Curcumin: A Culinary Herb and Its Health Benefits

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Abstract: Curcumin, present in *Curcuma longa*, a traditional Indian spice, has many important biological mechanisms to improve health of aging organisms. It inhibits nuclear factor kappa beta (NFkB) decreasing both inflammation and cell survival, which is important to avoid proliferation of cancer cells and decrease brain, endothelial and myocardial damage. Curcumin also decreases inflammation by other membrane systems, such as protein kinases. This traditional spice also elicites higher antioxidant activity that can potentially enhance neuronal survival, decreasing the risk of neurodegenerative disorders of the CNS (e.g. Alzheimer's disease). By its capability to trigger apoptosis of different target tumoral cells, curcumin has been considered as a new promise anti-cancer quimiopreventive agent. It is speculated that dietary curcumin could perform many important biological mechanisms affording a better quality of life during human lifespan.

Keywords: NFkB, inflammation, heme-oxygenase, antioxidant, brain, Alzheimer's disease, apoptosis, cardiovascular protection, cancer.

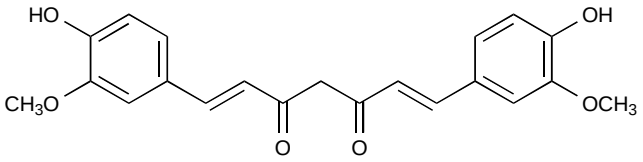
INTRODUCTION

A very traditional culinary herb, turmeric or curry has been used as a food or a medicine for more than 2500 years, especially in Asian Nations [1]. *Curcuma longa* L. is the major plant species, but curcumin sources also include *C. phaeocaulis*, *C. xanthorrhiza*, *C. mangga*, *C. zedoaria*, and *C. aromatica* [1].

It is important to emphasize that curry is also very used all over the world, since it was incorporated in Latin American and African cuisine.

From the rhizomes of Turmeric (*Curcuma longa L.*), the "Indian gold spice", it was isolated more than 235 compounds, such as 109 sesquiterpenes, 5 diterpenes, 3 triterpenoids, 68 monoterpenes, 22 diarylheptanoids, diarylpentanoids, 8 phenylpropenes, phenolic compounds, 4 sterols, 2 alkaloids, and 14 remaining compounds [2].

Commercial curcumin is usually a mixture of three curcuminoids: curcumin (71.5%), demethoxycurcumin (19.4%), and bisdemethoxycurcumin (9.1%) [3]. Curcumin (Figure **1**) is obtained by solvent (acetone, carbon dioxide, ethanol, and isopropanol) extraction from ground turmeric rhizomes and purification of the extract by crystallization. The commercial Curcumin extract is a yellowish to orange-red water-insoluble powder [3].



$C_{21}H_{20}O_6$; molecular weight: 368.38

Figure 1: Molecular structure of curcumin.

The most important cell and tissue protective mechanisms performed by curcumin comprise antioxidant and antinflammatory activities [4, 5].

The objective of this paper is to review the health benefits of curcumin (diferuloylmethane).

ANTIOXIDANT PROPERTIES OF CURCUMIN: LIVER PROTECTION

In aging as well as in many metabolic and disease states, because of mitochondrial overload, decay or failure, is common to found both oxidative stress (excessive reactive oxygen species/free radicals and poor intracellular antioxidant defenses, such superoxide dismutase-SOD, glutathione-GSH, glutathione peroxidase-GPX, catalase-CAT) and nitrosative stress, and consequently massive depletion of nutritional and cellular antioxidants [6-8].

Curcumin has powerful potential to scavenge free radicals and reactive species as well as to enhance synthesis of endogenous antioxidant enzyme systems, such as GSH and GPX [9]. Those aging-related oxidative changes are also implicated in liver aging [10]. Balasubramanyam *et al*. [11] had found that curcumin decreased protein kinase c and calcium

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influx, decreasing reactive oxygen species releasing and cell damage.

Curcumin administration to mice decreased both plasma and liver levels of lipid peroxidation [12]. Other study, confirmed the protective effects of curcumin against membrane phospholipid peroxidation [13]. Curcumin also protected mice against acetaminophen and mal-nutrition-induced liver peroxidation and also partially reversed the GSH decay induced by oxidative stress [14]. In this respect, experimental data have been supported the fact that curcumin can block oxidative damage to proteins and lipids in mitochondrial membrane [15].

