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TURMERIC: NOT SO SPICY AFTER ALL

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Turmeric, also known as saffron Indian, prepared from the rhizome of *Curcuma longa* L. has an aromatic pepper-like, but somewhat bitter taste and gives curry dishes their characteristic yellowish colour. Curcumin, a non-toxic constituent of turmeric is responsible for the yellow colour, but importantly also has pharmacological potential. Many trials investigating the efficacy of curcumin against cancer, Alzheimer's disease, cystic fibrosis and human immunodeficiency virus (HIV) among others have been carried out *in vitro* with encouraging results. These findings point to the antioxidant properties of curcumin as an important factor in its effectiveness. The problem of retention *in vivo*, however, and thus its bioavailability, is a major negative aspect which requires much further study.

Le curcuma, aussi appelé safran des Indes, produit à partir du rhizome de *Curcuma longa,* a un goût aromatique ressemblant à celui du poivre, mais quelque peu amer. C'est lui qui donne au curry sa couleur jaune caractéristique. Cette couleur jaune vient de la curcumine, une composante non toxique du curcuma, qui a par-dessus tout un potentiel pharmacologique. De nombreuses expériences *in vitro* entreprises pour étudier l'efficacité de la curcumine contre le cancer, la maladie d'Alzheimer, la mucoviscidose et le virus de l'immunodéficience humaine (VIH), entre autres, ont produit des résultats encourageants. Elles semblent indiquer que les propriétés antioxydantes de la curcumine jouent un rôle important dans son efficacité. Toutefois, le problème de la rétention *in vivo*, de la substance, et donc sa biodisponibilité, représente un facteur négatif majeur, nécessitant de bien plus amples études.

INTRODUCTION

Natural products often serve as a rich source of relatively non-toxic compounds with pronounced biological effects. Curcumin is one; a phytochemical that has been established as a lead molecule for the development of novel therapies for various pathological conditions, such as cancer (Sharma et al. 2005), Alzheimer's disease (Lim et al. 2001), cystic fibrosis (Zeitlin 2004), human immunodeficiency virus (De Clercq 2000, Mazumder et al. 1997), chronic inflammation (Lim et al. 2001), and oxidative stress (Kopani et al. 2006). Curcumin underwent clinical trials for cancer because of its prominent activity as an antitumor and preventive agent (NCI 1996). This trial, however, ceased because of the poor bioavailability of the molecule (Sharma et al. 2001, Shoba et al. 1998). Currently clinical trials are underway to test the efficacy of curcumin against Alzheimer's disease (NIA 2006)

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and cystic fibrosis (Ramsey 2005). Intense efforts are being undertaken to modify the structure of curcumin to increase its bioavailability and potency while maintaining the relatively non-toxic nature of the natural product. This review is a summary and recapitulation of the important scientific findings and developments regarding curcumin and its biological activities, chemical properties, and pharmacokinetics; the anticancer and chemopreventive (prevention of illness through pharmaceutical means) aspects of curcumin's bioactivity have been reviewed by Sharma et al. (2005).

Curcumin, or diferuloylmethane [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a polyphenol derived from the dried, ground rhizome of *Curcuma longa* L., a perennial herb and a member of the ginger family, known as turmeric in English, haldi in Hindi and ukon in Japanese. *Curcuma* spp contain turmerin, essential oils, and the phenolytic curcuminoids. The orange-yellow curcumin is the active ingredient in this commonly used spice (Sharma et al. 2005) which has long been used as a dye and therapeutic agent in Ayurveda, the traditional system of Indian medicine, to treat biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis (Sharma et al. 2005, Araujo & Leon 2001).

CHEMICAL PROPERTIES

Curcumin which is a bis-□,□-unsaturated □-diketone in equilibrium with its enol tautomer (Fig 1) contains three acidic hydrogen atoms in the form of two phenolic groups and an active methylene, which permit multiple modes for free radical scavenging activity. In neutral or acidic pH, or in the cell membrane, the bis-keto form (Fig 1a) exists predominately. The haptadienone linkage between the two methoxyphenol rings results in a highly activated carbon and the C-H bonds are very weak as a result of the delocalization of the unpaired electron on the adjacent oxygen atoms. Owing to these effects, curcumin acts as a powerful proton donor at pH 3-7. The heptatrienone structure (Fig 1b) is the major constituent in pH values above 8, and curcumin acts mainly as an electron donor, resulting in scavenging activity typical of phenolic antioxidants (Sharma et al. 2005).

