stabilisation[30]; ↑ antioxidant plasma concentrations[31]
Cancer	Induces apoptosis[36-45]; Inhibits metastasis[46]
Diabetes	↓ glucose, haemoglobin and glycated haemoglobin[48]; ↑ antioxidant protection[48]
Gastric diseases	↓ growth of some *Helicobacter* strains[49]; ↓ NF-κB and mitogenic response [50]; Antifungic properties[51]
Hepatic diseases	↓ lipid accumulation[52-54]; ↓ hepatic risk biomarkers[53,55]; ↓ NF-κB-dependent gene expression; ↓ inflammatory molecules expression[55,56]; ↓ oxidation[55]
Pancreatic diseases	↓ NF-κB activation and activator protein 1 expression; ↓ inflammatory molecules expression[57]; ↓ caspase-3 activation[57]; ↓ intra-pancreatic trypsin activation[57]
Intestinal diseases	↓ lipid peroxidation[58]; ↓ NF-κB activation[58,60]; ↓ nitric oxide levels[58]; immune function regulation[58]; ↓ MAPK p38[59]; ↓ inflammatory response[59,60]
Neurodegenerative diseases	Free radical scavenger[66, 67]; ↓ oxidative markers[70]; ↓ β-amyloid deposits [69]
Ocular diseases	Antioxidant activity[77-79]
Respiratory diseases	↓ fibrogenesis[80]; inflammatory markers[80]; calcium and chloride pump alteration[82,83]; Anti-asthmatic effect[84]
Tobacco smoke-induced injury	↓ NF-κB activation:↓ anti-inflammatory molecules[85]

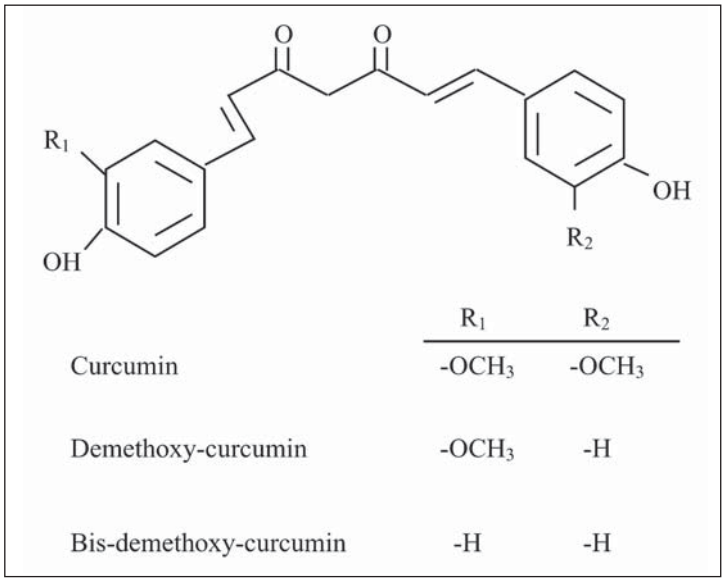

Fig. 1.—Structure of curcumin and its main derivatives.

Turmeric – approved as food additive

Curcumin, 1,7-bis (4-hydroxy-3-methoxyphenol)-1,6heptadiene-3,5-dione), or dipheruloylquinone (fig. 1), is the most abundant polyphenol present in the dietary spice turmeric and received from dried rhizozomes of the perennial herb *Curcuma longa* Linn, a member of the ginger family. Turmeric is mainly known for its excellent ability to 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 bioavailability on oral supplementation is low, but can be improved by dissolution in ambivalent solvents (glycerol, ethanol, DMSO).[6] It is also reported to be dramatically elevated by co-ingestion of peperine (a component of pepper), demonstrated both in experimental animals and humans.[7] 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.[8] Several studies has demonstrated that curcumin is atoxic, also in very high doses.[9-10] It is estimated that adult Indians consume daily 80-200 mg curcumin per day.[11] 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, since the content of curcumin in turmeric is usually 4-5%. Finally, it is noteworthy to mention that the treatment of humans during three months with 8,000 mg curcumin per day showed no side effects.[10]

Curcumin – an antioxidant and inhibitor of NF-κB, COX-2, LOX and iNOS and against stress-induced overinflammation

