Why Curcumin Is The World's Most Used Herb

A Five Hour CEU/PDA Course

By Dr. Harvey Kaltsas, AP (FL), D.O.M., Dipl. Ac. (NCCAOM)

Introduction - Why curcumin?

Wikipedia reports that Francis Galton, a 19 th century English statistician, *"was a keen observer. In 1906, visiting a livestock fair, he stumbled upon an intriguing contest. An ox was on display, and the villagers were invited to guess the animal's weight after it was slaughtered and dressed. Nearly 800 participated, and Galton was able to study their individual entries after the event. Galton stated that the middlemost estimate expresses the* vox populi*, every other estimate being condemned as too low or too high by a majority of the voters, and reported this value (the median, in terminology he himself had introduced, but chose not to use on this occasion) as 1,207 pounds. To his surprise, this was within 0.8% of the weight measured by the judges. Soon afterwards, in response to an enquiry, he reported the mean of the guesses as 1,197 pounds, but did not comment on its improved accuracy. Recent archival research has found some slips in transmitting Galton's calculations to the original article in* ***Nature****: the median was actually 1,208 pounds, and the dressed weight of the ox 1,197 pounds, so the mean estimate had zero error."*

The New Yorker essayist James Surowiecki retells Galton's tale in his book, **The Wisdom of Crowds**, to support his hypotheses that

> *"The averages of multiple guesses is usually better than the best individual guess,"*

and that there is indeed wisdom in crowds. The human race is just such a crowd, and it too makes guesses as to what herbs are useful to ingest for its own health. Given the wisdom of crowds, curcumin leads the pack.

Turmeric/curcumin is a key ingredient in the making of curry, which is the favororite food seasoning on the Indian sub-continent. That alone makes curcumin among the world's most popular herbs. Then consider for a moment the following copyrighted report:

Turmeric/curcumin supplement sales grow 26%, total herbal supplements sales top $6 billion for the first time

03-Sep-2014 By Stephen DANIELLS

"Sales of herbal dietary supplements with turmeric/curcumin as the primary ingredient grew by 26.2% in 2013 to take the top spot in the natural channel, says a new report published in the current issue of the American Botanical Council's HerbalGram."

HTTPS://WWW.NUTRAINGREDIENTS-USA.COM/ARTICLE/2014/09/03/TURMERIC-CURCUMIN-SUPPLEMENT-SALES-GROW-26-TOTAL-HERBAL-SUPPLEMENTS-SALES-TOP-6-BILLION-FOR-THE-FIRST-TIME

Also, consider this analysis based on 2016 data which shows that demand for curcumin has grown even more and is projected to rise much further:

The global curcumin market size was estimated at USD 44,246.3 thousand in 2016 and is projected to register a CAGR of 13.3% over the forecast period. Demand is projected to be driven by increasing use in cosmetic, food, and pharmaceutical industries. It exhibits advantageous anti-inflammatory and anti-oxidation properties, emerging as a go-to pain relief option for patients with arthritis and osteoarthritis. Increasing awareness among consumers, especially in developed economies such as U.S., Denmark, and Germany, is further fueling demand for curcumin over the forecast period. It is an active ingredient of turmeric extracted from the Curcuma longa plant. Turmeric is a widely used ingredient in food and medical products on account of its therapeutic qualities, particularly in the Asian subcontinent. Demand for ayurvedic medicinal formulations has been gaining momentum in a number of developed countries as well, and this trend is anticipated to significantly benefit the market over the forecast period.

What makes curcumin so popular? Simply put, it is good for your health, and the Chinese and Indians have known this for thousands of years. It is a staple of both Traditional Chinese Medicine (TCM) and Ayuveda, and this course will focus upon its role, sometimes miraculous, in TCM and modern health care.

…….

This course is divided into four parts, followed by an exam. Part four is optional and will not be tested on the exam.

Part One - Traditional Chinese Medical (TCM) Qualities of Curcumin

Part Two - Preparation Methods and Bio-Availability

Part 3 - Peer-Reviewed Clinical Studies on the Efficacy of Curcumin

Part Four – Supplemental Research Studies on Curcumin's Health Benefits. Optional Reading, Not Required. Read them for your pleasure…

Part One - Traditional Chinese Medical (TCM) Qualities of Curcumin

Curcumin comes from both the rhizome (Jiang Huang) and the root (Yu Jin) of the Curcuma Longa plant, commonly known as turmeric, from the Zingiberacea or ginger family. It's properties are as follows:

Jiang Huang:
Taste: Pungent and bitter
Property: Warm
Therapeutic channel: Spleen and liver
Function: To regulate circulation of blood and qi with qi and blood stasis
To remove stagnation
To relieve pain by clearing the channels and collaterals
To reduce swelling from accumulation of toxic heat with qi and blood stasis
Medical Uses:
1. Pain in the abdomen and chest, dysmennorhea
2. Traumatic injuries
3. Arthritis - Bi zheng syndrome, especially of the upper limbs
4. Hypochondriac pain from hepatitis
5. Sores and lesions caused by toxic heat buildup

Pharmacological Effects:
1. Reduces both cholesterol and triglyceride levels
2. Inhibits aggregation of platelets
3. Cholagogic – It increases bile production and excretion
4. Abortifacient – at levels of 10 gm/kg by stimulating and contracting the uterus

Contraindications:
For patients with no qi and blood stagnation or when pregnant
For patients taking anticoagulant or antiplatelet medications

Chemical composition:
Essential oil containing borneol, cineole phellandrene, sabinene, turmerone, and zingerene; arabinose, arturmerone, bisdemethoxycurcumin, caryophyllene, curcumin, curcumoids, demethoxyucurcumin, fatty oil, fructose, glucose, and starch

Dosage: 3 to 9 grams, depending on patient's body weight. 20 mg/kg for tumors

Yu Jin:
Taste: Pungent and bitter
Property: Cold
Therapeutic channel: Heart, lung, liver and gall bladder
Function:
To relieve pain by removing blood and qi stasis
To regulate circulation of qi and disperse stagnation
To clear pathogenic heat from the pericardium, cool the blood, calm shen
To increase bile production and excretion, reduce jaundice

Medical Uses:
1. Pain in the abdomen, chest, or intercostals; amennorhea or dysmennorhea;
2. Tumors
3. Angina, heart disease
4. Jaundice from hepatitis
5. convulsions, epilepsy, mania with delirium from phlegm in the heart

Pharmacological Effects:
1. Protects the liver, reduces SGOT and SGPT, stimulates the immune system
2. Reduces cholesterol and triglycerides
3. Cholagogic – It increases bile production and excretion
4. Lowers pH in the duodenum and stomach, increases stomach acid,

Contraindications:
For patients with no qi and blood stagnation or when pregnant. Not for patients with bleeding and/or qi deficiency. Not for patients taking anticoagulant medications such as Coumadin, enoxaparin, orheparin or or antiplatelets such as aspirin, Persantine, or Plavix

Chemical composition:
Essential oils: d-camphene, d-camphor, l-d-curcumene,l-B-curcume; bisdemethoxycurcumin, carvone, curcumin, demethoxycurcumin, fatty oil, p-tolylmethylcarbinolddifereryloymeethane, Ar-turmerone, starch, and turmerone.

Dosage: 3 to 9 grams, depending on patient's body weight. 20 mg/kg for tumors

Part Two - Preparation Methods and Bio-Availability

April 1, 2019 I presented the following observations about curcumin at the 2nd Annual International Conference of TCM and Acupuncture in Washington, D.C. It was attended by Doctors of Acupuncture and TCM from 15 countries and all 50 United States.

Much of the research presented later in this course confirms how important preparation methods are to achieving bio-availability and maximum clinical efficacy. The key to whether curcumin is remarkably effective is its bio-availability, which is directly a function of the methods used to prepare it, long known to be so important in traditional Chinese herbal medicine. Unfortunately, this has been a major stumbling block to the clinical efficacy of curcumin until very recently.

Walls and Barriers

In *Mending Wall*, Robert Frost once wrote: *"Good fences make good neighbors."*
In the same poem, he also observed: *"Something there is that doesn't love a wall."*

This dichotomy exists in the human body as well. Walls or barriers are important elements of human physiology, needed to keep out unwanted substances, but at times they also prevent the entry of healthy and crucially needed nutrients such as curcumin, which can prevent or cure even the most serious of ailments if adequately absorbed.

When it comes to Curcumin, the walls we are most concerned with are the wall of the intestinal tract and even more so the blood /brain barrier. It is very difficult for the body to absorb curcumin. Indian doctors found that the most they could see absorbed by a patient was **40 nanograms per milliliter of blood.** However, even at that low level, they saw dramatic improvement in 10% of patients with pancreatic cancer. The Indian doctors wished that more curcumin could be absorbed, because they saw it as key to curing pancreatic cancer, which has a very low survival rate.

In 2015, the Japanese Theracumin company developed a more easily absorbable form of curcumin labeled **Theracumin.** It delivers up to 40 nanograms per milliliter of blood.

https://doi.org/10.1016/j.phanu.2015.08.002

But it ONLY delivered 40 nanograms per milliliter of blood, the same level Indian docors thought was promising but still insuffucient to cure pancreatic cancer.
Several of the clinical studies cited in this course were funded in part by the Theracumin Company of Japan, and they used Theracumin in their studies. Even at the increased though still low bio-availability afforded by Theracumin, curcumin nevertheless showed

promising clinical results. Most studies, however, still lamented the limited bio-availability of curcumin, and one study by Verbeck and Kiselak observed that very little commercially available curcumin passed the blood/brain barrier.

Other nutritional companies have mixed curcumin with piperine from black pepper to increase absorption of curcumin. This works, except piperine inhibits the detoxification functions of the liver and makes the curcuminoids, although absorbed, much less effective. Such inhibition is discussed in the following study:

Piperine, a Major Constituent of Black Pepper, Inhibits Human P-glycoprotein and CYP3A4

Rajinder K. Bhardwaj, Hartmut Glaeser, Laurent Becquemont, Ulrich Klotz, Suresh K. Gupta and Martin F. Fromm

Journal of Pharmacology and Experimental Therapeutics August 2002, 302 (2) 645-650; DOI: https://doi.org/10.1124/jpet.102.034728

Blending curcumin with the alkaloid piperene from black pepper does increase absorption by 154%, but at a price. Piperene greatly inhibits the detoxification function of the liver. One National Institutes of Health report concluded as follows: “This study showed that there might have been a considerable damage to the liver with piperine extract. Further research may be required to prove this damage to liver function.”

https://www.ncbi.nlm.nih.gov/pubmed/26205799

Moreover, a study by Verbeck and Kiselak at the University of North Texas found that because piperine acts as a metabolism inhibitor, it actually weakens or prevents the effects of curcumin in the body. The same study, **“Determining Apparent Permeability of Curcumin and Curcumin bound to B-Lactoglobulin using a Parallel Artificial Membrane Permeability Assay (PAMPA),”** found a marked difference between how well the body absorbs unbound curcumin - the type commonly available in the marketplace of supplements – and curcumin bound to B-lactoglobulin - a form available in only very limited commercial supply:

“After consulting with the University of North Texas Molecular Chemistry Department, we determined a more scientific, and accurate, way to measure whether curcumin, or more specifically, our curcumin/protein conjugate, was transporting / assimilating in the body. We ran a Parallel Artificial Membrane Permeability Assay (PAMPA) study on the raw curcumin we use to make our products, and the CPRO conjugate we produce. This method provides an in-vitro model for passive diffusion. This is an important factor in

determining transport through the gastrointestinal tract (GI), penetration of the blood-brain barrier (BBB), as well as transport across cell membranes. This test is commonly used by the DEA in determining drug transport."

Verbeck and Kiselak determined that the amount of curcumoids from curcumin found in the blood after taking curcumin bound to B-lactoglobulin was 1000 nanograms per milliliter of blood – twenty-five times that of the curcumoids bio-available compared to even Theracumin's 40 nanograms per milliliter. That's a whopping increase in bio-availability of 2500%!

Guided by the conclusions of the Dhillon study - **Phase II trial of curcumin in patients with advanced pancreatic cancer –** I treated a patient with a golf ball sized pancreatic cancer tumor who was not responding to chemo. Her oncologists said she had three months to live. My protocol? I had her take 1800 mg. a day of curcumin bound to B-lactoglobulin, the form of curcumin tested in Kiselek and Verbeck's study. It is commercially available from Amazon as CurcuminPro® Complete®. I also recommended Health Concerns'Power Mushrooms (Ganoderma - Reishi), three capsules a day for three months. By that time, the pancreatic tumor had totally dissolved. She is alive and well now, fully three years later.

These results affirmed the hypothesis of the Dhillon study, that with enough absorbed curcuminoids, pancreatic cancers would reduce or disappear. I have since treated skin cancers successfully the same way. Also, the PAMPA studies by Kiselak and Verbeck at the University of North Texas show that while unbound curcumin itself did not significantly cross the gastrointestinal or blood-brain barrier, curcumin bound with B-lactoglubulin passed both barriers at levels significant for clinical efficacy. The implications are profound for treating both Alzheimers and Chronic Traumatic Encephalopathy (CTE) with curcumin bound with B-lactoglubulin. These ailments are much more widespread than pancreatic cancer.

In addition to binding curcumin with B-lactoglubulin, researchers have now found remarkable efficacy by delivering curcumin as **nanoparticles** or as **encapsulated in exosomes**. The implications for stroke prevention and treatment (discussed later in this course in a study entitled **Epigenetic Impact of Curcumin on Stroke Prevention,** are especially profound, since such delivery system cross the blood/brain barrier even more effectively than when curcumin is bound with B-lactoglubulin. However, curcumin as **nanoparticles** or as **encapsulated in exosomes** have not yet come onto the market. For now, curcumin bound with B-lactoglubulin is the best form available.

Part 3 - Peer-Reviewed Clinical Studies on the Efficacy of Curcumin

Let us take a look at abstracts from other peer-reviewed studies on the clinical efficacy of curcumin, starting with heart disease.

Research on Curcumin and Heart Disease

In this section I present excerpts from two studies on the efficacy of curcumin for heart disease, and I highlighted important passages in bold. HK

1. Acta Med Indones. 2008 Oct; 40(4):201-10.
The effect of curcumin on lipid level in patients with acute coronary syndrome.

Alwi I 1 , Santoso T , Suyono S , Sutrisna B , Suyatna FD , Kresno SB , Ernie S.
Author information

Abstract

"AIM: to evaluate the effects of curcumin on total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride in acute coronary syndrome patients.

"METHODS: This study was conducted at Dr. Cipto Mangunkusumo General Hospital (RSUPN-CM), Persahabatan Hospital, MMC Hospital and Medistra Hospital, Jakarta. The study started from 1 May 2005 to 5 May 2006. Study Design was an interventional study which was a randomized double blind controlled trial to evaluate the effects of curcumin administration at escalating doses (low dose 3 times 15 mg/day, moderate dose 3 times 30 mg/day, and high dose 3 times 60 mg/day) on total cholesterol level, LDL cholesterol level, HDL cholesterol level, and triglyceride level in ACS patients…

"…The effects of curcumin on total cholesterol level and LDL cholesterol level: There was a trend that the lower the dose of curcumin, the higher the effect of reduction. For HDL cholesterol level, there was also a trend that the lower the dose of curcumin, the higher the effect of increase in HDL cholesterol level. However, for triglyceride the pattern was not the same, and the group of moderate-dose curcumin showed the minimal effect of increase, followed by the low-dose curcumin and finally the high-dose curcumin that showed the highest effect of increase.

"CONCLUSION: The administration of low-dose curcumin showed a trend of reduction in total cholesterol level and LDL cholesterol level in ACS patients."

2. Effect of curcumin on permeability of coronary artery and expression of related proteins in rat coronary atherosclerosis heart disease model

Xiaolong Li, Yan Lu, Yi Sun, Qi Zhang

Int J Clin Exp Pathol. 2015; 8(6): 7247–7253. Published online 2015 Jun 1.

ABSTRACT

"**Objective**: Our objective is to explore the effect of curcumin on permeability of coronary artery and expression of related proteins in rat coronary atherosclerosis heart disease model.

"Methods: … The rats in the treatment group and model control group received high-fat diet for 12 weeks and intraperitoneal injection of VD_3 to establish rat coronary atherosclerosis heart disease model. After modeling, the rats in the treatment group received gavage of 100 mg/(kg·d) curcimin, and the rats in the model control group and blank control group received gavage of 5 ml/(kg·d) distilled water, the intervention time was 4 weeks.

"Conclusion: Rat coronary atherosclerosis heart disease model can be successfully established by feeding with high-fat diet and intraperitoneal injection of VD_3, the permeability of coronary artery in coronary heart disease rat model is significantly increased, which may be related to up-regulation of MMP-9, CD40L, TNF-α and CRP expression. **Application of curcumin can inhibit expression of MMP-9, CD40L, TNF-α and CRP to improve the permeability of coronary artery.**

3. Curcumin & Osteoarthritis - In this section I present excerpts from one study on the efficacy of curcumin for osteoarthritis and put important passages in bold. HK

J Orthop Sci. 2014 Nov;19(6):933-9. doi: 10.1007/s00776-014-0633-0. Epub 2014 Oct 13.

Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study.

Nakagawa Y[1], Mukai S, Yamada S, Matsuoka M, Tarumi E, Hashimoto T, Tamura C, Imaizumi A, Nishihira J, Nakamura T.

Author information

Abstract

BACKGROUND:

We previously developed a surface-controlled water-dispersible form of curcumin and named it Theracurmin(®) (Theracurmin; Theravalues, Tokyo, Japan). The area under the blood concentration-time curve of Theracurmin in humans was 27-fold higher than that of curcumin powder. We determined the clinical effects of orally administered Theracurmin in patients with knee osteoarthritis during 8 weeks of treatment.

METHODS:

Fifty patients with knee osteoarthritis of Kellgren-Lawrence grade II or III and who were aged more than 40 years were enrolled in this randomized, double-blind, placebo-controlled, prospective clinical study. Placebo or Theracurmin containing 180 mg/day of curcumin was administered orally every day for 8 weeks. To monitor adverse events, blood biochemistry analyses were performed before and after 8 weeks of each intervention. The patients' knee symptoms were evaluated at 0, 2, 4, 6, and 8 weeks by the Japanese Knee Osteoarthritis Measure, the knee pain visual analog scale (VAS), the knee scoring system of the Japanese Orthopedic Association, and the need for nonsteroidal anti-inflammatory drugs.

RESULTS:

At 8 weeks after treatment initiation, **knee pain VAS scores were significantly lower in the Theracurmin group than in the placebo group**, except in the patients with initial VAS scores of 0.15 or less. Theracurmin lowered the celecoxib dependence significantly more than placebo. No major side effects were observed with Theracurmin treatment.

CONCLUSION:

Theracurmin shows modest potential for the treatment of human knee osteoarthritis.

4. Chronic Traumatic Encephalopathy - In this section I present excerpts from a study on the efficacy of curcumin for reducing inflammation such as can affect Chronic Traumatic Encephalopathy, and I have put important passages in bold. HK

High bioavailability curcumin: an anti-inflammatory and neurosupportive bioactive nutrient for neurodegenerative diseases characterized by chronic neuroinflammation.

Ullah F[1], Liang A[1], Rangel A[1], Gyengesi E[1,2], Niedermayer G[3], Münch G[1,2].

Arch Toxicol. 2017 Apr;91(4):1623-1634. doi: 10.1007/s00204-017-1939-4. Epub 2017 Feb 15.

Abstract

“Neuroinflammation is a pathophysiological process present in a number of neurodegenerative disorders, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, stroke, traumatic brain injury including chronic traumatic encephalopathy and other age-related CNS disorders. Although there is still much debate about the initial trigger for some of these neurodegenerative disorders, during the progression of disease, broad range anti-inflammatory drugs including cytokine suppressive anti-inflammatory drugs (CSAIDs) might be promising therapeutic options to limit neuroinflammation and improve the clinical outcome. One of the most promising CSAIDs is curcumin, which modulates the activity of several transcription factors (e.g., STAT, NF-κB, AP-1) and their pro-inflammatory molecular signaling pathways. **However, normal curcumin preparations demonstrate low bioavailability in vivo.** To increase bioavailability, preparations of high bioavailability curcumin have been introduced to achieve therapeutically relevant concentrations in target tissues. This literature review aims to summarize the pharmacokinetic and toxicity profile of different curcumin formulations.”

5. Dysmennorhea and PMS - In this section I present excerpts from two studies on the efficacy of curcumin for treating gynecological disorders, and I have put important passages in bold. I have paraphrased the findings in this report. HK

https://www.sciencedirect.com/science/article/pii/S096522991500059X

Complementary Therapies in Medicine

Volume 23, Issue 3, June 2015, Pages 318-324

Curcumin attenuates severity of premenstrual syndrome symptoms: A randomized, double-blind, placebo-controlled trial

Authors: SamiraKhayat[b] HamedFanaei[cd] MasoomehKheirkhah[ef] Zahra Behboodi Moghadam[b] Amir Kasaeian[gh] ManiJavadimehr[i]

https://doi.org/10.1016/j.ctim.2015.04.001Get rights and content

This article reports that

- Many women experience PMS at their reproductive age.
- Curcumin has a therapeutic effect on the severity of premenstrual syndrome symptoms.
- Curcumin reduced severity of behavioral, mood, and physical symptoms of PMS significantly.

Background

Most women at their reproductive age experience premenstrual syndrome (PMS), a combination of behavioral physical, and psychological changes which interfere with personal relationships and social activities.

Methods

This study was a double-blinded clinical trial. PMS participants were allocated to curcumin (n = 35) and placebo (n = 35) groups. For three successive menstrual cycles ach PMS patient received two capsules a day for a week before menstruation and for three days after their menstruation. They the recorded the severity of their symptoms each day on a questionnaire.

Results

Before intervention there were no differences in the baseline levels of PMS symptoms which did not differ between groups. After three cycles in a row of treatment with curcumin, total PMS severity score reduced from 102.06 ± 39.64 to 42.47 ± 16.37 (mean change: 59.59) and in Placebo, total PMS severity score went from 106.06 ± 44.12 to 91.60 ± 43.56 (mean change: 14.45). Also, there was a significant difference between mean changes (mean difference: 45.14).

Conclusions

Results showed curcumin has a potentially beneficial effect in reducing the severity of symptoms of PMS, probably by modulating neurotransmitters and curcumin's anti-inflammatory effects of curcumin.

.....

6. "How I Fixed My Menstrual Cramps,"

from this website : https://livethewhole.com/cramps-and-curcumin/

In this article the unnamed author refers the reader to the following study, for an understanding of the anti-inflammatory cause of such cramps and the anti-inflammatory effect of curcumin:

Surg Neurol Int. 2010; 1: 80.

Published online 2010 Dec 13. doi: 10.4103/2152-7806.73804

Natural anti-inflammatory agents for pain relief

Joseph C. Maroon, Jeffrey W. Bost,* and Adara Maroon[1]

Abstract

"INTRODUCTION

"…..In most cases, the genesis of pain is inflammatory, regardless of the etiology. With the elucidation of the role of inflammatory cytokines, there is now a clear understanding of the pathways by which many anti-inflammatory drugs can alleviate inflammation and relieve pain.

“The use of non-steroidal anti-inflammatory drug (NSAID) medication is still the mainstay of most classically taught clinicians for joint and spine related inflammatory pain, despite their commonly known side effects [Table 1]. NSAID mechanisms are primarily through interaction with proinflammatory cytokines interleukin (IL)-1a, IL-1b, IL-6 and tumor necrosis factor (TNF-α). Increased concentrations of TNF-α are believed to cause the cardinal signs of inflammation to occur.[44]

“Curcumin (turmeric)

“Curcumin is a naturally occurring yellow pigment derived from turmeric (*Curcuma longa*), a flowering plant of the ginger family. It has traditionally been used as a coloring and flavoring spice in food products. Curcumin has long been used in both Ayurvedic and Chinese medicines as an anti-inflammatory agent, a treatment for digestive disorders, and to enhance wound healing. Several clinical trials have demonstrated curcumin’s antioxidant, anti-inflammatory, and antineoplastic effects. Results of a study by Zandi and Karin suggested that curcumin might be efficacious in the treatment of cystic fibrosis because of its anti-inflammatory effect.[121] Curcumin is known to inhibit inflammation by suppressing NF-kB, restricting various activators of NF-kB as well as stemming its expression.

“Curcumin has also been suggested as a treatment for colitis, chronic neurodegenerative diseases, arthritis, and cancer. In addition, it regulates the activity of several enzymes and cytokines by inhibiting both COX-1 and COX-2. Most studies to date have been performed in animals, but given the centuries of use of curcumin, as well as its now demonstrated activity in the NF-kB, COX-1, and COX-2 inflammatory pathways, it may be considered a viable natural alternative to nonsteroidal agents for the treatment of inflammation.

“The usual dosage of standardized turmeric powder is 400–600 mg taken three times per day.[13] Side effects are few, but with extended use, this agent can cause stomach upset, and in extreme cases gastric ulcers may occur at very high doses. Caution should be used if the patient is taking anticoagulant medications or high doses of nonsteroidal drugs. Studies have shown that curcumin may be used in combination with lower doses of nonsteroidal medications.[7–9,11,21,40,87,111,121]”

7. OSTEOPOROSIS - I have excerpted the relevant parts of this study on curcumin and osteoporosis and put the most important statements in bold. HK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921272/

J Korean Neurosurg Soc. 2013 Dec; 54(6): 461–466.

Published online 2013 Dec 31. doi: 10.3340/jkns.2013.54.6.461

Therapeutic Advantages of Treatment of High-Dose Curcumin in the Ovariectomized Rat

Dae-Chul Cho, M.D., Ph.D.,[1,*] Hyun-Sik Jung, M.D.,[1,*] Kyoung-Tae Kim, M.D., Ph.D.,[1] Younghoon Jeon, M.D., Ph.D.,[2] Joo-Kyung Sung, M.D., Ph.D.,[1] and Jeong-Hyun Hwang, M.D., Ph.D.[1]

Abstract

"…….**Osteoporosis is a chronic disease of the skeleton characterized by loss of bone mass and disruption of bone microarchitecture, increasing the risk of fracture**[11,18]. Nowadays, the incidence of osteoporosis is increasing rapidly in the elderly population, especially in postmenopausal women[16,17,20].

"Bisphosphonates (BPs) are potent antiresorptive agents widely used as the mainstay of treatment of osteoporosis. Because BPs accumulate in bone and are released for months or years after treatment is stopped, physicians need to be aware of the potential adverse effects of long-term use of BPs in osteoporosis[3,4,7,8,21]. 461Due to the possible undesirable effects associated with pharmacological treatments, natural alternatives for the prevention and treatment of osteoporosis are highly desirable[1,3,6,23].

"… It is well known that curcumin has diverse biologic effects, including anti-inflammatory, antioxidant, antiviral and anti-infectious[5,13,19]. In addition, some studies investigated the effects of curcumin on the regulation of bone remodeling. It has known as a therapeutic oriental plant that have shown to improve bone quality[9]. In a recent study by French et al.[6], the long-term effects of curcumin administration in ovariectomized rats were examined, and it was concluded that curcumin produced beneficial changes in bone turnover and an increase in bone strength in the ovariectomized mature rat model of postmenopausal osteoporosis.

"Curcumin has been consumed as a dietary spice at doses of up to approximately 1.5 mg/kg/day[19]. **However, according to the recent study of Folwarczna et al.[5], curcumin at a dietary achievable dose may not be useful for the prevention or treatment of osteoporosis.**

"Although curcumin has a protective effect on bone remodeling[2,5,6,9,13,19,22], appropriate therapeutic concentrations of curcumin are not well known as therapeutic drugs for osteoporosis…**Thus the aim of the present study was to compare the bone sparing effect of treatment of low-dose and high-dose curcumin after ovariectomy in rats.** We studied

normal female rats and rats with estrogen deficiency (bilaterally ovariectomized) as a model of postmenopausal osteoporosis."

DISCUSSION

"Although bisphosphonates, potent antiresorptive agents, have been the most popular first-line drugs for the treatment of osteoporosis for some time, many side effects have become evident in recent years[4,8,18,21]. Some reports suggested a link between BPs use and the development of atypical insufficiency fractures or osteonecrosis of the jaw[14,15]. These are thought to be due to long term oversuppression of bone turnover leading to impaired bone remodeling, accumulation of microdamage in bone and increased skeletal fragility. Therefore, there is increasing interest in the discovery of natural substances that could favorably affect the skeletal system, which could be used in place of pharmacological treatment for osteoporosis.

