The Effect of Curcumin and Tocotrienol on the Development of Eye Disease

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ABSTRACT

There is growing evidence that inflammation may be one of the causative factors of many chronic diseases especially which is related to eyes such as cataract, age-related macular degeneration and uveitis. Several cytokines such as IL-1, IL-6, RANKL, OPG, and M-CSF were implicated in the pathogenesis of chronic diseases. Anticytokine therapy using cytokine antagonists such as IL-receptor antagonist and TNF-binding protein was able to suppress the activity of the respective cytokines and prevent bone loss. Few animal studies have shown that vitamin E in the forms of palm-derived tocotrienol and α-tocopherol may prevent chronic eye disease in rat models by suppressing IL-1 and IL-6. Free radicals are known to activate transcription factor NFκB which leads to the production of bone resorbing cytokines. Tocotrienol, a potent antioxidant, may be able to neutralize free radicals before they could activate NFκB, therefore suppressing cytokine production and inflammatory reaction. Curcumin is widely reported to have potent anti-inflammatory and anti-carcinogenic effects. The anti-inflammatory action of curcumin seems to be closely related to inhibition of TNF-α and other inflammatory cytokines production and suppression of NF-xB activation by blocking phosphorylation of inhibitory factor I-kappa B kinase (IκB) Tocotrienol and curcumin have also been shown to inhibit COX-2, the enzyme involved in inflammatory reactions of the these studied, tocotrienol seemed to be better than tocopherols in terms of its ability to suppress inflammation induced by cytokines.

Keywords: Curcumin, Tocotrienol, Eye Disease, Inflammation.

INTRODUCTION

The free radical (ROS) defined as any atom or molecule possessing unpaired electrons. Molecular oxygen O2− is a biradical with two such unpaired electrons. The biologically relevant free radicals derived from oxygen are the superoxide anion (O2−), the perhydroxyl radical (protonated superoxide, HO2−), the hydroxyl radical (HO2−), and free radical nitric oxide (NO2−).

As antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Antioxidants action can terminate these chain reactions by removing free radicals intermediates (Sies et al., 1997). The use of antioxidants in pharmacology is intensively studied, particularly as treatments for stroke and neurodegenerative diseases. However, it is unknown whether oxidative stress is the cause or the consequence of disease (Bjelakovic et al., 2007).
Oxidative stress and free radicles

The eye is a highly metabolically active structure, continually bathed in light and the absorption and metabolism will be highly functioning. Thus, oxidative and particularly photo-oxidative processes are critical factors in ocular pathologic conditions but are often poorly recognized by investigating ocular disease regarding to (Jean et al., 1999; Jennifer et al., 2008). Oxidative stress is a key player in the mechanism of inflammation; thus, we should not be surprised that it is important in eye disease conjunctiva, cornea and uvea (Saraswathy and Rao, 2009). As well as in cataract formation in the lens, retinal degeneration and in optic nerve pathologic conditions, inflammatory in optic neuritis and degenerative in glaucoma due to oxidative stress which occurs throughout the eye and is involved in many different types of tissue damage (Wu et al., 2005; Ferreira et al., 2004; Biswas et al., 2005). This effect of oxidative stress has been increasingly recognized as important factor in pathologic conditions generally in ocular pathologic conditions specifically in the past decade (Mittag, 1984; Bacci et al., 2005; Kruzel et al., 2006).

In Ophthalmology, the relation between oxidative stress and aging has been given attention for some diseases to aging like age-related macular degeneration, cataract and dystrophy. Regarding to Imamura et al., (2006) the amount and activity of SOD were the highest among the in the human retina, it seemed reasonable to hypothesize that the lack of SOD would accelerate age-related pathological changes in the human retina (Liang & Godley, 2003; Taysi et al., 2007). In many experimental research of uveitis generally involve the posterior segment and retinal mitochondria that exhibit signs of oxidative stress, which seems to result from the up regulation of inducible nitric oxide synthase (iNOS) in photoreceptor mitochondria and retinal cytokine generation by antigen-specific infiltrating T cells (Rajendrum et al., 2007; David et al., 2008).