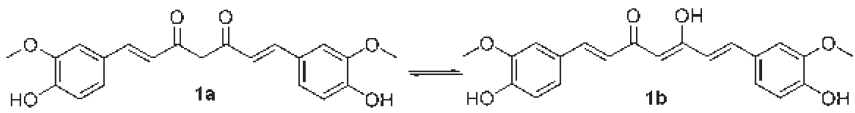


Fig 1 Tautomerism of curcumin with pH: 1a) bis-keto form (neutral or acidic pH values, 1b) heptatrienone form (values above pH 8)

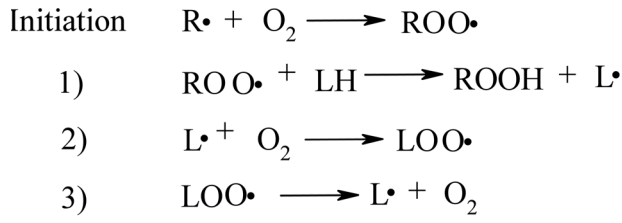
Antioxidant Activity

Curcumin derives its chemoprevention properties, at least in part, from its potent antioxidant behaviour (Lim et al. 2001). Research regarding oxidative

stress in the body suggests that natural polyphenols possess strong activity and curcumin stands at the forefront of the list of powerful antioxidants (Masella et al. 2005). Curcumin has been reported to significantly lower the concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the body by scavenging mechanisms (Lim et al. 2001). Many pathological conditions such as atherosclerosis, hypertension, ischemia-reperfusion injury, inflammation, cystic fibrosis, cancer, type-2 diabetes, Parkinson's disease, and Alzheimer's disease have strong relations to increased levels of oxidative stress (Jezek & Hlavata 2005). Oxidative stress stems from an increase in ROS and RNS to levels that are potentially harmful to biological molecules such as DNA, proteins, and lipids. Typical ROS are superoxide anions, hydroxyl radicals, and hydrogen peroxide, whereas common RNS include the nitric oxide radical and the nitrogen dioxide radical; excess ROS and RNS are detoxified by the action of various antioxidant machinery in normal, healthy cells. Superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX) are examples of typical antioxidant enzymes (Jezek & Hlavata 2005).

ROS are often generated during metabolism, during the body's inflammatory reaction mechanism, through various lifestyle stressors such as cigarette smoking, and in tandem with physiological conditions such as ischaemia (Kopani et al. 2006). RNS are observed to be a product of L-arginine and L-citrulline breakdown via nitric oxide synthase and as a side product associated with the inhalation of automobile exhaust (Drew & Leeuwenburgh 2002).

Another important aspect of the antioxidant properties of curcumin is the prevention of lipid peroxidation (Araujo & Leon 2001) which plays a critical role in the inflammation experienced in heart disease and cancer. The most common lipids to undergo peroxidation are polyunsaturated fatty acids (PUFA); this cyclic process generally occurs in four steps: 1) proton transfer from the PUFA to the initiating radical or chain carrying peroxyl radicals; 2) reaction of the created lipid radical with molecular oxygen, yielding a lipid peroxyl radical; 3) separation of the lipid peroxyl radical to give oxygen and a lipid radical; and 4) rearrangement of the peroxyl radical (Scheme 1).



Scheme 1 Cyclic process of lipid peroxidation

These steps give polymeric materials, complex products including hydroperoxides, and cleavage products such as aldehydes which implement cytotoxic and genotoxic effects (gene damage) leading to the development of various pathological conditions (Niki et al. 2005). Curcumin, by acting as a powerful antioxidant, removes these peroxyl radicals from the biological system which effectively stops the lipid peroxidation chain reaction in the first step (Araujo & Leon 2001).

Apoptotic Activity (Programmed Cell Death)

Apart from antioxidant activity, curcumin also exhibits the ability to induce apoptosis mechanisms (programmed cell death in which the cell death is regulated at the molecular level and does not cause the contents of dying cells to be exposed as in the familiar type of cell death labelled as necrosis). Curcumin-induced apoptosis, has been shown to occur in cancer cells without cytotoxic effects on healthy cells (Duvoix et al. 2005); it appears to be tissue dependant and includes several mitochondrial associated mechanisms (Sharma et al. 2005).