"Curcumin is a nonsteroidal, naturally occurring compound in the rhizomes of the popular Indian spice turmeric plant (*Curcumin longa L.*), which is commonly used as a dietary pigment. In addition to a variety of pharmacologic effects, including anti-inflammatory, anti-infectious and antioxidant activities, which are traditionally known[5,13,19], recent studies investigated the protective effects of curcumin on the regulation of bone remodeling. It is well known that curcumin has action similar to bisphosphonate, the inhibition of osteoclastogenesis[4-7,9,23]. Ozaki et al.[10] showed that curcumin is a potent stimulator of osteoclast apoptosis and also an inhibitor of bone resorption caused by rabbit osteoclast. It has also been shown in murine cells that curcumin inhibits osteoclastogenesis induced by receptor activation of NF-kB ligand[2].

"In the study by Folwarczna et al.[5], 10 mg/kg curcumin was administered po daily for 4 weeks to normal and bilaterally ovariectomized rats. In their study, although curcumin slightly improved some bone histomorphometric parameters impaired by estrogen deficiency, the effects on the skeletal system were ambiguous. **They concluded that curcumin at a dietary achievable dose may not be useful for the prevention or treatment of osteoporosis.**

"Curcumin has been consumed as a dietary spice at doses of up to 100 mg/day[19], i.e., approximately 1.5 mg/kg/day, assuming that human body mass is 65-70 kg. According to Phase I clinical trials, **humans can tolerate curcumin even at a dose of 8 g/day[2].**

"Because **it is known that the oral bioavailability of curcumin in rats is about 1%** and **the half-life of curcumin is rather short[22], we hypothesized that a relatively high concentration of curcumin would have a protective effect of bone remodeling**. **Thus in the present study, ovariectomized rats were treated either with low-dose (10 mg/kg) or high-dose (50 mg/kg) curcumin. We then compared the therapeutic effects on bone remodeling with different dose of curcumin treatment using bone turnover markers, histomorphometric parameters and bone strength.**

"French et al.[6] conducted a well-designed experiment about the bone sparing effect of curcumin or bisphosphonate (etidronate) in the ovariectomized rat. They used three different

doses of curcumin; 1.5 mg/kg, 3 mg/kg, 15 mg/kg, which are a relatively low concentration of curcumin compared with the doses of our study. In their study, there was no difference in lumbar spine BMD at two months after ovariectomy. At four months post-ovariectomy, all three curcumin groups demonstrated a sustained increase in spine BMD over ovariectomized animals, which was not statistically significant. There was a 50% increase in mechanical strength for all groups of animals that received curcumin. We think that this lack of a significant increase in spine BMD in the curcumin group in the study by French et al.[6] may be due to administration of a dose of curcumin that was too low to produce a significant increase in spine BMD.

"In our study using a relatively high dose of curcumin, the curcumin treated groups (low-dose and high-dose curcumin groups) showed a sustained increase in spine BMD and CrBMD compared with the untreated OVX group. In the comparison between the different doses of curcumin, the high-dose curcumin treated group had a significant increase in BMD and CrBMD compared with the low-dose curcumin treated group. Considering mechanical strength, the low-dose and high-dose curcumin treated groups had a greater maximal load value compared to the untreated OVX group, but only high-dose curcumin treated group had a significant difference from the untreated OVX group (p=0.015). Thus our study supported the results of Folwarczna et al.[5]. We strongly agree with their opinion, that curcumin at a dietary achievable dose may not be useful for the prevention or treatment of osteoporosis. **We think high-dose curcumin treatment could lead to more advantages in the bone sparing effect.**

"As mentioned above, curcumin has an action similar to bisphosphonate, the inhibition of bone resorption by osteoclast. Biochemical markers of bone turnover have been widely used as measures of the status of bone remodeling. The extent of bone resorption could be checked by CTX-1 level (a sensitive marker of bone resorption). French et al.[6] noted that the curcumin treated group showed CTX concentrations very similar to those of ovariectomized animals given etidronate. In our previous study about a synergistic bone sparing effect of curcumin (50 mg/kg, daily) and alendronate in ovariectomized rats, we achieved results comparable to French et al.[6] CTX-1 concentration in curcumin administered group was similar to those of the alendronate administered group. In addition, the combination therapy (50 mg/kg curcumin and alendronate) group had lower CTX-1 concentrations, which were statistically significant to the curcumin only and the alendronate only group[3].

"In the present study, the high-dose curcumin group had significantly lower CTX-1 concentration compared with the sham group and the low-dose curcumin group. This is further evidence of our hypothesis that **high-dose curcumin treatment could lead to better bone sparing effect."**

CONCLUSION

"The present study demonstrated that a high-dose curcumin has therapeutic advantages over a low-dose curcumin as to antiresorptive effect on bone remodeling, and improving bone mechanical strength."

References

1. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22:465–475. [PubMed] [Google Scholar]

2. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001;21:2895–2900. [PubMed] [Google Scholar]

3. Cho DC, Kim KT, Jeon Y, Sung JK. A synergistic bone sparing effect of curcumin and alendronate in ovariectomized rat. Acta Neurochir (Wien) 2012;154:2215–2223. [PubMed] [Google Scholar]

4. Fleisch H. Bisphosphonates : mechanisms of action. Endocr Rev. 1998;19:80–100. [PubMed] [Google Scholar]

5. Folwarczna J, Zych M, Trzeciak HI. Effects of curcumin on the skeletal system in rats. Pharmacol Rep. 2010;62:900–909. [PubMed] [Google Scholar]

6. French DL, Muir JM, Webber CE. The ovariectomized, mature rat model of postmenopausal osteoporosis : an assessment of the bone sparing effects of curcumin. Phytomedicine. 2008;15:1069–1078.[PubMed] [Google Scholar]

7. Kashii M, Hashimoto J, Nakano T, Umakoshi Y, Yoshikawa H. Alendronate treatment promotes bone formation with a less anisotropic microstructure during intramembranous ossification in rats. J Bone Miner Metab. 2008;26:24–33. [PubMed] [Google Scholar]

8. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover : a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294–1301.[PubMed] [Google Scholar]

9. Oh S, Kyung TW, Choi HS. Curcumin inhibits osteoclastogenesis by decreasing receptor activator of nuclear factor-kappaB ligand (RANKL) in bone marrow stromal cells. Mol Cells. 2008;26:486–489.[PubMed] [Google Scholar]

10. Ozaki K, Kawata Y, Amano S, Hanazawa S. Stimulatory effect of curcumin on osteoclast apoptosis. Biochem Pharmacol. 2000;59:1577–1581. [PubMed] [Google Scholar]

11. Palumbo C, Ferretti M, Bertoni L, Cavani F, Resca E, Casolari B, et al. Influence of ferutinin on bone metabolism in ovariectomized rats. I: role in preventing osteoporosis. J Bone Miner Metab. 2009;27:538–545. [PubMed] [Google Scholar]

12. Park SB, Lee YJ, Chung CK. Bone mineral density changes after ovariectomy in rats as an osteopenic model : stepwise description of double dorso-lateral approach. J Korean Neurosurg Soc. 2010;48:309–312.[PMC free article] [PubMed] [Google Scholar]

13. Park SK, Oh S, Shin HK, Kim SH, Ham J, Song JS, et al. Synthesis of substituted triazolyl curcumin mimics that inhibit RANKL-induced osteoclastogenesis. Bioorg Med Chem Lett. 2011;21:3573–3577.[PubMed] [Google Scholar]

14. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates : a review of 63 cases. J Oral Maxillofac Surg. 2004;62:527–534. [PubMed] [Google Scholar]

15. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics. 2006;61:31–33. [PubMed] [Google Scholar]

16. Sheng ZF, Dai RC, Wang P, Yao XF, Feng XQ, Fang LN, et al. [Nanomechanical properties of vertebral trabeculae in ovariectomized rats] Zhonghua Yi Xue Za Zhi. 2006;86:515–519. [PubMed] [Google Scholar]

17. Shin YH, Cho DC, Yu SH, Kim KT, Cho HJ, Sung JK. Histomorphometric analysis of the spine and femur in ovariectomized rats using micro-computed tomographic scan. J Korean Neurosurg Soc. 2012;52:1–6. [PMC free article] [PubMed] [Google Scholar]

18. Shiraishi A, Miyabe S, Nakano T, Umakoshi Y, Ito M, Mihara M. The combination therapy with alfacalcidol and risedronate improves the mechanical property in lumbar spine by affecting the material properties in an ovariectomized rat model of osteoporosis. BMC Musculoskelet Disord. 2009;10:66.[PMC free article] [PubMed] [Google Scholar]

19. Shishodia S, Sethi G, Aggarwal BB. Curcumin : getting back to the roots. Ann N Y Acad Sci. 2005;1056:206–217. [PubMed] [Google Scholar]

20. Szulc P, Delmas PD. Biochemical markers of bone turnover : potential use in the investigation and management of postmenopausal osteoporosis. Osteoporos Int. 2008;19:1683–1704. [PubMed] [Google Scholar]

21. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab. 2010;95:1555–1565. [PubMed] [Google Scholar]

22. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;853:183–189. [PubMed] [Google Scholar]

23. Yang MW, Wang TH, Yan PP, Chu LW, Yu J, Gao ZD, et al. Curcumin improves bone microarchitecture and enhances mineral density in APP/PS1 transgenic mice. Phytomedicine. 2011;18:205–213. [PubMed] [Google Scholar]

8. Relief from Arthritic Pain - I have excerpted the relevant parts of this study on curcumin and pain and put the most important statements in bold. HK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5003001/

JOURNAL OF MEDICINAL FOOD

J Med Food. 2016 Aug 1; 19(8): 717–729.

Published online 2016 Aug 1. doi: 10.1089/jmf.2016.3705

Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

James W. Daily,[1] Mini Yang,[2] and Sunmin Park[2]

Abstract - Introduction

"THE TERM ARTHRITIS is derived from the Greek words "artho" and "itis," meaning joint and inflammation, respectively. Arthritis is a form of joint disorder characterized by chronic inflammation in one or more joints that usually results in pain and is often disabling.[1,2] Arthritis includes more than 100 different forms: the most common form is osteoarthritis, but other forms include rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases.[1,2] Although the causes of these diseases are different, their symptoms and treatments are similar. As osteoarthritis is a degenerative joint disease, the number of people with arthritis is also growing with the increase in the aging population.[1] The worldwide prevalence of knee osteoarthritis increased 26.6% from 1990 to 2010, and it affects about 9.6% of men and 18% of women more than 60 years of age.[3] The occurrence of osteoarthritis increases with age due to the decreased capacity to suppress inflammation, age-related sarcopenia, and increased bone turnover.[1] Rheumatoid arthritis is a systemic inflammatory and destructive joint disease with a prevalence of about 1–2% of the adult population worldwide.[2]

"Although arthritis is associated with inflammation and pain, the exact cause of arthritis remains uncertain, and there is no treatment for its fundamental causes. The major goal of arthritis treatment is to reduce joint pain induced by inflammation in the joints, daily wear and tear of joints, and muscle strains.[4] The existing pharmaceuticals for treating arthritis are analgesics, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), which reduce the symptoms such as severe pain and inflammation.[5] Classical NSAIDs are cyclooxygenase (COX) inhibitors that inhibit prostaglandin and thromboxane synthesis, thereby reducing inflammation.[5] New NSAIDs selectively inhibit COX-2 and are usually specific to inflamed tissue, which decreases the risk of peptic ulcer.[5] However, their long-term use cannot be sustained due to inadequate pain relief, immune disturbances, and serious gastrointestinal and cardiovascular adverse events.[6] Therefore, herbal therapies with anti-inflammatory properties and minimum side effects are needed for the treatment of arthritis, including

rheumatoid arthritis and osteoarthritis, especially after the withdrawal of many Food and Drug Administration-approved anti-inflammatory drugs.[7]

*"**Curcuma longa* and *Zingiber officinale*, both of which belong to the Ziangiberaceae family, are potential alternative medicines for arthritis.**[8,9] They have been used as seasonings in many ethnic cuisines in various countries such as Bangladesh, India, and Pakistan. **They have long been used as anti-inflammatory treatments in traditional Chinese and Ayurvedic medicines**.[10] The effective components of *Z. officinale*: gingerols, shogaols, zingerone, and paradol, and ginger itself have been reported to exert anti-inflammatory effects by inhibiting COX-1 and COX-2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and 5-lipoxygenase (5-LOX).[11] Several systematic reviews of clinical trials have shown that ginger may reduce the subjective experience of pain in some conditions such as muscular diseases.[12] In addition, turmeric extracts have activities similar to ginger although they have different effective compounds. Several studies have evaluated the efficacy of turmeric extracts for the treatment of musculoskeletal disorders.[13]

"Although turmeric belongs to the Zingiberaceae family, turmeric contains different bioactive components, mainly curcumin and demethoxycurcumin, bis-demethoxycurcumin, and turmeric essential oils. When used as an alternative medicine or dietary supplement, turmeric is typically used as an extract that is standardized to 80–95% curcuminoids, primarily curcumin. Turmeric and its derivatives have anti-inflammatory activities. Unlike ginger, turmeric and curcumin do not modulate COX-1 activity,[14,15] but modify NF-κB signaling, proinflammatory cytokines such as interleukin production and phospholipase A2, COX-2, and 5-LOX activities. Curcumin also modulates the expressions of various transcription factors involved in energy metabolism such as signal transducer and activator of transcription, peroxisome proliferator-activated receptor-γ, activator protein-1, cAMP responding element binding protein, estrogen response element, and others.[15] **As a result, turmeric and its components have been reported to exert beneficial effects on osteoarthritis, type 2 diabetes, and dyslipidemia.** Turmeric is better tolerated than ginger and pepper due to being less hot and spicy. Therefore, it is important to conduct a systematic review of the antiarthritis effects of curcuma.

"The purpose of this review was to systemically evaluate all randomized clinical trials (RCTs) of turmeric and curcumin for treating arthritis symptoms and to elucidate the efficacy of curcuma for alleviating the symptoms of arthritis. **To the best of our knowledge, this is the first systematic review and meta-analysis of RCTs on the efficacy of turmeric for arthritis symptoms.**

Adverse events: **"… turmeric preparations and curcumin were considered to be safe at doses not exceeding 1200 mg/day for up to 4 months.**

Discussion

"Although the exact biochemical cause of osteoarthritis remains unknown, it is associated with inflammation in articular cartilage, which can cause abnormal joint structure in the knee

and hip and it is accompanied with pain. The most common treatments are analgesics and NSAIDs.[5] However, the drugs have serious adverse events in the gastrointestinal tract and cardiovascular system.[6] Therefore, herbal treatments that can mitigate the pain and inflammation have been investigated as potential primary or adjunct therapies for relieving arthritis symptoms. This systematic review and meta-analysis provided scientific evidence that 8–12 weeks of standardized turmeric extracts (typically 1000 mg/day of curcumin) treatment can reduce arthritis symptoms (mainly pain and inflammation-related symptoms) and result in similar improvements of the symptoms as ibuprofen and diclofenac sodium. Therefore, turmeric extracts and curcumin can be cautiously recommended for alleviating the symptoms of arthritis, especially osteoarthritis. However, the sample sizes (45–124) of the studies included in this review were insufficient to be conclusive, and some studies represented moderate quality. Further high-quality RCT studies with more subjects are needed to confirm the therapeutic efficacy of turmeric and curcumin for arthritis.

“The article by Pinsornsak and Niempoog[21] was not included in the meta-analyses because its design did not permit its data to be merged with any of the other studies. That RCT was a comparison of diclofenac (75 mg/day) with or without curcumin (1000 mg/day). Both groups made significant improvements over the 3-month course of the study, but although **the group that included curcumin seemed to improve more**, there was no significant differences between groups. Since diclofenac is an NSAID, it is possible that its mechanisms of action are similar to those of curcumin and the redundancy of action resulted in little additional benefit. The authors also suggested that the lack of statistical significance might have been influenced by the drop-out rate of 9% due to difficulty in traveling for follow up in the rural area. They also suggested that the dose may have been too low; however, other studies included in this review found significant improvements at lower dosages. However, **the design of this study did not permit a determination of the effectiveness of curcumin alone.**

“The study by Madhu *et al.*[22] was unique in using a turmeric extract that contained only polar substances, especially polysaccharides, and no curcumin. This study had four groups: placebo, turmeric, chondroitin sulfate, and turmeric plus chondroitin sulfate. Turmeric and chondroitin sulfate both provided significant benefits by both PVAS and WOMAC score, with turmeric performing significantly better. However, combining turmeric and chondroitin provided no added benefit, which may be due to redundant effects as already suggested for curcumin and diclofenac. The most important contribution of this study, however, may be that it demonstrated potent anti-inflammatory and/or analgesic benefits for turmeric components other than curcumin.

“Osteoarthritis is exacerbated by the activation of NF-κB, which is initiated by a host of stress-related stimuli, including proinflammatory cytokines, excessive mechanical stress, and extracellular matrix degradation products.[4,30] These actions reduce the amount of articular cartilage in the joints and wear out the bones near the joints to induce pain and difficulty in movements. As a result, osteoarthritis treatment focuses on relieving pain and swelling, improving joint mobility and stiffness, increasing the strength of the joints, and minimizing the disabling effects of the disease.[31] Thus, the severity of arthritis is mostly measured by PVAS and WOMAC as symptomatic end-point results in RCTs.

“The approved drugs commonly used to treat arthritis, such as NSAIDs, have adverse effects, and alternative treatments have been investigated. NSAIDs increase the risk of gastrointestinal bleeding, vascular adverse events, and allergic responses.[32] Symptomatic slow-acting drugs for osteoarthritis such as glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, hyaluronic acid, avocado soybean unsaponifiables, and diacerein are common alternative medicines for treating osteoarthritis symptoms.[33–36]In systematic reviews, glucosamine and diacerein were found to reduce pain but did not alleviate joint space narrowing.[33,36] In addition, they also caused some gastrointestinal and metabolic disturbances, although the adverse effects were less than NSAIDs.[37] People with impaired glucose tolerance or insulin resistance are more likely to exhibit severely impaired glucose metabolism with glucosamine treatment for osteoarthritis.[33,37] Therefore, these drugs cannot be used for long-term treatment, although osteoarthritis is a chronic long-term disease. Herbal medicine is often recommended for osteoarthritis treatment. Herbal and complementary therapies are safer to use and can be taken for longer periods, but they are also subject to widespread advertising and attractive, but unsubstantiated, claims that are often made for many natural products. Promising therapeutic agents for treating osteoarthritis can be compounds that block NF-κB signaling.[38] Several candidates for naturally occurring NF-κB inhibitors are phytochemicals such as flavonoids and catechins from green tea, rosehip, curcumin, and resveratrol.[38,39]

“Turmeric (*C. longa*) has a long history of safe use as food and it has long been used as in anti-inflammatory treatment in traditional Chinese and Ayurvedic medicine.[30] Turmeric contains a yellow-pigmented fraction that mainly consists of curcuminoids. The principal ingredient of curcuminoids is curcumin, which is reported to have beneficial effects on osteoarthritis, type 2 diabetes, and dyslipidemia due to its antioxidant and anti-inflammatory activities. **However, the systemic bioavailability of curcumin is known to be poor.[40]Several studies have reported that curcumin concentrations are extremely low or nonexistent in serum and tissues at 1, 2, 3, and 4 h after taking a single oral dose of 500–8000 mg in humans**, and also after long-term oral administration of 440–2200 mg curcumin or curcuma extracts per day.[41–43] This is associated with the low stability of curcumin in aqueous solution at physiological pH, and within 30 min, curcumin is degraded into trans-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal, ferulic aldehyde, ferulic acid, feruloyl methane, vanillin, vanillic acid, and other dimerization end products.[44,45] **The metabolites of curcumin are present in high concentrations in the circulation after curcumin consumption. These curcumin metabolites may be responsible for the anti-inflammatory and antioxidant activities that reduce the symptoms of metabolic diseases including osteoarthritis**.[44,45] However, Gupta *et al.* reported that curcumin is low but detectable in the circulation as the forms of glucuronide and sulfate conjugates in the patients with oral consumption of 8 g/day curcumin for more than 2 months.[46] **Thus, curcumin itself can be a therapeutic agent for relieving arthritis.**

“Korea Food and Drug Safety administration has declared turmeric roots as “generally regarded as safe.” Turmeric and curcumin have been found to be safe and tolerable in human clinical trials and systematic reviews.[47] No long-term studies with curcumin have revealed toxic or adverse effects.[48] However, some clinical studies in humans with high doses (8–12 g)

of curcumin have shown a few side effects, with some subjects reporting mild nausea or diarrhea.[49] The studies used in this systematic review and meta-analyses used several types of turmeric and curcumin preparations and all appeared to provide efficacy for treating arthritis.

"Recently, high doses of curcumin was found to alter iron metabolism by chelating iron and suppressing the protein hepcidin, potentially causing iron deficiency in susceptible patients.[40] However, overall, the dosage required to improve osteoarthritis was less than 2000 mg/day and this dosage did not show any noticeable adverse effects in this review. Thus, turmeric and curcumin can be safely used as a therapeutic agent for osteoarthritis.

"To the best of our knowledge, this is the first systematic review and meta-analysis of RCTs on the effectiveness of turmeric extract or curcumin for arthritis. Although **the present meta-analysis of RCTs suggested that oral administration of curcumin reduced arthritis symptoms, as measured by PVAS and WOMAC, as much as pain medicine**, it is difficult to recommend curcumin and turmeric as a good therapeutic agent for arthritis due to the limitations of the RCT studies included in this systematic review. The limitations of the studies are as follows: first, the number of RCTs ($n = 8$) and sample sizes ($n = 45–124$) of the primary studies are low. RCTs had either a placebo control or pain medicine control, and they also utilized different end-point measurements such as PVAS and/or WOMAC. Thus, total sample size of each meta-analysis was low: PVAS for curcuma and placebo was 60 curcuma and 62 placebo; WOMAC score for curcuma and placebo was 308 curcuma and 291 placebo; PVAS for curcuma and pain medicine was 258 curcuma and 242 pain medicine. Furthermore, there were various turmeric preparations, some designed to increase absorption, that complicate drawing firm conclusions about the most effective preparation method and dose. However, **this is also a strength of the study because it demonstrates that turmeric contains multiple functional compounds and their metabolites that have efficacy for arthritis**. In addition, the RCTs included in the systematic review had overall low-to-moderate ROB. Four RCTs were classified as high quality[17,18,20,23] and four RCTs had a moderate quality.[16,21,22,24] Some studies did not report randomization of the subjects and allocation of the groups,[17,20,24] whereas two RCTs did not mention their blindness to the practitioners.[17,21] In addition, two RCTs did not report drop-out rates and reasons for withdrawals from the trials.[23,24] However, it is difficult to detect bias resulting from authors not publishing negative results that are considered uninteresting, so there is still some possibility of publication bias.

"In conclusion, although the studies used in this meta-analysis do not have sufficient number of subjects to permit a definitive recommendation for the use of curcumin as a treatment for arthritis, they do provide a compelling justification for its use as a dietary adjunct to conventional therapy. Furthermore, they also provide sufficient evidence to support larger clinical trials that could eventually lead to its acceptance as a standard therapy for many forms of arthritis and possibly other inflammatory conditions."

"Acknowledgment - This work was supported by a grant from the Korea Institute of Oriental Medicine (grant no. K16291)."

9. STROKE - I have excerpted the relevant parts of this study on curcumin and stroke and put the most important statements in bold. HK

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4216637/

Metab Brain Dis. 2015 Apr; 30(2): 427–435.

Published online 2014 May 1. doi: 10.1007/s11011-014-9537-0

Epigenetic impact of curcumin on stroke prevention

Anuradha Kalani,[1] Pradip K Kamat,[1] Komal Kalani,[2] and Neetu Tyagi[1]

Author information Copyright and License information Disclaimer

"Abstract - Introduction

Cerebral stroke or "brain attack" is caused by interruption of blood supply to the brain which leads to the loss of brain functions (Langhorne et al. 2013). Cerebral stroke can be classified into ischemic (blockage of blood supply) or hemorrhagic (bursting of blood vessels). Thrombolytic agents, anti-platelet drugs, and neuro-surgery are the only available options for the treatment of stroke (Adams, Jr. et al. 2007); however the protective therapy against cerebral stroke is yet to be discovered. Dietary components have found to exert immense impacts on normal functioning of the brain (Alamy and Bengelloun, 2012; Bedi, 2003; Gomez-Pinilla, 2008) and contribute to the prevention of a series of brain diseases including stroke (Psaltopoulou et al. 2013). Reports indicate that dietary components not only evoke genetic, but also epigenetic components to compensate stroke, or stroke-like pathologies (Gallou-Kabani et al. 2007; Kalani et al. 2013a). In that regard **the potential of curcumin, which also exhibits genetic and epigenetic influences, cannot be ignored.** Curcumin is derived from the roots of *Curcumin longa* and due to remarkable medicinal properties; curcumin (diferuloylmethane) is termed as yellow gold. **Curcumin treatment provides vascular protective effects in persons at risk for stroke** (Ovbiagele, 2008). **The stroke preventive properties of curcumin can be attributed to: 1) neuro-protection via free radical scavenging, inhibiting nitric oxide synthase and lipid peroxidation (Strimpakos and Sharma, 2008); 2) anti-inflammatory property by suppressing the production of IL-1, IL-8 and TNF-α (Strimpakos and Sharma, 2008); 3) anti-lipidemic property by lowering cholesterol and boosting up HDL (Soni and Kuttan, 1992) and; 4) anti-aggregation property by inhibiting platelet aggregation and inducing platelet aggregation factor (Strimpakos and Sharma, 2008). The ability of curcumin to cross blood-brain-barrier (BBB) also favors its selection over other therapeutic agents/molecules during cerebral stroke** (Mishra and Palanivelu, 2008; Tsai et al. 2011). In addition**, curcumin appears to have potential to inhibit amyloid beta oligomers and**

fibrils formation in mice (Yang et al. 2005). The therapeutic efficacy of curcumin in middle cerebral artery occlusion (MCAO) models of rat and mice has also been explored (Lapchak et al. 2011; Shukla et al. 2008; Tyagi et al. 2012; Zhao et al. 2010). **Studies suggest that curcumin overcomes cerebral ischemia by its neuro-protective and anti-oxidative properties** (Strimpakos and Sharma, 2008; Tyagi et al. 2012). Besides exhibiting anti-inflammtory, anti-lipidemic, and anti-oxidative properties, curcumin also induces signs of epigenetic changes (Chiu et al. 2013; Hardy and Tollefsbol, 2011; Martin et al. 2013; Teiten et al. 2013); however the epigenetic influence of curcumin on stroke epigenetics is needed to be explored. In this present review, we propose that curcumin affect molecular processes such as DNA methylation, histone modification, nucleosome remodeling, and small noncoding RNAs (ncRNAs) (e.g., miRNAs) that modulate gene expression and impart an important role in amelioration of stroke pathogenesis. Since, curcumin possesses potential therapeutic effects and therefore, it has been recommended for clinical trials to prevent / treat brain disease, including stroke (Goel and Aggarwal, 2010; Ovbiagele, 2008; Perry and Howes, 2011). **Phase I clinical trials on curcumin were not successful due to its low bioavailability** (Anand et al. 2007). The factors that limit curcumin bioavailability include; poor absorption, quick metabolism, and rapid systemic elimination. However, recent studies suggest that curcumin-encapsulated exosomes are more stable, highly soluble, highly concentrated in the blood and possess therapeutic potentials (Sun et al. 2010; Zhuang et al. 2011). Exosomes are the nano-vesicles (<200 nm) derived from the fusion of multivesicular body to the plasma membrane and found in the extracellular body fluids (serum, plasma, saliva, urine, breast milk, brancheo-alveoli lavage) including culture conditioned media (Kalani et al. 2014; Thery et al. 2002; Thery et al. 2006). These nano-units have been employed for the treatment of stroke in rat (Xin et al. 2013). Targeted delivery of curcumin-encapsulated exosomes to the brain through intra-nasal routes has been shown to be effective for brain inflammatory diseases (Zhuang et al. 2011). Interestingly, preliminary studies from our lab explored that curcumin-primed exosomes (CUR-EXO), derived from culture conditioned media of mouse brain endothelial cells (MBEC) treated with curcumin, might equally benefit since these units alleviate tight junction proteins and endothelial cell layer permeability in MBECs (unpublished data). These results concomitantly show the therapeutic aspects in CUR-primed, or CUR-encapsulated exosomes and provide a promising area to explore their potentials to recover cerebral ischemic stroke probably by amelioration of epigenetic and molecular events.

“Hence, the present review suggests the possible epigenetic mechanisms induced with curcumin along with a short discussion on molecular designing to enhance its bioavailability and impacts of curcumin encapsulated/curcumin-primed exosomes on stroke therapy.