NF-κB plays a critical role in several signal transduction pathways involved in chronic inflammatory diseases[12] such as asthma and arthritis and various cancers.[13] 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, lipoxygenase (LOX), matrix mettaloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), interleukin-8 (IL-8), eotaxin, cell surface adhesion molecules and anti-apoptotic proteins are regulated by NF-κB.[14] 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. COX-2 synthesizes series-2 prostaglandins (PGE_2, PGF_2-α), which contribute to inflammation, swelling and pain. PGE_2 promotes production of IL-10, a potent immuno-suppressive cytokine produced especially by lymphocytes and macrophages, and suppression of IL-12.[15] Inducible nitric oxide synthase (iNOS), activated by NF-κB, is another enzyme that plays 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,[16] it is also a potent inducer of heat shock proteins (HSPs) and potential cytoprotector.[17,18] Curcumin does not only inhibit

COX-2, it also inhibits lipooxygenases (LOX) and leukotreines such as LBT_4 and 5-hydroxieicosenoic (5-HETE),[19] especially when bound to phosphatidylcholine micelles.[20] It is also reported to inhibit cytochrome P450 isoenzymes and thereby activation of carcinogens.[21] Curcumin has the ability to intercept and neutralize potent prooxidants and carcinogens, both ROS (superoxide, peroxyl, hydroxyl radicals) and NOS (nitric oxide —NO—, peroxynitrite).[22] It is also a potent inhibitor of tissue growth factor beta (TGF-β) and fibrogenesis,[23] 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.[24] Finally, 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.[25]

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another, and interactions between herbs and drugs, even if structurally un-related, may increase or decrease the pharmacological and toxicological effects of either component.[26,27] 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.[28]

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 are 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 were compared with a defined antioxidant butylated hydroxy anisole (BHA), capsaisin, quercetin.[29] 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.[30] 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 coenzyme Q, retinol and α-tocopherol and reductions in LDL conjugated dienes and in thiobarbituric acid-reactive substances (TBARS), an expression of ongoing oxidation.[31]

Cancer: Cancer is a group of more than 100 different diseases, which manifest itself in uncontrolled cellular reproduction, tissue invasion and distant metastases.[32] 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 (23 X), melanoma skin cancer (male 14 X, female 9 X), colorectal cancer (male 11 X, female 10 X), endometrial cancer (9 X), lung cancer (male 7 X, female 17 X), bladder cancer (male 7 X, female 8 X) breast cancer (5 X), renal cancer (male 9 X, female 12 X).[35] 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.[34] Curcumin induces *in vitro* apoptosis of various tumour cell lines: breast cancer cells,[34,35] lung cancer cells,[36] human melanoma cells,[37] human myeloma cells,[38] human leukemia cell lines,[39] human neuroblastoma cells,[40] oral cancer cells,[41] prostatic cancer cells.[42-45] Curcumin has, in experimental models also demonstrated ability to inhibit intrahepatic metastases.[46] Few in vivo experimental studies and no clinical controlled trials are this far concluded. However, a recent phase I study reported histologic improvement of precancerous 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.[47] 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 mg/day.

Diabetes: Turmeric (1 g/kg body weight) or curcumin (0.08 g/kg body weight) were in a recent study supplied daily for three weeks to rats with alloxan-induced diabetes and compared to controls.[48] Significant improvements were observed in blood glucose, hemoglobin and glycosylated hemoglobin as well than in plasma and liver TBARS and glutathione. On the other hand, 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 premalignant 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.[49] 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), extracellular signal regulating kinases 1/2 (ERK1/2) and p38. *H pylori*-induced mitogenic response was completely blocked by curcumin.[50] Significant antifungal properties against various fungal, especially phytopathogenic, organisms by curcumin are also reported.[51]