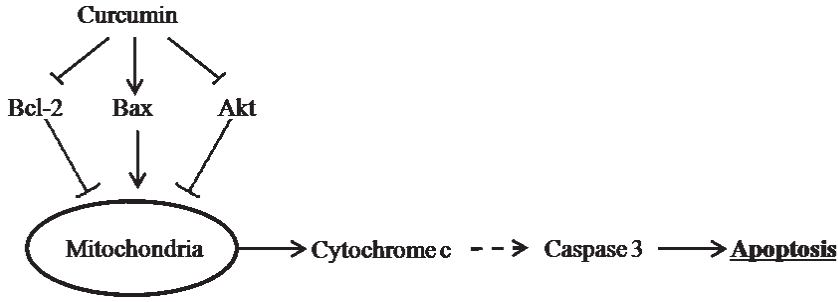


Fig 2 Overview of curcumin induced apoptosis.

Woo et al. (2003) have shown that curcumin-induced apoptosis of human renal carcinoma Caki tissue culture cells is directly linked to the sequential dephosphorylation of Akt (also known as protein kinase B, a serine/threonine kinase), release of cytochrome *c*, and activation of caspase 3 (a proteolytic enzyme that cleaves cysteine-aspartate linkages), and promotion of pore formation in the mitochondrial membranes (Woo et al. 2003, Conrad 2006). By dephosphorlyating Akt, curcumin effectively allows cytochrome *c* release from the mitochondria through the mitochondrial pore which is a key step in curcumin-induced apoptosis. Cytochrome *c* effectively activates caspases during the apoptotic response - an essential step because the caspases are close mediators of the apoptotic reaction (Woo et al. 2003).

Pore formation is regulated by the Bax and Bcl-2 protein families. Ultimately, these proteins establish the cell's response to various apoptotic stimuli. Curcumin significantly reduces the level of the antiapoptotic pro-

teins Bcl-2 and Bcl-X_L in the treated cells, allowing for increased action by the proapoptotic protein Bax (Woo et al. 2003). Pal et al. (2001) have also reported that in Ehrlich's Ascites carcinoma cells the apoptotic effects of curcumin are not a result of the down-regulation of the antiapoptotic protein Bcl-2, but by the up-regulation of the proapoptotic protein Bax. The general increase in the overall ratio of Bax/Bcl-2 leads to equivalent results, i.e. curcumin-induced apoptosis.

SPECIFIC DISEASE-RELATED ACTIVITIES

Alzheimer's Disease

Alzheimer's disease (AD) has been characterized by the accumulation of amyloid □ peptide (A□), oxidative damage, and inflammation (Lim et al. 2001, Yang et al. 2005). A□ is derived from the amyloid precursor protein (APP) through consecutive proteolysis by the aspartyl protease □-secretase and presenilin-dependent □-secretase cleavage. It is believed that this accumulation of A□ is one of the essential triggering factors initiating a cascade of events such as neurotoxicity, oxidative damage, and inflammation, leading to the progression of AD. Currently, clearance or prevention of A□ is the central target for many AD therapeutic agents (Yang et al. 2005).

Curcumin, as previously discussed, is a potent antioxidant through the scavenging of free radicals. This activity effectively protects the brain from damage as a result of lipid peroxidation, ROS, and NO-based radicals (Lim et al. 2001). High levels of interleukin-1□ are often associated with inflammation reactions in the brain. Curcumin has been shown to successfully down-regulate nuclear factor kappa B (NF-□B)-mediated transcription of inflammatory cytokines, inducible nitric oxide synthase, and cyclooxygenase 2. These results can be directly linked with the anti-inflammatory properties associated with curcumin treatment of AD. Assessing protein carbonyl formation is a technique used to detect oxidative damage to the brain (Lim et al. 2001). Protein carbonyls are formed from direct oxidation of amino acid side chains by ROS or lipid peroxidation products. This oxidation can result in the direct loss of function of the protein. Therefore, protein carbonyl levels are capable of serving as biomarkers for general oxidative stress (Zusterzeel et al. 2000). Curcumin has been shown to greatly suppress the levels of protein carbonyls in the brain, which is consistent with curcumin's known antioxidant capabilities.