“….Epigenetic impact of curcumin

“Fu et al. have suggested that curcumin may exert its biological activities through epigenetic modulation, even at lower concentrations (Fu and Kurzrock, 2010). Epigenetic mechanisms regulate functional gene environment by regulating gene expressions without altering gene sequence or structure. The normal genetic expressions are under the control of various mechanisms such as: DNA methylation, histone modifications, non-coding small RNA

(micro RNA, miR), and RNA editing (Kalani et al. 2013b; Qureshi and Mehler, 2010b; Qureshi and Mehler, 2012). These associated mechanisms may play immense role in normal physiological functions of the brain. Curcumin as an epigenetic agent can be used for stroke protection and therapeutics by reversing erroneous epigenetic mechanisms or inducing/controlling normal epigenetic mechanisms.

"Curcumin for stroke prevention

"Curcumin possess multiple pharmacological properties (anti-inflammatory, anti-thrombotic, and anti-oxidative) and these properties further add on to its anti-ischemic property. The anti-ischemic effect of curcumin is believed to be contributed by its free radical scavenging activity which is unique upon having phenolic and diketonic groups present in its structure. However, other natural anti-oxidants lack the presence of two groups together and possess either of these. The neuroprotective effect of curcumin is well documented over different neurotoxicants; such as Hcy (Kalani et al. 2013a). These protective effects not only rescue the metabolite alterations but also improve brain edema, Evans Blue leakage and infarct size during ischemic brain injury (stroke) (Tyagi et al. 2012). The beneficiary effect of curcumin is also reported to be executed by lowering lipid peroxidation, when administered orally or intraperitoneally (Ghoneim et al. 2002; Thiyagarajan and Sharma, 2004). Hence, the major advantages that lay with curcumin treatment have been explored as its non-toxic effect (even at high doses), ability to cross BBB in aged mice and gerbils, and its cerebro-protective behavior (Thiyagarajan and Sharma, 2004; Tyagi et al. 2012; Wang et al. 2005).

".....Curcumin Bioavailability

"Although curcumin demonstrated efficient and safe in nature, its limited bioavailability continues to be a major concern. Due to its rapid metabolism and elimination, low levels are found in serum and tissue irrespective of the route of administration. Low solubility in water probably reduces its effective action in the target protein site. Different attempts were tried to enhance its bioavailability including; modulation of the administering route, medium of curcumin administration, structural medications and encapsulation in exosomes.

".....Exosomes and Curcumin

"A recent report by Tiwari et al (2014) has shown **nanoparticle mediated delivery of curcumin to be neuroregenerative which strengthens the therapeutic link towards stroke therapy.** Xin et al. describes the potential of exosomes in rat MCAO model (Xin et al. 2013). The investigators derived exosomes from mesenchymal stromal cells (MSC) and used these nano-units against MCAO injury through tail vein injection. They find functional improvements; neurite remodeling, neurogenesis and angiogenesis post MCAO with MSC-exosome treatment which suggests therapeutic efficacy of exosomes. Although exosomes have been implicated in stroke therapeutics, encapsulation of curcumin in exosomes further enhances its protective effects. Investigators have found that curcumin-encapsulated exosomes are highly concentrated in the blood with increased solubility and stability (Sun et al. 2010; Zhuang et al. 2011). Authors confirmed that delivery of curcumin-encapsulated

exosomes is beneficial for inflammatory diseases since the approach has no significant side effects (Sun et al. 2010). Interestingly, another report suggests targeted delivery of curcumin-encapsulated exosomes to the brain through nasal route as a promising, non-invasive and novel therapeutic approach for treating brain inflammatory diseases (Zhuang et al. 2011). We have also observed that curcumin-primed exosomes have potential to recover junction proteins and permeability of endothelial cells (fig. 3). These novel therapeutic options should be tried in order to alleviate stroke pathology.

“

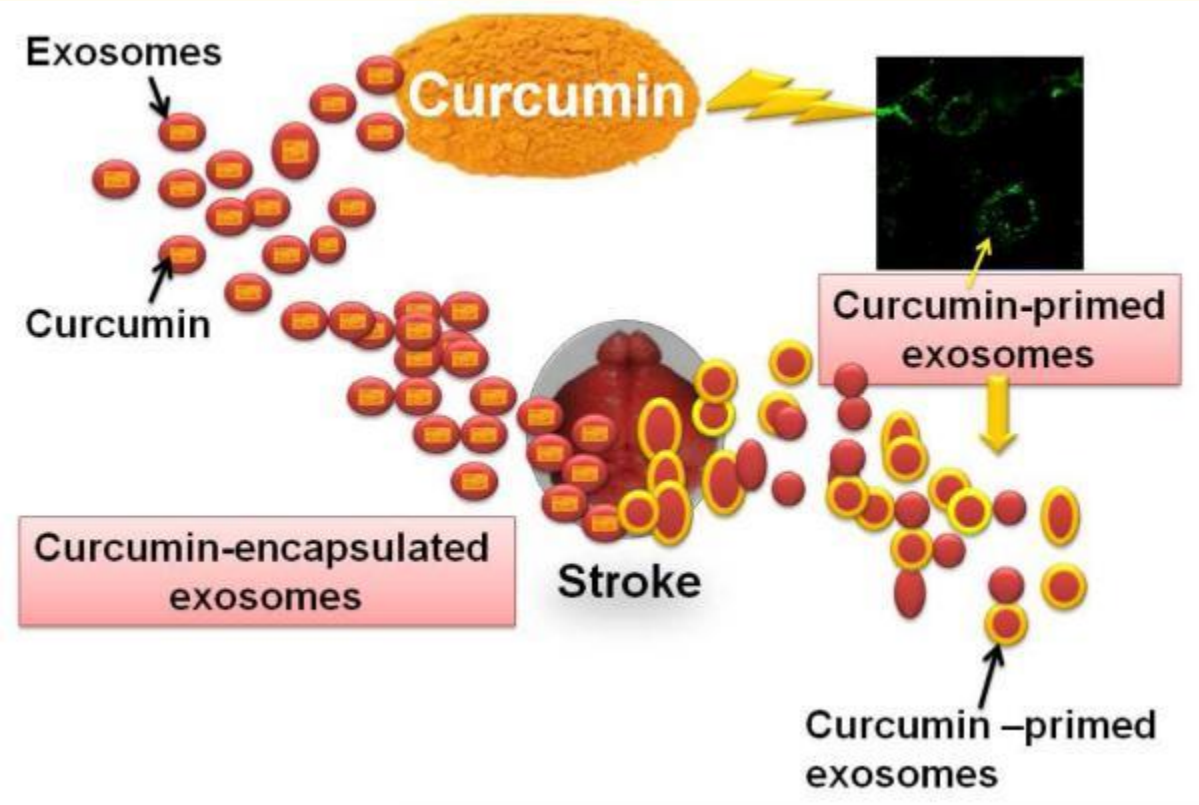

Fig. 3

Image showing protective potential of curcumin-encapsulated exosomes (left) and curcumin-primed exosomes (right) during stroke. Curcumin-primed exosomes (labeled with PKH67) are shown as green dots in the image.”

“Conclusion and Future direction

“Although curcumin possess anti-inflammatory, anti-oxidative, neuro-protective, and anti-cancer properties mediated through multiple intercellular/regulatory signaling mechanisms; very little is known about the effect of curcumin on epigenetic aspect during cerebral ischemia stroke. It has been suspected through earlier literature that curcumin possess epigenetic modulation properties and that’s how it affects epigenetic factors, such as HDAC, HAT, DNMTs, and miRNAs. Exploring epigenetic properties of curcumin in neuroprotection potentiates its use in stroke therapeutics. Nonetheless **the question that still**

exists is whether the protective mechanism of curcumin is epigenetically regulated or it has only potential impact? If the epigenetic aspect of curcumin to rescue ischemia stroke becomes clearer, more exciting results can come and give direction for the protective efficacy and therapy. **To cope with decreased bioavailability issue, discovery of the novel lead molecule might hopefully bring advancement in the safe and effective treatment of stroke.** However, further, QSAR and docking guided lead optimization is under progress, which will assist in elucidating the precise mechanism of action. Alongside, **exciting results on the use of curcumin-encapsulated / curcumin-derived exosomes pave the way to the future novel therapeutics in cerebral stroke where drug target is still a challenge."**

10. Curcumin for Asthma - the reader may find the extensive footnotes to be informative, but they are not required reading.

J Clin Diagn Res. 2014 Aug; 8(8): HC19–HC24.
Published online 2014 Aug 20. doi: 10.7860/JCDR/2014/9273.4705

PMCID: PMC4190737
PMID: 25302215

Evaluation of Efficacy of Curcumin as an Add-on therapy in Patients of Bronchial Asthma

Afroz Abidi, 1 Surabhi Gupta , 2 Manu Agarwal, 3 H.L. Bhalla, 4 and Mahip Saluja 5

“Abstract - Introduction

“**Bronchial asthma affects 100-150 million people worldwide** and approximately 180,000 deaths annually are attributed to asthma [1]. According to WHO, India is home to 15-20 million asthmatics. Asthma is a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing due to reversible airway obstruction, cellular inflammation, mucus hypersecretion, airway remodeling, blood vessel proliferation and mucous gland hyperplasia and hypersecretion. The broncho- constrictor and inflammatory mediators of asthma include cytokines, chemokines, cysteinyl leukotrines, histamine, nitric oxide, PGD2 adhesion molecules, enzymes and kinases which are mostly regulated by NF-kB pathway. This pathway has now been recognized to be involved in asthma and mediates the complex inflammatory response in the airways. Therefore the agents that downregulate NF-kB pathway could have a potential efficacy against the disease [2]. The diagnosis of asthma is established by demonstrating reversible airway obstruction.

“Conclusion

This study evaluated the clinical efficacy and safety of curcumin capsules as an add on therapy in patients of mild to moderate asthma and proved therapeutic improvement in FEV1 values along with improvement in concerned hematological parameters. This corroborates the fact that there is a definite improvement in lung function due to the anti-inflammatory effect of curcumin though there is no visible clinical efficacy. Therefore a further clinical evaluation is needed with more number of subjects, a higher tolerated dose and for a longer duration. Absence of any clinically significant adverse events indicates dependable safety profile of curcumin. **Therefore, it is concluded that**

curcumin is effective and safe as an add-on therapy for the treatment of bronchial asthma."

References

[1] Bronchial asthma http://www.who.int/mediacentre/factsheets/fs206/en/ accessed on 2014 Feb 4 .

[2] PJ Barnes. Cytokine modulators as novel therapies for asthma. Annu Rev Pharmacol Toxicol. 2002;42:81–98. [PubMed] [Google Scholar]

[3] PJ Barnes. J Oral Med. 12th Edition. New York: McGraw-Hill; 2011. Pulmonary pharmacotogy. In: Brunton LL editor. Goodman & Gilman's The pharmacological basis of therapeutics. pp. 1031–65. [Google Scholar]

[4] W Mitzner, RO Cooley, NH Olsen, JJ Hefferren. Bronchial thermoplasty in asthma. Allergology International. 2006;55:225–34. [PubMed] [Google Scholar]

[5] PD Blanc, L Trupin, G Earnest, PP Katz, EH Yelin, MD Eisner. Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: a data from a population basedsurvey. Chest. 2001;120:1461–67. [PubMed] [Google Scholar]

[6] H Itokawa, Q Shi, T Akiyama, SL Morris-Natschke, KH Lee. Recent advances in the investigation of Curcuminoids. Chin Med. 2008:3–11. [PMC free article] [PubMed] [Google Scholar]

[7] JS Jurenka. Anti-inflammatory properties of Curcumin, a major constituent of Curcuma longa: A review of preclinical and clinical research. Alternative medicine review. 2009;l4:141–53.[PubMed] [Google Scholar]

[8] C Jobin, CA Bradham, MP Russo, B Juma, AS Narula, DA Brenner, et al. Curcumin blocks cytokine-mediated NF-kappaB activation and pro-inflammatory gene expression by inhibiting inhibitory factor I-kappaB kinase activity. J Immunol. 1999;163:3474–83. [PubMed] [Google Scholar]

[9] Y Cheng, J Ping, LM Xu. Effects of Curcumin on peroxisome proliferator- activated receptor gamma expression and nuclear translocation/redis- tribution in culture activated rat hepatic stellate cells. Chinese Med J. 2007;120:794–801. [PubMed] [Google Scholar]

[10] HP Ammon, MA Wahl. Pharmacology of Curcuma longa. Planta Med. 1991;57:1–7.[PubMed] [Google Scholar]

[11] N Chainani-Wu. Safety and anti-inflammatory activity of Curcumin: A component of turmeric (Curcuma longa). J Altern Complement Med. 2003;9:161–68. [PubMed] [Google Scholar]

[12] KK Meja, S Rajendrasozhan, D Adenuga, SK Biswas, IK Sundar, G Spooner, et al. Curcumin restores corticosteroid function in monocytes exposed to oxidants by maintaining HDAC2. Am J Respir cell Mol Biol. 2008;39:312–23. [PMC free article] [PubMed] [Google Scholar]

[13] T Kobayashi, S Hashimoto, T Horie. Curcumin inhibition of Dermatophagoides farinea-induced interleukin-5 (IL-5) and granulocyte macrophage- colony stimulating factor (GM-CSF) production by lymphocytes from bronchial asthmatics. Biochem Pharmacol. . 1997;54:819–24.[PubMed] [Google Scholar]
[14] EH South, IH Exon, K Hendrix. Dietary Curcumin enhances antibody response in rats. Immunopharmacol Immunotoxicol. 1997;19:105–19. [PubMed] [Google Scholar]
[15] A Ram, M Das, B Ghosh. Curcumin attenuates allergen-induced airway hyperresponsiveness in sensitized guinea pigs. Biol Pharm Bull. 2003;26:1021–24. [PubMed] [Google Scholar]
[16] Kohli K, Ali J, Ansari M J, Raheman Z. Curcumin: A natural antiinflammatory agent. Indian J Pharmacol. 2005;37:141–47. [Google Scholar]
[17] VP Kurup, CS Barrios, R Raju, BD Johnson, MB Levy, JN Fink. Immune response modulation by Curcumin in a latex allergy model. Clin MolAllergt. 2007;5:1. [PMC free article][PubMed] [Google Scholar]
[18] DO Moon, MO Kim, HJ Lee, YH Choi, YM Park, MS Heo, et al. Curcumin attenuates ovalbumin-induced airway inflammation by regulating nitric oxide. Biochem Biophys Res Commun. 2008;375:275–79. [PubMed] [Google Scholar]
[19] BB Aggarwal, KB Harikumar. Potential therapeutic effects of Curcumin, the anti-inflammatory agent,against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41:40–59. [PMC free article][PubMed] [Google Scholar]
[20] SW Oh, JY Cha, JE Jung, BC Chang, HJ Kwon, BR Lee, et al. Curcumin attenuates allergic airway inflammation and hyper-responsiveness in mice through NF-κB inhibition. J Ethnopharmacol. 2011;136:414–21. [PubMed] [Google Scholar]
[21] M Karaman, Z Arikan Ayyildiz, F Firinci, M Kiray, A Bagriyanik, O Yilmaz, et al. Effects of Curcumin on lung histopathology and fungal burden in a mouse model of chronic asthma and oropharyngeal candidiasis. Archives of medical research. 2011;42:79–87. [PubMed] [Google Scholar]
[22] Zeng Xin, Cheng Ying, Qu Yuejun, Xu Jide, Han Zhiyuan , Zhang Tingting . Curcumin inhibits the proliferation of airway smooth muscle cells in vitro and in vivo. Int J Mol Med. 2013;32:629–36. [PubMed] [Google Scholar]
[23] Kang BY, Song YJ, Kim KM, Choe YK, Hwang Y, Kim TS. Curcumin inhibits Th1 cytokine profile in CD4+T cells by suppressing interleukin-12 production in macrophages. Br J Pharmacol. 1999;128:380–84. [PMC free article] [PubMed] [Google Scholar]
[24] J Hong, M Bose, J Ju, JH Ryu, X Chen, S Sang, et al. Modulation of arachidonic acid metabolism by Curcumin and related β-diketone derivatives: Effects on

cytosolic phospholipase A2, cyclooxygenases and 5 lipoxygenase. Carcinogenesis. 2004;25:1671–79. [PubMed] [Google Scholar]
[25] GC Jagetia, BB Aggarwal. Spicing up of the immune system by curcumin. J Clin Immunol. 2007;27:19–35. [PubMed] [Google Scholar]
[26] S Biswas, I Rahman. Modulation of steroid activity in chronic inflammation: a novel anti-inflammatory role for Curcumin. Mol Nutr Food Res.. 2008;52:987–94. [PubMed] [Google Scholar]
[27] M Schatz, S Clark, CA Camargo Jr. Sex Differences in the presentation and course of asthma hospitalizations. Chest. 2006;129:50–5. [PubMed] [Google Scholar]
[28] SK Vemula, PR Turapati, RSR Ponugoti, P Garrepally. Asthma: Alternative management approaches.Asian J Pharm Clin Res. 2011;4:1–8. [Google Scholar]
[29] TP Ng, M Niti, KB Yap, WC Tan. Curcumins-Rich Curry Diet and Pulmonary Function in Asian Older Adults. PLoS ONE. 2012;7(12):e51753. [PMC free article] [PubMed] [Google Scholar]
[30] V Vachharajani, SW Wang, N Mishra, M El-Gazzar, B Yoza, C McCall. Curcumin modulates leukocyte and platelet adhesion in murine sepsis. Microcirculation. 2010;17:407–16.[PMC free article] [PubMed] [Google Scholar]

11. Curcumin as an Anti-Inflammatory Agent

Int J Biochem Cell Biol. Author manuscript; available in PMC 2010 Jan 1.
Published in final edited form as: Int J Biochem Cell Biol. 2009; 41(1): 40–59.
Published online 2008 Jul 9. doi: 10.1016/j.biocel.2008.06.010

PMCID: PMC2637808
NIHMSID: NIHMS88681
PMID: 18662800

Potential Therapeutic Effects of Curcumin, the Anti-inflammatory Agent, Against Neurodegenerative, Cardiovascular, Pulmonary, Metabolic, Autoimmune and Neoplastic Diseases

Bharat B. Aggarwal 1 and Kuzhuvelil B. Harikumar

Abstract

"Although safe in most cases, ancient treatments are ignored because neither their active component nor their molecular targets are well defined. This is not the case, however, with curcumin, a yellow-pigment substance and component of turmeric (Curcuma longa), which was identified more than a century ago. For centuries it has been known that turmeric exhibits anti-inflammatory activity, but extensive research performed within the past two decades has shown that the this activity of turmeric is due to **curcumin, a diferuloylmethane. This agent has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation.** The process of inflammation has been shown to play a major role in most chronic illnesses, including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. In the current review, we provide evidence for **the potential role ofcurcumin in the prevention and treatment of various pro-inflammatory chronic diseases**.These features, combined with the pharmacological safety and negligible cost, rendercurcumin an attractive agent to explore further."

- Journal List
- Pharmacogn Mag
- v.10(37); Jan-Mar 2014

12. Curcumin vs. Fluoride Toxicity

Curcumin attenuates neurotoxicity induced by fluoride: An *in vivo* evidence

Chhavi Sharma, Pooja Suhalka, Piyu Sukhwal, Neha Jaiswal, and Maheep Bhatnagar

Pharmacogn Mag. 2014 Jan-Mar; 10(37): 61–65.

doi: 10.4103/0973-1296.126663

PMCID: PMC3969660

PMID: 24696547

Abstract - Background:

"Curcumin (Cur), an active ingredient of turmeric is known to have multiple activities, including an antioxidant property and has been suggested to be useful in treatment of several neurological diseases.

"Objective:

"To investigate the neuroprotective effects of Cur to mitigate the effect of the Fluoride (F) induced neurotoxicity in mice brain using the histological and the biochemical parameters.

"Materials and Methods:

Exposure of mice (30 days old male) to F (120 ppm) daily for 30 days.

"Result and Discussion:

"Treatment with the F causes an increase in lipid peroxidation (LPO) and also increase in the neurodegenerative cells in the hippocampal sub-regions. Interestingly, co-treatment with Cur (30 mg/kg BW) with F (120 ppm) for 30 days results in significant decreases in LPO with a concomitant decrease in neurodegeneration as compared with those treated with F alone.

"Conclusion:

"Our study reveals that Cur is useful in ameliorating degenerative effects of F in mice brain."

Note: Fluoride calcifies the pineal gland, subverting its ability to regulate the hormonal system and to connect us with the cosmos. HK

13. Curcumin and Parkinson's - In this section I present excerpts from studies on curcumin's efficacy for Parkinson's, and I put important passages in bold. HK

Neuroprotective properties of curcumin in toxin-base animal models of Parkinson's disease: a systematic experiment literatures review

- Xin-Shi Wang†,
- Zeng-Rui Zhang†,
- Man-Man Zhang,
- Miao-Xuan Sun,
- Wen-Wen Wang Email author and
- Cheng-Long Xie Email author

†Contributed equally

BMC Complementary and Alternative Medicine BMC series 2017**17**:412
https://doi.org/10.1186/s12906-017-1922-x

Abstract - Background

"Curcumin (diferuloylmethane), a polyphenol extracted from the plant *Curcuma longa*, is widely used in Southeast Asia, China and India in food preparation and for medicinal purposes. Meanwhile, **the neuroprotective actions of curcumin have been documented for experimental therapy in Parkinson's disease (PD).**

"Methods -"In this study, we used a systematic review to comprehensively assess the efficacy of curcumin in experimental PD. Using electronic and manual search for the literatures, we identified studies describing the efficacy of curcumin in animal models of PD.

"Results - We identified 13 studies with a total of 298 animals describing the efficacy of curcumin in animal models of PD. The methodological quality of all preclinical trials is ranged from 2 to 5. The majority of the experiment studies demonstrated that curcumin was more significantly neuroprotection effective than control groups for treating PD. Among them, five studies indicated that curcumin had an anti-inflammatory effect in the PD animal models ($p < 0.05$). Meanwhile, four studies showed the antioxidant capability of curcumin, by which it protected substantia nigra neurons and improved striatal dopamine levels. Furthermore, two studies in this review displayed that curcumin treatment was also effective in reducing neuronal apoptosis and improving functional outcome in animal models of PD. Most of the preclinical studies demonstrated the positive findings while one study reported that curcumin had no beneficial effects against Mn-induced disruption of hippocampal metal and neurotransmitter homeostasis.

" **Conclusions -** The results demonstrated a marked efficacy of curcumin in experimental model of PD, suggesting curcumin probably a candidate neuroprotective drug for human PD patients."

14. a. Curcumin and Alzheimer's - In this section I present excerpts from two studies on curcumin's efficacy for Alzheimer's, and I put important passages in bold. HK

Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial

Gary W. Small, M.D., Prabha Siddarth, Ph.D., Zhaoping Li, M.D., Ph.D., Karen J. Miller, Ph.D., Linda Ercoli, Ph.D., Natacha D. Emerson, M.A., Jacqueline Martinez, M.B.A., M.S., Koon-Pong Wong, Ph.D., Jie Liu, Ph.D., David A. Merrill, M.D., Ph.D., Stephen T. Chen, M.D., Susanne M. Henning, Ph.D., R.D., Nagichettiar Satyamurthy, Ph.D., Sung-Cheng Huang, D.Sc., David Heber, M.D., Ph.D., Jorge R. Barrio, Ph.D.
https://doi.org/10.1016/j.jagp.2017.10.010

" **Objective**: Because curcumin's anti-inflammatory properties may protect the brain from neurodegeneration, we studied its effect on memory in non-demented adults and explored its impact on brain amyloid and tau accumulation using 2-(1-{6-[(2-[F18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile positron emission tomography (FDDNP-PET).

" Methods: Forty subjects (age 51–84 years) were randomized to a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily [N = 21]) or placebo (N = 19) for 18 months.Primary outcomes were verbal (Buschke Selective Reminding Test [SRT]) and visual (Brief Visual Memory TestRevised [BVMT-R]) memory, and attention (Trail Making A) was a secondary outcome. FDDNP-PET signals (15 curcumin, 15 placebo) were determined in amygdala, hypothalamus, medial and lateral temporal, posterior cingulate, parietal, frontal, and motor (reference) regions. Mixed effects general linear models controlling for age and education, and effect sizes (ES; Cohen's d) were estimated.

"Results: SRT Consistent LongTerm Retrieval improved with curcumin (ES = 0.63, p = 0.002) but not with placebo (ES = 0.06, p = 0.8; between-group: ES = 0.68, p = 0.05). Curcumin also improved SRT Total (ES = 0.53, p = 0.002), visual memory (BVMT-R Recall: ES = 0.50, p = 0.01; BVMT-R Delay:ES = 0.51, p = 0.006), and attention (ES = 0.96, p < 0.0001) compared with placebo (ES = 0.28, p = 0.1; between-group: ES = 0.67, p = 0.04). FDDNP binding decreased significantly in the amygdala with curcumin (ES = −0.41, p = 0.04) compared with placebo (ES = 0.08,

p = 0.6; between-group: ES = 0.48, p = 0.07). In the hypothalamus, FDDNP binding did not change with curcumin (ES = −0.30, p = 0.2), but increased with placebo (ES = 0.26, p = 0.05; between-group: ES = 0.55, p = 0.02).

"Conclusions: Daily oral Theracurmin may lead to improved memory and attention in nondemented adults.The FDDNP-PET findings suggest that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory. (Am J Geriatr Psychiatry 2018; 26:266–277)

…. "Highlights:

• This is the first long-term (18 months) double-blind, placebo controlled trial of a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily) in non-demented adults.

• We found that daily oral Theracurmin led to significant memory and attention benefits.

• FDDNP-PET scans performed pre- and post-treatment suggested that behavioral and cognitive benefits are associated with decreases in plaque and tangle accumulation in brain regions modulating mood and memory.

• Curcumin's cognitive benefits may stem from its anti-inflammatory and/or antiamyloid brain effects.

"Received July 16, 2017; revised September 8, 2017; accepted October 13, 2017.

From the Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior (GWS, PS, KJM, LE, NDE, JM, DAM, STC), UCLA Longevity Center (GWS, KJM, LE, JM), Department of Molecular and Medical Pharmacology (K-PW, JL, NS, S-CH, JRB), and Center for Human Nutrition (ZL, SMH, DH), David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA.

Send correspondence and reprint requests to Gary W. Small, M.D., UCLA Semel Institute, 760 Westwood Plaza, Los Angeles, CA 90024. e-mail: gsmall@mednet.ucla.edu Presented in part at the 2017 Alzheimer's Association International Conference, London, UK. *https://doi.org/10.1016/j.jagp.2017.10.010 REGULAR RESEARCH ARTICLES 266 Am J Geriatr Psychiatry 26:3, March 2018"*

14.b. The effect of curcumin (turmeric) on Alzheimer's disease: An overview

Shrikant Mishra and Kalpana Palanivelu

Ann Indian Acad Neurol. 2008 Jan-Mar; 11(1): 13–19. PMCID: PMC2781139, PMID: 19966973

doi: 10.4103/0972-2327.40220

Abstract – Introduction:

Alzheimer's disease

"Alzheimer's disease (AD) is a progressive neurodegenerative disease. It is characterized by progressive cognitive deterioration together with declining activities of daily living and behavioral changes. It is the most common type of pre-senile and senile dementia. According to the World Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide.[1] In India, the total prevalence of dementia per 1000 people is 33.6%, of which AD constitutes approximately 54% and vascular dementia constitutes approximately 39%. AD affects approximately 4.5 million people in the United States or approximately 10% of the population over the age of 65, and this number is projected to reach four times by 2050. **The frequency increases to 50% by the age of 80 years.** Every year more than $100 billion is spent for health care in the U.S. to treat AD in primary care settings alone."

"Neuropathology of AD:

"The neuropathological process consists of neuronal loss and atrophy, principally in the temporoparietal and frontal cortex, with an inflammatory response to the deposition of amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibres (neurofibillary tangles). Neurotic plaques are relatively insoluble dense cores of 5-10 nm thick amyloid fibrils with a pallor staining "halo" surrounded by dystrophic neuritis, reactive astrocytes and activated microglia. There is an increased presence of monocytes/macrophages in the cerebral vessel wall and reactive or activated microglial cells in the adjacent parenchyma.[2,3] The main protein component of amyloid in AD is the 39-42 amino acid (beta) amyloid peptide (A-beta) …"

Curcumin - "Curcumin ... has been used extensively in Ayurveda (Indian system of Medicine) for centuries as a pain relieving, anti-inflammatory agent to relieve pain and inflammation in the skin and muscles. It has also proven to have anti-cancer properties.[4,5] Curcumin holds a high place in Ayurvedic medicine as a "cleanser of the body," ...

