

## ABSTRACTS

Page 1 of 4

## Curcumin

Curcumin protects against 4-hydroxy-2-trans-nonenal-induced cataract formation in rat lenses.

Age-related cataractogenesis is a significant health problem worldwide. Oxidative stress has been suggested to be a common underlying mechanism of cataractogenesis, and augmentation of the antioxidant defenses of the ocular lens has been shown to prevent or delay cataractogenesis. The present studies were designed to test the efficacy of curcumin, an antioxidant present in the commonly used spice turmeric, in preventing cataractogenesis in an in vitro rat model. Rats were maintained on an AIN-76 diet (ICN Pharmaceuticals Inc, Cleveland) for 2 wk, after which they were given a daily dose of corn oil alone or 75 mg curcumin/kg in corn oil for 14 d. Their lenses were removed and cultured for 72 h in vitro in the presence or absence of 100  $\mu$ mol 4-hydroxy-2-nonenal (4-HNE)/L, a highly electrophilic product of lipid peroxidation. The results of these studies showed that 4-HNE caused opacifications of cultured lenses as indicated by the measurements of transmitted light intensity using digital image analysis. However, the lenses from curcumin-treated rats were much more resistant to 4-HNE-induced opacification than were lenses from control animals. Curcumin treatment caused a significant induction of the glutathione S-transferase (GST) isozyme rGST8-8 in rat lens epithelium. Because rGST8-8 utilizes 4-HNE as a preferred substrate, we suggest that the protective effect of curcumin may be mediated through the induction of this GST isozyme. These studies suggest that curcumin may be an effective protective agent against cataractogenesis induced by lipid peroxidation.

Am J Clin Nutr 1996 Nov;64(5):761-6

Efficacy of curcumin in the management of chronic anterior uveitis.

Curcumin, obtained from rhizomes of *Curcuma longa*, was administered orally to patients suffering from chronic anterior uveitis (CAU) at a dose of 375 mg three times a day for 12 weeks. Of 53 patients enrolled, 32 completed the 12-week study. They were divided into two groups: one group of 18 patients received curcumin alone, whereas the other group of 14 patients, who had a strong PPD reaction, in addition received antitubercular treatment. The patients in both the groups started improving after 2 weeks of treatment. All the patients who received curcumin alone improved, whereas the group receiving antitubercular therapy along with curcumin had a response rate of 86%. Follow up of all the patients for the next 3 years indicated a recurrence rate of 55% in the first group and of 36% in the second group. Four of 18 (22%) patients in the first group and 3 of 14 patients (21%) in the second group lost their vision in the follow up period due to various complications in the eyes, e.g. vitritis, macular oedema, central venous block, cataract formation, glaucomatous optic nerve damage etc. None of the patients reported any side effect of the drug. The efficacy of curcumin and recurrences following treatment are comparable to corticosteroid therapy which is presently the only available standard treatment for this disease. The lack of side effects with curcumin is its greatest advantage compared with corticosteroids. A double blind multi-centric clinical trial with this drug in CAU is highly desirable to further validate the results of the present study.

Phytother Res 1999 Jun;13(4):318-22

Dietary curcumin prevents ocular toxicity of naphthalene in rats.

Administration of naphthalene is known to cause cataract formation in rats and rabbits and naphthalene-initiated cataract is frequently used as a model for studies on senile cataract in humans. Oxidative stress has been implicated in the mechanism of naphthalene-induced cataract. Curcumin, a constituent of turmeric, a spice used in Indian curry dishes, is an effective antioxidant and is known to induce the enzymes of glutathione-linked detoxification pathways in rats. During the present studies, we have examined whether low levels of dietary curcumin could prevent naphthalene-induced opacification of rat lens. The presence of apoptotic cells in lens epithelial cells was also examined by catalytically incorporating labeled nucleotide to DNA with either Klenow fragment of DNA polymerase or by terminal deoxynucleotidyl transferase (TdT), which forms polymeric tail using the principle of TUNEL assay. The results of these studies demonstrated that the rats treated with naphthalene and kept on a diet supplemented with only 0.005% (w/w) curcumin had significantly less opacification of lenses as compared to that observed in rats treated only with naphthalene. Our studies also demonstrate, for the first time, that naphthalene-initiated cataract in lens is

accompanied and perhaps preceded by apoptosis of lens epithelial cells and that curcumin attenuates this apoptotic effect of naphthalene.

Toxicol Lett 2000 Jun 5;115(3):195-204

Enhancement of wound healing by curcumin in animals.

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and remodeling of the tissue. In this study, we evaluated the *in vivo* effects of curcumin (diferuloylmethane), a natural product obtained from the rhizomes of *Curcuma longa* on wound healing in rats and guinea pigs. We observed faster wound closure of punch wounds in curcumin-treated animals in comparison with untreated controls. Biopsies of the wound showed reepithelialization of the epidermis and increased migration of various cells including myofibroblasts, fibroblasts, and macrophages in the wound bed. Multiple areas within the dermis showed extensive neovascularization, and Masson's Trichrome staining showed greater collagen deposition in curcumin-treated wounds. Immunohistochemical localization of transforming growth factor-beta1 showed an increase in curcumin-treated wounds as compared with untreated wounds. *In situ* hybridization and polymerase chain reaction analysis also showed an increase in the mRNA transcripts of transforming growth factor-beta1 and fibronectin in curcumin-treated wounds. Because transforming growth factor-beta1 is known to enhance wound healing, it may be possible that transforming growth factor-beta1 plays an important role in the enhancement of wound healing by curcumin.