High concentrations of metal ions, e.g. Cu (II), have also been associated with AD. Curcumin has been shown to be an effective Cu (II) chelating agent comparable in magnitude to that of clioquinol, an efficient Cu (II) chelating agent with promising treatment effects for moderately severe AD patients. This 1:2 Cu (II) to curcumin complex (2, Fig 3) has four phenolic hydroxyl groups that participate in the ROS-scavenging characteristics typical of curcumin. This complex has been shown to be less reactive than the parent curcumin molecule in scavenging ROS via the H-atom donating

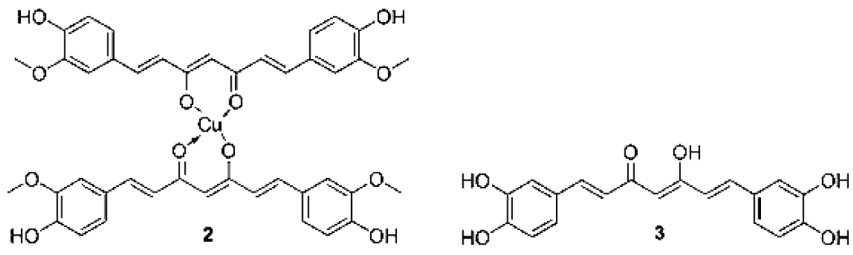


Fig 3 Curcumin-Cu (II) complex (2) and dicaffeoylmethane (3).

mechanism but more active through electron donation (Shen et al. 2005). These findings indicate curcumin acts via several modes to combat AD.

Cystic Fibrosis

Cystic fibrosis (CF) is a result of a dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) (Davis & Drumm 2004). The CFTR is a cyclic adenosine 3'5' monophosphate (cAMP)-activated chloride channel expressed in the apical membranes of many epithelia (Tabary et al. 2006). CF can lead to different pathological problems in various tissues, but the most prominent morbidity and mortality occurs when the disease is present in the airways. Dysfunction of CFTRs in this region leads to reduced water content, increased bacteria retention, and the severe inflammatory response associated with increased levels of bacteria. Restoration of the normal function of the mutant forms of the CFTR could restore normal lung function and normal life expectancy (Davis & Drumm 2004).

CF is most commonly associated with mutation in the ΔF508 allele. In CF patients, this allele is missing the codon for the amino acid, phenylalanine, in the first nucleotide-binding fold. This mutation causes the protein to misfold and become ubiquinated i.e., linked to ubiquitin, a small protein which marks proteins for destruction by proteasomes (i.e. large multiprotein complexes that catalyze the ATP-dependent breakdown of a variety of ubiquitin-linked proteins) (Davis & Drumm 2004). In CF patients with a mutation in the ΔF508 allele, there is incidence also of increased and prolonged activity of NF-□B, which is associated with the transcription of various inflammatory cytokines (Tabary et al. 2006). Possible mechanisms of action of curcumin-mediated restoration of ion exchange in ΔF508 CF patients involve the requirements of calcium for both destruction and increased inflammatory response (Courtney et al. 2004). The proteasomes responsible for the destruction of the CFTR protein are calcium dependent and by decreasing the concentration of calcium, the amount of ubiquinated protein would also decrease (Davis & Drumm 2004). As this mechanism has not been proven, it remains speculative. Tabary et al. (2006), however, have

shown that calcium is a key regulator of NF-□B activation and by regulating calcium levels it is possible to control the action of NF-□B.

It has been reported that when ΔF508 CF mice were administered curcumin orally, they regained normal nasal potential-difference measurements, indicating normal ion transfer; these mice were less likely to die through intestinal plugging (a result of inadequate salt and water transport into the gut) (Davis & Drumm 2004). These results, however, could not be reproduced by Dragomir et al. (2004), indicating the need for further investigation.