"Curcumin and Alzheimer's Disease

Worldwide, there are over 1000 published animal and human studies, both *in vivo* and *in vitro* in which the effects of curcumin on various diseases have been examined. Studies include epidemiological, basic and clinical research on AD.

"Epidemiological Studies

"Various studies and research[9,10] results indicate a lower incidence and prevalence of AD in India. **The prevalence of AD among adults aged 70-79 years in India is 4.4 times less than that of adults aged 70-79 years in the United States.[**9] Researchers investigated the association between the curry consumption and cognitive level in 1010 Asians between 60 and 93 years of age. The study found that **those who occasionally ate curry (less than once a month) and often (more than once a month) performed better on a standard test (MMSE) of cognitive function** than those who ate curry never or rarely.[10]"

"Mechanism of action of curcumin on Alzheimer's disease:

The process through which AD degrades the nerve cells is believed to involve certain properties: inflammation, oxidative damage and most notably, the formation of beta-amyloid plaques, metal toxicity [Figure 3]. There have been several studies on effects of curcumin on AD. Outlined below are some of the studies and their conclusions.

"Effects of Curcumin on Macrophages

"A study conducted at UCLA found that curcumin may help the macrophages to clear the amyloid plaques found in Alzheimer's disease. …"11]

"Curcumin on glial cells:

"Recent histological studies reveal the **presence of activated microglia and reactive astrocytes around A-beta plaques in brains from patients with AD.** The chronic activation of microglia secretes cytokines and some reactive substances that exacerbate A-beta pathology. So neuroglia is an important part in the pathogenesis of AD. Curcumin has a lipophilic property and can pass through all cell membranes and thus exerts its intracellular effects. **Curcumin has anti-proliferative actions on microglia. A minimal dose of curcumin affects neuroglial proliferation and differentiation.** Its inhibition of microglial proliferation and differentiation were studied and researched by the University of Southern California Los Angeles (UCLA). …The overall effect of curcumin on neuroglial cells involves decreased astrocytes proliferation, improved myelogenesis and increased activity and differentiation of oligodendrocytes."

"Curcumin as an Anti Inflammatory in Alzheimer's

"One of the important pathogenesis in Alzheimer's disease is the chronic inflammation of nerve cells. … Curcumin has a potent anti-inflammatory effect. Through its various anti-inflammatory effects, it may have a role in the cure of AD. …The chemotaxis of monocytes, which can occur in response to chemokines from activated microglia and astrocytes in the brain, can be decreased by curcumin.[13,14]

“Curcumin is found to inhibit cyclooxygenase (COX-2), phospholipases, transcription factor and enzymes involved in metabolizing the membrane phospholipids into prostaglandins….The exposure to curcumin also impaired the production of pro-inflammatory cytokines (IL-1, IL-6 and TNF-). **These studies indicate a potent inhibitor of pro-inflammatory cytokine production by curcumin** and it may differ according to the nature of the target cells.”

“Curcumin as an Anti-oxidant

‘Curcumin inhibits the activity of AP-1, a transcription factor involved in expression of amyloid, which is linked to AD. Curcuminoids are proven to have strong antioxidant action demonstrated by the inhibition of the formation and propagation of free radicals. It decreases the low-density lipoprotein oxidation and the free radicals that cause the deterioration of neurons, not only in AD but also in other neuron degenerative disorders such as Huntington's and Parkinson's disease.[16] In one study, curcuma oil (500 mg Kg(-1) i.p.) was given 15 min before 2 h middle cerebral artery occlusion, followed by 24 h reflow in rats. This significantly diminished the infarct volume, improved neurological deficit and counteracted oxidative stress.[17]

“A study conducted at Nanjing Medical University (China) showed that a single injection of curcumin (1 and 2 mg/kg, i.v.) after focal cerebral ischemia/reperfusion in rats significantly diminished the infarct volume, improved neurological deficit, decreased mortality and reduced the water content in the brain.[18]

Curcumin has powerful antioxidant and anti-inflammatory properties; according to the scientists, these properties believe help ease Alzheimer's symptoms caused by oxidation and inflammation.[19] … Pre-treatment with curcumin protects brain mitochondria against peroxynitrite (a product of the reaction of nitric oxide with superoxide) a potent and versatile oxidant that can attack a wide range of cells *in vitro* by direct detoxification and *in vivo* by the elevation of total cellular glutathione levels.[22]”

“…Beta-Amyloid Plaques

“The most prominent characteristic feature in AD is the presence of beta-amyloid plaques. These plaques are basically an accumulation of small fibers called beta amyloid fibrils. Because the deposition of beta-amyloid protein is a consistent pathological hallmark of brains affected by AD, the inhibition of A-beta generation, prevention of A-beta fibril formation, destabilization of pre-formed A-beta would be an attractive therapeutic strategy for the treatment of AD. **The levels of beta-amyloid in AD mice that were given low doses of curcumin were decreased by around 40% in comparison to those that were not treated with curcumin.** In addition, low doses of curcumin also caused a 43% decrease in the so-called “plaque burden” that these beta-amyloid have on the brains of AD mice. Surprisingly low doses of curcumin given over longer period were actually more effective than high doses in combating the neurodegenerative process of AD.[26] At higher concentration, curcumin binds to amyloid beta and blocks its self assembly activity.

“Because of the lipophilic nature of curcumin, it crosses the blood brain barrier and binds to plaques. …Curcumin given to APPswe/PS1dE9 mice for 7 days crosses the blood-brain barrier as demonstrated by muliti-photon microscopy and reduces the existing senile plaques.[29] In another study, **curcumin has been shown to increase the phagocytosis of amyloid-beta, effectively clearing them from the brains of patients with AD**.[30]”

“Metal Chelation

“Studies showed that metals can induce A-beta aggregation and toxicity and are concentrated on Alzheimer's brain….**Curcumin, by interaction with heavy metals such as cadmium and lead, prevents neurotoxicity caused by these metals.** The intraperitoneal injection of lead acetate in rats in the presence of curcumin was studied microscopically. The results show lead-induced damage to neurons was significantly reduced in rats injected with curcumin.[34] A study at Chinese University of Hong Kong showed that by using spectrophotometry, the curcumin effectively binds to copper, zinc and iron. In addition, curcumin binds more effectively with redox-active metals such as iron and copper than the redox-inactive zinc. It is suggested that curcumin suppresses inflammatory damage by preventing metal induction of NF-kappa.[35,36]”

“Cholesterol Lowering Effect

“High-fat diets and increased blood cholesterol are linked to increased amyloid plaques by the intracellular accumulation of cholestryl esters.[37] Researchers believe that by inhibiting cholesterol formation and decreasing serum peroxides, curcumin might exert beneficial effects on AD.[38]”

“…Oral bioavailability:

“Curcumin has poor bioavailability. Because curcumin readily conjugated in the intestine and liver to form curcumin glucuronides.[39] In a clinical trial conducted in Taiwan, serum curcumin concentrations peaked one to two hours after an oral dose.”

“Conclusion

“Based on the main findings detailed above, **curcumin will lead to a promising treatment for Alzheimer's disease. …however, large-scale human studies are required to identify the prophylactic and therapeutic effect of curcumin.”**

“ References [Not Required Reading]

1. Fratiglioni L, De Ronchi D, Agüero-Torres H. Worldwide prevalence and incidence of dementia. Drugs Aging. 1999;15:365–75. [PubMed] [Google Scholar]

2. Bamberger ME, Landreth GE. Inflammation, apoptosis and Alzheimer's disease. Neuroscientist. 2002;8:276–83. [PubMed] [Google Scholar]

3. Di Patre PL, Read SL, Cummings JL, Tomiyasu U, Vartavarian LM, Secor DL, et al. Progression of clinical deterioration and pathological changes in patients with Alzheimers Disease evaluated at biopsy and autopsy. Arch Neurol. 1999;56:1254–61. [PubMed] [Google Scholar]

4. Shishodia S, Sethi G, Aggarwal BB. Getting back to roots. Ann NY Acad Sci. 2005;1056:206–17.[PubMed] [Google Scholar]

5. Ammon HP, Wahl MA. Pharmacology of curcuma longa. Planta Med. 1991;57:1–7. [PubMed] [Google Scholar]

6. Youssef KM, El-Sherbeny MA. Synthesis and antitumor activity of some curcumin analogs. Arch Pharm (Weinheim) 2005;338:181–9. [PubMed] [Google Scholar]

7. Kolev TM, Velcheva EA, Stamboliyska BA, Spiteller M. DFT and experimental studies of the structure and vibrational spectra of curcumin. Int J Quantum Chem. 2005;102:1069–79. [Google Scholar]

8. Payton F, Sandusky P. Alworth NMR study of the solution structure of curcumin WL PMID: 17315954(Pub Med) [PubMed] [Google Scholar]

9. Pandav R, Belle SH, DeKosky ST. Apolipoprotein E polymorphism and Alzheimer's disease: The Indo-US cross-national dementia study. Arch Neurol. 2000;57:824–30. [PubMed] [Google Scholar]

10. Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. Curry consumption and cognitive function in the elderly. Am J Epidemiol. 2006;164:898–906. [PubMed] [Google Scholar]

11. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, et al. Curcuminoids enhance amyloid -beta uptake by macrophages of Alzheimer's disease patients. J Alzheimers Dis. 2006;10:1–7. [PubMed] [Google Scholar]

12. Ambegaokar SS, Wu L, Alamshahi K, Lau J, Jazayeri L, Chan S, et al. Curcumin inhibits dose-dependently and time-dependently neuroglial proliferation and growth. Neuro Endocrinol Lett. 2003;24:469–73. [PubMed] [Google Scholar]

13. Giri RK, Rajagopal V, Kalra VK. Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor. J Neurochem. 2004;91:1199–210. [PubMed] [Google Scholar]

14. Pendurthi UR, Rao LV. Suppression of transcription factor Egr-1 by curcumin. Thromb Res. 2000;97:179–89. [PubMed] [Google Scholar]

15. Park SY, Kim DS. Discovery of natural products from Curcuma longa that protect cells from beta-amyloid insult: A drug discovery effort against Alzheimers disease. J Nat Prod. 2002;65:1227–31.[PubMed] [Google Scholar]

16. Kim GY, Kim KH, Lee SH, Yoon MS, Lee HJ, Moon DO. Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-B as potential targets. J Immunol. 2005;174:8116–24. [PubMed] [Google Scholar]

17. Rathore P, Dohare P, Varma S, Ray A, Sharma U, Jaganathanan NR, et al. Curcuma oil: Reduces early accumulation of oxidative product and is anti-apoptogenic in transient focal ischemia in rat brain. Neurochem Res. 2007 Oct 23; [PubMed] [Google Scholar]

18. Jiang J, Wang W, Sun YJ, Hu M, Li F, Zhu DY. Neuroprotective effect of curcumin on focal cerebral ischemic rats by preventing blood-brain barrier damage. Eur J Pharmacol. 2007;30:54–62. [PubMed] [Google Scholar]

19. Frautschy SA, Hu W. Phenolic anti inflammatory antioxidant reversal of b induced cognitive deficits and neuropathology. Neurobiol Aging. 2001;22:993–1005. [PubMed] [Google Scholar]

20. Bala K, Tripathy BC, Sharma D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. Biogerontology. 2006;7:81–9. [PubMed] [Google Scholar]

21. Kim DS, Park SY, Kim JK. Curcuminoids from Curcuma longa L. (Zingiberaceae) that protect PC rat pheochromocytoma and normal human umbilical vein endothelial cells from betaA(1-42) insult. Neurosci Lett. 2001;303:57–61. [PubMed] [Google Scholar]

22. Mythri RB, Jagatha B, Pradhan N, Andersen J, Bharath MM. Mitochondrial complex I inhibition in Parkinsons disease: How can curcumin protect mitochondria? Antioxid Redox Signal. 2007;9:399–408.[PubMed] [Google Scholar]

23. Scapagnini G, Foresti R, Calabrese V, Giuffrida Stella AM, Green CJ, Motterlini R. Caffeic acid, phenethyl ester and curcumin: A novel class of heme oxygenase 1 inducer. Mol Pharmacol. 2002;61:554–61. [PubMed] [Google Scholar]

24. Jeong GS, Pal HO, Jeong SO, Kim YL, Shin MK, Seo BY, et al. Comparative effects of curcuminoids on endothelial heme oxygenase-1 expression: Ortho-methoxy groups are

essential to enhance heme oxygenase activity and protection. Exp Mol Med. 2006;38:393–400. [PubMed] [Google Scholar]

25. Calabrese V, Butterfield DA, Stella AM. Nutritional antioxidants and the heme oxygenase pathway of stress tolerance: Novel targets for neuroprotection in Alzheimer's disease. Ital J Biochem. 2003;52:177–81.[PubMed] [Google Scholar]

26. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. J Biol Chem. 2005;280:5892–901. [PubMed] [Google Scholar]

27. Ono K, Hasegawa K, Naiki H, Yamada MJ. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta fibrils *in vitro*. Neurosci Res. 2004;75:742–50. [PubMed] [Google Scholar]

28. Narlawar R, Pickhardt M, Leuchtenberger S, Baumann K, Krause S, Dyrks T, et al. Curcumin-derived pyrazoles and isoxazoles: Swiss army knives or blunt tools for Alzheimers disease? Chem Med Chem. 2008;3:165–72. [PubMed] [Google Scholar]

29. Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology *in vivo*, disrupts existing plaques and partially restores distorted neurites in an Alzheimer mouse model. J Neurochem. 2007;102:1095–104. [PubMed] [Google Scholar]

30. Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, et al. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimers disease patients are improved by bisdemethoxycurcumin. Proc Natl Acad Sci USA. 2007;104:12849–54. [PMC free article] [PubMed] [Google Scholar]

31. Perry G, Sayre LM, Atwood CS, Castellani RJ, Cash AD, Rottkamp CA, et al. The role of iron and copper in the aetiology of neurodegenerative disorders. CNS Drugs. 2002;16:339–52. [PubMed] [Google Scholar]

32. DAI, Xueling, SUN, Yaxuan, JIANG Zhaofeng Copper (2) potentiation of Alzheimers A-(beta)1-40 cytotoxicity and transition on its secondary structure. Acta Biochimica et Biophysica Sinica. 1938;11:765–72. [PubMed] [Google Scholar]

33. Liu G, Huang W, Moir RD, Vanderburg CR, Barry AI, Zicheng P, et al. Metal exposure and Alzheimers pathogenesis. J Structural Biol. 2005;155:45–51. [PubMed] [Google Scholar]

34. Daniel S, Limson JL, Dairam A, Watkins GM, Daya S. Through metal binding, curcumin protects against lead- and cadmium-induced lipid peroxidation in rat brain homogenates

and against lead-induced tissue damage in rat brain. J Inorg Biochem. 2004;98:266–75. [PubMed] [Google Scholar]

35. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. Alzheimer's Dis. 2004;6:367–77. [PubMed] [Google Scholar]

36. Shukla PK, Khanna VK, Khan MY, Srimal RC. Protective effect of curcumin against lead neurotoxicity in rat. Hum Exp Toxicol. 2003;22:653–8. [PubMed] [Google Scholar]

37. Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: The cholesterol connection. Nat Neurosci. 2003;6:345–51. [PubMed] [Google Scholar]

38. Soni KB, Kuttan R. Effect of oral curcumin administration on serum peroxides and cholesterol in human volunteers. Indian J Physiol Pharmacol. 1992;36:273–5. [PubMed] [Google Scholar]

39. Ireson CR, Jones DJ, Orr Sl. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Biomarkers Prev. 2002;11:105–11. [PubMed] [Google Scholar]

40. Cheng AL, Hsu CH, Lin JK. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001;21:2895–900. [PubMed] [Google Scholar]

41. Liddle M, Hull C, Liu C. Powell D Contact urticaria from curcumin. Dermatitis. 2006;17:196–7.[PubMed] [Google Scholar]

42. Chainani N. Safety and anti-inflammatory activity of Curcumin component of turmeric (curcuma longa) J Alter Compl Med. 2003;9:161–8. [PubMed] [Google Scholar]

43. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64:353–6. [PubMed] [Google Scholar]

44. Rasyid A, Lelo A. The effect of curcumin and placebo on human gall-bladder function: An ultrasound study. Aliment Pharmacol Ther. 1999;13:245–9. [PubMed] [Google Scholar]

45. Rasyid A, Rahman AR, Jaalam K, Lelo A. Effect of different curcumin dosages on human gall bladder. Asia Pac J Clin Nutr. 2002;11:314–8. [PubMed] [Google Scholar]

46. Lim GP, Chu T, Yang F, Beech W, Frautschy SA. Cole GM The curry spice curcumin reduces oxidative damage and amyloid pathogenesis on Alzheimer's transgenic mouse. J Neurosci. 2001;21:8370–7.[PubMed] [Google Scholar]

47. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity and cognition. Exp Neurol. 2006;197:309–17. [PubMed] [Google Scholar]

48. Suri AA. The anti-oxidative effects of curcumin on memory curves of planaria: A model for the treatment of Alzheimer's disease. 2003. p. S1425. Available from: http://www.usc.edu. [Google Scholar]

49. Jorm AF, Jolley D. The incidence of dementia: A meta analysis. Neurology. 1998;51:728–33.[PubMed] [Google Scholar]

50. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL. A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res. 2005;2:131–6. [PMC free article] [PubMed] [Google Scholar]"

Part Four – Supplemental Research Studies on Curcumin's Health Benefits. Optional Reading, Not Required. Read them for your pleasure…

A. Heart Health and Curcumin

Effect of curcumin on high-sensitivity C-reactive protein and blood-lipids in patients with coronary heart disease. **Zhang, Qing-bin and Liu, Fu-yuan.** 2, s.l.: CNKI, February 2007, Chinese Traditional Patent Medicine, Vol. 2007, pp. 164-167. ISSN: 1001-1528.

The Role of Chronic Inflammation in Cardiovascular Disease and its Regulation by Nutrients. **Osiecki, Henry.** [ed.] Kathleen A. Head. 1, Napa: Thorne Research, Inc., March 2004, Alternative Medicine Review, Vol. 9, pp. 32-53. ISSN: 1089-5159.

An hydroalcoholic extract of Curcuma longa lowers the apo B:apo A ratio Implications for atherogenesis prevention. **Ramírez-Boscá, Ana, et al., et al.** [ed.] Bernard L. Strehler. 1-2, Los Angeles: Elsevier Science Ireland Ltd., October 20, 2000, Mechanisms of Ageing and Development, Vol. 119, pp. 41-47. DOI: 10.1016/S0047-6374(00)00169-X; http://www.sciencedirect.com/science/article/pii/S004763740000169X. ISSN: 0047-6374.

Blaylock, Russell L. What Drug Companies Don't Want You to Know about Heart Disease, Cholesterol, and Obesity. *The Blaylock Wellness Report.* February 2008, Vol. 5, 2.

Cardiovascular Protection by Curcumin: Molecular Aspects. **Kapakos, Georgia, Youreva, Viktoria and Srivastava, Ashok K.** [ed.] S.C. Sharma. New Delhi: National Institute of Science Communication and Information Resources, October 2012, Indian Journal of Biochemistry & Biophysics, Vol. 49, pp. 306-315. ISSN: 0301-1208.

Protective Effect of Curcumin on Pulmonary and Cardiovascular Effects Induced by Repeated Exposure to Diesel Exhaust Particles in Mice. **Nemmar, Abderrahim, Subramaniyan, Deepa and Ali, Badreldin H.** [ed.] Mauricio Rojas. 6, s.l.: Public Library of Science, June 22, 2012, PLoS One, Vol. 7, p. e39554. DOI: 10.1371/journal.pone.0039554; http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0039554. ISSN: 1932-6203.

Curcumin maintains cardiac and mitochondrial function in chronic kidney disease. **Correa, Francisco, et al., et al.** [ed.] Kelvin Davies. Los Angeles: Elsevier Inc., August 2013, Free Radical Biology and Medicine, Vol. 61, pp. 119-129. DOI: 10.1016/j.freeradbiomed.2013.03.017; http://www.sciencedirect.com/science/article/pii/S0891584913001226. ISSN: 0891-5849.

Anti-platelet effects of Curcuma oil in experimental models of myocardial ischemia-reperfusion and thrombosis. **Prakash, Prem, et al., et al.** [ed.] Charles Francis and Per Morten Sandset. 2, Rochester; Oslo: European Thrombosis Research Organisation, February 2011, Thrombosis Research, Vol. 127, pp. 111-118. DOI: 10.1016/j.thromres.2010.11.007; http://www.thrombosisresearch.com/article/S0049-3848(10)00603-1/abstract. ISSN: 0049-3848.

Protective effect of curcumin against cardiac dysfunction in sepsis rats. **Yang, Cheng, et al., et al.** [ed.] John M. Pezzuto. 4, London: Informa Healthcare, April 2013, Pharmaceutical Biology, Vol. 51, pp. 482-487. DOI: 10.3109/13880209.2012.742116; http://informahealthcare.com/doi/abs/10.3109/13880209.2012.742116. ISSN: 1388-0209.

University of Minnesota Medical School. U of M Medical School researchers find natural antioxidant can protect against cardiovascular disease. *American Association for the Advancement of Science (AAAS): Eureka Alert!* [Online] June 15, 2012. [Cited: March 25, 2015.] http://health.umn.edu/media/releases/GPx3/.

Apolipoproteins A-I and B: biosynthesis, role in the development of atherosclerosis and targets for intervention against cardiovascular disease. **Olofsson, Sven-Olof, Wiklund, Olov and Borén, Jan.** [ed.] Roland Asmar. 4, Paris: Dove Medical Press Limited: International Society of Vascular Health, August 2007, Vascular Health and Risk Management, Vol. 3, pp. 491-502. ISSN: 1178-2048.

Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. **Shin, Su-Kyung, et al., et al.** [ed.] Hans-Ulrich Humpf. 12, Weinheim: WILEY-VCH Verlag GmbH & Co., December 2011, Molecular Nutrition & Food Research, Vol. 55, pp. 1829-1840. DOI: 10.1002/mnfr.201100440; http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201100440/abstract. eISSN: 1613-4133.

Curcumin Improves Hemodynamic Status and Attenuates Arterial Remodeling in L-NAME-Induced Hypertensive Rats. **Boonla, Orachorn, et al., et al.** Bangkok: Journal of Physiological and Biomedical Sciences, 2012. 41st Annual Scientific Meeting of The Physiological Society of Thailand. Vol. 25, p. 38. O-04.

The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. **Morimoto, Tatsuya, et al., et al.** [ed.] Howard Rockman. 3, Durham: American Society for Clinical Investigation, March 3, 2008, The Journal of Clinical Investigation, Vol. 118, pp. 868–878. DOI: 10.1172/JCI33160; http://www.jci.org/articles/view/33160. ISSN: 0021-9738.

The Sonodynamic Effect of Curcumin on THP-1 Cell-Derived Macrophages. **Wang, Fengping, et al., et al.** [ed.] Leandro Machado Rocha. Article ID 737264, Harbin: Hindawi Publishing Corporation, 2013, BioMed Research International, Vol. 2013, pp. 1-9. DOI: 10.1155/2013/737264; http://www.hindawi.com/journals/bmri/2013/737264/. eISSN: 2314-6141.

Curcumin Suppresses Gelatinase B Mediated Norepinephrine Induced Stress in H9c2 Cardiomyocytes. **Kohli, Shrey, et al., et al.** [ed.] Effie C. Tsilibary. 10, Demokritos: Public Library of Science, October 7, 2013, PLoS One, Vol. 8, p. e76519. DOI: 10.1371/journal.pone.0076519; http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0076519. eISSN: 1932-6203.

Miriyala, Sumitra, Panchatcharam, Manikandan and Rengarajulu, Puvanakrishnan. Cardioprotective Effects of Curcumin. [ed.] Bharat B. Aggarwal, Young-Joon Surh and Shishir Shishodia. *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease.* New York: Springer Science+Business Media, LLC, 2007, pp. 359-378. ISBN-13: 978-0-387-46400-8.

Effect of Tetrahydrocurcumin on Aortic Stiffening in Mice Exposed to Cadmium. **Donpunha, Wanida, et al., et al.** Bangkok: Journal of Physiological and Biomedical Sciences, 2012. 41st Annual Scientific Meeting of The Physiological Society of Thailand. Vol. 25, p. 36. O-02.

Curcuma oil ameliorates hyperlipidaemia and associated deleterious effects in golden Syrian hamsters. **Singh, Vishal, et al., et al.** [ed.] G.C. Burdge. 3, Southampton: Cambridge University Press, August 2013, British Journal of Nutrition, Vol. 110, pp. 437-446. DOI: http://dx.doi.org/10.1017/S0007114512005363; http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8957513&fileId=S0007114512005363. ISSN: 0007-1145.

Curcumin increases vasodilatory effect of cilostazol in diabetic rat aorta. **Nurullahoğlu-Atalik, K.E., et al., et al.** [ed.] Ashok Agarwal. 2, New Delhi: CSIR-National Institute of Science Communication and Information Resources, February 2012, Indian Journal of Experimental Biology, Vol. 50, pp. 128-132. ISSN: 0019-5189.

Anti-Inflammatory Polymeric Coatings for Implantable Biomaterials and Devices. **Bridges, Amanda W. and Andrés J. García, Ph.D.** [ed.] David C. Klonoff. 6, Burlingame: Diabetes Technology Society, November 2008, Journal of Diabetes Science and Technology, Vol. 2, pp. 984-994. ISSN: 1932-2968.

Sefton, Michael V., Gemmell, Cynthia H. and Gorbet, Maud B. Nonthrombogenic Treatments and Strategies. [ed.] Buddy D. Ratner, et al., et al. *Biomaterials Science.* 3. Oxford: Academic Press: Elsevier Inc., 2013, Appendix E: Chapter II.5.2, pp. 1488-1509. ISBN: 978-0-12-374626-9.

Curcumin (diferuloylmethane) delivery methods: A review. **Angelo Azzi.** 1, Boston: John Wiley & Sons, Inc.: International Union of Biochemistry and Molecular Biology, Inc., January/February 2013, Biofactors, Vol. 39, pp. 21-26. DOI: 10.1002/biof.1080; http://onlinelibrary.wiley.com/doi/10.1002/biof.1080/abstract. eISSN: 1872-8081.

Preparation and blood compatibility of electrospun PLA/curcumin composite membranes. **Chen, Yan, et al., et al.** [ed.] Won Ho Jo. 10, Seoul: The Korean Fiber Society, December 2012, Fibers and Polymers, Vol. 13, pp. 1254-1258. DOI: 10.1007/s12221-012-1254-x; http://link.springer.com/article/10.1007%2Fs12221-012-1254-x. ISSN: 1229-9197.

Demethoxycurcumin, a major active curcuminoid from Curcuma longa, suppresses balloon injury induced vascular smooth muscle cell migration and neointima formation: An in vitro and in vivo study. **Sheu, Ming-Jyh, et al., et al.** [ed.] Hans-Ulrich Humpf. 9, KGaA, Weinheim: WILEY-VCH Verlag GmbH & Co., September 2013, Molecular Nutrition & Food

Research, Vol. 57, pp. 1586-1597. DOI: 10.1002/mnfr.201200462; http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201200462/abstract. eISSN: 1613-4133.

Forming of Demethoxycurcumin Nanocrystallite-Chitosan Nanocarrier for Controlled Low Dose Cellular Release for Inhibition of the Migration of Vascular Smooth Muscle Cells. **Wang, Yen-Jen, et al., et al.** [ed.] Gordon L. Amidon. 8, Washington, D.C.: American Chemical Society, August 6, 2012, Molecular Pharmaceutics, Vol. 9, pp. 2268-2279. DOI: 10.1021/mp300150q; http://pubs.acs.org/doi/abs/10.1021/mp300150q. ISSN: 1543-8384.

In vitro mutagenicity and blood compatibility of paclitaxel and curcumin in poly (dl-lactide-co-glicolide) films. **Vieira, Iara Lucia Barbosa Fernandes, et al., et al.** [ed.] Daniel Acosta, Frank A. Barile and Bas J. Blaauboer. 1, Cincinnati; Queens; Utrecht: Elsevier Ltd., February 2013, Toxicology in Vitro, Vol. 27, pp. 198-203. ISSN: 0887-2333.

Natural wound healing and bioactive natural products. **Tsala, David Emery, Amadou, Dawe and Habtemariam, Solomon.** [ed.] T. Efferth. 3, Surrey: Inforesights Publishing, 2013, Phytopharmacology, Vol. 4, pp. 532-560. e2046-1194.

Combined effect of PLGA and curcumin on wound healing activity. **Chereddy, Kiran Kumar, et al., et al.** [ed.] K. Park. 2, West Lafayette: Elsevier B.V., October 28, 2013, Journal of Controlled Release, Vol. 171, pp. 208-215. ISSN: 0168-3659.