Wound Repair Regen 1998 Mar-Apr;6(2):167-77

Curcumin enhances wound healing in streptozotocin induced diabetic rats and genetically diabetic mice.

Tissue repair and wound healing are complex processes that involve inflammation, granulation and tissue remodeling. Interactions of different cells, extra cellular matrix proteins and their receptors are involved in wound healing, and are mediated by cytokines and growth factors. Previous studies from our laboratory have shown that curcumin (diferuloylmethane), a natural product obtained from the rhizomes of *Curcuma longa*, enhanced cutaneous wound healing in rats and guinea pigs. In this study, we have evaluated the efficacy of curcumin treatment by oral and topical applications on impaired wound healing in diabetic rats and genetically diabetic mice using a full thickness cutaneous punch wound model. Wounds of animals treated with curcumin showed earlier reepithelialization, improved neovascularization, increased migration of various cells including dermal myofibroblasts, fibroblasts, and macrophages into the wound bed, and a higher collagen content. Immunohistochemical localization showed an increase in transforming growth factor-beta1 in curcumin-treated wounds compared to controls. Enhanced transforming growth factor-beta1 mRNA expression in treated wounds was confirmed by *in situ* hybridization, and laser scan cytometry. A delay in the apoptosis patterns was seen in diabetic wounds compared to curcumin treated wounds as shown by terminal deoxynucleotidyl transferase-mediated deoxyuridyl triphosphate nick end labeling analysis. Curcumin was effective both orally and topically. These results show that curcumin enhanced wound repair in diabetic impaired healing, and could be developed as a pharmacological agent in such clinical settings.

Wound Repair Regen 1999 Sep-Oct;7(5):362-74

Systemic administration of the NF-kappaB inhibitor curcumin stimulates muscle regeneration after traumatic injury.

Skeletal muscle is often the site of tissue injury due to trauma, disease, developmental defects or surgery. Yet, to date, no effective treatment is available to stimulate the repair of skeletal muscle. We show that the kinetics and extent of muscle regeneration *in vivo* after trauma are greatly enhanced following systemic administration of curcumin, a pharmacological inhibitor of the transcription factor NF-kappaB. Biochemical and histological analyses indicate an effect of curcumin after only 4 days of daily intraperitoneal injection compared with controls that require >2 wk to restore normal tissue architecture. Curcumin can act directly on cultured muscle precursor cells to stimulate both cell proliferation and differentiation under appropriate conditions. Other pharmacological and genetic inhibitors of NF-kappaB also stimulate muscle differentiation *in vitro*. Inhibition of NF-kappaB-mediated transcription was confirmed using reporter gene assays. We conclude that NF-kappaB exerts a role in regulating myogenesis and that modulation of NF-kappaB activity within muscle tissue is beneficial for muscle repair. The striking effects of curcumin on myogenesis suggest therapeutic applications for treating muscle injuries.

Am J Physiol 1999 Aug;277(2 Pt 1):C320-9

Inhibition of ligand-induced activation of epidermal growth factor receptor tyrosine phosphorylation by curcumin.

We explored the regulation of epidermal growth factor (EGF)-mediated activation of EGF receptor (EGF-R) phosphorylation by curcumin (diferuloyl-methane), a recently identified kinase inhibitor, in cultured NIH 3T3 cells expressing human EGF-R. Treatment of cells with a saturating concentration of EGF for 5-15 min induced increased EGF-R tyrosine phosphorylation by 4- to 11-fold and this was inhibited in a dose- and time-dependent manner by up to 90% by curcumin, which also inhibited the growth of EGF-stimulated cells. There was no effect of curcumin treatment on the amount of surface expression of labeled EGF-R and inhibition of

EGF-mediated tyrosine phosphorylation of EGF-R by curcumin was mediated by a reversible mechanism. In addition, curcumin also inhibited EGF-induced, but not bradykinin-induced, calcium release. These findings demonstrate that curcumin is a potent inhibitor of a growth stimulatory pathway, the ligand-induced activation of EGF-R, and may potentially be useful in developing anti-proliferative strategies to control tumor cell growth.

Carcinogenesis 1995 Aug;16(8):1741-5

Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells.

Curcumin, a potent antioxidant and chemopreventive agent, has recently been found to be capable of inducing apoptosis in human hepatoma and leukemia cells by way of an elusive mechanism. Here, we demonstrate that curcumin also induces apoptosis in human basal cell carcinoma cells in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic change. In our study, consistent with the occurrence of DNA fragmentation, nuclear p53 protein initially increased at 12 h and peaked at 48 h after curcumin treatment. Prior treatment of cells with cycloheximide or actinomycin D abolished the p53 increase and apoptosis induced by curcumin, suggesting that either de novo p53 protein synthesis or some proteins synthesis for stabilization of p53 is required for apoptosis. In electrophoretic mobility gel-shift assays, nuclear extracts of cells treated with curcumin displayed distinct patterns of binding between p53 and its consensus binding site. Supportive of these findings, p53 downstream targets, including p21(CIP1/WAF1) and Gadd45, could be induced to localize on the nucleus by curcumin with similar p53 kinetics. Moreover, we immunoprecipitated extracts from basal cell carcinoma cells with different anti-p53 antibodies, which are known to be specific for wild-type or mutant p53 protein. The results reveal that basal cell carcinoma cells contain exclusively wild-type p53; however, curcumin treatment did not interfere with cell cycling. Similarly, the apoptosis suppressor Bcl-2 and promoter Bax were not changed with the curcumin treatment. Finally, treatment of cells with p53 antisense oligonucleotide could effectively prevent curcumin-induced intracellular p53 protein increase and apoptosis, but sense p53 oligonucleotide could not. Thus, our data suggest that the p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. This evidence also suggests that curcumin may be a potent agent for skin cancer prevention or therapy.