The relevance to the anterior uveitis seen more commonly, oxidative stress is also seen in models of anterior uveitis, such as that induced by endotoxin (Bhattachjerie et al., 1983; Yan Guex et al., 1996; Satici et al., 2004; Yadav., et al., 2009). The level of malondialdehyde (MDA) in aqueous humor which is consider important key marker of oxidative stress (Rahman and Biswas, 2004). The trophic factor pigment epithelial-derived factor (PEDF) is produced by the retinal pigment epithelium and also by the epithelium of the ciliary body, from whence it is secreted into the aqueous humor (Ortego et al., 1996; Neiderkorn et al., 2007).

Imamura et al., (2006) have been investigated the age-related changes of the retinas of mice and found that these mice have many of the key elements of human age-related macular degeneration including thickened Bruch's membrane, and retina neovascularization. Moreover, the retinal pigment epithelium (RPE) cells of these mice showed signs of oxidative stress damage, and their junction integrities have been damaged (Bilgihan et al., 2003). In the other hand some studies revealed that the mechanism of causative role of oxidative stress in the pathogenesis of retinal degeneration and demonstrated a critical role of SOD in protecting the RPE from age-related degeneration (Imamura et al., 2006; Wakamatsu et al., 2008). In vivo studies, it provides a steady supply of free radicals since it is a chain reaction leading to the formation of organic peroxides. The accumulation of peroxides can lead to damage effect on cellular vitality, which might be developing to degeneration and necrosis (Chung et al., 1999; Tezel et al., 2001; Tezel, 2006).

The eye is unique in possessing abundant quantities of antioxidant enzymes and other antioxidant agents. The antioxidant enzymes which include superoxide dismutase (SD), catalase (CAT), glutathione peroxidase (GPX), and glutathione transferase (Delcourt. et al., 2003; Gritz et al., 2006; Jennifer et al., 2008), all of these enzymes are distributed in the corneal epithelium and endothelium, lens epithelium, retina and retinal pigment epithelium. The eye also contains other antioxidants, such as ascorbate, vitamin E, ceruloplasmin, and transferrin (Behndig et al., 2001). These agents and the enzymes are contributed to prevent the damaging effects of oxygen and its metabolites (Koh et al., 2000; Balci et al., 2007). As the balance between the production and catabolism of oxidants by cells and tissue is critical for maintenance of the biologic and structural integrity of the tissue, the role of free radical generation in initiation of retinal or other intraocular tissue damage should be studied in clinically relevant models of uveitis in vivo (Barry et al., 2007).

Tocotrienol: Evidences of antioxidant and anti-inflammatory effects

Tocotrienol are capable of scavenging and reducing reactive oxygen species. The antioxidative activity resides mainly with its “chain-breaking” property, which neutralizes peroxy and alkoxyl radicals generated during lipid peroxidation (Yoshida, et al., 2007). Tocotrienol on the other hand, found in abundance in palm oil used for frying and consider as a potent antioxidant. The main role of the antioxidants represent by mopping up reactive oxygen species (ROS) which is consider one of the potent activator of oxidative stress-induced inflammation (Kamat and Devasagayam, 1995). Tocotrienol is one of the active compounds found in palm oil, together with the more abundant tocopherol (Yoshida, et al., 2007).

Tocopherol has been widely researched and recently was found to control the levels of pro-inflammatory cytokines such as interleukin (IL)-6 by down regulating its expression (Noriko et al., 1999; Sharma and Vinayak, 2011). δ-tocotrienol has been shown to block LPS-induced expression of TNF-α, IL-1β, IL-6 and iNOS in macrophages (Qureshi et al., 2010). The average level of vitamin E (alpha tocopherol) was lower in individuals with macular degeneration than in age and risk matched controls (Satici et al., 2003; Williams, 2006). In placebo-controlled studies, oral vitamin E was able to increase the glutathione levels in the aqueous humor and lenses of humans, rabbits and rats (Bilgihan et al., 2003). Oxidative processes have been implicated in the causation of both cataracts and the age-related disorder of the retina, maculopathy. Cataracts occur when the transparent material in the lens of the eye becomes cloudy and opaque. Oxidation, induced mainly by
exposure to ultraviolet light, is believed to be a major cause of damage to the proteins of the lens. Garrett et al., (1999) reported that the average level of vitamin E (alpha tocopherol) was lower in individuals with macular degeneration than in age and risk matched controls in placebo-controlled studies, oral vitamin E was able to increase the glutathione levels in the aqueous humor and lenses of humans, rabbits and rats. Supplementation of 400IU vitamin E (as natural D-α-tocopherol) is commonly recommended to all individuals to help with the ‘normal’ oxidative load (Seddon et al., 2005). All three of the major dietary antioxidants (vitamin C, vitamin E and carotenoids) have been associated with decreased cataract risk through the retardation of lens opacity (Leeuwen et al., 2005). Therefore the low plasma levels of vitamin E were associated with the worsening of early cortical lens opacities (Chiu and Taylor, 2007; Sanz et al., 2007).