In three experimental models of tissue injury, e.g., edematous inflammation, granulomatous inflammation, and carbon tetrachloride (CCl_4)-induced liver injury, previous administration of curcumin partially restored the levels of cellular antioxidants (GSH, GPX, SOD) and reversed liver damage [16]. Then, curcumin decreases hepatic lipid peroxidation products (lipid hydroperoxides, malonaldehyde), biomarkers of oxidative damage, inflammation, and liver fibrosis [5, 16, 17].

ANTIOXIDANT AND CARDIOVASCULAR PROTECTION OF CURCUMIN

Cardiovascular protection is an important issue and curcumin seems to positively modulate this system.

Curcumin administration (200mg/Kg) inhibited (30mg/100g) rat myocardial necrosis, decreasing collagen degradation and re-synthesis, effects mediated by scavenging of free radicals and blocking of lysosomal enzymes releasing [18]. In an isoproterenol induced myocardial injury experimental model, previous administration of curcumin partially restored the levels of cellular antioxidants (GSH, GPX, SOD) and reversed myocardial injury [16].

Curcumin can also decrease the vascular risk of atherosclerosis and thrombosis.

Oral curcumin intake (20mg) during 60 days decreased both HDL and LDL cholesterol lipoperoxidation in healthy humans [19]. Curcumin was also important to inhibit smooth muscle cells migration, proliferation and collagen synthesis [20], a crucial sequence of events to atherothrombotic plaque formation [21, 22]. Another study re-enforced the potential role of curcumin against atherosclerosis, since the herb partially reduced vascular oxidative stress and aortic fatty streak formation in rabbits [23].

Excessive prostagandin E_2 endothelial releasing increases the risk for both thrombosis and atherothrombosis [24], effects that could be suppressed by curcumin [25, 26]. It has also been suggested that curcumin possess anti-thrombotic properties *in vivo* [27].

Curcumin can also suppress oxidative stress-induced endothelial dysfunction conserving normal vasodilatory actions which are important in order to avoid artery stiffness and artery occlusion by coagula or fatty streak [28].

Curcumin seems to be effective also in human cardiac patients. Administration of curcumin (4g *per* day) previously to coronary bypass surgery in 121 patients strongly decreased myocardial infarction rates. The authors observed curcumin decreased cardiomyocyte apoptosis, lipid peroxidation (malonaldehyde), N-terminal B-type natriuretic peptide, and inflammation as measured by C reactive protein levels [29].

ANTIOXIDANT AND BRAIN PROTECTIVE EFFECTS OF CURCUMIN

Frequent curry consumption has been associated to increased scores on Mini-Mental State Examination Test, suggesting that curry's curcumin protects against brain aging and preserves mental performance in older people [30].

Curcumin administration to young and old rats protected brain by enhancing SOD, GPx and Na^+,K^+–ATPase levels; on the other side, it potentially decreased lipofuscin, the senescence pigment, and lipoperoxide levels, a marker of lipid peroxidation [31].

In the same context, curcumin had partially inhibited ischemic-induced neuronal cell death, decreased oxidative stress, lipid peroxidation, and mitochondrial dysfunction, effects associated with better locomotor activity in Mongolian gerbils [32]. Another study revealed that curcumin protected against mitochondrial dysruption and loss of cytochrome c as well as activation of caspase-3 and apoptosis of cortical neurons [33]. This finding is in agreement with the fact that curcumin decreases cerebral ischemia, neuronal apoptosis, lipid peroxidation, oxidative stress, and mitochondrial dysfunction [32, 34]. Curcumin could also trigger GSH and GPX synthesis protecting astrocytes

from neurotoxicity as well as protecting brain against Parkinson's disease, and other neurodegenerative diseases [35-37]. Because of its capacity to activate cell antioxidant systems (GSH, GPX, SOD) and decrease lipid peroxidation, curcumin seems to be a promise in spinal cord injury studies [38].

Curcumin has other important cell protective pathways. Heme-oxygenase enzyme (isoforms 1 and 2) is important to convert erithrocyte free HEME proteins into biliverdin (further transformed in bilirrubin), CO and Fe^{2+} (incorporated into ferritin) and it is expression, during aging and many cellular stresses, affords protection agaisnt neuronal oxidative damage and other cell injuries [39-41]. Many studies have been suggested that curcumin can protect astrocytes and neurons through activation of heme-oxygenase [42, 43].