J Invest Dermatol 1998 Oct;111(4):656-61

Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers.

The medicinal properties of curcumin obtained from *Curcuma longa* L. cannot be utilised because of poor bioavailability due to its rapid metabolism in the liver and intestinal wall. In this study, the effect of combining piperine, a known inhibitor of hepatic and intestinal glucuronidation, was evaluated on the bioavailability of curcumin in rats and healthy human volunteers. When curcumin was given alone, in the dose 2 g/kg to rats, moderate serum concentrations were achieved over a period of 4 h. Concomitant administration of piperine 20 mg/kg increased the serum concentration of curcumin for a short period of 1-2 h post drug. Time to maximum was significantly increased ( $P < 0.02$ ) while elimination half life and clearance significantly decreased ( $P < 0.02$ ), and the bioavailability was increased by 154%. On the other hand in humans after a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine 20 mg produced much higher concentrations from 0.25 to 1 h post drug ( $P < 0.01$  at 0.25 and 0.5 h;  $P < 0.001$  at 1 h), the increase in bioavailability was 2000%. The study shows that in the dosages used, piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects.

Planta Med 1998 May;64(4):353-6

Continued on Page 2 of 4

[Back to the Magazine Forum](#)

## ABSTRACTS

Page 2 of 4

Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines.

Curcumin, which is a widely used dietary pigment and spice, has been demonstrated to be an effective inhibitor of tumor promotion in mouse skin carcinogenesis. We report that curcumin induces cell shrinkage, chromatin condensation, and DNA fragmentation, characteristics of apoptosis, in immortalized mouse embryo fibroblast NIH 3T3 erb B2 oncogene-transformed NIH 3T3, mouse sarcoma S180, human colon cancer cell HT-29, human kidney cancer cell 293, and human hepatocellular carcinoma Hep G2 cells, but not in primary culture of mouse embryonic fibroblast C3H 10T1/2, rat embryonic fibroblast, and human foreskin fibroblast cells in a concentration- and time-dependent manner. Many cellular and biochemical effects of curcumin in mouse fibroblast cells have been reported, such as inhibition of protein kinase C (PKC) activity induced by phorbol 12-myristate 13-acetate treatment, inhibition of tyrosine protein kinase activity, and inhibition of arachidonic acid (AA) metabolism. Treatment of NIH 3T3 cells with the PKC inhibitor staurosporine, the tyrosine kinase inhibitor herbimycin A, and the AA metabolism inhibitor quinacrine induces apoptotic cell death. These results suggest that, in some immortalized and transformed cells, blocking the cellular signal transduction might trigger the induction of apoptosis.

Nutr Cancer 1996;26(1):111-20

Inhibitory effects of curcumin on tumorigenesis in mice.

Curcumin (diferuloylmethane), the naturally occurring yellow pigment in turmeric and curry, is isolated from the rhizomes of the plant *Curcuma longa* Linn. Curcumin inhibits tumorigenesis during both initiation and promotion (post-initiation) periods in several experimental animal models. Topical application of curcumin inhibits benzo[a]pyrene (B[a]P)-mediated formation of DNA-B[a]P adducts in the epidermis. It also reduces 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal DNA synthesis, ornithine decarboxylase (ODC) mRNA level, ODC activity, hyperplasia, formation of c-Fos, and c-Jun proteins, hydrogen peroxide, and the oxidized DNA base 5-hydroxymethyl-2'-deoxyuridine (HmdU). Topical application of curcumin inhibits TPA-induced increases in the percent of epidermal cells in synthetic (S) phase of the cell cycle. Curcumin is a strong inhibitor of arachidonic acid-induced edema of mouse ears in vivo and epidermal cyclooxygenase and lipoxygenase activities in vitro. Commercial curcumin isolated from the rhizome of the plant *Curcuma longa* Linn contains 3 major curcuminoids (approximately 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin). Commercial curcumin, pure curcumin, and demethoxycurcumin are about equipotent as inhibitors of TPA-induced tumor promotion in mouse skin, whereas bisdemethoxycurcumin is somewhat less active. Topical application of curcumin inhibits tumor initiation by B[a]P and tumor promotion by TPA in mouse skin. Dietary curcumin (commercial grade) inhibits B[a]P-induced forestomach carcinogenesis, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)-induced duodenal carcinogenesis, and azoxymethane (AOM)-induced colon carcinogenesis. Dietary curcumin had little or no effect on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis and 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast carcinogenesis in mice. Poor circulating bioavailability of curcumin may account for the lack of lung and breast carcinogenesis inhibition.

J Cell Biochem Suppl 1997;27:26-34

Curcumin is an in vivo inhibitor of angiogenesis.

**BACKGROUND:** Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In animal models, curcumin and its derivatives have been shown to inhibit the progression of chemically induced colon and skin cancers. The genetic changes in carcinogenesis in these organs involve different genes, but curcumin is effective in preventing carcinogenesis in both organs. A possible explanation for this finding is that curcumin may inhibit angiogenesis. **MATERIALS AND METHODS:** Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin and its derivatives were subsequently tested for their ability to inhibit bFGF-induced corneal neovascularization in the mouse cornea. Finally, curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production. **RESULTS:** Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin and its derivatives demonstrated significant inhibition of bFGF-mediated corneal neovascularization in the mouse. Curcumin had no effect on phorbol ester-stimulated VEGF production. **CONCLUSIONS:** These results indicate that curcumin has direct antiangiogenic activity in vitro and in vivo. The activity of curcumin in inhibiting carcinogenesis in diverse organs such as the skin and colon may be mediated in part through angiogenesis inhibition.

Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress.

Curcumin, a widely used spice and coloring agent in food, has been shown to possess potent antioxidant, antitumor promoting and anti-inflammatory properties in vitro and in vivo. The mechanism(s) of such pleiotropic action by this yellow pigment is unknown; whether induction of distinct antioxidant genes contributes to the beneficial activities mediated by curcumin remains to be investigated. In the present study we examined the effect of curcumin on endothelial heme oxygenase-1 (HO-1 or HSP32), an inducible stress protein that degrades heme to the vasoactive molecule carbon monoxide and the antioxidant biliverdin. Exposure of bovine aortic endothelial cells to curcumin (5-15 microM) resulted in both a concentration- and time-dependent increase in HO-1 mRNA, protein expression and heme oxygenase activity. Hypoxia (18 h) also caused a significant ( $P < 0.05$ ) increase in heme oxygenase activity which was markedly potentiated by the presence of low concentrations of curcumin (5 microM). Interestingly, prolonged incubation (18 h) with curcumin in normoxic or hypoxic conditions resulted in enhanced cellular resistance to oxidative damage; this cytoprotective effect was considerably attenuated by tin protoporphyrin IX, an inhibitor of heme oxygenase activity. In contrast, exposure of cells to curcumin for a period of time insufficient to up-regulate HO-1 (1.5 h) did not prevent oxidant-mediated injury. These data indicate that curcumin is a potent inducer of HO-1 in vascular endothelial cells and that increased heme oxygenase activity is an important component in curcumin-mediated cytoprotection against oxidative stress.

Free Radic Biol Med 2000 Apr 15;28(8):1303-12

Mechanisms of cancer chemoprevention by curcumin.

Curcumin is a major component of the *Curcuma* species, which is commonly used as a yellow coloring and flavoring agent in foods. Curcumin has shown anti-carcinogenic activity in animals as indicated by its ability to block colon tumor initiation by azoxymethane and skin tumor promotion induced by phorbol ester TPA. Recently, curcumin has been considered by oncologists as a potential third generation cancer chemopreventive agent, and clinical trials using it have been carried out in several laboratories. Curcumin possesses anti-inflammatory activity and is a potent inhibitor of reactive oxygen-generating enzymes, such as lipoxygenase/cyclooxygenase, xanthine dehydrogenase/oxidase and inducible nitric oxide synthase. Curcumin is also a potent inhibitor of protein kinase C, EGF-receptor tyrosine kinase and I $\kappa$ B kinase. In addition, curcumin inhibits the activation of NF $\kappa$ B and the expression of c-jun, c-fos, c-myc and iNOS. It is proposed that curcumin may suppress tumor promotion by blocking signal transduction pathways in the target cells. Curcumin was first biotransformed to dihydrocurcumin and tetrahydrocurcumin, and these compounds were subsequently conjugated into monoglucuronide conjugates. The experimental results suggest that curcumin-glucuronide, dihydrocurcumin-glucuronide, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin are major metabolites of curcumin in mice.

Proc Natl Sci Counc Repub China B 2001 Apr;25(2):59-66

Neuroprotective role of curcumin from *curcuma longa* on ethanol-induced brain damage.

In the present study, curcumin from *Curcuma longa* was screened for neuroprotective activity using ethanol as a model of brain injury. Oral administration of curcumin to rats caused a significant reversal in lipid peroxidation, brain lipids and produced enhancement of glutathione, a non-enzymic antioxidant in ethanol intoxicated rats, revealing that the antioxidative and hypolipidaemic action of curcumin is responsible for its protective role against ethanol induced brain injury.

Phytother Res 1999 Nov;13(7):571-4

The inhibitory effect of curcumin, genistein, quercetin and cisplatin on the growth of oral cancer cells in vitro.

Epidemiological evidence indicates that plant derived flavonoids and other phenolic antioxidants protect against heart disease and cancer. In the current investigation utilizing human oral squamous carcinoma cell line (SCC-25), we have evaluated the potency of three different plant phenolics, viz., curcumin, genistein and quercetin in comparison with that of cisplatin on growth and proliferation of SCC-25. Test agents were dissolved in DMSO and incubated in triplicates in 25 cm<sup>2</sup> flasks in DMEM- HAM's F-12 (50:50) supplemented with 10% calf serum and antibiotics in an atmosphere 5% CO<sub>2</sub> in air for 72 hours cell growth was determined by counting the number of cells in a hemocytometer. Cell proliferation was determined by measuring DNA synthesis by the incorporation of [3H]-thymidine in nuclear DNA. Cisplatin (0.1, 1.0, 10.0 microM) and curcumin (0.1, 1.0, 10.0 microM) induced significant dose-dependent inhibition in both cell growth as well as cell proliferation. Genistein and quercetin (1.0, 10.0, 100.0 microM) had biphasic effect, depending on their concentrations, on cell growth as well as cell proliferation. Based on these findings, it is concluded that curcumin is considerably more potent than genistein and quercetin, but cisplatin is five fold more potent than curcumin in inhibition of growth and DNA synthesis in SCC-25.

Anticancer Res 2000 May-Jun;20(3A):1733-8

Effect of curcumin on the apoptosis of rodent and human nonproliferating and proliferating lymphoid cells.