Taylor et al., (2002) investigated the effects of the combined antioxidant vitamins A, C, and E and zinc on the development of cataract and (age-related macular degeneration) AMD and showed some partial protective effect of antioxidants supplements on the progression of moderately advanced AMD (Washington et al., 2001). Age-related eye disease study group (AREDS) (2001), used a randomized, placebo-controlled clinical trial, comprising 3640 participants, using supplementation with high-dose antioxidants (average follow-up 6.5 years) showed a significant reduction in rates of at least moderate visual loss in certain categories of ARM. Participants were randomized to daily antioxidants (vitamin C 500 mg, vitamin E 400 IU, b-carotene 15 mg, zinc 80 mg and copper 2 mg) or placebo. Subjects with extensive intermediate size drusen, at least one large druse, non-central geographic atrophy in one or both eyes, or advanced ARM in one eye had statistically significant odds reduction for the development of advanced (late) ARM. At 5 years, the estimated probability of progression to advanced ARM (neovascular ARM, geographic atrophy) was 28% for those assigned to placebo, and 20% for those assigned to antioxidants plus zinc.

Vague effects of the natural antioxidant vitamin E have been described in its relation to cataract development in rodents: a significant prevention of cataractogenesis and an improvement of lens biochemical indices, without affecting the visual cataract score (Ohta et al., 2000). A randomized controlled trial of vitamin E supplementation has not shown any effect on the incidence of early AMD after 4 years of follow-up (Flood et al., 2002). In contrast with the aforementioned studies, our results were based on long-term follow-up of a large, population-based cohort with thorough baseline assessment of dietary intake. Recently, a meta-analysis of 19 clinical trials including AREDS showed that high-dose (400 IU/d) vitamin E supplementation may increase in all-cause mortality (Miller et al., 2005). Tocotrienols also displayed potent anti-inflammatory activity by inhibiting IL-6 and TNF-α. These are the major pro-inflammatory cytokines released by activated macrophages. IL-6 has been massively studied due to its correlation with poor prognosis and resistance to therapy, interestingly; δ-tocotrienol demonstrated a 51% reduction in IL-6 levels in LPS-stimulated macrophages (Mun et al., 2009; Ndlovu et al., 2009).

Curcumin: Evidences of anti-inflammatory effects

Curcumin, a yellow coloured phenolic pigment extracted from the rhizome of herb Curcuma longa, is widely reported to have potent anti-oxidative, anti-inflammatory and anticarcinogenic effects. The anti-inflammatory action of curcumin seems to be closely related to inhibition of TNF-α and other inflammatory cytokines production and suppression of NF-kB activation by blocking phosphorylation of inhibitory factor I-kappa B kinase (IkB) (Kim et al., 2003). Curcumin is widely used for our preparation of food. Curcumin can be found in turmeric, which is the powdered form of Curcuma longa rhizomes, Curcumin has been shown to have anti-inflammatory activity when applied topically in EIU (Gupta et al., 2008). Curcumin exerts its anti-inflammatory effects by up-regulating the expression of PPARγ (Siddiqui et al., 2006) and by direct action on PPARγ receptor (Rinwa et al., 2011) thus leading to inhibition of the NF-kB pathway (Zhong et al., 2011). Curcumin was also noted to increase neutrophil apoptosis (Siddiqui et al., 2006). Although topical preparation of curcumin has been shown to reduce the level of tumour necrosis factor-α (TNF-α, one of several pro-inflammatory cytokines) (Gupta et al., 2008), the direct effect of curcumin on the expression of pro-inflammatory cytokines has not been demonstrated. Ukl et al (2003) investigated the protective effects of curcumin on 2, 4, 6-trinitrobenzenesulphonic acid (TNBS)-induced colitis in mice which is a model of inflammatory bowel disease (IBD). It also had been shown in curcumin-pretreated mice; there was a significant reduction in the degree of both neutrophil infiltration and lipid peroxidation in the inflamed colon as well as decreased serine protease activity (Bereswill et al., 2010; Lin et al., 2011). Curcumin also reduced the levels of NO and O2− associated with the favorable expression of Th1 and Th2 cytokines and inducible NOS. Consistent with these observations, NF-kB activation in colonic mucosa was suppressed in the curcumin treated mice; therefore the studies suggested that curcumin can exert beneficial effects in experimental colitis (Aggarwal et al., 2003; Kunsch et al., 2004; Sikora et al., 2010). The curcumin also have been shown an inhibitory effect on protein kinase C and xanthine oxidase (Kuo et al., 1996; Chao et al., 2007).