In Alzheimer´s disease, a defective lysis of amyloid precursor protein (APP) leads to the formation of β-amyloid proteins which aggregate into neurotoxic neurofibrilary tangles capable of inducing chronic inflammatory and oxidative stress reactions, including increased nitric oxide production and mitochondrial dysfunction, that results in death and progressive loss of hipocampal neurons [44, 45]. Lim *et al*. [46] reported that curcumin administration decreased β-amyloid protein and neurofibrilary tangles by 43%; however, the authors did observe no decrease on APP. Same anti-β-amyloid effects of curcumin *in vitro* and/or *in vivo* were also respectively observed by Ono *et al*. [47] and by Yang *et al*. [48]. A recent study also confirmed suppressing effects of curcumin on neurofibrilary tangles and neuronal cytotoxicity in an AD model [49]. Pleothropic mechanisms developed by curcumin are represented in Figure **1**.

DOES CURCUMIN HELP TO PREVENT CATARACT?

Dietary curcumin seems to decrease the risk for cataract due to its antioxidant and anti-lipoperoxidative actions on eye lenses [50-53]. In this regard, in many experimental cataract models, curcumin was found to decrease oxidative stress, to improve antioxidant molecular defenses, and to inhibit calcium-dependent calpain-induced lens opacification decreasing cataract formation [54-56]. However, more studies are needed on this issue.

MOLECULAR TARGETS OF CURCUMIN: PROTECTING AGAINST AGE-RELATED DISEASES AND CANCER

Curcumin induced apoptosis of promyelocyte leukemia HL-60 cells, an effect mediated by increasing intracellular reactive oxygen species and partial inhibition of Bcl-2 protein [57]. Curcumin can also induce apoptosis in human hepatocellular carcinoma cells, lung adenocarcinoma cells, colon cancer cells, chronic lymphocytic leukemia B Cells, medulloblastoma cells, and many other cell types (Table **1**) [58-70].

Curcumin seems to inhibit nuclear factor-kappa beta (NFkB), an important cell messenger for activation of nuclear inflammatory genes, oncogenes and anti-

Table 1: Effect of Curcumin on Cancer Cell Lines

Tumor cell line	reference
Curcumin induced apoptosis in rat colon cancer cells	Kawamori *et al*. (1999)
It induced apoptosis of human lung adenocarcinoma cells through caspase-3 induction	Ye *et al*. (2012)
Curcumin induced apoptosis on multidrug-resistant acute leukemia cell line (CEM-CCRF)	Piwocka *et al*. (2002)
It induced apoptosis of chronic lymphocytic leukemia B cells	Gosh *et al*. (2009)
It triggered apoptosis on LNCaP prostate cancer cells	Deeb *et al*. (2003)
It promoted apoptosis of medulloblastoma cells *via* activation of anaphase/cyclosome protein Cdc27	Lee and Langhans (2012)
It induced apoptosis of human multiple myeloma cells	Bharti *et al*. (2003)
Curcumin induced p38-dependent apoptosis of human hepatocellular carcinoma cells	Wang *et al*. (2013)
It induced apoptosis on MCF-7, HepG2 and MDAMB tumor cells but not kill normal rat hepatocytes	Syng-Ai *et al*. (2004)
It triggered apoptosis on human renal cancer cells	Jung *et al*. (2005)
It triggered cell death of both neck and head human squamous cell carcinoma lines	LoTempio *et al*. (2005)
It induced apoptosis on colon cancer cells	Moussavi *et al*. (2006)
Curcumin induced apoptosis of colon cancer cells *via* activation of p53-dependent and independent pathways	Majumdar *et al*. (2009)

apoptotic genes [71, 72], which can aggravate infection, inflammatory disorders, burns and photodamaged skin, and stimulates tumor initiation [73-76]. Then, curcumin can block cell proliferation, inflammation (leukotrienes and prostaglandins synthesis) and induces apoptosis by suppressing NFkB in many cancer cell lines [77-81]. Curcumin can also decrease apoptosis of by suppressing proteosome activity [82], which at least in part explains the 11.7% increased longevity in curcumin fed mice [83]. This study contrasts with data from Jana *et al*. which observed suppression of the ubiquitin-proteosome system by curcumin was related to mitochondrial dysfunction and apoptosis of neurons [84].

In fact, curcumin has a pivotal role on cell survival and death (Figure **2**). Many different studies, summarized on Table **1**, on tumor cell lines revealed that curcumin could induce apoptosis avoiding tumor survival [57]. However, curcumin can inhibit chemotherapy-triggered apoptosis of human breast cancer cells [85].