Proteins mediating collagen biosynthesis and accumulation in arterial repair: novel targets for anti-restenosis therapy. **Osherov, Azriel B., et al., et al.** [ed.] H. Michael Piper and David Garcia-Dorado. 1, Düsseldorf; Barcelona: Oxford University Press: European Society of Cardiology, July 1, 2011, Cardiovascular Research, Vol. 91, pp. 16-26. DOI: 10.1093/cvr/cvr012; http://cardiovascres.oxfordjournals.org/content/91/1/16.full. ISSN: 0008-6363.

Dysregulation of the Ubiquitin-Proteasome System by Curcumin Suppresses Coxsackievirus B3 Replication. **Si, Xiaoning, et al., et al.** [ed.] Lynn W. Enquist. 7, Washington DC: American Society for Microbiology, January 2007, Journal of Virology, Vol. 81, pp. 3142-3150. DOI: 10.1128/JVI.02028-06; http://jvi.asm.org/content/81/7/3142. ISSN: 0022-538X.

Curcumin Protects Mice From Coxsackievirus B3-Induced Myocarditis by Inhibiting the Phosphatidylinositol 3 kinase/Akt/Nuclear Factor-κB Pathway. **Song, Yunxiao, et al., et al.** [ed.] Robert A. Kloner. 6, Los Angeles: SAGE Publications, September 19, 2013, Journal of Cardiovascular Pharmacology and Therapeutics, Vol. 18, pp. 560-569. DOI: 10.1177/1074248413503044; http://cpt.sagepub.com/content/18/6/560. ISSN: 1074-2484.

Non-HDL-C is a Better Predictor for the Severity of Coronary Atherosclerosis Compared with LDL-C. **Zhang, Yan, et al., et al.** [ed.] A. Robert Denniss. 10, Sydney: Elsevier B.V.: Australian and New Zealand Society of Cardiac and Thoracic Surgeons; Cardiac Society of Australia and New Zealand, October 2016, Heart, Lung and Circulation, Vol. 25, pp. 975-981. DOI:10.1016/j.hlc.2016.04.025; http://linkinghub.elsevier.com/retrieve/pii/S1443950616302608. ISSN: 1443-9506; PMID: 27634241.

B. Curcumin Studies for Colon Health, Diabetes, Hyperlipidemia, and Obesity - In this section I present excerpts from four studies on the efficacy of curcumin for treating colon health, diabetes, hyperlipidemia, and obesity. Thereafter I present many further studies on these subjects for the reader's pleasure and further information. **Optional.**

1. *Preventive Effects of Curcumin on the Development of Azoxymethane-Induced Colonic Preneoplastic Lesions in Male C57BL/KsJ-db/db Obese Mice*.

Kubota, Masaya, et al., et al. [ed.] Leonard A. Cohen. 1, Valhalla: Taylor and Francis, 2012, Nutrition and Cancer, Vol. 64, pp. 72-79. DOI: 10.1080/01635581.2012.630554; http://www.tandfonline.com/doi/abs/10.1080/01635581.2012.630554#.VDq8izZOVD8. ISSN: 0163-5581.

Abstract - **I have excerpted quotes from the abstract of this study from the journal Nutrition and Cancer** Volume 64, 2012 - Issue 1 **I have added bold for emphasis. HK**

"**Obesity-related metabolic abnormalities include a state of chronic inflammation and adipocytokine imbalance, which increase the risk of colon cancer. Curcumin, a component of turmeric, exerts both cancer preventive and antiinflammatory properties. Curcumin is also expected to have the ability to reverse obesity-related metabolic derangements…**

"….Feeding with a diet containing 0.2% and 2.0% curcumin caused a significant reduction in the total number of colonic premalignant lesions compared with basal diet-fed mice…

"….**In conclusion, curcumin inhibits the development of colonic premalignant lesions in an obesity-related colorectal carcinogenesis model**…Curcumin may be useful in the chemoprevention of colorectal carcinogenesis in obese individuals

"ACKNOWLEDGMENTS

"This work was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan (No. 18790457 to M. S. and No. 17015016 to H. M.) and by Grant-in-Aid for the 3rd Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan."

2. Hypoglycemic Effects of Turmeric (*Curcuma longa* L. Rhizomes) on Genetically Diabetic KK-A^{y} Mice

Minpei Kuroda, Yoshihiro Mimaki, Tozo Nishiyama, Tatsumasa Mae, Hideyuki Kishida, Misuzu Tsukagawa, Kazuma Takahashi, Teruo Kawada, Kaku Nakagawa, Mikio Kitahara

Abstract is from *the Biological and Pharmaceutical Bulletin* of Japan

JOURNALS FREE ACCESS

2005 Volume 28 Issue 5 Pages 937-939

DOI https://doi.org/10.1248/bpb.28.937

Abstract

Abstract

The turmeric (*Curcuma longa* L. rhizomes) EtOH extract significantly suppressed an increase in blood glucose level in type 2 diabetic KK-A^{y} mice. In an *in vitro* evaluation, the extract stimulated human adipocyte differentiation in a dose-dependent manner and showed human peroxisome proliferator-activated receptor (PPAR)-γ ligand-binding activity in a GAL4-PPAR-γ chimera assay. The main constituents of the extract were identified as curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone, which had also PPAR-γ ligand-binding activity. **These results indicate that turmeric is a promising ingredient of functional food for the prevention and/or amelioration of type 2 diabetes and that curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone mainly contribute to the effects *via* PPAR-γ activation.**

3. I have excerpted quotes from the abstract of this study which is from **BioFactors**. I have added bold for emphasis. HK

Molecular mechanisms of hypolipidemic effects of curcumin

Jean-Marc Zingg, Syeda T. Hasan, Mohsen Meydani

First published: 22 January 2013
https://doi.org/10.1002/biof.1072

Read the full text PDF

Abstract

"**Recent evidence suggests potential benefits from phytochemicals and micronutrients in reducing the elevated oxidative and lipid-mediated stress associated with inflammation, obesity, and atherosclerosis.** …

"…**curcumin, a polyphenol present in the rhizomes of turmeric (*Curcuma longa*) spice, influences oxidative and lipid-mediated stress in the vascular system…**

"…**curcumin may act chemically as scavenger of free radicals…**

"…**The resulting lower oxidative and lipid-mediated stress may not only explain the beneficial effects of curcumin on inflammation, cardiovascular, and neurodegenerative disease, but may also contribute to the increase in maximum life-span observed in animal models.** © 2013 BioFactors, 39(1):101–121, 2013"

For the full abstract, visit https://iubmb.onlinelibrary.wiley.com/doi/abs/10.1002/biof.1072

or read **BioFactors,** Volume**39**, Issue**1**

Special Issue: CURCUMIN

January/February 2013

Pages 101-121

4. This abstract is from *Nutrients.* I have added emphasis in bold. HK

Dietary Polyphenols and Obesity

Mohsen Meydani * **and** Syeda T. Hasan

Vascular Biology Laboratory, Jean Mayer USDA- Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111, USA

Author to whom correspondence should be addressed.
Nutrients **2010**, *2*(7), 737-751; https://doi.org/10.3390/nu2070737
Received: 4 June 2010 / Revised: 1 July 2010 / Accepted: 7 July 2010 / Published: 8 July 2010
(This article belongs to the Special Issue Dietary Antioxidants)

Full-Text

PDF [138 KB, uploaded 8 July 2010]

Abstract

"The prevalence of overweight and obesity and their associated metabolic disorders are considered a major threat to the public's health. While several diet and exercise programs are available for weight loss and prevention of weight regain, progress is often slow and disappointing. Recently, natural bioactive phytochemicals present in foods have been discovered for their potential health benefit effects on the prevention of chronic disorders such as cancer, cardiovascular disease, inflammatory and metabolic diseases including obesity. Polyphenols are a class of naturally-occurring phytochemicals, of which some such as catechins, anthocynines, resveratrol and **curcumin have been shown to modulate physiological and molecular pathways that are involved in energy metabolism, adiposity, and obesity**. The potential in vivo, beneficial effects of these polyphenols on adiposity and obesity as complementary agents in the up-regulation of energy expenditure have emerged by investigating these compounds in cell cultures, animal models of obesity and in some human clinical and epidemiological studies. In this brief review, the efficacy of the above-named polyphenols and **their potential efficacy to modulate obesity and some associated disorders are discussed.** View Full-Text

[Excerpted from full text] 5. Curcumin

"Curcumin is the major, bioactive polyphenol present in the spice turmeric, which is the ground rhizome of the perennial herb Curcuma longa. In addition to being used as a spice and colorant, turmeric has been used in Asian medicine since the second millennium BC [76]. Curcumin is a low molecular polyphenol with several biological properties. **It has been shown to possess antioxidant, anti-inflammatory, anticancer, anti-angiogenesis, chemopreventive and chemotherapeutic properties** [77]. The first report referring to curcumin's effect on disease in humans was published in The Lancet about 80 years ago [78]. Rao et al. reported that curcumin supplementation at the dose of 500-1,000 mg/kg in rat diet **reduced liver cholesterol**

and increased bile acid excretion [79]. At a dose of 250 mg/kg, curcumin was also **reported to reduce weight gain in rats after 4 weeks** and tended to reduce liver weight as well as blood triglyceride and free fatty acids levels [80].

“In addition to the above-mentioned earlier studies, recent cell culture and animal studies have explored the impact of curcumin on lipid metabolism, adiposity, and inflammation in more detail. **Curcumin may have a significant effect on adiposity and lipid metabolism through several mechanisms including modulation of energy metabolism, inflammation, and suppression of angiogenesis.** It has been well established that angiogenesis plays pivotal roles in the growth and expansion of adipose tissue (reviewed in [81,82,83,84]) was also reported to reduce weight to suppress angiogenesis, it has mainly been investigated for its effect on cancerous tumor growth. However, it may play an important role in the growth and expansion of adipose tissue as well. It is known that through down-regulation of several factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), as well as angiopoietin and hypoxia-inducible factors (HIF)-1α, **curcumin suppresses angiogenesis and restricts the growth of tumors** [85,86]. Therefore, curcumin may contribute to the prevention of adipogenesis through suppression of angiogenesis into the adipose tissue [87]. In adipose tissue, angiogenesis is mediated by adipose tissue secretion of adipokines including leptin, adiponectin, resistin, visfatin, tumor necrosis factor (TNF)-α, interleukin(IL)-6, IL-1, and VEGF [88]. Therefore, **the inhibition of angiogenesis in adipose tissue can be used as a strategy to prevent the growth of adipose tissue and thus, obesity. We have demonstrated this effect of curcumin in our recent study** [89] where supplementing a high fat diet of C57BL/6J mice with curcumin reduced microvessel density as an indication of suppression of angiogenesis in adipose tissue.

“Like other polyphenols reviewed above, we in our recent study found that curcumin activated AMPK and down-regulated ACC activity through phosphorylation of this enzyme, which in turn down-regulated the flow of acetyl CoA to malonyl CoA leading to up-regulation of carnitine palmitoyltransferase-1 (CPT-1), which transfers cytosolic long-chain fatty acyl CoA into the mitochondria for oxidation [90]. In addition, through activation of AMPK, curcumin down-regulated synthesis of glycerol lipids by inhibiting glycerol-3-phosphate acyl transferase-1 (GPAT-1) activity, which esterifies fatty acids to glycerol to form triglycerides for storage [89].

“These effects of curcumin on energy metabolism were observed both in adipocyte cultures and in adipose tissue of mice fed a high fat diet. **Several other studies in animal models of obesity have reported the beneficial effects of curcumin on body weight and fat, adiposity, and energy metabolism.** Asai and Miyazawa [91] reported that **relatively high dietary curcumin supplementation (2 and 10 g/kg diet)**

for two weeks in rats reduced epididymal adipose tissue, attenuated liver fatty acid synthesis, and increased rat liver acetyl CoA oxidase activity, which is the first catalytic enzyme in fatty acid β-oxidation. Recently, it was reported that **supplementing the high fat diet of hamsters with 500 mg/kg curcumin reduced the levels of free fatty acid, total cholesterol, triglycerides, and leptin as well as the insulin resistance index** [92]. The hypoglycemic effect of ethanolic extract of turmeric has also been reported in genetically diabetic KK-Ay/Ta mice [93]. Jang et al. also reported that in hamsters fed a high fat diet, curcumin supplementation increased the hepatic β-oxidation and decreased fatty acid and cholesterol synthesis [92]. These observations are in support of our findings that curcumin supplementation suppressed a high fat diet-induced fatty liver in mice and reduced plasma levels of cholesterol, triglycerides, glucose, and free fatty acids. In a mouse model of insulin resistant obesity, Weisberg et al. [94] recently reported that **inclusion of a generous amount of curcumin in the diet significantly ameliorated type 2 diabetes** and inflammation in the liver as detected by a lower expression of nuclear factor (NF)-κB and reduced the infiltration of macrophages in adipose tissues. They also reported that although mice consumed more curcumin-supplemented food (i.e., more calories), they nevertheless displayed a lower body weight and a lower body fat as measured by nuclear magnetic resonance (NMR).

“In our study, [89] we also found that curcumin supplementation suppressed expression of PPARγ and C/EBPα, transcription factors that are mainly found in adipose tissue and are the key transcription factors in adipogenesis and lipogenesis [95]. Curcumin also suppressed differentiation of pre-adipocytes to adipocytes, which in turn attenuated adipose tissue growth and expansion. This effect of curcumin might have been mediated through suppressing the expression of PPARγ transcription factor because a PPARγ agonist, such as thiazolidinedione, induces differentiation of human pre-adipocytes and increases subcutaneous adiposity [96]. Therefore, suppression of these transcription factors by curcumin is another potential mechanism by which **curcumin contributes to the suppression of adipogenesis**.

“It is worth mentioning that studies on the **effect of curcumin on metabolic syndrome and obesity have been conducted in the experimental animals, whereas supplementation studies on humans are mainly limited to investigations related to curcumin’s anti-inflammatory and anti-cancer properties**. Therefore, curcumin’s anti-obesity effect in humans remains to be demonstrated after establishing its safety after long-term use.

YOU ARE NOT EXPECTED TO READ ANY OF THESE ADDITIONAL STUDIES ON Curcumin for Colon Health, Diabetes, Hyperlipidemia, and Obesity AS PART OF THIS COURSE! Optional. For pleasure only. HK

Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals. **Aggarwal, Bharat B.** [ed.] Robert J. Cousins. Gainesville: Annual Reviews, August 2010, Annual Review of Nutrition, Vol. 30, pp. 173-199. DOI: 10.1146/annurev.nutr.012809.104755; http://www.annualreviews.org/doi/abs/10.1146/annurev.nutr.012809.104755. ISSN: 0199-9885.

Obesity, Inflammation, and the Potential Application of Pharmaconutrition. **Cave, Matt C., et al., et al.** [ed.] Jeanette Hasse. 1, Dallas: SAGE Publications: American Society for Parenteral and Enteral Nutrition, February 2008, Nutrition in Clinical Practice, Vol. 23, pp. 16-34. DOI: 10.1177/0115426508023001116; http://ncp.sagepub.com/content/23/1/16. ISSN: 0884-5336.

Iqbal, Muzamal, et al., et al. Phytochemicals as a potential source for TNF-α inhibitors. [book auth.] Muzamal Iqbal. *NMR-based metabolomics to identify bioactive compounds in herbs and fruits.* Leiden: Natural Products Laboratory (NPL), Institute of Biology (IBL), Faculty of Science, Leiden University, 2013, 2, pp. 9-64. ISBN: 978-94-6203-348-1.

Preventive Effects of Curcumin on the Development of Azoxymethane-Induced Colonic Preneoplastic Lesions in Male C57BL/KsJ-db/db Obese Mice. **Kubota, Masaya, et al., et al.** [ed.] Leonard A. Cohen. 1, Valhalla: Taylor and Francis, 2012, Nutrition and Cancer, Vol. 64, pp. 72-79. DOI: 10.1080/01635581.2012.630554; http://www.tandfonline.com/doi/abs/10.1080/01635581.2012.630554#.VDq8izZOVD8. ISSN: 0163-5581.

Molecular mechanisms of hypolipidemic effects of curcumin. **Zingg, Jean-Marc, Hasan, Syeda T. and Meydani, Mohsen.** [ed.] Angelo Azzi. 1, Boston: John Wiley & Sons, Inc.: International Union of Biochemistry and Molecular Biology, Inc., January/February 2013, Biofactors, Vol. 39, pp. 101-121. DOI: 10.1002/biof.1072; http://onlinelibrary.wiley.com/doi/10.1002/biof.1072/abstract. ISSN: 1872-8081.

Curcumin Inhibits Adipogenesis in 3T3-L1 Adipocytes and Angiogenesis and Obesity in C57/BL Mice. **Ejaz, Asma, et al., et al.** [ed.] A. Catharine Ross. 5, University Park: American Society for Nutrition, May 2009, The Journal of Nutrition, Vol. 139, pp. 919-925. DOI: 10.3945/jn.108.100966; http://jn.nutrition.org/content/139/5/919. ISSN: 0022-3166.

The study of insulin resistance and leptin resistance on the model of simplicity obesity rats by curcumin. **Yu, Y., Hu, S.K. and Yan, H.**[ed.] Junshi Chen. 11, Beijing: Chinese Medical Association, November 2008, Chinese Journal of Preventive Medicine, Vol. 42, pp. 818-822. ISSN: 0253-9624.

Recent advances in the investigation of curcuminoids. **Itokawa, Hideji, et al., et al.** [ed.] Siu-wai Leung. 11, Macao: BioMed Central Ltd.: International Society for Chinese Medicine, September 17, 2008, Chinese Medicine, Vol. 3. DOI: 10.1186/1749-8546-3-11; http://www.cmjournal.org/content/3/1/11. ISSN: 1749-8546.

Impaired Preadipocyte Differentiation in Human Abdominal Obesity - Role of Wnt, Tumor Necrosis Factor-α, and Inflammation **Isakson, Petter, et al., et al.** [ed.] Peter C. Butler. 7, Los Angeles: American Diabetes Association, July 2009, Diabetes, Vol. 58, pp. 1550-1557. DOI: 10.2337/db08-1770; http://diabetes.diabetesjournals.org/content/58/7/1550. ISSN: 1939-327X.

Attenuation of fatty liver and prevention of hypercholesterolemia by extract of Curcuma longa through regulating the expression of CYP7A1, LDL-receptor, HO-1, and HMG-CoA reductase. **Yiu, Wing-Fat, et al., et al.** [ed.] Daryl B. Lund. 3, Madison: John Wiley & Sons, Inc.: Institute of Food Technologists®, April 2011, Journal of Food Science, Vol. 76, pp. H80-H89. DOI: 10.1111/j.1750-3841.2011.02042.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1750-3841.2011.02042.x/abstract. ISSN: 0022-1147.

Prasad, Sahdeo and Aggarwal, Bharat B. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. [ed.] Iris F.F. Benzie and Sissi Wachtel-Galor. *Herbal Medicine: Biomolecular and Clinical Aspects.* 2. Boca Raton: CRC Press: Taylor and Francis Group, LLC, 2011, 13, pp. 263-288. ISBN: 978-1-4398-0713-2.

Nahar, Lutfun and Sarker, Satyajit D. Phytochemistry of the Genus Curcuma. [ed.] P. N. Ravindran, K. Nirmal Babu and K. Sivaraman. *Turmeric: The Genus Curcuma.* Boca Raton: CRC Press: Taylor & Francis Group, LLC, 2007, 3, pp. 71-106. ISBN-13: 978-0-8493-7034-2.

Nutraceuticals in dyslipidemia management. **Kota, Sunil K., et al., et al**. [ed.] Manash P. Baruah. 1, Mumbai: Medknow: ALLIANCE, January 1, 2013, Journal of Medical Nutrition and Nutraceuticals, Vol. 2, pp. 26-40. DOI: 10.4103/2278-019X.105328; http://www.jmnn.org/article.asp?issn=2278-019X;year=2013;volume=2;issue=1;spage=26;epage=40;aulast=Kota. ISSN: 2278-1870.

Balakrishnan, K.V. Postharvest Technology and Processing of Turmeric. [ed.] P. N. Ravindran, K. Nirmal Babu and K. Sivaraman. *Turmeric: The Genus Curcuma.* Boca Raton: CRC Press: Taylor & Francis Group, LLC, 2007, 8, pp. 193-256. ISBN-13: 978-0-8493-7034-2.

Phytochemicals with potential effects in metabolic syndrome prevention and therapy. **Holubková, Andrea, et al., et al.** [ed.] Aleksander Pavko. 2, Slovenija: Slovenian Chemical Society, 2012, Acta Chimica Slovaca, Vol. 5, pp. 186-199. ISSN: 1318-0207.

Aggarwal, Bharat B., et al., et al. Curcumin — Biological and Medicinal Properties. [ed.] P. N. Ravindran, K. Nirmal Babu and K. Sivaraman. *Turmeric: The Genus Curcuma.* Boca

Raton: CRC Press: Taylor & Francis Group, 2007, 10, pp. 298-348. ISBN-13: 978-0-8493-7034-2.

Foods for the prevention of diabetes: how do they work? **Thomas, Theodoros and Pfeiffer, Andreas F.H.** [ed.] Jesse Roth. 1, Manhasset: John Wiley & Sons, Ltd., January 3, 2012, Diabetes Metabolism Research and Reviews, Vol. 28, pp. 25-49. DOI: 10.1002/dmrr.1229; http://onlinelibrary.wiley.com/doi/10.1002/dmrr.1229/abstract. ISSN: 1520-7552.

Hypoglycemic Effects of Turmeric (Curcuma longa L. Rhizomes) on Genetically Diabetic KK-Ay Mice. **Kuroda, Minpei, et al., et al.** 5, Tokyo: International Academic Printing Co., Ltd.: The Pharmaceutical Society of Japan, May 2005, Biological and Pharmaceutical Bulletin, Vol. 28, pp. 937-939. DOI: 10.1248/bpb.28.937; https://www.jstage.jst.go.jp/article/bpb/28/5/28_5_937/_article. ISSN: 0918-6158.

Modulation of PPAR-γ by Nutraceutics as Complementary Treatment for Obesity-Related Disorders and Inflammatory Diseases. **Sahagún, D. Ortuño, et al., et al.** [ed.] Bruce Blumberg. Article ID 318613, Guadalajara: Hindawi Publishing Corporation, October 23, 2012, PPAR Research, Vol. 2012, pp. 1-17. DOI: 10.1155/2012/318613; http://www.hindawi.com/journals/ppar/2012/318613/. ISSN: 1687-4757.

Chemical Composition and Product Quality Control of Turmeric (Curcuma longa L.). **Li, Shiyou, et al., et al.** [ed.] Shiyou Li and Shilin Chen. Nacogdoches; Beijing: Bentham Open, 2011, Pharmaceutical Crops, Vol. 2, pp. 28-54. DOI: 10.2174/2210290601102010028; http://benthamopen.com/ABSTRACT/TOPHARMCJ-2-28. ISSN: 2210-2906.

Screening of selected Asian spices for anti obesity-related bioactivities. **Yuliana, Nancy Dewi, et al., et al.** [ed.] G.G. Birch. 4, Reading: Elsevier Ltd., June 15, 2011, Food Chemistry, Vol. 126, pp. 1724-1729. DOI: 10.1016/j.foodchem.2010.12.066; http://www.sciencedirect.com/science/article/pii/S0308814610016870. ISSN: 0308-8146.

A Review on Anti-Inflammatory Activity of Monoterpenes. **Sá, Rita de Cássia da Silveira e, Andrade, Luciana Nalone and Sousa, Damião Pergentino de.** [ed.] Derek J. McPhee. 18, Emeryville: MDPI AG, January 18, 2013, Molecules, Vol. 2013, pp. 1227-1254. DOI: 10.3390/molecules18011227; http://www.mdpi.com/1420-3049/18/1/1227. ISSN: 1420-3049.

Studies on Chemistry and Biological Activities of Curcuma Longa Linn - A Review. **Reddy, Y. Surendra, et al., et al.** [ed.] M. William Carey. 1, Andhra Pradesh: KMR Pharma Welfare Association, January 24, 2011, International Journal of Advances in Pharmaceutical Research, Vol. 2, pp. 26-36. eISSN: 2230-7583.

Duke, James A., Bogenschutz-Godwin, Mary Jo and duCellier, Judi. *CRC Handbook of Medicinal Spices.* Boca Raton: CRC Press LLC, 2003. ISBN: 0-8493-1279-5.

Dietary Polyphenols and Their Biological Significance. **Han, Xiuzhen, Shen, Tao and Lou, Hongxiang.** [ed.] Michael N. Hall. 9, Basel: MDPI - Open Access Publishing, September 12, 2007, International Journal of Molecular Sciences, Vol. 8, pp. 950-988. DOI: 10.3390/i8090950; http://www.mdpi.com/1422-0067/8/9/950. ISSN: 1422-0067.

Sarker, Satyajit D. and Nahar, Lutfun. Bioactivity of Turmeric. [ed.] P. N. Ravindran, K. Nirmal Babu and K. Sivaraman. *Turmeric: The Genus Curcuma.* Boca Raton: CRC Press: Taylor & Francis Group, LLC, 2007, 9, pp. 258-285. ISBN-13: 978-0-8493-7034-2.

Ferulic Acid - A Comprehensive Pharmacology of an Important Bioflavonoid. **Gohil, Kashmira J., Kshirsagar, Shashank B. and Sahane, Rajkumari S.** [ed.] Shashi Alok. 1, Jhansi: Society of Pharmaceutical Sciences & Research, March 2012, International Journal of Pharmaceutical Sciences and Research, Vol. 3, pp. 700-710. ISSN: 0975-8232. [FERULIC ACID COMBINES WELL WITH CURCUMIN TO PREVENT DEMENTIA]

Attokaran, Mathew. Turmeric: Curcuma longa L (Zingiberaceae). *Natural Food Flavors and Colorants.* Ames: Blackwell Publishing Ltd. and Institute of Food Technologists, 2011, 98, pp. 391-398. ISBN: 978-0-8138-2110-8.

Natural plant products and extracts that reduce immunoexcitotoxicity-associated neurodegeneration and promote repair within the central nervous system. **Blaylock, Russell L. and Maroon, Joseph.** [ed.] James I. Ausman. 19, Los Angeles: Medknow, February 15, 2012, Surgical Neurology International®, Vol. 3. DOI: 10.4103/2152-7806.92935; http://www.surgicalneurologyint.com/article.asp?issn=2152-7806;year=2012;volume=3;issue=1;spage=19;epage=19;aulast=Blaylock. ISSN: 2152-7806.

Molecular Pathways of Endothelial Cell Activation for (Targeted) Pharmacological Intervention of Chronic Inflammatory Diseases. **Kuldo, Joanna M., et al., et al.** [ed.] Dimitri P. Mikhailidis. 1, London: Bentham Science Publishers, January 2005, Current Vascular Pharmacology, Vol. 3, pp. 11-39. DOI: 10.2174/1570161052773898; http://www.eurekaselect.com/80027/article. 1570-1611.

Nrf2, a Guardian of Healthspan and Gatekeeper of Species Longevity. **Lewis, Kaitlyn N., et al., et al.** [ed.] Harold Heatwole. 5, Raleigh: Oxford University Press: The Society for Integrative and Comparative Biology, November 2010, Integrative and Comparative Biology, Vol. 50, pp. 829-843. DOI: 10.1093/icb/icq034; http://icb.oxfordjournals.org/content/50/5/829. 1540-7063.

Dietary phenolics: chemistry, bioavailability and effects on health. **Crozier, Alan, Jaganath, Indu B. and Clifford, Michael N.** 8, s.l.: The Royal Society of Chemistry, August 2009, Natural Product Reports, Vol. 26, pp. 1001-1043. DOI: 10.1039/b802662a; http://pubs.rsc.org/en/Content/ArticleLanding/2009/NP/b802662a#!divAbstract. ISSN: 0265-0568.

Chempakam, B. and Parthasarathy, V.A. Turmeric. [ed.] V.A. Parthasarathy, B. Chempakam and T. John Zachariah. *Chemistry of Spices.*Oxfordshire: CAB International, 2008, 6, pp. 97-123. ISBN: 978-1-84593-405-7.

The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia. **Houston, Mark.** [ed.] Michael A. Weber. 2, Greenwich: John Wiley & Sons, Inc., February 2012, The Journal of Clinical Hypertension, Vol. 14, pp. 121-132. DOI: 10.1111/j.1751-7176.2011.00576.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1751-7176.2011.00576.x/abstract. eISSN: 1751-7176.