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.[54] Ethanol-induced steatosis is known to be further aggravated by supply of polyunsaturated fatty acids (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, showed extensive histopathological changes with focal and feathery degeneration, micronecroses 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 or particularly photo-irradiated curcumin, e.g. curcumin kept in bright sunshine for five hours.[53] Both products were supplied in a dose of 80 mg/kg body weight. Both products did significantly inhibit elevations in alkaline phasphatases (ALP) and γ-glutamyl transferase (γGT). Similar beneficial effects were observed on histology in various tissues and in hepatic content of cholesterol, triglycerides free fatty acids and phospholipids.[53] Rats were, in another study for four weeks, fed with fish oil and ethanol 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.[54] 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 (CCl_4)-induced injuries. Pretreatment during four days with curcumin (100 mg/kg body weight) before intraperitoneal injection of CCl_4 prevented significantly subsequent increases in TBARS, alanine aminotransferase (ALT) and aspertate aminotransferase (AST) and in hydroxyproline (μg/g liver tissue).[55] A recent study has shown that curcumin administration prevent the reduction of cytochrome enzyme P450 expression induced in inflammatory situations.[56]

Pancreatic diseases: The effect of curcumin to reduce the damage to pancreas was studied in two different models; cerulein-induced and ethanol and colecistokinin (CCK)-induced pancreatitis.[57] 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 intrapancreatic activation of trypsin, the hyperamylasemia and hyperlipasemia, 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.[57]

Intestinal diseases: Pretreatment 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 myeloperoxidase activity) and lipid peroxidation (measured as decrease in malondialdehyde activity) in the inflamed colon, as well as in a decreased serine protease activity.[58] A significant reduction in NF-κB activation and reduced levels of NO, superoxide anion and a regulation of the immune function were also found. Specifically, a marked suppression of Th1 functions, through a lower expression of interferon gamma (IFNγ) mRNA and a better Th2 protective expression improved colonic mucosa induced damage.[58] In another similarly designed study curcumin was added to the diet during 24 h before and 2 wk after the induction of TNBS colitis. A significant reduction in COX-2 and iNOS expression could be attributed to the lower activation of MAPK p38.[59] Indeed, curcumin modulates proinflammatory cytokines expression, attenuating IL-1β TNBS-induced damage, and increase IL-10 expression.[60] Curcumin was also supplied in combination with caffeic acid phenethyl ester to animals treated with cytostatic drugs (arabinose cytosine and methotrexate). 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 to the cytostatic agents.[61] However, a recent study has shown that the effect of curcumin of TNBS-induced damage on intestinal mucosa depend on the experimental model. These authors concluded that the therapeutic value of curcumin depends on the nature of the immune alteration during intestinal bowel disease.[62]

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 in all NDD, which in the case of Alzheimer disease (AD) leads to extracellular deposition of β-amyloid (Aβ) as senile plaques.

Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen has proven effective to prevent progress of AD in animal models,[63] but gastrointestinal and occasional liver and kidney toxicity induced by inhibition of COX-1 precludes widespread chronic use of the drug.[64] Use of antioxidants such as vitamin E (α-tocopherol) has proven rather unsuccessful even when high doses were used.[65] Vitamin E, α-tocopherol, is in contrast to γ-tocopherol a poor scavenger of NO-based free radicals. However, Curcumin is a several times more potent scavenger than vitamin E,[66] and in addition also a specific scavenger of NO-based radicals.[67] When tried in a transgenic mouse model of AD a modest dose (24 mg/kg body weight), but not a > 30 times higher dose (750 mg/kg body weight) of curcumin did significantly reduce oxidative damage and amyloid pathology.[68] Similar observations, reductions in both Aβ deposits and in memory deficits are also made in Sprague Dawley rats.[69] The age-adjusted prevalence of both AD[70] and Parkinson's disease[71] is in India, with its significantly higher intake of turmeric, much lower than in Western countries, especially the USA. 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 g of dried extract/kg body weight were demonstrated effective in reversing age-related deficits in both neuronal and behavioural parameters.[72] A study from 1999 is of special interest. Rats on chronic ethanol supply were randomized to 80 mg/kg body weight of curcumin or control and compared to non-intoxicated normal rats.[73] The degree of histopathological changes and levels of TBARS, cholesterol, phospholipids, and free fatty acids 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.[74] 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.[75] However, the age-adjusted prevalence of cataract in India is, however, three times that of the United States,[76] despite that have three different experimental studies reported significant preventive effects of curcumin against cataracts induced by naphthalene,[77] galactose,[78] and selenium.[79]