Curcumin, a major active component of turmeric, has been recognized as an anticarcinogenic agent because of its propensity to induce apoptosis in vivo and in vitro. Previously, we showed that curcumin protects cells against oligonucleosomal DNA fragmentation and induces a novel apoptosis-like pathway in Jurkat cells (Piwocka et al. *Exp Cell Res* 249, 299-307, 1999). Here, we have studied the ability of curcumin to induce cell death in other human and rodent transformed as well as normal cells. Normal cells were quiescent or stimulated to proliferate. We showed that 50 microM pigment is able to induce cell death in all studied cells, but cell death symptoms varied for different cells. All the cells died as assessed by the TdT-mediated UTP nick end labeling method or trypan blue exclusion test. No one type of cells showed oligonucleosomal DNA fragmentation (DNA "ladder") due to curcumin action, although in HL-60 cells, we were able to observe sub-G1 formation and caspase-3 activation. Together, these data showed that curcumin induces cell death in all tested cells that can be classified as apoptosis-like, and only in HL-60 cells can it be recognized as classical apoptosis.

*Nutr Cancer* 2000;38(1):131-8

Suppressive effect of curcumin on trichloroethylene-induced oxidative stress.

In vivo antioxidative effects of curcumin were investigated using a trichloroethylene (TCE)-induced oxidative stress model in mouse liver. Increases in the contents of peroxisome and thiobarbituric acid reactive substances (TBARS) and decreases in GSH content of mouse liver by the TCE administration were suppressed by the pre-administration of curcumin. TCE-induced changes in the activities of antioxidative enzyme, such as Cu/Zn-SOD, catalase, glutathione reductase, glutathione peroxidase (GPx) and D-glucose-6-phosphate dehydrogenase (G6PD), were also diminished by curcumin. These results indicate that curcumin significantly suppresses TCE-induced oxidative stress by scavenging various free radicals, and its antioxidative activity seems to be derived from its suppressive effects on the increase in peroxisome content and decrease in GPx and G6PD activities.

*J Nutr Sci Vitaminol (Tokyo)* 2000 Oct;46(5):230-4

Continued on Page 3 of 4

[Back to the Magazine Forum](#)

## ABSTRACTS

## Metformin

Prevention of type 2 diabetes: role of metformin.

Metformin lowers moderate (nondiabetic) fasting hyperglycaemia in individuals at risk for type 2 diabetes without causing hypoglycaemia. In addition, it has demonstrated favourable action on several cardiovascular risk factors that are often present in these individuals: it favours the maintenance of diet-induced weight loss and its associated improvement in fibrinolysis; and it lowers plasma concentrations of fasting insulin, total and low density lipoprotein-cholesterol, free fatty acids, and of two markers of endothelial damage-tissue plasminogen activator antigen and von Willebrand factor. These effects together with the good tolerability profile of the drug position metformin as a first-line agent for the prevention of type 2 diabetes.

Drugs 1999;58 Suppl 1:71-3; discussion 75-82

The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group.

**OBJECTIVE:** The constellation of anomalies associated with insulin resistance is a plausible additional cause of ischemic cardiovascular disease and of NIDDM. To test this hypothesis in a primary prevention trial, the effects of metformin as a potential candidate for intervention in the insulin resistance syndrome (IRS) were evaluated in 324 middle-aged subjects with upper-body obesity. **RESEARCH DESIGN AND METHODS:** Trial patients were selected on the basis of a high waist-to-hip ratio. They were randomly allocated to receive either metformin or placebo, following a double-blind procedure. After 1 year of treatment, the main clinical and biological parameters of the IRS were assessed and their evolution compared between treatment groups. **RESULTS:** Compared with placebo, metformin induced a significant weight loss, a better maintenance of fasting blood glucose, total and LDL cholesterol levels, and a greater decrease of fasting plasma insulin concentration. Moreover, tissue-type plasminogen activator antigen, a marker of fibrinolytic impairment, showed a significant decrease under metformin. By contrast, metformin treatment had no significant effect on blood pressure or serum triglyceride and HDL cholesterol concentrations. The main side effect of metformin was diarrhea. **CONCLUSIONS:** The BIGuanides and Prevention of Risks in Obesity (BIGPRO1) results suggest that metformin would be a suitable candidate for long-term intervention for the prevention of diabetes but that its use in a trial of primary prevention of cardiovascular diseases requires either a reevaluation of its properties toward the most potentially atherogenic anomalies of the IRS or a better definition of the target population.

Diabetes Care 1996 Sep;19(9):920-6

Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome.

In 43 amenorrheic women with polycystic ovary syndrome (PCOS), 31 (74%) with fasting hyperinsulinemia ( $>$  or  $=20$  microU/mL), our aim was to determine whether metformin (Bristol-Myers Squibb, Princeton, NJ), which reduces hyperinsulinemia, would reverse the endocrinopathy of PCOS, allowing resumption of regular normal menses. A second aim was to assess the effects of weight loss versus other metformin-induced effects on ovarian function, and to determine if there were different responses to metformin between those who lost weight and those who did not. A third aim was to assess associations between PCOS, 4G/5G polymorphism in the promoter sequence of the plasminogen activator inhibitor-1 gene (PAI-1 gene), and PAI activity (PAI-Fx). Of the 43 women, 40 (93%) had normal fasting blood glucose and 37 had normal hemoglobin A1C (HgA1C); only three (7%) had type 2 diabetes mellitus. Metformin (1.5 to 2.25 g/d) was given for  $6.1 \pm 5.1$  months (range, 1.5 to 24), to 16 patients for less than 3 months, to 12 for 3 to 6 months, and to 15 for at least 6 months. On metformin, 39 of 43 patients (91%) resumed normal menses. The percentage of women resuming normal menses did not differ among treatment duration groups ( $P < .1$ ) or among dose groups ( $P > .1$ ). The body mass index (BMI) decreased from  $36.4 \pm 7$  Kg/m<sup>2</sup> at study entry to  $35.1 \pm 6.7$  on metformin ( $P = .0008$ ). Of 43 patients, 28 (67%) lost weight (1 to 69 pounds), with nine (21%) losing at least 12 pounds. On metformin, the median fasting serum insulin decreased from 26 microU/mL to 22 ( $P = .019$ ), testosterone decreased from 61 ng/dL to 47 ( $P = .003$ ), and estradiol increased from 41 pg/mL to 71 ( $P = .0001$ ). Metformin-induced improvements in ovarian function were independent of weight loss (testosterone decrease,  $P < .002$ ; estradiol increase,  $P < .0004$ ). The change in response variables on metformin did not differ ( $P > .05$ ) between those who lost weight and those who did not, excepting Lp(a), which increased 4 mg/dL in those who lost weight and decreased 9 mg/dL in those who did not ( $P = .003$ ). The change in response variables on metformin did not differ among the five quintiles of weight loss, excepting fasting glucose ( $P < .05$ ), which increased 6 mg/dL in those who lost the least weight on metformin versus those in the 60th to 80th percentile for weight loss, in whom glucose decreased 33 mg/dL. Although the