Molecular mechanisms for anti-aging by natural dietary compounds. **Pan, Min-Hsiung, et al., et al.** [ed.] Hans-Ulrich Humpf. 1, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, January 2012, Molecular Nutrition & Food Research, Vol. 56, pp. 88-115. DOI: 10.1002/mnfr.201100509; http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201100509/abstract. ISSN: 1613-4133.

Druggability of lead compounds from turmeric (Curcuma longa). **Wilson, M., Balaji, S. and Eapen, S.J.** 2006, Journal of Medicinal and Aromatic Plant Sciences, Vol. 28, pp. 384-390. ISSN: 0253-7125.

Composition and Antioxidant Properties of Essential Oils from Curcuma rhizome. **Tsai, Snu-Yao, et al., et al.** [ed.] Shian-Shyong Tseng. 1, Taichung City: Asia University, June 2011, Asian Journal of Arts and Sciences, Vol. 2, pp. 57-66. ISSN: 2221-4224.

Phytochemistry and mode of action of some tropical spices in the management of type-2 diabetes and hypertension. **Adefegha, Stephen Adeniyi and Oboh, Ganiyu.** [ed.] Himanshu Gupta, et al., et al. 7, s.l.: Academic Journals, February 22, 2013, African Journal of Pharmacy and Pharmacology, Vol. 7, pp. 332-346. ISSN: 1996-0816.

Amelioration of Obesity, Glucose Intolerance, and Oxidative Stress in High-Fat Diet and Low-Dose Streptozotocin-Induced Diabetic Rats by Combination Consisting of "Curcumin with Piperine and Quercetin". **Kaur, Ginpreet and Chintamaneni, Meena.** [ed.] T. Kumai and M.A. Prendergast. Article ID 957283, Mumbai: Hindawi Publishing Corporation, March 8, 2012, ISRN Pharmacology, Vol. 2012, pp. 1-7. DOI: 10.5402/2012/957283; http://www.hindawi.com/journals/isrn/2012/957283/. ISSN: 2090-5165.

Curcumin inhibits hepatic protein-tyrosine phosphatase 1B and prevents hypertriglyceridemia and hepatic steatosis in fructose-fed rats. **Li, Jian-Mei, et al., et al.** [ed.] Michael H. Nathanson. 5, New Haven: John Wiley & Sons, Inc.: American Association for the Study of Liver Diseases, May 2010, Hepatology, Vol. 51, pp. 1555-1566. DOI: 10.1002/hep.23524; http://onlinelibrary.wiley.com/doi/10.1002/hep.23524/abstract. eISSN: 1527-3350.

Impact of Dietary Polyphenols on Carbohydrate Metabolism. **Hanhineva, Kati, et al., et al.** [ed.] Andrei Alexandrescu. 4, Basel: MDPI AG, March 31, 2010, International Journal of

Molecular Sciences, Vol. 11, pp. 1365-1402. DOI: 10.3390/ijms11041365; http://www.mdpi.com/1422-0067/11/4/1365. ISSN: 1422-0067.

Dietary Polyphenols and Obesity. **Meydani, Mohsen and Hasan, Syeda T.** [ed.] Peter Howe and Jonathan Buckley. 7, Callaghan; Adelaide: MDPI - Open Access Publishing, July 8, 2010, Nutrients, Vol. 2, pp. 737-751. DOI: 10.3390/nu2070737; http://www.mdpi.com/2072-6643/2/7/737. ISSN: 2072-6643.

mTOR-regulated senescence and autophagy during reprogramming of somatic cells to pluripotency: A roadmap from energy metabolism to stem cell renewal and aging. **Menendez, Javier A., et al., et al**. [ed.] M.V. Blagosklonny. 21, Buffalo: Landes Bioscience, November 1, 2011, Cell Cycle, Vol. 10, pp. 3658-3677. DOI: 10.4161/cc.10.21.18128; http://www.tandfonline.com/doi/abs/10.4161/cc.10.21.18128#.VPTMJjZOWpo. ISSN: 1538-4101.

Effect of Plant Polyphenols on Adipokine Secretion from Human SGBS Adipocytes. **Derdemezis, Christos S., et al., et al.** [ed.] Tzi-Bunb Ng. Article ID 285618, Hong Kong: Hindawi Publishing Corporation, July 23, 2011, Biochemistry Research International, Vol. 2011, pp. 1-5. DOI: 10.1155/2011/285618; http://www.hindawi.com/journals/bri/2011/285618/. eISSN: 2090-2247.

Curcumin Extract for Prevention of Type 2 Diabetes. **Chuengsamarn, Somlak, et al., et al.** [ed.] William T. Cefalu. 11, Alexandria: American Diabetes Association, November 2012, Diabetes Care, Vol. 35, pp. 2111-2112. DOI: 10.2337/dc12-0116; http://care.diabetesjournals.org/content/35/11/2121. ISSN: 1935-5548.

Committee on Herbal Medicinal Products. *Assessment Report on Curcuma Longa L. Rhizoma.* London: European Medicines Agency, 2009. EMEA/HMPC/456848/2008.

Diabetes Epidemic in India: Risk Factors, Symptoms and Treatment. **Abhinov, T., et al., et al.** [ed.] B. Pragati Kumar. 2, Vijayawada: Pragati Publication PVT Ltd., March-April 2013, Indian Journal of Research in Pharmacy and Biotechnology , Vol. 1, pp. 234-243. eISSN: 2320-3471.

Adiponectin Levels and Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis. **Li, Shanshan, et al., et al.** [ed.] Catherine D. DeAngelis. 2, Baltimore: American Medical Association, July 8, 2009, JAMA, Vol. 302, pp. 179-188. DOI: 10.1001/jama.2009.976; http://jama.jamanetwork.com/article.aspx?articleid=184206. ISSN: 0098-7484.

Curcumin Improves Insulin Sensitivity and Ameliorates Serum Pro-inflammatory Cytokines Levels in Diabetes Rat model Irrespective of type of Diabetes. **Mahfouz, Mohamed Khaled Mohamed.** [ed.] Hongbao Ma. 6, East Lansing: Marsland Press, June 25, 2011, Journal of American Science, Vol. 7, pp. 794-799. ISSN: 1545-1003.

Retinal Redox Stress and Remodeling in Cardiometabolic Syndrome and Diabetes. **Yang, Ying, et al., et al.** [ed.] Kenneth Maiese. 6, New York; Cairo: Hindawi Publishing Corporation, Nov-Dec 2010, Oxidative Medicine and Cellular Longevity, Vol. 3, pp. 392-403. DOI: 10.4161/oxim.3.6.14786; http://www.hindawi.com/journals/omcl/2010/193157/abs/. ISSN: 1942-0900.

Antidiabetic and antioxidant potentials of spent turmeric oleoresin, a by-product from curcumin production industry. **Nampoothiri, Suresh V, et al., et al.** [ed.] Jeffrey M. Bethony, et al., et al. Supplement 1, Washington, D.C.; Livorno; Leicester: Elsevier (Singapore) Pte Ltd., October 2012, Asian Pacific Journal of Tropical Disease, Vol. 2, pp. S169-S172. DOI: 10.1016/S2222-1808(12)60146-7; http://www.sciencedirect.com/science/article/pii/S2222180812601467. ISSN: 2222-1808.

Turmeric (Curcuma longa L.) volatile oil inhibits key enzymes linked to type 2 diabetes. **Lekshmi, P.C., et al., et al.** [ed.] Furio Brighenti. 7, Parma: Informa Plc, November 2012, International Journal of Food Sciences and Nutrition, Vol. 63, pp. 832-834. DOI: 10.3109/09637486.2011.607156; http://informahealthcare.com/doi/abs/10.3109/09637486.2011.607156. ISSN: 0963-7486.

Turmerin, the antioxidant protein from turmeric (Curcuma longa) exhibits antihyperglycaemic effects. **Lekshmi, P.C., et al., et al.** [ed.] Armandodoriano Bianco. 17, Roma: Taylor & Francis Group, 2012, Natural Product Research, Vol. 26, pp. 1654-1658. DOI: 10.1080/14786419.2011.589386; http://www.tandfonline.com/doi/abs/10.1080/14786419.2011.589386#.VPDcmTZOWpp. ISSN: 1478-6419.

Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. **Wickenberg, Jennie, Ingemansson, Sandra Lindstedt and Hlebowicz, Joanna.** [ed.] Nehme Gabriel. 43, Leesburg: BioMed Central Ltd, October 12, 2010, Nutrition Journal, Vol. 9. DOI: 10.1186/1475-2891-9-43; http://www.nutritionj.com/content/9/1/43. ISSN: 1475-2891.

Remadevi, R., Surendran, E. and Kimura, Takeatsu. Turmeric in Traditional Medicine. [ed.] P. N. Ravindran, K. Nirmal Babu and K. Sivaraman. *Turmeric: The Genus Curcuma.* Boca Raton: CRC Press: Taylor & Francis Group, 2007, 12, pp. 409-436. ISBN-13: 978-0-8493-7034-2.

Clinical Study of Turmeric (Curcuma longa L.) and Garlic (Allium sativum L.) Extracts as Antihyperglycemic and Antihyperlipidemic Agent in Type-2 Diabetes-Dyslipidemia Patients. **Sukandar, E.Y., et al., et al.**[ed.] Majid Y. Moridani. 4, Denver: Asian Network for Scientific Information, 2010, International Journal of Pharmacology, Vol. 6, pp. 456-463. ISSN: 1811-7775.

Evaluation of Traditional Indian Antidiabetic Medicinal Plants for Human Pancreatic Amylase Inhibitory Effect In Vitro. **Ponnusamy, Sudha, et al., et al.** Article ID 515647, New York; Cairo: Hindawi Publishing Corporation, 2011, Evidence-Based Complementary and

Alternative Medicine, Vol. 2011, pp. 1-10. DOI: 10.1155/2011/515647; http://www.hindawi.com/journals/ecam/2011/515647/. eISSN: 1741-4288.

Dietary Curcumin Significantly Improves Obesity-Associated Inflammation and Diabetes in Mouse Models of Diabesity. **Weisberg, Stuart P., Leibel, Rudolph and Tortoriello, Drew V.** [ed.] Jeffrey D. Blaustein. 7, Boston: The Endocrine Society, July 2008, Endocrinology, Vol. 149, pp. 3549-3558. DOI: 10.1210/en.2008-0262; http://press.endocrine.org/doi/abs/10.1210/en.2008-0262. ISSN: 0013-7227.

Curcumin diminishes the impacts of hyperglycemia on the activation of hepatic stellate cells by suppressing membrane translocation and gene expression of glucose transporter-2. **Lin, Jianguo and Chen, Anping.** [ed.] I.T. Huhtaniemi. 2, London: Elsevier Ireland Ltd., February 20, 2010, Molecular and Cellular Endocrinology, Vol. 333, pp. 160-171. DOI: 10.1016/j.mce.2010.12.028; http://www.sciencedirect.com/science/article/pii/S0303720710006210. ISSN: 0303-7207.

Effects of ingested turmeric oleoresin on glucose and lipid metabolisms in obese diabetic mice: a DNA microarray study. **Honda, Shinichi, et al., et al.** [ed.] James N. Seiber. 24, Davis: American Chemical Society, November 29, 2006, Journal of Agricultural and Food Chemistry, Vol. 54, pp. 9055-9062. DOI: 10.1021/jf061788t; http://pubs.acs.org/doi/abs/10.1021/jf061788t. ISSN: 0021-8561.

Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β1 activity in streptozotocin-induced type I diabetic rats. **Soetikno, Vivian, et al., et al.** [ed.] Hans-Ulrich Humpf. 11, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, November 2011, Molecular Nutrition & Food Research, Vol. 55, pp. 1655-1665. DOI: 10.1002/mnfr.201100080; http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201100080/abstract. eISSN: 1613-4133.

Curcumin and Turmeric Delay Streptozotocin-Induced Diabetic Cataract in Rats. **Suryanarayana, Palla, et al., et al.** [ed.] Robert N. Frank. 6, Detroit: Association for Research in Vision and Ophthalmology, June 2005, Investigative Ophthalmology & Visual Science, Vol. 46, pp. 2092-2099. DOI: 10.1167/iovs.04-1304; http://www.iovs.org/content/46/6/2092. eISSN: 1552-5783.

A pilot study on the effects of a polyherbal formulation cream on diabetic foot ulcers. **Viswanathan, Vijay, et al., et al.** [ed.] K. Satyanarayana. 2, New Delhi: Indian Council of Medical Research , August 2011, Indian Journal of Medical Research , Vol. 134, pp. 168-173. ISSN: 0971-5916.

Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. **Na, Li-Xin, et al., et al.** [ed.] Hans-Ulrich Humpf. 9, Weinheim: WILEY-VCH Verlag GmbH & Co. KGaA, September 2013, Molecular Nutrition & Food Research, Vol. 57, pp. 1569-1577. DOI:

10.1002/mnfr.201200131; http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201200131/abstract. ISSN: 1613-4133.

Curcumin/Irbesartan Combination Improves Insulin Sensitivity and Ameliorates Serum Pro-inflammatory Cytokines levels in Diabetes Rat model. **Mahfouz, Mohamed Khaled Mohamed.** [ed.] Hongbao Ma. 11, East Lansing: Marsland Press, 2010, Journal of American Science, Vol. 6, pp. 1051-1059. ISSN: 1545-1003.

Caldecott, Todd. *Ayurveda: The Divine Science of Life.* s.l.: Elsevier Health Sciences, 2006. ISBN: 978-0-7234-3410-8.

Murray, Michael T. and Pizzorno, Joseph E. Curcuma longa (turmeric). *Textbook of Natural Medicine.* 2. Edinburgh: Harcourt Publishers Limited: Churchill Livingstone, 1999, Vol. Pharmacology of natural medicines, 80, pp. 690-694. ISBN: 0-443-05945-4.

Turmeric: A Herbal and Traditional Medicine. **Bhowmik, Debjit, et al., et al.** [ed.] Eno E. Ebenso. 2, Mmabatho: Scholars Research Library, 2009, Archives of Applied Science Research, Vol. 1, pp. 86-108. ISSN: 0975-508X.

Turmeric and curcumin: Biological actions and medicinal applications. **Chattopadhyay, Ishita, et al., et al.** [ed.] P. Balaram. 1, Bangalore: Indian Academy of Sciences, July 10, 2004, Current Science, Vol. 87, pp. 44-53. ISSN: 0011-3891.

Herbal medicinal products for non-ulcer dyspepsia. **Coon, J. Thompson and Ernst, E.** [ed.] Roy E. Pounder and Walter L. Peterson. 10, London; Dallas: John Wiley & Sons Ltd, October 2002, Alimentary Pharmacology & Therapeutics, Vol. 16, pp. 1689-1699. DOI: 10.1046/j.1365-2036.2002.01339.x; http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2036.2002.01339.x/abstract. eISSN: 1365-2036.

Comparative clinical evaluation of Kshara Sutra ligation and hemorrhoidectomy in Arsha (hemorrhoids). **Gupta, Meva Lal, Gupta, S.K. and Bhuyan, Chaturbhuja.** [ed.] M.S. Baghel. 2, Gujarat: Institute for Post Graduate Teaching & Research in Ayurveda, Gujarat Ayurved University, Apr-Jun 2011, International Quarterly Journal of Research in Ayurveda, Vol. 32, pp. 225-229. DOI: 10.4103/0974-8520.92591; http://www.ayujournal.org/article.asp?issn=0974-8520;year=2011;volume=32;issue=2;spage=225;epage=229;aulast=Gupta. ISSN: 0974-8520.

Thornton, Scott C., Perry, Kyle R. and Rosh, Adam J. Hemorrhoids Treatment & Management: Overview, Treatment. *Medscape Reference: Drugs, Diseases & Procedures.* [Online] November 3, 2014. [Cited: January 13, 2015.] http://emedicine.medscape.com/article/775407-overview#showall..

Curcumin for Inflammatory Bowel Disease: A Review of Human Studies. **Taylor, Rebecca A. and Leonard, Mandy C.** [ed.] Kathleen A. Head. 2, Napa: Alternative Medicine Review, LLC, June 2011, Alternative Medicine Review, Vol. 16, pp. 152-156. ISSN: 1089-5159..

Curcumin Protects Intestinal Mucosal Barrier Function of Rat Enteritis via Activation of MKP-1 and Attenuation of p38 and NF-κB Activation. **Song, Wei-Bing, et al., et al.** [ed.] Stefan Bereswill. 9, Berlin: Public Library of Science, September 24, 2010, PLoS One, Vol. 5, p. e12969. DOI: 10.1371/journal.pone.0012969; http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0012969. ISSN: 1932-6203.

Curcumin Regulates Expression and Activity of Matrix Metalloproteinases 9 and 2 during Prevention and Healing of Indomethacin-induced Gastric Ulcer. **Swarnakar, Snehasikta, et al., et al.** [ed.] Herbert Tabor. 10, Rockville: American Society for Biochemistry and Molecular Biology, March 11, 2005, The Journal of Biological Chemistry, Vol. 280, pp. 9409-9415. DOI: 10.1074/jbc.M413398200;http://www.jbc.org/content/280/10/9409. ISSN: 0021-9258.

A curcumin-based 1-week triple therapy for eradication of Helicobacter pylori infection: something to learn from failure?. **Di Mario, Francesco, et al., et al.** [ed.] David Y Graham. 3, Houston: John Wiley & Sons, Inc., June 2007, Helicobacter, Vol. 12, pp. 238-243. DOI: 10.1111/j.1523-5378.2007.00497.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1523-5378.2007.00497.x/abstract. ISSN: 1083-4389.

Effect of curcumin on Helicobacter pylori biofilm formation. **Pattiyathanee, Panan, Vilaichone, Ratha-korn and Chaichanawongsaroj, Nuntaree.** [ed.] George Nkem Ude. 19, Bowie: African Journals Online, October 9, 2009, African Journal of Biotechnology, Vol. 8, pp. 5106-5115. ISSN: 1684-5315.

Curcuma longa Extract Protects against Gastric Ulcers by Blocking H2 Histamine Receptors. **Kim, Dong-Chan, et al., et al.** [ed.] Naoto Oku. 12, Shizuoka: The Pharmaceutical Society of Japan, December 2005, Biological & Pharmaceutical Bulletin, Vol. 28, pp. 2220-4. DOI: 10.1248/bpb.28.2220; https://www.jstage.jst.go.jp/article/bpb/28/12/28_12_2220/_article. ISSN: 0918-6158.

Natural products in treatment of ulcerative colitis and peptic ulcer. **Awaad, Amani S., El-Meligy, Reham M. and Soliman, Gamal A.** [ed.] Abdullah M. AlMayouf. 1, Riyadh: Elsevier B.V.: King Saud University, January 2013, Journal of Saudi Chemical Society, Vol. 17, pp. 101-124. DOI: 10.1016/j.jscs.2012.03.002; http://www.sciencedirect.com/science/article/pii/S1319610312000397. ISSN: 1319-6103.

Effects of Turmeric in Peptic Ulcer and Helicobacter pylori. **Aljamal, Abdulrahim.** [ed.] Muhammad Sohail. 3, s.l.: Medwell Journals, 2011, Plant Sciences Research, Vol. 3, pp. 25-28. ISSN: 1995-476X.

Phase II Clinical Trial on Effect of the Long Turmeric (Curcuma Longa Linn) on Healing of Peptic Ulcer. **Prucksunand, Chaweewan, et al., et al.** [ed.] Suvanee Supavej. 1, Bangkok: SEAMEO Regional Tropical Medicine and Public Health Network, March 2001, The

Southeast Asian Journal of Tropical Medicine and Public Health, Vol. 32, pp. 208-215. ISSN: 0125-1562.

Investigation of the anti-inflammatory effect of Curcuma longa in Helicobacter pylori-infected patients. **Koosirirat, Chucart, et al., et al.** [ed.] J.E. Talmadge. 7, Omaha: Elsevier B.V., July 2010, International Immunopharmacology, Vol. 10, pp. 815-818. DOI: 10.1016/j.intimp.2010.04.021; http://www.sciencedirect.com/science/article/pii/S1567576910001359. ISSN: 1567-5769.

The effects of a traditional drug, turmeric (Curcuma longa), and placebo on the healing of duodenal ulcer. **Van Dau, N., et al., et al.**[ed.] N.R. Farnsworth and H. Wagner. 1, Chicago, Munich: Elsevier GmbH: Gusav Fischer Verlag, March 1998, Phytomedicine, Vol. 5, pp. 29-34. DOI: 10.1016/S0944-7113(98)80056-1; http://www.sciencedirect.com/science/article/pii/S0944711398800561. ISSN: 0944-7113.

Shishodia, Shishir, Singh, Tulika and Chaturvedi, Madan M. *Modulation of Transcription Factors by Curcumin.* [ed.] Bharat B. Aggarwal, Young-Joon Surh and Shishir Shishodia. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. New York: Springer Science+Business Media, LLC, 2007, pp. 127-148. ISBN-13: 978-0-387-46400-8.

Oral Supplementation of Turmeric Decreases Proteinuria, Hematuria, and Systolic Blood Pressure in Patients Suffering From Relapsing or Refractory Lupus Nephritis: A Randomized and Placebo-controlled Study. **Khajehdehi, Parviz, et al., et al.** [ed.] Jerrilynn D. Burrowes and Christoph Wanner. 1, Brookville; Wüerzburg: Elsevier Inc.: National Kidney Foundation, Inc., January 2012, Journal of Renal Nutrition, Vol. 22, pp. 50-57. DOI: 10.1053/j.jrn.2011.03.002; http://www.jrnjournal.org/article/S1051-2276(11)00064-1/abstract. ISSN: 1051-2276.

Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. **DiSilvestro, Robert A, et al., et al.** [ed.] Nehme Gabriel. 79, Leesburg: BioMed Central Ltd., September 26, 2012, Nutrition Journal, Vol. 11. DOI: 10.1186/1475-2891-11-79; http://www.nutritionj.com/content/11/1/79. ISSN: 1475-2891.

Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers. **Soni, K.B. and Kuttan, R.** [ed.] K.K. Deepak. 4, Delhi: Association of Physiologists and Pharmacologists of India, October 1992, Indian Journal of Physiology and Pharmacology, Vol. 36, pp. 273-275. ISSN: 0019-5499.

Effects of Supplementation with Curcuminoids on Dyslipidemia in Obese Patients: A Randomized Crossover Trial. **Mohammadi, Akram, et al., et al.** [ed.] Elizabeth M. Williamson, et al., et al. 3, Reading; Naples; Seoul; Charleston: John Wiley & Sons, Ltd., May 21, 2012, Phytotherapy Research, Vol. 27, pp. 374-379. DOI: 10.1002/ptr.4715; http://onlinelibrary.wiley.com/doi/10.1002/ptr.4715/abstract. eISSN: 1099-1573.

Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: Results of a randomized controlled trial. **Panahi, Yunes, et al., et al.** [ed.] Robbert van Haselen. 5, Kingston, Surrey: Elsevier Inc., October 2014, Complementary Therapies in Medicine, Vol. 22, pp. 851-857. DOI: 10.1016/j.ctim.2014.07.006; http://www.complementarytherapiesinmedicine.com/article/S0965-2299(14)00114-9/abstract. ISSN: 0965-2299.

Curcumin improves intestinal barrier function: Modulation of intracellular signaling and organization of tight junctions. **Wang, Jing, Ghosh, Siddhartha S. and Ghosh, Shobha.** [ed.] Josephine Adams. 4, Bristol: American Physiological Society, March 1, 2017, American Journal of Physiology - Cell Physiology®, Vol. 314, pp. C438-C445. DOI: 10.1152/ajpcell.00235.2016; http://ajpcell.physiology.org/content/early/2017/02/23/ajpcell.00235.2016. ISSN: 0363-6143; PMID: 28249988.

Turmeric-based beverage blunted acute high fat meal-induced oxidative stress by lowering serum malondialdehyde (MDA) levels: a randomized cross-over study. **Zanzer, Yoghatama Cindya, et al., et al.** [ed.] Veronika Butterweck. S01, Muttenz: Georg Thieme Verlag KG, December 14, 2016, Planta Medica, Vol. 82, pp. S1-S381. DOI: 10.1055/s-0036-1596975; https://www.thieme-connect.de/DOI/DOI?10.1055/s-0036-1596975. ISSN: 0032-0943.

Curcumin for maintenance of remission in ulcerative colitis. **Garg, Sushil K., et al., et al.** [ed.] Cochrane IBD Group. s.l.: John Wiley & Sons, Ltd., October 17, 2012, Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD008424.pub2; http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008424.pub2/abstract. ISSN: 1469-493X; PMID: 23076948.

Curcumin in Combination With Mesalamine Induces Remission in Patients With Mild-to-Moderate Ulcerative Colitis in a Randomized Controlled Trial. **Salomon, Nir, et al., et al.** [ed.] Hashem B. El-Serag. 8, Houston: Elselvier: Saunders, August 2015, Clinical Gastroenterology and Hepatology, Vol. 13, pp. 1444-1449.e1. DOI: 10.1016/j.cgh.2015.02.019; http://www.cghjournal.org/article/S1542-3565(15)00158-5/fulltext. ISSN: 1542-3565; PMID: 25724700.

Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial. **Kedia, Saurabh, et al., et al.** [ed.] Hugh J. Freeman. 2, Vancouver: Baishideng Publishing Group Co., Limited, May 6, 2017, World Journal of Gastrointestinal Pharmacology and Therapeutics, Vol. 8, pp. 147-154. DOI: 10.4292/wjgpt.v8.i2.147; https://www.wjgnet.com/2150-5349/full/v8/i2/147.htm. eISSN: 2150-5349; PMID: 28533925.

C. Curcumin for the Kidneys

In this section I present excerpts from two studies on the efficacy of curcumin for treating kidney disease. I have added the bold emphasis. HK. **YOU ARE NOT EXPECTED TO READ ANY OFTHESE ADDITIONAL STUDIES AS PART OF THIS COURSE! For PLEASURE ONLY!**

1. Renoprotective effect of the antioxidant curcumin: Recent findings.

Trujillo, Joyce, et al., et al. [ed.] V.M. Darley-Usmar and T. Grune. 1, Birmingham; Jena: Elsevier B.V., 2013, Redox Biology, Vol. 1, pp. 448-456. DOI: 10.1016/j.redox.2013.09.003; http://www.sciencedirect.com/science/article/pii/S2213231713000670. ISSN: 2213-2317.

Redox Biology
Volume 1, Issue 1, 2013, Pages 448-456

Mini Review

Renoprotective effect of the antioxidant curcumin: Recent findings

Author links open overlay panelJoyceTrujillo[a]Yolanda IrasemaChirino[b]EduardoMolina-Jijón[c]Ana CristinaAndérica-Romero[a]EdiliaTapia[d]JoséPedraza-Chaverrí[a]

https://doi.org/10.1016/j.redox.2013.09.003Get rights and content

“Highlights”

- “Curcumin prevents mitochondrial dysfunction in nephrotoxicity.”
- “Curcumin prevents renal hemodynamic alterations in chronic renal failure.”
- “Curcumin is a therapeutic agent in chronic renal failure.”

-

“Curcumin induces renal Nrf2 translocation.”

-

“Curcumin is an antiinflammatory agent in renal injury.”

Abstract

“… **Numerous studies have shown that curcumin has broad biological functions particularly antioxidant and antiinflammatory.** ..

…**The renoprotective effect of curcumin has been evaluated in several** experimental models **including diabetic nephropathy, chronic renal failure, ischemia and** reperfusion **and nephrotoxicity induced by compounds such as** gentamicin**, adriamycin, chloroquine, iron nitrilotriacetate, sodium fluoride,** hexavalent chromium **and** cisplatin**.** ..

“…It has been shown recently **in a model of chronic renal failure that curcumin exerts a therapeutic effect; in fact it reverts not only systemic alterations but also glomerular** hemodynamic **changes…. Another recent finding shows that the renoprotective effect of curcumin is associated to preservation of function and redox balance of** mitochondria**….**

“… these studies attribute the protective effect of curcumin in the kidney to the induction of the master regulator of antioxidant response nuclear factor erythroid-derived 2 (Nrf2), inhibition of mitochondrial dysfunction, attenuation of inflammatory response, preservation of antioxidant enzymes and prevention of oxidative stress. …**this paper identifies curcumin as a promising renoprotective molecule against renal injury.”**

2. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: A randomized, double-blind and placebo-controlled study.

Khajehdehi, Parviz, et al., et al. [ed.] Per-Uno Malmström. 5, Stockholm: Informa Plc, November 2011, Scandinavian Journal of Urology, Vol. 45, pp. 365-370. DOI: 10.3109/00365599.2011.585622; http://informahealthcare.com/doi/abs/10.3109/00365599.2011.585622. ISSN: 2168-1805.