Anti-HIV Activity

Human immunodeficiency virus type 1 (HIV-1) and 2 (HIV-2) are both causative agents of acquired immunodeficiency syndrome (AIDS) (Mazumder et al. 1997). HIV-1 is the more common and virulent of the two, with HIV-2 having a longer latency period, fewer immunological abnormalities in individuals that are asymptomatic, and lower sexual transmission and perinatal rates than is associated with HIV-1 (Reid et al. 2005). HIV type 1 and 2 are retroviruses that offer a unique replication mechanism that provides many potential targets for chemotherapeutic intervention. Three key enzymes are evident in the replication of the retrovirus, post-infection: 1) the deoxyribonucleic acid (DNA) polymerase, reverse transcriptase (RT), is used to transcribe the viral ribonucleic acid (RNA) to proviral DNA prior to incorporation into the host DNA; 2) to catalyze 3'-preprocessing of the viral DNA and its insertion into the host DNA, the enzyme integrase (IN) is used; and 3) processing new viral particles is controlled by the enzyme HIV protease (PR). The current standard clinical treatment for HIV infection and AIDS is a combination of inhibitors of the RT and PR. Targets of these mechanisms, however, do not effectively remove the virus from the host and it is therefore desirable to investigate other targets of action, *i.e.* the HIV IN enzyme, as it occurs early in the lifecycle of the virus (Vajragupta et al. 2005).

Curcumin is a reported IN inhibitor with a 50% inhibition concentration ($IC_{50)}$ of 40μM, while that of the curcumin analogue, dicaffeoylmethane (see 3 in Fig 3) is under 10μM (Mazumder et al. 1997). Vajragupta et al. (2005) used computational docking to simulate models of the interaction of curcumin with IN and PR. Similar binding mechanisms with the active sites of both IN and PR were modelled. Results obtained in this study indicate that the keto-enol tautomerization of curcumin (see Fig 1a, b) and both *o*-hydroxyl structures are important for inhibition of the PR protein, while the keto-enol and only one side of the *o*-hydroxyl exhibited tight binding during inhibition of the IN protein. The binding mechanisms obtained by this simulation provide potential targets for future modification of curcumin.

Anti-Inflammatory Activity

Chronic inflammation can last for long periods (weeks, months or years) as a result of the persistence of the causative inflammatory stimulus. Chronic inflammation can lead to tissue damage and has been reported to

predispose the patient to cancer as indicated by the association between inflammatory bowel disease and colon cancer, chronic pancreatitis and pancreatic adenocarcinoma, and hepatitis with hepatocellular carcinoma (Baniyash 2006).

Possible chemopreventive agents in response to chronic inflammation involve downregulation of tumor necrosis factor-α (TNF-□), interleukin-1 (IL-1), NF-□B (Sharma et al. 2005), and cyclooxygenase-2 (COX-2) (Lim et al. 2001), increasing levels of SOD and GPX (Manikandan et al. 2004), and act as a potent antioxidant. Evidently, curcumin possesses mechanisms of action that complement all of the chemopreventive methods put forth; indicating curcumin is an excellent prototype for chemotherapy of both chronic inflammation and cancer.

Pharmacokinetics

Although curcumin exhibits many potentially beneficial characteristics, it has not yet become a clinical solution to any pathological conditions because of its poor pharmacokinetic properties. Initially, it was found that curcumin administered in the diet of rats was excreted mainly in the feces (Sharma et al. 2001). When administered orally to rats, curcumin, again, appeared to be mainly excreted in the feces, along with metabolites such as curcumin sulphate and curcumin glucuronide in the urine and plasma, along with smaller levels of reduced products such as dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin and hexahydrocurcuminol. Preclinical studies using suspensions of isolated human hepatocytes, liver or gut microsomes suggest that curcumin is metabolically reduced within minutes. Another study indicated that co-administration of piperine with curcumin may increase the bioavailability of curcumin by as much as 154% by inhibiting xenobiotic glucuronidation (Shoba et al. 1998).

As shown in rodents, curcumin essentially undergoes intestinal metabolism resulting in low bioavailability. Any absorbed curcumin appears to undergo rapid fast-pass metabolism and excretion in the bile (Sharma et al. 2001). The consequence of these mechanisms is that curcumin is unable to perform *in vivo* the biological activity observed in *in vitro* studies.

CONCLUSIONS

It is clear curcumin holds promise in the development of new therapies for cancer, Alzheimer's disease, cystic fibrosis, inflammation, and HIV infection. Although curcumin possesses wide ranging anti-inflammatory and anti-cancer properties its low systemic bioavailability upon oral dosing limits the tissues it can reach at concentrations sufficient to be effective. In view of the pharmacological properties reported, however, "its clinical evaluation in individuals at risk of developing cancer, especially of the gastrointestinal tract, appears opportune" (Sharma et al. 2005).

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