pretreatment fasting serum insulin was not significantly correlated with testosterone ( $r=.24$ ,  $P=.13$ ) or androstenedione ( $r=.27$ ,  $P=.09$ ), on metformin, the change in insulin correlated positively with the change in testosterone ( $r=.35$ ,  $P=.047$ ) and with the change in androstenedione ( $r=.48$ ,  $P=.01$ ). Patients were more likely than normal controls (83% v 64%,  $P=.016$ ) to be heterozygous or homozygous for 4G polymorphism of the PAI-1 gene and were also more likely to have high PAI-Fx ( $>$  or  $=22$  U/mL, 28% v 3%,  $\chi^2(2)=10.1$ ,  $P=.001$ ). Metformin reduces the endocrinopathy of PCOS, allowing resumption of normal menses in most (91%) previously amenorrheic women with PCOS.

Metabolism 1999 Apr;48(4):511-9

Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy.

Using polycystic ovary syndrome (PCOS) as a model of insulin resistance and hyperandrogenism, our specific aim was to assess the effect of metformin on lipoproteins, sex hormones, gonadotropins, and blood pressure in 26 women with PCOS who were studied at baseline, received metformin 1.5 g/d for 8 weeks, and were then restudied. None of the women had normal menstrual cycles, 100% had multiple subcapsular follicles by pelvic ultrasound, 90% were hirsute, and 85% had high free testosterone. Comparing post-metformin versus baseline levels, the Quetelet Index (QI) decreased 1.5% ( $P = .04$ ) and the waist to hip ratio (WHR) decreased 2.8% ( $P = .003$ ). After covariance adjusting for changes in the QI and WHR, on metformin the area under the insulin curve (IA) during oral glucose tolerance testing decreased 35% ( $P = .04$ ), and the insulin area to glucose area ratio decreased 31% ( $P = .03$ ). On metformin, covariance-adjusted systolic blood pressure (SBP) decreased ( $P = .04$ ) and apo A-1 increased ( $P = .05$ ). On metformin, with improvement in insulin sensitivity, there were sharp reductions in covariance-adjusted luteinizing hormone ([LH]  $P = .0007$ ), total testosterone ([T]  $P = .0004$ ), free T ( $P = .0001$ ), androstenedione ( $P = .002$ ), dehydroepiandrosterone sulfate ([DHEAS]  $P = .006$ ), and the free androgen index ([FAI]  $P = .0005$ ), with increments in follicle-stimulating hormone ([FSH]  $P = .04$ ) and sex hormone-binding globulin ([SHBG]  $P = .04$ ).

Metabolism 1994 May;43(5):647-54

Alzheimer's disease

Causative genes in Alzheimer's disease.

Recently, some Alzheimer-associated genes have been found: amyloid precursor protein (APP), apolipoprotein E (apoE), presenilin 1 (PS-1) and presenilin 2 (PS-2). First, we examined mutations of APP, PS-1, and PS-2 genes in familial Alzheimer's disease (FAD) (7 cases) found in San-in district by single-strand conformation polymorphism and sequence analysis. These seven cases with FAD did not show any mutations of APP, PS-1, and PS-2 genes. Other susceptibility genes of FAD still remain to be not identified. Many reports have established that apoE genotype distribution for the epsilon 4 allele is a susceptibility factor for the earlier onset and more rapid progression of Alzheimer's disease (AD). However, the cause of sporadic AD (SAD) has not been elucidated fully. Other genetic factors may be associated with development of SAD. Second, we investigated the association between polymorphisms of the estrogen receptor (ER) alpha gene and SAD. The frequencies of P and X alleles in SAD were significantly higher than those in the control group ( $p < 0.05$ ). Polymorphisms of the ER alpha gene may be a genetic risk factor for SAD. The apoE genotype is a genetic factor closely related SAD, but it is not full by appreciated how apoE has an effect on developing AD. There are few reports on the quantitative change of apoE, namely the expression of apoE mRNA. Third, ApoE mRNA level in the brains of patients with Alzheimer's disease (27 cases) and Down's syndrome (11 cases) was determined by reverse transcriptase-polymerase chain reaction (RT-PCR). ApoE mRNA level in the DS as well as AD was significantly higher than that in control group ( $p < 0.05$ ,  $p < 0.05$ , respectively). High levels of apoE mRNA in AD and DS may play an important role in the development of Alzheimer pathology.