Abstract

"Objective. End-stage renal disease (ESRD) due to type 2 diabetic nephropathy is a very common condition which is increasing in prevalence, and is associated with high global levels of mortality and morbidity. Both proteinuria and transforming growth factor-β (TGF-β) may contribute to the development of ESRD in patients with diabetic nephropathy. Experimental studies indicate that turmeric improves diabetic nephropathy by suppressing TGF-β. Therefore, this study investigated the effects of turmeric on serum and urinary TGF-β, interleukin-8 (IL-8) and tumour necrosis factor-α (TNF-α), as well as proteinuria, in patients with overt type 2 diabetic nephropathy."

"*Material and methods.* A randomized, double-blind and placebo-controlled study was carried out … **Each patient in the trial group received one capsule with each meal containing 500 mg turmeric, of which 22.1 mg was the active ingredient curcumin (three capsules daily) for 2 months…"**

"Results. **Serum levels of TGF-β and IL-8 and urinary protein excretion and IL-8 decreased significantly comparing the pre- and post-turmeric supplementation values**. No adverse effects…"

" *Conclusion.* **Short-term turmeric supplementation can attenuate proteinuria**, TGF-β and IL-8 in patients with overt type 2 diabetic nephropathy and can be administered as a safe adjuvant therapy for these patients."

More optional research on curcumin for the kidneys:

Effect of Turmeric and its Active Principle Curcumin on T3-Induced Oxidative Stress and Hyperplasia in Rat Kidney: A Comparison. **Samanta, Luna, et al., et al.** [ed.] Praveen Sharma. 4, Jaipur: Springer-Verlag, October 1, 2010, Indian Journal of Clinical Biochemistry, Vol. 25, pp. 393-397. DOI: 10.1007/s12291-010-0046-6; http://link.springer.com/article/10.1007%2Fs12291-010-0046-6. ISSN: 0970-1915..

Moreillon, Jennifer Josephine. *Effects of eight weeks of curcumin and Boswellia serrata supplementation on plasma markers of inflammation and antioxidant activity in chronic kidney disease patients.* Dept. of Health, Human Performance and Recreation, Baylor University. Waco: Baylor University's Digital Repository, 2010. Ph.D. Thesis.

Curcumin Induces Nrf2 Nuclear Translocation and Prevents Glomerular Hypertension, Hyperfiltration, Oxidant Stress, and the Decrease in Antioxidant Enzymes in 5/6 Nephrectomized Rats. **Tapia, Edilia, et al., et al.** [ed.] Felipe Dal-Pizzol. Article ID 269039, Rio de Janeiro: Hindawi Publishing Corporation, June 4, 2012, Oxidative Medicine and Cellular Longevity, Vol. 2012, pp. 1-14. DOI: 10.1155/2012/269039; http://www.hindawi.com/journals/omcl/2012/269039/. ISSN: 1942-0900.

Curcumin and enalapril ameliorate renal failure by antagonizing inflammation in 5/6 nephrectomized rats: role of phospholipase and cyclooxygenase. **Ghosh, S.S., et al., et al.** [ed.] Thomas R. Kleyman. 4, Pittsburgh: The American Physiological Society, February 15, 2012, American Journal of Physiology - Renal Physiology, Vol. 302, pp. F439-F454. DOI: 10.1152/ajprenal.00356.2010; http://ajprenal.physiology.org/content/302/4/F439. ISSN: 1931-857X.

Amelioration of renal ischaemia-reperfusion injury by liposomal delivery of curcumin to renal tubular epithelial and antigen presenting cells. **Rogers, N.M., et al., et al.** [ed.] David R Poyner and Debbie L Hay. 1, Glasgow: John Wiley & Sons, Inc.: The British Pharmacological Society, May 2012, British Journal of Pharmacology, Vol. 166, pp. 194-209. DOI: 10.1111/j.1476-5381.2011.01590.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2011.01590.x/abstract. eISSN: 1476-5381.

Beneficial Effects of the Bioflavonoids Curcumin and Quercetin on Early Function in Cadaveric Renal Transplantation: A Randomized Placebo Controlled Trial. **Shoskes, Daniel, et al., et al.** 11, s.l.: Lippincott Williams & Wilkins, December 15, 2005, Transplantation, Vol. 80, pp. 1556-1559. DOI: 10.1097/01.tp.0000183290.64309.21; http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2005&issue=12150&article=00008&type=abstract. ISSN: 0041-1337.

Curcumin Pretreatment Prevents Potassium Dichromate-Induced Hepatotoxicity, Oxidative Stress, Decreased Respiratory Complex I Activity, and Membrane Permeability Transition Pore Opening. **García-Niño, Wylly Ramsés, et al., et al.** [ed.] Shrikant Anant. Article ID 424692, Kansas City: Hindawi Publishing Corporation, July 17, 2013, Evidence-Based Complementary and Alternative Medicine, Vol. 2013, pp. 1-19. DOI: 10.1155/2013/424692; http://www.hindawi.com/journals/ecam/2013/424692/. eISSN: 1741-4288.

Oral nanoparticulate curcumin combating arsenic-induced oxidative damage in kidney and brain of rats. **Sankar, Palanisamy.** [ed.] Alan M. Hoberman. Horsham: SAGE Publications, October 8, 2013, Toxicology and Industrial Health. DOI:

10.1177/0748233713498455; http://tih.sagepub.com/content/early/2013/10/04/0748233713498455. eISSN: 1477-0393.

Protective effects of the dietary supplementation of turmeric (Curcuma longa L.) on sodium arsenite-induced biochemical perturbation in mice. **Karim, Rezaul, et al., et al.** [ed.] A.K. Khan. 3, Dhaka: Bangladesh Medical Research Council, December 2010, Bangladesh Medical Research Council Bulletin, Vol. 36, pp. 82-88. DOI: 10.3329/bmrcb.v36i3.7287; http://www.banglajol.info/index.php/BMRCB/article/view/7287. ISSN: 0377-9238.

Curcumin and analog 2a inhibit â-catenin pathway and ADPKD cyst growth. **Bello-Reuss, Elsa, et al., et al.** [ed.] Gerald Weissmann. Meeting Abstract Supplement 910.19, New York: Federation of American Societies for Experimental Biology, April 2013, The FASEB Journal, Vol. 27, p. 910.19. ISSN: 0892-6638.

Pharmacological and clinical properties of curcumin. **Beevers, Christopher S. and Huang, Shile.** [ed.] Ayse Kuruuzum-Uz. Ankara: Dove Medical Press Ltd., June 23, 2011, Botanics: Targets and Therapy, Vol. 1, pp. 5-18. DOI: 10.2147/BTAT.S17244; http://www.dovepress.com/pharmacological-and-clinical-properties-of-curcumin-peer-reviewed-article-BTAT. ISSN: 1179-9897.

A Pilot Study on Intravesical Administration of Curcumin for Cystitis Glandularis. **Lu, Qiong, et al., et al.** [ed.] Alfredo Vannacci. Article ID 269745, Prato: Hindawi Publishing Corporation, May 22, 2013, Evidence-Based Complementary and Alternative Medicine, Vol. 2013, pp. 1-5. DOI: 10.1155/2013/269745; http://www.hindawi.com/journals/ecam/2013/269745/. eISSN: 1741-4288.

*Antimicrobial Activity of Three Different Rhizomes of Curcuma Longa & Curcuma Aromatica on Uropathogens of Diabetic Patients.***Saleem, Mehvish, Daniel, Betty and K, Murli.** [ed.] Manish S. Bhatia. 4, Pune: Academic Sciences, Oct-Dec 2011, International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 3, pp. 273-279. ISSN: 0975-1491.

Capsicum, Rosemary, and Turmeric. [book auth.] Manuchair Ebadi. *Pharmacodynamic Basis of Herbal Medicine.* 2. Boca Raton: CRC Press: Taylor & Francis Group, LLC, 2007, 19, pp. 237-238. ISBN: 0-8493-7050-7.

D. Curcumin and the Liver

In this section I present excerpts from one study on the efficacy of curcumin for treating the liver. I have added **bold** for emphasis. The reader may want to explore the many articles provided in the footnotes but they will NOT be subject to examination in this course. Also, thereafter I present many further studies on this subject for the reader's pleasure and further information. **Optional reading.**

1. Pharmacological actions of curcumin in liver diseases or damage.

Rivera-Espinoza, Yadira and Muriel, Pablo. [ed.] Rajiv Jalan. 10, Calgary: John Wiley & Sons Ltd, November 2009, Liver International, Vol. 29, pp. 1457-1466. DOI: 10.1111/j.1478-3231.2009.02086.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1478-3231.2009.02086.x/abstract. eISSN: 1478-3231.

Free Access

Correspondence
Pablo Muriel, PhD, Sección Externa de Farmacología, Cinvestav-I.P.N., Apdo. Postal 14-740, México 07000, D.F., México
Tel: +5255 5747 3303
Fax: +5255 5747 3394
e-mail: pamuriel@cinvestav.mx

PDF

Abstract

Since 1900 BC, several therapeutic activities have been attributed to the rhizomes of the plant *Curcuma longa* for a variety of diseases, including liver disorders. Curcumin, the main active compound obtained from this plant, was first isolated two centuries ago and its structure as diferuloylmethane was determined in 1910. **Curcumin has shown anti-inflammatory, anti-oxidant, antifungal, antibacterial and anticancer activities.** The pharmacological properties of curcumin were reviewed recently and focused mainly on its anticancer properties. However, its beneficial activity on liver diseases (known centuries ago, and demonstrated recently utilizing animal models) has not being reviewed in depth until now. The curcumin ability to inhibit several factors like nuclear factor-κB, which modulates several pro-inflammatory and profibrotic cytokines as well as its anti-oxidant properties, provide a rational molecular basis to use it in hepatic disorders. **Curcumin attenuates liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis and acute, subchronic and chronic carbon**

tetrachloride (CCl_4) intoxication; moreover, it reverses CCl_4 cirrhosis to some extent. Unfortunately, the number of studies of curcumin on liver diseases is still very low and investigations in this area must be encouraged because hepatic disorders constitute one of the main causes of worldwide mortality.

Traditional agents derived from ancient Hindu medicine, such as curcumin, have been shown to have biological activity at physiologically relevant concentrations in preclinical studies. Dozens of medicinal properties of curcumin have been described that have been reviewed recently (1-3). The most studied beneficial properties of curcumin are perhaps its anti-oxidant, anticarcinogenic, anti-inflammatory and immunomodulatory activities, among others. However, the pharmacological hepatoprotective properties of curcumin known to Indians in the traditional medicine hundreds of years ago, and tested recently on the basis of modern scientific methods, have not been reviewed in depth. Therefore, this review summarized the most important and general actions of curcumin but focused on its effects on liver diseases.

Curcumin botany

Curcumin, a polyphenol (diferuloylmethane), is the main active compound found in the perennial plant *Curcuma longa* (commonly known as turmeric). The *Curcuma* genus belongs to the division of Magnoliophyta, class of Liliopsyda, subclass of Zingiberidae, order Zingiberales and family Zingiberaceae. Turmeric is a short-stemmed plant that grows around 1 m in height; it has curved leaves and oblong, ovate or cylindrical rhizomes (Fig. 1). *Curcuma longa* grows naturally throughout the Indian subcontinent and in Southeast Asia and other tropical countries.

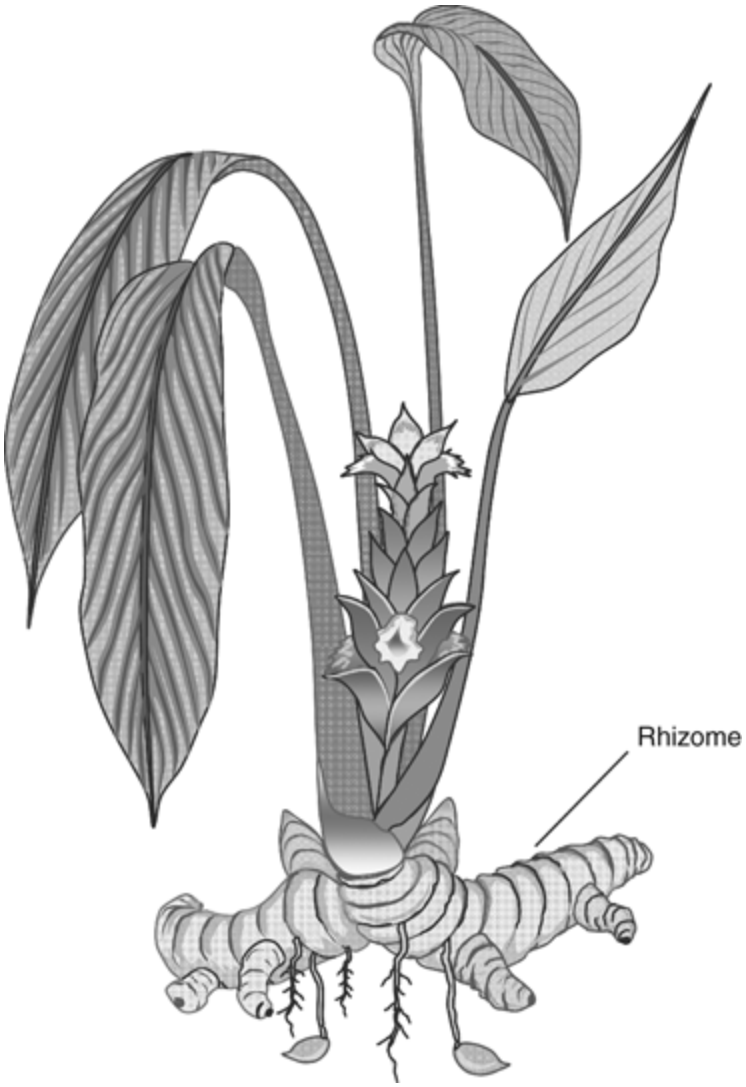

Figure 1

Open in figure viewerPowerPoint

Curcuma longa plant.

Curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin are the four principal curcuminoids obtained from the coloured extracts of dried roots from turmeric (Fig. 2). Whether all four analogues exhibit equal activity is not clear. Although in most systems curcumin was found to be the most potent (4, 5), in some systems bisdemethoxycurcumin was found to exhibit higher activity (6, 7). There are also suggestions that the mixture of all three is more potent than either one alone (8, 9).

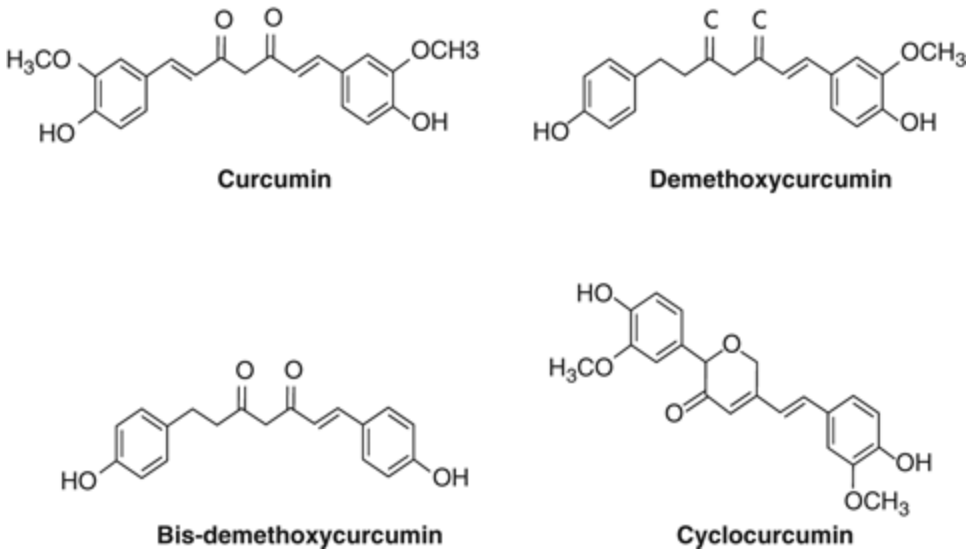

Figure 2

Open in figure viewerPowerPoint

The major curcuminoids present in the rhizome of the plant *Curcuma longa*.

India is the main producer of turmeric and consumes about 90% of it and exports the remainder (10). *Curcuma longa* and its constituents have been used in Asian cookery and traditional medicine for thousands of years: at present, they are used by the food industry as additives, like curry in England, flavourings, preservatives and colouring agents, in soft drinks, mustard and margarine.

Safety

One of the most prominent features of curcumin is its extremely good tolerance and its very low toxicity and side effects. However, although turmeric and curcumin are natural products used in the diet, the doses used in clinical trials exceed those consumed in the diet; therefore, systematic toxicity studies are needed. Curcumin is Generally Recognized As Safe by the Food and Drug Administration, and this compound has been granted an Acceptable Daily Intake level of up to 3 mg/kg by the Joint FAO and WHO Expert Committee on Food Additives, 1996 (11). No studies in either animals (12, 13) or humans (14) have found any toxicity associated with the consumption of curcumin even at very high doses.

Molecular targets

Curcumin possesses a diverse range of molecular targets; among them are transcription and growth factors, cytokines, enzymes and genes regulating cell proliferation and apoptosis. It binds to and inhibits the activity of enzymes, growth factor receptors, metals, albumin and other molecules. Curcumin binds *p*-glycoprotein (15, 16), multidrug resistance proteins 1 and 2 (MRP1 and MRP2) (17), glutathione (18), protein kinase C (PKC), ATPase (19, 20) and α-1-acid glycoprotein (21). It also blocks fibril formation *in vitro* and *in vivo* by directly binding small β-amyloid species (22). Curcumin binds CD13/aminopeptidase N and prevents angiogenesis and tumour invasion (23). It inhibits the activity of lipoxygenase by binding to it (24) or binding to phosphatidylcholine micelles and thereby inhibiting lipoxygenase 1 (25).

Various transcription factors are strongly inhibited by curcumin, including nuclear factor-κB (NF-κB), signal transducer and activator of transcription proteins, activated protein-1, β-catenin and peroxisome proliferator-activated receptor-γ (26). These transcription factors regulate the expression of genes that contribute to cell survival, inflammation, tumorigenesis, angiogenesis, cell proliferation and invasion. Curcumin also downregulates the activity of multiple kinases [for a review, please see Goel *et al*. (2, 3)].

Curcumin and liver damage

To date, there is no cure for cirrhosis, which is a leading worldwide cause of death (27). Some beneficial drugs for liver diseases have been studied but we are far from finding effective treatments. **In this scenario, curcumin appears as a drug with possibilities to cure/ameliorate hepatic disorders.**

Effects on iron-induced hepatic toxicity in rats

Iron is an essential constituent of the body and can be found in a functional form in cytochromes, haemoglobin, myoglobin and enzymes with iron–sulphur complexes and other iron-dependent enzymes. However, an excess of iron in the body is associated with toxic effects, leading to diseases (28). Because the body lacks any effective means to eliminate excessive iron, the toxic consequence of iron accumulation is determined by the rate, magnitude and distribution of iron in various compartments. Liver damage is the most common toxic effect observed with iron overloading. Excessive deposition of iron in hepatocytes produces fibrosis and cirrhosis (29, 30). Dietary curcumin lowers lipid peroxidation induced by Fe^{2+} intoxication to rats by enhancing the activities of anti-oxidant enzymes (31). Moreover, it has been demonstrated that curcumin and

other spice ingredients can inhibit the oxidation of Fe^{2+} by H_2O_2 in the Fenton reaction (32), which generates ·OH radicals, involved in the initiation of lipid peroxidation (33). Based on these observations, Reddy and Lokesh (34) assessed whether the injury caused to hepatic parenchyma by iron intoxication could be normalized by curcumin. They found that administration of 30 mg/kg, p.o., of curcumin daily for 10 days to Wistar rats significantly reduced the lipid peroxidation degree induced by iron [30 mg/kg, intraperitoneal (i.p.)]. Serum enzyme activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are very important adjuncts to diagnosis and to measure liver injury; iron administration significantly elevated the hepatic lipid peroxides and serum AST, ALT and lactate dehydrogenase. Importantly, curcumin significantly prevented the serum levels of AST and ALT in iron-treated rats, indicating that this spice principle reduced the severity of iron toxicity by reducing the lipid peroxidation (34). Other targets of curcumin, like NF-κB inactivation (35), cannot be discarded to contribute to the beneficial effects of curcumin on iron toxicity. Recently, it was found that curcumin reduces the toxic effects of iron loading in rat liver epithelial cells (36). In summary, there is evidence that curcumin possesses beneficial properties on iron toxicity; however, more studies are needed to confirm this effect. New studies should include histopathological analysis and more in depth investigations of the action mechanism of curcumin in the light of their many and new described properties (1-3).

Ethanol administration resulted in biochemical, histopathological changes in the liver, kidney and brain that were reverted when curcumin and *N*-acetylcysteine were given to rats intoxicated with ethanol (37).

Evidence shows that alcohol-induced changes can cause a significant decrease in arachidonic acid in human plasma, erythrocytes, platelets and liver tissue (38-40). Arachidonic acid is released from phospholipids inserted into the plasma membrane by the action of Ca^{2+}-dependent phospholipase 2 (PLA_2) (41). There are two routes for arachidonic acid metabolism. One is the cycloxygenase (COX) pathway that produces prostaglandins (PGs), thromboxanes (TXs) and prostacyclins. The other pathway produces hydroxyeicosatetraenoic acids, and leukotrienes that are well-known mediators of the acute vascular changes that accompany the process of inflammation (42).

Researchers have demonstrated that chronic exposure to ethanol increases, progressively, PLA_2 activity (43, 44). In turn, PLA_2 activity increases the formation of arachidonic acid release from phospholipids, which is then converted to physiologically relevant eicosanoids (45). Interestingly, curcumin has been shown to inhibit the production of arachidonic acid in the liver, kidney and brain (46). Moreover, curcumin inhibits PLA_2 activity (47).

Oral alcohol administration to rats increases the levels of COX mRNA, which in turn enhances the production of PGs (48). Rajakrishnan *et al*. (46) found a significant increase in the levels of PGE_1, PGE_2, $PGF_{2\alpha}$ and PGD_2 in the liver, kidney and brain in alcohol-fed rats, while cotreatment with curcumin decreased the level of PGs significantly.

It has been reported that curcumin decreases the PG formation of PGE_2, $PGF_{2\alpha}$, PGD_2, $TXB_2$and 6-keto-PGF_1 in azoxymethane-induced colon carcinogenesis (49). The mechanism by which curcumin decreases the production of PGs is through inhibition of PLA_2, lipoxygenase and COX activities (50). In addition, curcumin administration to rats intoxicated chronically with ethanol resulted in a decrease in PGs. This decrease in PGs suggests that increased arachidonic acid may be utilized for the synthesis of phospholipids, which can be useful for plasma membrane synthesis (46). In fact, Rajakrishnan *et al*. (46) administered curcumin after 1 month of ethanol administration; because ethanol may have resulted in membrane hydrolysis and dysfunction, administration of curcumin may result in the resynthesis of plasma membrane, as evident from decreased PG synthesis, an increased arachidonic acid level and an increased phospholipid concentration. Therefore, evidence strongly suggests that curcumin helps in maintaining the membrane structure, integrity and function, protecting the liver, brain and kidney from alcohol toxicity.

Attenuation of thioacetamide-induced hepatitis by curcumin

The liver has a remarkable ability to metabolize and aid in the excretion of xenobiotics. However, this organ is susceptible to damage from several drugs and toxins (51). Hepatic damage following the intake of such agents can be reversible and subclinical, but may also cause fulminant hepatic failure (FHF) and death (51, 52). Experimental models of toxic liver injury are utilized to evaluate the biochemical processes involved in many forms of liver disease and to evaluate the possible pharmacological effects of candidate hepatoprotectants. The administration of thioacetamide (TAA) to rats causes FHF or cirrhosis, depending on the dose used and the duration of administration (53, 54). Animals treated with TAA exhibit, in their livers, enhanced formation of reactive oxygen species (ROS) and lipid peroxides (55), stimulation of NF-κB and the resultant production of pro-inflammatory molecules (56, 57), mechanisms that have an established role in FHF (52).

One of the most known mechanisms underlying curcumin's beneficial effects on several illnesses is its pleiotropic anti-oxidant activity (58). It prevents formation and scavenges ROS (59, 60) and

reactive nitrogen species (61, 62). Furthermore, curcumin was shown to induce several enzymatic anti-oxidants, like glutathione transferase (63), haeme-oxygenase-1 (64) and catalase (63). Curcumin inhibits the activation of NF-κB by ROS, PKC and pro-inflammatory cytokines. NF-κB-mediated expression of inducible nitric oxide synthase (iNOS) is also inhibited by curcumin (35, 65).

The information presented above prompted Shapiro *et al*. (66) to evaluate whether curcumin's ability to inhibit iNOS and NF-κB, and to scavenge free radicals would protect from TAA-induced acute liver damage in rats. In their work, FHF was induced by two i.p. injections of 300 mg/kg of TAA at 24-h intervals. Two doses of curcumin were evaluated, a low dose (200 mg/kg per day, i.p.) or a high dose (400 mg/kg per day), initiated 48 h before the first TAA injection. Appropriate controls were performed. Survival was higher in the curcumin-treated groups compared with the TAA-only-treated animals. Liver necrosis and blood ammonia were reduced by curcumin, and the effect was better in the high-dose group. Lipid peroxidation, NF-κB activation and iNOS expression were increased by TAA and reduced by curcumin. The findings of the Shapiro *et al*. (66) study confirm a role for ROS, nitric oxide and NF-κB activation in the pathogenesis of TAA-induced liver damage and indicate that a blockade of their formation or activation by curcumin administration has a potent anti-inflammatory effect. Because curcumin is safe in humans (67), its use in patients with acute liver injury can be evaluated based on these results.

Attenuation of thioacetamide-induced cirrhosis by curcumin

Although progress has been made in the management of liver cirrhosis and its complications, preventive strategies should be beneficial in reducing the burden of this disease. Based on these facts, Bruck *et al*. (68) studied the preventive effect of curcumin on TAA-induced cirrhosis. TAA, although not toxic in itself, is converted into potent toxic substances by cytochromes (69). Hepatic damage is produced by the action of these reactive compounds (70) and possibly by activating NF-κB (66, 71). The type of liver injury induced by TAA depends on the dosage and duration of its administration: high doses can produce FHF (72), whereas lower doses administered periodically can lead to cirrhosis (54). In the study of Bruck *et al*. (68), rats that received biweekly, i.p. injections of TAA for 12 weeks developed liver cirrhosis, manifested by a gross macroscopic appearance, liver histopathology, hepatic hydroxyproline content and increased spleen weight; the liver showed hepatic stellate cells (HSC) activation determined as increased expression of α-smooth muscle actin and type I collagen gene expression. Curcumin

(300 mg/kg/day/12 weeks) co-administration to TAA-treated rats resulted in a significant improvement of all alterations observed in the group receiving TAA alone. The protective effect of curcumin against liver fibrosis may be associated with its ability to inhibit NF-κB in Kupffer cells and infiltrating macrophages (35), therefore preventing liver inflammation, necrosis and apoptosis.

In order to further explore the potential antifibrotic actions of curcumin, Bruck *et al*. (68) studied whether curcumin would have a fibrolytic effect on established TAA cirrhosis. Unfortunately, administration of curcumin for 4 or 6 weeks to rats that already received TAA for 12 weeks did not reduce hepatic hydroxyproline levels or spleen weights, suggesting that curcumin exerts no beneficial effects on pre-established TAA-induced cirrhosis. This is in agreement with the observations in the same study that curcumin showed no *in vitro* effect on HSC. The failure of curcumin to inhibit HSC profibrogenic activity observed by Bruck *et al*. (68) is not in agreement with a previous study (72); the use of different HSC cell lines may explain this discrepancy. The most relevant result of this study is that curcumin prevented the development of hepatic cirrhosis induced by TAA. Because curcumin is safe for consumption by humans, it may have a beneficial role in chronic liver diseases characterized by ongoing necroinflammation.

Effects on cholestasis and biliary cirrhosis

Cirrhosis produced by bile duct ligation (BDL) in the rat is a useful model to evaluate possible beneficial drugs (73). Cirrhosis is accompanied by a perturbation in liver homeostasis with the release of cytokines and signalling molecules (74). One of the most important profibrogenic cytokines, transforming growth factor- β (TGF-β), is central to the development of fibrosis through its stimulating properties on ECM production and inhibitory effect on its removal (75). TGF-β plays an important role in initiating and promoting the activation of HSC to myofibroblasts during hepatic fibrogenesis. The TGF-β expression is elevated in experimental and human liver diseases ranging from hepatitis and cholestasis to cirrhosis (76, 77).