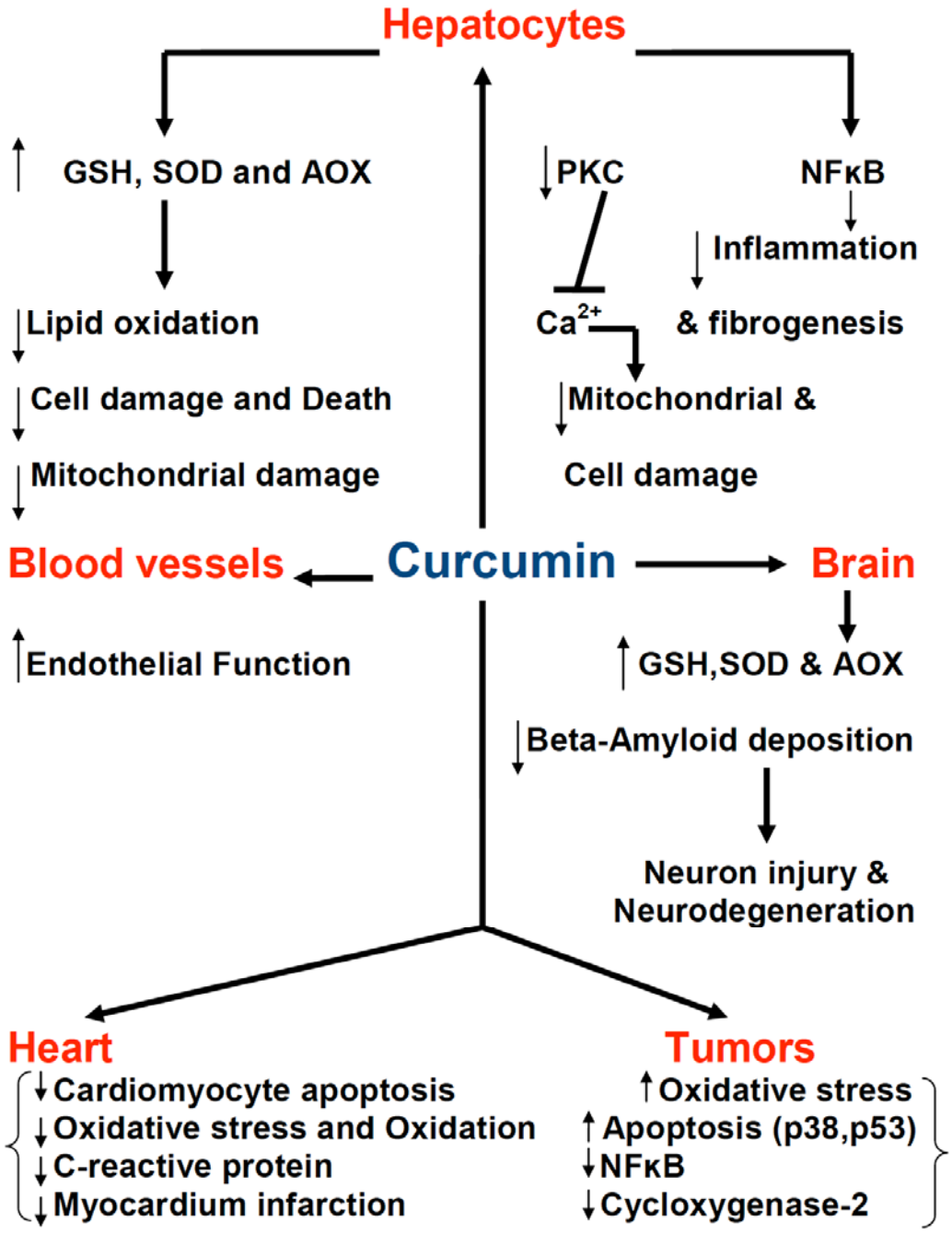

Figure 2: Pleiothropic Mechanisms and Effects of Curcumin.

In an experimental of benzopyrene-induced lung cancer, curcumin inhibit cycloxygenase-2 expression in tumoral lungs [86].

It is important to note that curcumin can be helpful for adjuvant treatment of some but not all cancers. In fact, in some studies curcumin has very weak anticancer activities [87, 88]. Sebastià *et al*. [89] had found curcumin caused genotoxic effects human peripheral blood lymphocytes.

CONCLUSION

Curcumin should be added to human diet, inside a healthy lifestyle, because it can help to decrease free radical damage and cell death, improve hepatic metabolism, protect brain and cardiovascular system, and it can trigger tumor cell death.

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