Nippon Ronen Igakkai Zasshi 2001 Mar;38(2):117-20

Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease.

The major known genetic risk for Alzheimer's disease (AD), apolipoprotein E-4 (APOE-4), is associated with lowered parietal, temporal, and posterior cingulate cerebral glucose metabolism in patients with a clinical diagnosis of AD. To determine cognitive and metabolic decline patterns according to genetic risk, we investigated cerebral metabolic rates by using positron emission tomography in middle-aged and older nondemented persons with normal memory performance. A single copy of the APOE-4 allele was associated with lowered inferior parietal, lateral temporal, and posterior cingulate metabolism, which predicted cognitive decline after 2 years of longitudinal follow-up. For the 20 nondemented subjects followed longitudinally, memory performance scores did not decline significantly, but cortical metabolic rates did. In APOE-4 carriers, a 4% left posterior cingulate metabolic decline was observed, and inferior parietal and lateral temporal regions demonstrated the greatest magnitude (5%) of metabolic decline after 2 years. These results indicate that the combination of cerebral metabolic rates and genetic risk factors provides a means for preclinical AD detection that will assist in response monitoring during experimental treatments.

Beta-amyloid therapies in Alzheimer's disease.

Neurons in the brain produce beta-amyloid fragments from a larger precursor molecule termed the amyloid precursor protein (APP). When released from the cell, these protein fragments may accumulate in extracellular amyloid plaques and consequently hasten the onset and progression of Alzheimer's disease (AD). Amyloid-beta fragments are generated through the action of specific proteases within the cell. Two of these enzymes, beta- and gamma-secretase, are particularly important in the formation of beta-amyloid as they cleave within the APP protein to give rise to the N-terminal and C-terminal ends of the beta-amyloid fragment, respectively. Consequently, many researchers are investigating therapeutic approaches that inhibit either beta- or gamma-secretase activity, with the ultimate goal of limiting amyloid-beta production. An alternative AD therapeutic approach that is being investigated is to employ anti-beta-amyloid antibodies to dissolve plaques that have already formed. Both of these approaches focus on the possibility that accrual of amyloid-beta leads to neuronal degeneration and cognitive impairment characterized by AD and test the hypothesis that limiting amyloid-beta deposition in neuritic plaques may be an effective treatment for AD.

Expert Opin Investig Drugs 2001 Apr;10(4):593-605

Continued on Page 4 of 4

[Back to the Magazine Forum](#)

## ABSTRACTS

Page 4 of 4

Nicastrin modulates presenilin-mediated notch/glp-1 signal transduction and betaAPP processing.

Nicastrin, a transmembrane glycoprotein, forms high molecular weight complexes with presenilin 1 and presenilin 2. Suppression of nicastrin expression in *Caenorhabditis elegans* embryos induces a subset of notch/glp-1 phenotypes similar to those induced by simultaneous null mutations in both presenilin homologues of *C. elegans* (*sel-12* and *hop-1*). Nicastrin also binds carboxy-terminal derivatives of beta-amyloid precursor protein (betaAPP), and modulates the production of the amyloid beta-peptide (A beta) from these derivatives. Missense mutations in a conserved hydrophilic domain of nicastrin increase A beta42 and A beta40 peptide secretion. Deletions in this domain inhibit A beta production. Nicastrin and presenilins are therefore likely to be functional components of a multimeric complex necessary for the intramembranous proteolysis of proteins such as Notch/GLP-1 and betaAPP.

Nature 2000 Sep 7;407(6800):48-54

A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging.

Previous reports have suggested that estrogen replacement therapy (ERT) in women may exert a protective effect on their risk of developing Alzheimer's disease (AD). We investigated this relationship in the Baltimore Longitudinal Study of Aging (BLSA), a prospective multidisciplinary study of normal aging conducted by the National Institute on Aging. The sample consisted of 472 post- or perimenopausal women followed for up to 16 years in the BLSA. We documented ERT prospectively at each BLSA visit, and we categorized women who had used oral or transdermal estrogens at anytime as ERT users. We used Cox proportional hazards models with time-dependent covariates to estimate the relative risk of developing AD after ERT as compared with women who had not used estrogen replacement. Approximately 45% of the women in the cohort had used ERT, and we diagnosed 34 incident cases of AD (NINCDS/ADRDA criteria) during follow-up, including nine estrogen users. After adjusting for education, the relative risk for AD in ERT users as compared with nonusers was 0.46 (95% CI, 0.209-0.997), indicating a reduced risk of AD for women who had reported the use of estrogen. Our data did not show an effect for duration of ERT usage. Our finding offers additional support for a protective influence of estrogen in AD. Randomized clinical trials are necessary to confirm this association, which could have significant public health impact.

Neurology 1997 Jun;48(6):1517-21

Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline.