Curcumin blocks the profibrotic actions of TGF-β and has been reported to prevent fibrosis in a TGF-β-driven model of fibrotic lung (78) and kidney (79) disease. Recently, we showed that curcumin protects against inflammation and oxidative stress in carbon tetrachloride (CCl_4)-induced acute hepatic injury (80). It was also found that curcumin prevents TAA-induced cirrhosis (68), but the role of TGF-β was not studied. Therefore, Reyes-Gordillo *et al*. (80) studied the effect of curcumin on BDL-induced cirrhosis and possible mechanisms like TGF-β downregulation and oxidative stress participation. Rats were bile duct obstructed for 4 weeks and curcumin was administered at a dose of 100 mg/kg, p.o., daily. Serum ALT activity increased

about two-fold after BDL; as expected in a model of cholestasis, γ-GTP and bilirubins were highly increased by BDL (22.5- and seven-fold respectively). Curcumin treatment partially, but significantly, prevented the increase of these serum markers of liver damage. Haematoxylin and eosin staining of liver sections showed important areas of necrosis in the BDL group that were absent in the BDL+curcumin group, confirming the ALT observations. Liver glutathione levels were measured as an indicator of oxidative stress at the hydrophilic level. GSH, GSH/GSSG ratio and total (GSH+GSSH) glutathione decreased significantly in the BDL group; in contrast, curcumin administration increased glutathione levels in BDL and in rats administered curcumin alone. The main source of energy in the liver, glycogen, was depleted by BDL, while curcumin maintained the normal levels. Fibrosis, measured by the liver content of hydroxyproline and visualized by trichromic staining, increased five-fold by BDL; this effect was prevented partially but significantly by curcumin. Numerous studies have shown that TGF-β treatment upregulates the expression of various profibrotic genes (75). The results of Reyes-Gordillo *et al*. (80) show increases in TGF-β mRNA in livers from BDL rats; importantly, curcumin treatment markedly inhibited this increase. TGF-β protein was also increased by BDL, but significantly inhibited by curcumin.

It can be concluded that curcumin attenuates experimental fibrosis of various aetiologies including biliary cirrhosis and that some of the mechanisms include NF-κB and TGF-β downregulation and its anti-oxidant properties.

Effects on acute and subacute carbon tetrachloride toxicity

Acute toxicity to the liver induces necrosis, inflammation and oxidative stress of hepatocytes (73). Recently, it has been suggested that hepatocellular injury is because of the inflammatory cells that have been attacked by the stressed hepatocytes (74). The inflammatory response is mediated by cytokines, mainly interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α); these cytokines may induce an acute-phase response or modulate the effects of IL-6 (81). The relevance of these cytokines in liver damage is demonstrated by evidence that circulating levels of IL-1β and TNF-α are elevated in rats that develop hepatic injury (74). It is also known that inflammatory events are regulated by NF-κB activation by the release of IL-1β and TNF-α (82). NF-κB is an important regulator of the expression of genes encoding cytokines (71) including IL-1β and TNF-α. Therefore, a vicious cycle is established in the damaged liver: IL-1β and TNF-α induce NF-κB activity and these factors increase the production of additional IL-1β and TNF-α. This cycle destroys the hepatic parenchyma and impairs liver function. Therefore,

NF-κB is a suitable target to treat liver diseases (71). Studies involving systemic curcumin administration have demonstrated its beneficial effects by modulating NF-κB activity (35); in addition, the ability of curcumin to scavenge a variety of ROX (83) makes this compound a suitable tool to be studied in CCl_4-induced liver damage.

Park *et al*. (84) studied the protective effect of curcumin in acute and subacute rat liver injury induced by CCl_4. In acutely liver-damaged rats (0.2 ml/kg, i.p.), AST and ALT serum activities were increased to 340 and 397% as compared with control animals. Treatment with curcumin (100 or 200 mg/kg) significantly prevented the increase of these enzymes. In the subchronic liver damage, CCl_4 was administered by gavage (1 ml/kg, mixed with an equal volume of corn oil) twice a week for 4 weeks; curcumin (50 or 100 mg/kg, daily) was administered along with CCl_4. Serum activities of alkaline phosphatase, AST and ALT increased by subacute CCl_4 intoxication, 1041, 840 and 1653%, respectively, while serum albumin levels decreased 22%. Curcumin (100 mg/kg) prevented partially, but significantly, these alterations. A 50 mg/kg dose of curcumin showed modest and no significant effects on these parameters.

The liver hydroxyproline content increased to 277% in subacutely intoxicated rats as compared with controls; daily administration of 100 mg/kg of curcumin maintained the liver hydroxyproline content within normal levels. The malondialdehyde in the livers of CCl_4-treated animals for 4 weeks increased significantly, but again, curcumin maintained normal lipid peroxidation degree.

In summary, the study of Park *et al*. (84) demonstrated that curcumin can effectively inhibit the hepatic damage produced by either acute or subacute CCl_4 treatment as monitored by serum biochemical parameters, fibrosis and lipid peroxides in the liver.

The ability of oral curcumin (200 mg/kg) to prevent acute CCl_4 (4 g/kg, p.o.) intoxication was studied recently (85). Acute CCl_4 administration produced liver injury measured by serum ALT, γ-GTP and bilirubins, and by histopathological analysis. The damage was associated with a decreased hepatic GSH/GSSG ratio, indicating oxidative stress. Furthermore, NF-κB was activated and pro-inflammatory cytokines upregulated by this factor, IL-1β, TNF-α and IL-6, increased several fold**. Curcumin treatment prevented all the alterations induced by acute CCl_4 intoxication (85).** It seems likely that the anti-oxidant properties of curcumin (83) and its ability to inactivate NF-κB (35), and thus pro-inflammatory cytokine production (86), are the most important mechanisms of action of curcumin to prevent acute CCl_4-induced liver injury.

Reversion of carbon tetrachloride cirrhosis

As shown previously, the ability of curcumin to prevent acute and chronic liver damage has been demonstrated in different models (CCl_4, TAA and BDL). However, the capacity of this compound to reverse well-established cirrhosis was not demonstrated. This is a very interesting point because usually patients are treated when the disease is already present.

Advanced cirrhosis is generally considered to be an irreversible process even after removal of the causative agent. The disease seems to be characterized by the inability of the damaged liver to remodel the fibrotic parenchyma (75). Discontinuation of CCl_4 after 2 months of chronic (three times per week) treatment is usually followed by rapid fibrosis remission (87). Therefore, based on previous observations (88), we decided to perform the evaluation of curcumin to reverse CCl_4 well-established cirrhosis by using a prolonged CCl_4treatment (3 months vs. the 2 months normally used in experimental protocols); after 3 months of chronic CCl_4 administration, the toxin was discontinued and curcumin (100 mg/kg, p.o., daily) was administered for 2 months; a group receiving vehicle was studied to monitor spontaneous resolution of liver damage (80). ALT activity increased significantly after 3 months of chronic CCl_4 administration. Importantly, discontinuation of CCl_4 produced a further increase in plasma ALT; curcumin treatment for 2 months of rats pretreated with CCl_4 restored the levels of ALT enzyme activity to normal values. Because it is well known that oxidative stress participates in the damage caused by CCl_4, glutathione was evaluated: an important decrement in GSH, GSH/GSSG ratio and total glutathione produced by CCl_4administration for 3 months was observed. Interestingly, discontinuation of the toxin increased oxidative stress at the hydrophilic level as the GSH, GSH/GSSG ratio and GSH+GSSG were lower than those in rats treated with CCl_4 for 3 months. **Very importantly, administration of curcumin for 2 months resulted in normalization of glutathione levels.**

Hepatic fibrosis occurs as a result of an imbalance between fibrogenesis and fibrolysis and is a major factor contributing to liver failure in cirrhotic patients. Administration of CCl_4 for 3 months led to a five-fold increase in the collagen content; curcumin administration to these rats for 2 months produced a partial but significant reversion of CCl_4-induced fibrosis. Liver glycogen content was found to be decreased because of CCl_4 administration and discontinuation of CCl_4 led to a further decrease of glycogen; **importantly, curcumin-restored control glycogen levels (80).**

It has been considered that the beneficial effects of curcumin are mediated, in part, by its anti-oxidant defence ability and the scavenging of free radicals; furthermore, curcumin is 10 times more active as an anti-oxidant than vitamin E (89). CCl_4 decreases the anti-oxidant capacity of the liver (73, 90) even after CCl_4 discontinuation for 2 months (80); thus, **the anti-oxidant activity of curcumin may account for its beneficial properties in the reversion of cirrhosis.** Curcumin also demonstrated its ability to restore glycogen levels previously depleted by hepatic injury induced by CCl_4 administration; Pari and Murugan (91) reported the ability of curcumin to preserve blood glucose levels. They attributed this action to the ability of curcumin to restore the altered activities of the enzymes 6-phosphate dehydrogenase and glucose-6-phosphatase that participate in gluconeogenesis and glucogenolysis. The same mechanism may be responsible for the recuperation of glycogen in the liver.

Liver recovery from fibrosis involves the degradation of fibrous bands. Metalloproteinase enzymes (MMPs), especially pro-MMP-2 and proMMP-9, as well as their active forms, are responsible for the degradation of matrix proteins like gelatin, collagen IV, collagen V, fibronectin and elastin (92, 93). It has been reported that curcumin upregulates the expression and activity of matrix pro-MMP-2 and proMMP-9 in human bronchial epithelial cells, and during the prevention and healing of indomethacin-induced gastric ulcers (94, 95). Thus, the reversion of liver fibrosis observed by Reyes-Gordillo *et al*. (80) may be explained through modulation of MMPs; in addition, downregulation of NF-κB and TGF-β and other cytokines may provide likely antifibrotic and fibrolytic mechanisms (71, 85). Furthermore, Kang *et al*. (96) reported that curcumin inhibits collagen synthesis and HSC activation *in vivo*and *in vitro*, supporting the ability of curcumin to reverse CCl_4 fibrosis (85).

Conclusions

Curcumin has shown beneficial properties in diverse experimental models of liver damage. It prevents liver damage induced by aflatoxins, iron overdose, erythromycin estolate, ethanol, TAA acute and chronic intoxication, cholestasis (BDL) and acute, subacute and chronic CCl_4 intoxication; moreover, **it reverses CCl_4 cirrhosis to some extent. Curcumin may act at several molecular targets, but two have been utilized the most to explain its pharmacological properties: one is its anti-oxidant effect and the other is its ability to inhibit NF-κB factors.** Oxidative stress plays a causative role in most liver disorders and models of hepatic injury, while NF-κB is responsible for the transcription of the fundamental mediators of inflammation and liver damage.

In the case of acute CCl_4 intoxication, for example, oxidative stress and expression of pro-inflammatory cytokines like TNF-α, IL-1β and IL-6 (all of them upregulated by NF-κB) and activation of NF-κB were associated with increases in several markers of liver damage and distortion in the hepatic microscopical structure; curcumin pretreatment prevented oxidative stress, activation of NF-κB and liver damage. Similarly, in biliary cirrhosis, curcumin showed antifibrogenic properties associated with a downregulation of the most profibrotic cytokine, TGF-β. **Reversion of CCl_4-induced cirrhosis by curcumin is, perhaps, the most exciting discovery due to its possible implications in human chronic liver disease.** However, there is only one report supporting the ability of the compound to reverse the disease. Therefore, more basic and even clinical (due to the low toxicity of curcumin) studies are urgently needed before this drug can be recommended for the treatment of human acute and chronic liver disorders.

Acknowledgements

The authors are grateful to Alfredo Padilla for preparing the figures, and to Biol. Mario G. Moreno and Liseth Rubí Aldaba Muruato for their careful review of the manuscript.

More optional research reading on curcumin for the liver:

A Current Update on the Role of Alternative and Complementary Medicine in the Treatment of Liver Diseases. **Guan, Yong-Song and He, Qing.** [ed.] Mohammad Ahmad Al-Shatouri. Article ID 321234, Ismaileya: Hindawi Publishing Corporation, September 10, 2013, Evidence-Based Complementary and Alternative Medicine, Vol. 2013, pp. 1-10. DOI: 10.1155/2013/321234; http://www.hindawi.com/journals/ecam/2013/321234/. eISSN 1741-4288.

Curcumin eliminates oxidized LDL roles in activating hepatic stellate cells by suppressing gene expression of lectin-like oxidized LDL receptor-1. **Kang, Qiaohua and Chen, Anping.** [ed.] Gene P. Siegal. 11, Birmingham: Nature Publishing Group: United States and Canadian Academy of Pathology, November 2009, Laboratory Investigation, Vol. 89, pp. 1275-1290. DOI: 10.1038/labinvest.2009.93; http://www.nature.com/labinvest/journal/v89/n11/full/labinvest200993a.html. ISSN: 0023-6837.

Pharmacological actions of curcumin in liver diseases or damage. **Rivera-Espinoza, Yadira and Muriel, Pablo.** [ed.] Rajiv Jalan. 10, Calgary: John Wiley & Sons Ltd, November 2009, Liver International, Vol. 29, pp. 1457-1466. DOI: 10.1111/j.1478-3231.2009.02086.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1478-3231.2009.02086.x/abstract. eISSN: 1478-3231.

Activation of peroxisome proliferator-activated receptor-γ contributes to the inhibitory effects of curcumin on rat hepatic stellate cell growth. **Xu, Jianye, Fu, Yumei and Chen,**

Anping. [ed.] Marshall Montrose. 1, Bethesda: The American Physiological Society, July 1, 2003, AJP - Gastrointestinal and Liver Physiology, Vol. 285, pp. G20-G30. DOI: 10.1152/ajpgi.00474.2002; http://ajpgi.physiology.org/content/285/1/G20. ISSN: 0193-1857.

The effectiveness of fermented turmeric powder in subjects with elevated alanine transaminase levels: a randomised controlled study. **Kim, Sang-Wook, et al., et al.** [ed.] Tom Rowles. 58, London: BioMed Central Ltd.: International Society for Complementary Medicine Research, March 8, 2013, BMC Complementary and Alternative Medicine, Vol. 13. DOI: 10.1186/1472-6882-13-58; http://www.biomedcentral.com/1472-6882/13/58. ISSN: 1472-6882.

Comparative effects of curcumin and resveratrol on aflatoxin B1-induced liver injury in rats. **El-Agamy, Dina S.** [ed.] Jan G. Hengstler. 5, Dortmund: Springer-Verlag, May 2010, Archives of Toxicology, Vol. 84, pp. 389-396. DOI: 10.1007/s00204-010-0511-2; http://link.springer.com/article/10.1007%2Fs00204-010-0511-2. ISSN: 0340-5761.

Biochemical Studies on the Role of Curcumin in the Protection of Liver and Kidney Damage by Anti-Malaria Drug, Chloroquine. **Al-Jassabi, S., Azirun, Mohd Sofian and Saad, Ali.** [ed.] Rachid Rouabhi. 1, Tebessa: IDOSI Publications, 2011, American-Eurasian Journal of Toxicological Sciences, Vol. 3, pp. 17-22. ISSN: 2079-2050.

Protective and modulatory effects of Curcumin and L-Carnitine against Methotrexate-induced Oxidative stress in albino rats. **Abdel-Ghaffar, Faten R., et al., et al.** [ed.] P. Gopkumar and K. Girish. 1, Surat: GVGS, January-March 2013, Research Journal of Pharmaceutical, Biological and Chemical Sciences, Vol. 4, pp. 744-754. ISSN: 0975-8585.

Curcumin protects rats against acetaminophen-induced hepatorenal damages and shows synergistic activity with N-acetyl cysteine. **Kheradpezhouh, Ehsan, et al., et al.** [ed.] F.P. Nijkamp. 1-3, Utrecht: Elsevier B.V., February 25, 2010, European Journal of Pharmacology, Vol. 628, pp. 274-281. DOI: 10.1016/j.ejphar.2009.11.027; http://www.sciencedirect.com/science/article/pii/S0014299909010425. ISSN: 0014-2999.

Piperine and Quercetin Enhances Antioxidant and Hepatoprotective effect of Curcumin in Paracetamol Induced Oxidative Stress. **Mehta, Astha, Kaur, Ginpreet and Chintamaneni, Meena.** [ed.] Majid Y. Moridani. 2, Denver: Asian Network for Scientific Information, 2012, International Journal of Pharmacology, Vol. 8, pp. 101-107. ISSN: 1811-7775.

Curcumin Exposure Modulates Multiple Pro-Apoptotic and Anti-Apoptotic Signaling Pathways to Antagonize Acetaminophen-Induced Toxicity. **Bulku, Elida, et al., et al.** [ed.] Kenneth Maiese. 1, Newark: Bentham Science Publishers, February 1, 2012, Current Neurovascular Research, Vol. 9, pp. 58-71. DOI: 10.2174/156720212799297083; http://www.eurekaselect.com/76453/article. ISSN: 1567-2026..

Effect of Curcuma longa or parziquantel on Schistoma mansoni infected mice liver - Histological and histochemical study. **El-Banhawey, Mahmoud A, et al., et al.** [ed.] K.

Satyanarayana. 10, New Delhi: Indian Council of Medical Research, October 2007, Indian Journal of Medical Research, Vol. 45, pp. 877-889. ISSN: 0971-5916.

Curcumin prevents and reverses cirrhosis induced by bile duct obstruction or CCl4 in rats: role of TGF-beta modulation and oxidative stress. **Reyes-Gordillo, Karina, et al., et al.** [ed.] Pascal Bousquet and Faiez Zannad. 4, Strasbourg; Nancy: Blackwell Publishing Ltd, August 2008, Fundamental & Clinical Pharmacology, Vol. 22, pp. 417-427. DOI: 10.1111/j.1472-8206.2008.00611.x; http://onlinelibrary.wiley.com/doi/10.1111/j.1472-8206.2008.00611.x/abstract. eISSN: 1472-8206.

OC-053 Curcumin, Anti-Oxidant, and Pioglitazone Therapy with Inclusion of Vitamin E in Non Alcoholic Fatty Liver Disease-A Randomized open Label Placebo Controlled Clinical Prospective Trial (Captive). **Basu, P, et al., et al.** [ed.] Emad El-Omar. Supplement 1, Aberdeen: BMJ Publishing Group Ltd & British Society of Gastroenterology, June 2013, Gut, Vol. 62, p. A23. DOI: 10.1136/gutjnl-2013-304907.052; http://gut.bmj.com/content/62/Suppl_1/A23.2. eISSN: 1468-3288.

Curcumin Inhibits srebp-2 Expression in Activated Hepatic Stellate Cells in Vitro by Reducing the Activity of Specificity Protein-1. **Kang, Qiaohua and Chen, Anping.** [ed.] Jeffrey D. Blaustein. 12, Boston: The Endocrine Society, December 1, 2009, Endocrinology, Vol. 150, pp. 5384-5394. DOI: 10.1210/en.2009-0517; http://press.endocrine.org/doi/abs/10.1210/en.2009-0517. ISSN: 0013-7227.

Curcumin Eliminates Leptin's Effects on Hepatic Stellate Cell Activation via Interrupting Leptin Signaling. **Tang, Youcai, Zheng, Shizhong and Chen, Anping.** [ed.] Jeffrey D. Blaustein. 7, Boston: The Endocrine Society, July 1, 2009, Endocrinology, Vol. 150, pp. 3011-3020. DOI: 10.1210/en.2008-1601; http://press.endocrine.org/doi/abs/10.1210/en.2008-1601. ISSN: 0013-7227.

High Fat Diet Induces Liver Steatosis and Early Dysregulation of Iron Metabolism in Rats. **Meli, Rosaria, et al., et al.** [ed.] Silvana Gaetani. 6, Rome: Public Library of Science, June 21, 2013, PLoS ONE, Vol. 8, p. e66570. DOI: 10.1371/journal.pone.0066570; http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0066570. ISSN: 1932-6203.

Curcumin inhibits hepatitis C virus replication via suppressing the Akt-SREBP-1 pathway. **Kim, KyeongJin, et al., et al.** [ed.] Felix Wieland. 4, Heidelberg: Elsevier B.V., February 19, 2010, FEBS Letters, Vol. 584, pp. 707-712. DOI: 10.1016/j.febslet.2009.12.019; http://www.febsletters.org/article/S0014-5793(09)01065-5/abstract. ISSN: 0014-5793.

Curcumin inhibits hepatitis B virus via down-regulation of the metabolic coactivator PGC-1α. **Rechtman, Maya Mouler, et al., et al.** [ed.] Hans-Dieter Klenk. 11, Marburg: Elsevier B.V., June 3, 2010, FEBS Letters, Vol. 584, pp. 2485-2490. DOI: 10.1016/j.febslet.2010.04.067; http://www.febsletters.org/article/S0014-5793(10)00352-2/abstract. ISSN: 0014-5793.

Delang, Leen, et al., et al. Hepatitis C Virus-Specific Directly Acting Antiviral Drugs. [ed.] Ralf Bartenschlager. *Hepatitis C Virus: From Molecular Virology to Antiviral Therapy.* Heidelberg: Springer-Verlag Berlin Heidelberg, 2013, Vol. 369, pp. 289-320. ISBN: 978-3-642-27339-1.

Antiviral effect of Curcuma longa Linn extract against hepatitis B virus replication. **Kim, Hye Jin, et al., et al.** [ed.] R. Verpoorte. 2, Leiden: Elsevier Ireland Ltd., July 15, 2009, Journal of Ethnopharmacology, Vol. 124, pp. 189-196. DOI: 10.1016/j.jep.2009.04.046; http://www.sciencedirect.com/science/article/pii/S0378874109002700. ISSN: 0378-8741.

Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. **Anggakusuma, et al., et al.** [ed.] Emad El-Omar. 7, Aberdeen: BMJ Publishing Group Ltd & British Society of Gastroenterology, July 13, 2014, Gut, Vol. 63, pp. 11374-1149. DOI: 10.1136/gutjnl-2012-304299; http://gut.bmj.com/content/63/7/1137. eISSN: 1468-3288.

A Controlled Clinical Study between Hepatic Arterial Infusion with Embolized Curcuma Aromatic Oil and Chemical Drugs in Treating Primary Liver Cancer. **Cheng, Jian-hua, et al., et al.** [ed.] Chen Ke-ji. 2, Beijing: Chinese Association of Traditional and Western Medicine, China Academy of Chinese Medical Sciences, June 1, 2001, Chinese Journal of Integrated Traditional and Western Medicine, Vol. 7, p. 141. ISSN: 1006-6497.

Curcumin inhibits HCV replication by induction of heme oxygenase-1 and suppression of AKT. **Chen, Ming-Ho, et al., et al.** [ed.] Demetrios A. Spandidos. 5, Athens: Spandidos Publications, November 2012, International Journal of Molecular Medicine, Vol. 30, pp. 1021-1028. DOI: 10.3892/ijmm.2012.1096; http://www.spandidos-publications.com/10.3892/ijmm.2012.1096. ISSN: 1107-3756.

Calabrese, Vittorio, et al., et al. Phenolics in Aging and Neurodegenerative Disorders. [ed.] Cesar G. Fraga. *Plant Phenolics and Human Health: Biochemistry, Nutrition, and Pharmacology.* Hoboken: John Wiley & Sons, Inc., 2010, 18, pp. 427-452. ISBN: 978-0-470-28721-7.

Inhibitory effects of crude extracts from some edible Thai plants against replication of hepatitis B virus and human liver cancer cells. **Waiyaput, Wanwisa, et al., et al.** [ed.] Tom Rowles. 246, London: BioMed Central Ltd., December 6, 2012, BMC Complementary and Alternative Medicine, Vol. 12. DOI: 10.1186/1472-6882-12-246; http://www.biomedcentral.com/1472-6882/12/246. ISSN: 1472-6882.

Chemopreventive Effect of Curcuma longa Linn on Liver Pathology in HBx Transgenic Mice. **Kim, Jungsun, et al., et al.** [ed.] Keith I. Block. 2, Chicago: Sage Publications, December 29, 2010, Integrative Cancer Therapies, Vol. 10, pp. 168-177. DOI: 10.1177/1534735410380613; http://ict.sagepub.com/content/10/2/168. ISSN: 1534-7354.

Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. **Panahi, Yunes, et al., et al.** [ed.] Kathi J. Kemper. Columbus: Elsevier Inc., August 2017, Complementary Therapies in Medicine, Vol. 33, pp. 1-5. DOI:

10.1016/j.ctim.2017.05.006; http://linkinghub.elsevier.com/retrieve/pii/S0965229917303370. ISSN: 0965-2299.

E. Curcumin for the Thyroid

Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial

Gary W. Small, M.D., Prabha Siddarth, Ph.D., Zhaoping Li, M.D., Ph.D., Karen J. Miller, Ph.D., Linda Ercoli, Ph.D., Natacha D. Emerson, M.A., Jacqueline Martinez, M.B.A., M.S., Koon-Pong Wong, Ph.D., Jie Liu, Ph.D., David A. Merrill, M.D., Ph.D., Stephen T. Chen, M.D., Susanne M. Henning, Ph.D., R.D., Nagichettiar Satyamurthy, Ph.D., Sung-Cheng Huang, D.Sc., David Heber, M.D., Ph.D., Jorge R. Barrio, Ph.D. https://doi.org/10.1016/j.jagp.2017.10.010

“ **Objective**: Because curcumin’s anti-inflammatory properties may protect the brain from neurodegeneration, we studied its effect on memory in non-demented adults and explored its impact on brain amyloid and tau accumulation using 2-(1-{6-[(2-[F18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile positron emission tomography (FDDNP-PET).

“ Methods: Forty subjects (age 51–84 years) were randomized to a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily [N = 21]) or placebo (N = 19) for 18 months.Primary outcomes were verbal (Buschke Selective Reminding Test [SRT]) and visual (Brief Visual Memory TestRevised [BVMT-R]) memory, and attention (Trail Making A) was a secondary outcome. FDDNP-PET signals (15 curcumin, 15 placebo) were determined in amygdala, hypothalamus, medial and lateral temporal, posterior cingulate, parietal, frontal, and motor (reference) regions. Mixed effects general linear models controlling for age and education, and effect sizes (ES; Cohen’s d) were estimated.

“Results: SRT Consistent LongTerm Retrieval improved with curcumin (ES = 0.63, p = 0.002) but not with placebo (ES = 0.06, p = 0.8; between-group: ES = 0.68, p = 0.05). Curcumin also improved SRT Total (ES = 0.53, p = 0.002), visual memory (BVMT-R Recall: ES = 0.50, p = 0.01; BVMT-R Delay:ES = 0.51, p = 0.006), and attention (ES = 0.96, p < 0.0001) compared with placebo (ES = 0.28, p = 0.1; between-group: ES = 0.67, p = 0.04). FDDNP binding decreased significantly in the amygdala with curcumin (ES = −0.41, p = 0.04) compared with placebo (ES = 0.08, p = 0.6; between-group: ES = 0.48, p = 0.07). In the hypothalamus, FDDNP binding did not change with curcumin (ES = −0.30, p = 0.2), but increased with placebo (ES = 0.26, p = 0.05; between-group: ES = 0.55, p = 0.02).

“Conclusions: Daily oral Theracurmin may lead to improved memory and attention in nondemented adults.The FDDNP-PET findings suggest that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory. (Am J Geriatr Psychiatry 2018; 26:266–277)

“Key Words: Bioavailable curcumin, normal aging, memory, cognition, positron emission tomography

“Highlights:

• This is the first long-term (18 months) double-blind, placebo controlled trial of a bioavailable form of curcumin (Theracurmin® containing 90 mg of curcumin twice daily) in non-demented adults.

• We found that daily oral Theracurmin led to significant memory and attention benefits.

• FDDNP-PET scans performed pre- and post-treatment suggested that behavioral and cognitive benefits are associated with decreases in plaque and tangle accumulation in brain regions modulating mood and memory.

• Curcumin’s cognitive benefits may stem from its anti-inflammatory and/or antiamyloid brain effects.

“Received July 16, 2017; revised September 8, 2017; accepted October 13, 2017.

From the Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior (GWS, PS, KJM, LE, NDE, JM, DAM, STC), UCLA Longevity Center (GWS, KJM, LE, JM), Department of Molecular and Medical Pharmacology (K-PW, JL, NS, S-CH, JRB), and Center for Human Nutrition (ZL, SMH, DH), David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, CA.

Send correspondence and reprint requests to Gary W. Small, M.D., UCLA Semel Institute, 760 Westwood Plaza, Los Angeles, CA 90024. e-mail: gsmall@mednet.ucla.edu Presented in part at the 2017 Alzheimer’s Association International Conference, London, UK. *https://doi.org/10.1016/j.jagp.2017.10.010 REGULAR RESEARCH ARTICLES 266 Am J Geriatr Psychiatry 26:3, March 2018”*