Pan et al., (2000) demonstrated that the nuclear factor kappa B (NF-κB2) which consider the master factor playing a role in the inflammatory and immune response, was suppressed by curcumin through inhibiting the activity of I-κB kinase (IKK). In principle, curcumin has been widely demonstrated to have potent antioxidant activities. It is well known that reactive oxygen species (ROS) play a key role in enhancing inflammation through the activation of stress kinases and redox sensitive transcription factors such as NF-κB. Oxidative stress activates NF-κB-mediated transcription of pro-inflammatory mediators either through the activation of its activating inhibitor IKK or the enhanced recruitment or activation of transcriptional co-activators (Samuhassaneeto et al., 2009; Naik et al., 2011).
Although numerous different pathways are activated during the inflammatory response, NF-κB is thought to be of the most importance in cancer-related inflammation (Philip and Rowley, 2004). However, curcumin acts as ROS scavenger, increases antioxidant glutathione levels by induction of glutamate cysteine ligase and acts as an anti-inflammatory agent by inhibition of NF-κB signaling (Biswa et al., 2005). Persistent activation of NF-κB has been observed in many different cancers research. Interestingly, Lu et al., (2004) have been identified that the sustained kinase (IKK) activation is achieved to activate NF-κB pathway in many types of human cancer, indicating the activation of NF-κB is likely to result from alterations in its upstream signaling components. In addition, cytotoxic studies in different cell lines have indicated that the toxicity of curcumin was significantly higher in tumor cells if compared to the normal cells (Kunwar et al., 2008).

Basically, curcumin prevents tissue damage by at least two mechanisms: acting as an antioxidant and by inhibiting NF-κB activation to minimized oxidative stress (Shapiro et al., 2006; Reyes-Gordillo et al., 2007). Interestingly, feeding curcumin to the diabetic rats controls oxidative stress by inhibiting the increase in thiobarbituric acid reactive substances (TBARS) and protein carbonyls by reversing altered antioxidant enzyme activities without altering the hyperglycemic state (Suryanarayana et al., 2007). By inhibiting ROS generation, curcumin also protects pancreatic islets against β cell toxins (Kanitkar and Bhonde, 2008).

All evidence shows that curcumin appears to be beneficial in preventing diabetes-induced oxidative stress, and the inhibition of NF-κB-dependent pathway is at least in part involved in the anti-diabetic mechanisms. Curcumin has long been expected to be a therapeutic or preventive agent for several major human diseases because of its anti-oxidative, anti-inflammatory, and anti-cancerous effects. As well as the absorption, bioavailability and metabolism of curcumin have been studied in humans (Chen et al., 2010). In 2001 research have been demonstrated that curcumin is not toxic to humans up to 8,000 mg/day when taken for 3 months (Cheng et al., 2001; Fu et al., 2008). In considering all of these discoveries, therefore, curcumin can be considered as an ideal lead compound for anti-inflammatory and anticancer drug development. In one small study, curcumin was given orally to 32 chronic anterior uveitis patients who were divided into two groups. The first group received curcumin alone, whereas the second group received a combination of curcumin and antitubercular treatment, all the patients treated with curcumin alone improved, compared to a response rate of 86% among those receiving the combination therapy (Lal et al., 1999).