**CONTEXT:** Alzheimer disease (AD) is characterized neuropathologically by the presence of amyloid beta-peptide (Abeta)-containing plaques and neurofibrillary tangles composed of abnormal tau protein. Considerable controversy exists as to whether the extent of accumulation of Abeta correlates with dementia and whether Abeta alterations precede or follow changes in tau. **OBJECTIVES:** To determine whether accumulation of Abeta correlates with the earliest signs of cognitive deterioration and to define the relationship between Abeta accumulation and early tau changes. **DESIGN, SETTING, AND PATIENTS:** Postmortem cross-sectional study of 79 nursing home residents with Clinical Dementia Rating (CDR) scale scores of 0.0 to 5.0 who died between 1986 and 1997, comparing the levels of Abeta variants in the cortices of the subjects with no (CDR score, 0.0 [n = 16]), questionable (CDR score, 0.5 [n = 11]), mild (CDR score, 1.0 [n = 22]), moderate (CDR score, 2.0 [n = 15]), or severe (CDR score, 4.0 or 5.0 [n = 15]) dementia. **MAIN OUTCOME MEASURES:** Levels of total Abeta peptides with intact or truncated amino termini and ending in either amino acid 40 (A(beta)x-40) or 42 (A(beta)x-42) in 5 neocortical brain regions as well as levels of tau protein undergoing early conformational changes in frontal cortex, as a function of CDR score. **RESULTS:** The levels of both A(beta)x-40 and A(beta)x-42 were elevated even in cases classified as having questionable dementia (CDR score = 0.5), and increases of both peptides correlated with progression of dementia. Levels of the more fibril-prone A(beta)x-42 peptide were higher than those of A(beta)x-40 in nondemented cases and remained higher throughout progression of disease in all regions examined. Finally, increases in A(beta)x-40 and A(beta)x-42 precede significant tau pathology at least in the frontal cortex, an area chosen for examination because of the absence of neuritic changes in the absence of disease. **CONCLUSIONS:** In this study, levels of total A(beta)x-40 and A(beta)x-42 were elevated early in dementia and levels of both peptides were strongly correlated with cognitive decline. Of particular interest, in the frontal cortex, Abeta was elevated before the occurrence of significant tau pathology. These results support an important role for Abeta in mediating initial pathogenic events in AD dementia and suggest that treatment strategies targeting the formation, accumulation, or cytotoxic effects of Abeta should be pursued.

TGF-beta1 promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice.

Abnormal accumulation of the amyloid-beta peptide (Abeta) in the brain appears crucial to pathogenesis in all forms of Alzheimer disease (AD), but the underlying mechanisms in the sporadic forms of AD remain unknown. Transforming growth factor beta1 (TGF-beta1), a key regulator of the brain's responses to injury and inflammation, has been implicated in Abeta deposition in vivo. Here we demonstrate that a modest increase in astroglial TGF-beta1 production in aged transgenic mice expressing the human beta-amyloid precursor protein (hAPP) results in a three-fold reduction in the number of parenchymal amyloid plaques, a 50% reduction in the overall Abeta load in the hippocampus and neocortex, and a decrease in the number of dystrophic neurites. In mice expressing hAPP and TGF-beta1, Abeta accumulated substantially in cerebral blood vessels, but not in parenchymal plaques. In human cases of AD, Abeta immunoreactivity associated with parenchymal plaques was inversely correlated with Abeta in blood vessels and cortical TGF-beta1 mRNA levels. The reduction of parenchymal plaques in hAPP/TGF-beta1 mice was associated with a strong activation of microglia and an increase in inflammatory mediators. Recombinant TGF-beta1 stimulated Abeta clearance in microglial cell cultures. These results demonstrate that TGF-beta1 is an important modifier of amyloid deposition in vivo and indicate that TGF-beta1 might promote microglial processes that inhibit the accumulation of Abeta in the brain parenchyma.

Nat Med 2001 May;7(5):612-8

Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.

Amyloid-beta peptide (Abeta) seems to have a central role in the neuropathology of Alzheimer's disease (AD). Familial forms of the disease have been linked to mutations in the amyloid precursor protein (APP) and the presenilin genes. Disease-linked mutations in these genes result in increased production of the 42-amino-acid form of the peptide (Abeta42), which is the predominant form found in the amyloid plaques of Alzheimer's disease. The PDAPP transgenic mouse, which overexpresses mutant human APP (in which the amino acid at position 717 is phenylalanine instead of the normal valine), progressively develops many of the neuropathological hallmarks of Alzheimer's disease in an age- and brain-region-dependent manner. In the present study, transgenic animals were immunized with Abeta42, either before the onset of AD-type neuropathologies (at 6 weeks of age) or at an older age (11 months), when amyloid-beta deposition and several of the subsequent neuropathological changes were well established. We report that immunization of the young animals essentially prevented the development of beta-amyloid-plaque formation, neuritic dystrophy and astrogliosis. Treatment of the older animals also markedly reduced the extent and progression of these AD-like neuropathologies. Our results raise the possibility that immunization with amyloid-beta may be effective in preventing and treating Alzheimer's disease.

Nature 1999 Jul 8;400(6740):173-7

A beta peptide immunization reduces behavioral impairment and plaques in a model of Alzheimer's disease.

Much evidence indicates that abnormal processing and extra cellular deposition of amyloid-beta peptide (A beta), a proteolytic derivative of the beta-amyloid precursor protein (betaAPP), is central to the pathogenesis of Alzheimer's disease (reviewed in ref. 1). In the PDAPP transgenic mouse model of Alzheimer's disease, immunization with A beta causes a marked reduction in burden of the brain amyloid. Evidence that A beta immunization also reduces cognitive dysfunction in murine models of Alzheimer's disease would support the hypothesis that abnormal A beta processing is essential to the pathogenesis of Alzheimer's disease, and would encourage the development of other strategies directed at the 'amyloid cascade'. Here we show that A beta immunization reduces both deposition of cerebral fibrillar A beta and cognitive dysfunction in the TgCRND8 murine model of Alzheimer's disease without, however, altering total levels of A beta in the brain. This implies that either a approximately 50% reduction in dense-cored A beta plaques is sufficient to affect cognition, or that vaccination may modulate the activity/abundance of a small subpopulation of especially toxic A beta species.

Nature 2000 Dec 21-28;408(6815):979-82

[Back to the Magazine Forum](#)

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