Respiratory diseases: As mentioned above, curcumin is a potent inhibitor of TGF-α and fibrogenesis,[24] and suggested to have positive effects in fibrotic diseases in kidneys, liver, intestine (Crohn's Disease), body cavities (prevention of fibrous adhesions)[18] and on conditions with lung fibrosis,[80] 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.[80] Significant inhibition of lactate dehydrogenase (LDH) activity, infiltration of neutrophils, eosinophils and macrophages in lung tissue, lipopolysaccharide (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 intratracheal instillation of 6.25 mg/kg body weight of amiodarone.[80]

Curcumin exhibits structural similarities to isoflavonoid compounds that seem to bind directly to the CFTR protein and alter its channel properties.[79] Egan et al,[80] who had previously observed that curcumin inhibits a calcium pump in endoplasmic reticulum, thought that reducing the calcium levels might liberate the mutant Cystic fibrosis transmembrane conductance regulator (CFTR) and increase its odds of reaching the cell surface- see also.[81] Previously, Egan et al observed that curcumin inhibits endoplasmic reticulum calcium bomb and proposed that calcium reduction may release a mutated CFTR that is able to reach cell surface.[82] The ΔF508 mutation, the most common cause of cystic fibrosis, will induce a misprocess in the endoplasmatic reticulum of a mutant 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.[83] No human studies are yet reported and it is 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 recently tested in guinea-pigs sensitized with ovalbumin and significant reductions observed both in airway constriction and in airway hyperreactivity to histamine.[84]

Tobacco/cigarette smoke-induced injuries: Cigarette smoke is suggested to cause 20% of all deaths and ~30% of all deaths from cancer. This smoke contains thousands of compounds of which about hundred are known carcinogens, co-carcinogens, mutagens and/or tumor 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 tumorigenesis through activation of several genes such as COX-2, iNOS, 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.[85]

Plant antioxidants - released by gastrointestinal microbiota

All chronic diseases are in a way related, they develop all as a result of a prolonged and exaggerated

inflammation.[86] Their development can most likely be prevented or at least delayed by extensive consumption of antioxidants such as curcumin. It is important to remember, that it is almost exclusively through microbial fermentation of the different plants that bioactive antioxidants 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 inflammatory bowel disease.[87] A study from 1983 demonstrated that *Lb. plantarum,* a strong fibre fermentor, is found in only 25 % of omnivorous Americans and in about 2/3 of vegetarian Americans.[88] 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 Parkistani children a much reduced flora.[89]

Astronauts, who return from space flights have during the flight lost most of their commensal flora including *lactobacillus* species such as *Lb. plantarum* (lost to almost 100%), *Lb. casei* (lost to almost 100%), *Lb. fermentum* (reduced by 43%), *Lb. acidophilus* (reduced by 27%), *Lb. salivarius* (reduced by 22%) and *Lb. brevis* (reduced by 12%),[90] changes most likely attributed to poor eating (dried food, no fresh fruits and vegetables) and a much reduced intake of plant fibers 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.[91] A recent Scandinavian study suggest that fiber-fermenting lactobacilli such as *Lb. plantarum, Lb. rhamnosus* and *Lb. 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.[92] These lactobacilli are present in all with more rural lifestyle. The lack of these lactobacilli is probably negative as these lactobacilli are unique in their ability to ferment important fibers such as inulin and phlein, otherwise resistant to fermentation by most *lactobacillus* species,[93] and superior to other *lactobacillus* in their ability to eliminate pathogenic microorganisms such as *Clostridium difficile*.[94] Thus, the lower presence of intestinal bacteria may influence the production of bioactive antioxidants from vegetables.

Conclusive remarks

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. Within them, curcuminoids, such as curcumin, are chemopreventive agents from turmeric curry foods. Its bioavailability on oral supplementation is low but also its toxicity. Several studies has demonstrated a number of beneficial properties on inflammatory chronic diseases such as atherosclerosis, cancer, diabetes, gastric, hepatic, pancreatic, intestinal neurodegenerative, ocular and respiratory diseases as well as on tobacco smoke-induced injuries.

Mechanisms of action are related to its antioxidant activity, able to neutralise oxygen and nitrogen reactive species, antiinflamatory properties, by decreasing activation of NF-κB and inhibiting COS-2, iNOS, LOX, LT, cytochrome P450 isoenzymes, TGF-β and fibrogenesis, and also to its immunosuppressive capacity, able to modulate cytokine and chemokine production. On the other hand, curcumin is able to prevent carcinogen activation.

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