Similar research conducted on rats and rabbits found that curcumin effectively inhibited chemically induced cataract formation, even at very low dietary levels (Pandya et al., 2000). Awasthi et al., (1996) found the as a potential cataract therapy, researchers fed two groups of rats diets that included corn oil, or a combination of curcumin and corn oil for 14 days. Afterward, their lenses were removed and examined for the presence of lipid peroxidation. The scientists discovered that "the lenses from curcumin-treated rats were much more resistant to induced opacification than were lenses from control animals (Chen et al., 2010). Curcumin have also found exhibited anti-inflammatory effects in standard animal models used for testing anti-inflammatory activity as well inhibit leukotriene formation in rat peritoneal polymorphonuclear neutrophils (Lal et al., 1999; Reyes et al., 2007). Possible benefits of oral curcumin supplementation have been observed in cases of chronic anterior uveitis as in the case of berberine, curcumin exhibits an ability to suppress TNF-α activity and cytokine production in experimental acute liver injury (Chen et al., 2010).

Gupta et al., (2008) demonstrated a significant anti-inflammatory effect including improvement of chronic uveitis by oral supplementation. The reduced severity of inflammatory changes observed in histopathologic examination and clinical manifestations in the inflamed eye was the result of significant inhibition of vascular and cellular inflammatory responses. The release of chemical mediators of inflammation was also suppressed secondary to inhibition of the cellular response. The suppression of vascular and cellular inflammatory responses by herbal extracts was evidenced by significantly lower levels of inflammatory cells, proteins, and TNF-α levels in aqueous humor of treated animals. Significantly reduced protein levels in aqueous humor also indicate a possible inhibitory role of extract constituents on leukocyte adherence to the vascular endothelium (Allegri et al., 2010).

Kumar et al., (2005) reported that curcumin feeding to rats with chemical-induced hyperglycemia can reduce oxidative stress that is the main cause of progression of cataract (Bengmark, 2006). The beneficial effects of this drug appear now to be related to the effect on regulation of peroxisome proliferator-activated receptor-γ (PPAR-γ), which is a ligand-inducible transcription factor involved mainly in controlling inflammation in peripheral organs. Activation of PPAR-γ has been shown to control the response in microglial cells and limit inflammation (Brigh, 2007; Jacob et al., 2007; Nonn et al., 2007). Curcumin also has been shown significant effect to prevent choroidal and retinal neurovascularization in several experimental animal models, notably through the inhibition of VEGF receptor expression (Jacob et al., 2007; Shakibaei et al., 2007; Allegri et al., 2010).

**CONCLUSION**

Vitamin E, especially the Tocotrienol and regulation of disease has been extensively studied in humans, animal models and cell systems. Most of these studies focus on the tocopherol isoform of vitamin E. These reports indicate contradictory outcomes for anti-inflammatory functions of the tocopherol isoform of vitamin E. These seemingly disparate clinical results are consistent with recently reported unrecognized properties of isomers of vitamin E. The anti-inflammatory potential of tocotrienols looks promising and further studies should be spearheaded. Understanding of the properties of tocotrienols would lead to greater benefits and provide good options when planning for the health of the public. Tocotrienol treatment has several anti-inflammatory effects that could be mechanistically analogous to the modulation of proteasomal
activity by lactacystin, a well-established proteasome inhibitor that can either increase or decrease proteasomal activity under different conditions and finally will lead to give good prognosis for chronic disease (Qureshi et al., 2010). In other hand the supplementation of curcumin has been shown to be safe in humans. The mechanism by which curcumin induces its anti-inflammatory effects is yet to be fully elucidated, but many studies have shown its relevance as a potent anti-inflammatory and immuno-modulating agent. PPARY agonists (like curcumin) act on microglia and immune cells systems modulating both innate and adaptive immune responses, and can have a profound effect on the inflammatory cascade. The positive results of the previous study show that Norflo (curcuminophosphatidylcholinecomplex) can play an important role in the adjunctive therapy of chronic disease in various origins and gives a contribution to the clinical potential efficacy of this plant-derived product in medicine (Allegri et al., 2010).

REFERENCES


Barr S, Winkler, Michael E. Boulton, John D. Gottsch, and Paul Sterberg.Oxidative damage and age-related macular degeneration, Mol Vis. Author manuscript; available in PMC 2007 January 17


Chao JW, Lee KS, Kim CW. Curcumin attenuates the expression of IL-1, IL-6, and TNF-as well as cyclin E in TNF-treated HaCaT cells; NF-B and MAPKs as potential upstream targets. Int J Mol Med 19: 469-474, 2007.


Renu Sharma and Manjula Vinayak.α-Tocopherol attenuates NF-xβ activation and pro-inflammatory cytokine IL-6 secretion in cancer-bearing mice. Bioscience Reports (2011) 31, 421–428


