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Enhanced Bioavailability: Concentrated Standardised Turmeric Extract Combined with Fenugreek Galactomannosides

Key Points at a Glance

Curcuminoids

- yellow pigments, major components of Turmeric
- curcumin (majority constituent), demethoxycurcumin and bisdemethoxycurcumin – 'curcumin' is often used as shorthand for (total) curcuminoids
- extensively studied, including clinical trials; main actions: anti-inflammatory, antioxidant, anticancer
- mechanism of action is diverse, such as induction of antioxidant defense mechanisms and phase II enzymes, and involves the regulation of many molecular targets including NF-kB, Nrf2 and inflammatory cytokines
- known however to have low bioavailability

Increased Curcumin Bioavailability: Combine with Galactomannosides

- bioavailability of curcumin/curcuminoids increased substantially by combining with galactomannosides from Fenugreek seed, possibly by slowing or inhibiting the metabolism of curcuminoids
  - increased levels of curcuminoids in brain tissues
- increased bioavailability verified in healthy volunteers: increase in the absorption of curcuminoids from a proprietary curcumin galactomannosides formulation was 24.8 and 45.6 times higher than from the same dosage of curcuminoids alone, for doses of curcuminoids equivalent to 97.7 mg and 391 mg respectively

Curcumin Galactomannosides Formulation: Clinical Results

- proprietary formulation: curcumin-impregnated soluble fibre (galactomannans) derived from Fenugreek seed
- clinically demonstrated:
  - to improve fatigue, concentration and anxiety in those experiencing occupational stress (1 g/day of the formulation providing 391 mg/day of curcuminoids)
  - antioxidant effect in those experiencing stress (1 g/day of the formulation providing 391 mg/day of curcuminoids)

to reduce aortic stiffness in a subset of young obese men (500 mg/day of the formulation providing 193 mg/day of curcuminoids)

Potential Uses: Curcumin Trials

- clinical trials using curcumin, especially at high doses, may provide applications for formulations of concentrated, standardised Turmeric extract combined with galactomannosides
- anti-inflammatory activity and/or symptom improvement in inflammatory conditions, including arthritis, and in type 2 diabetes (0.09–4 g/day)
- reduced muscle pain induced by intense exercise (5 g/day)
- antioxidant activity in patients, healthy volunteers and those exercising (0.09–4 g/day), although mixed results in cancer patients (up to 4 g/day)
- beneficial for prediabetes, type 2 diabetes, ulcerative colitis (dose dependent), irritable bowel syndrome, patients undergoing heart surgery, Takayasu arteritis, systemic lupus erythematosus with hypovitamin D, depression, oral lichen planus (dose dependent), reflux, gastrointestinal symptoms in HIV, premenstrual syndrome, orbital pseudotumour, allergic rhinitis (0.06–6 g/day)
- some benefit in cancer patients (0.5–8 g/day), including the difficult to treat advanced pancreatic cancer, and premalignant lesions
- anti-inflammatory activity in chronic kidney disease (combined with Boswellia)
- beneficial for dialysis-dependent kidney transplant recipients and familial adenomatous polyposis patients (combined with quercetin)

Potential Uses: Trials of Another Bioavailability-Enhanced Curcumin Product

- clinical trials using curcuminoid phosphatidylcholine complex (providing enhanced bioavailability) may provide additional applications
- concentrated, standardised Turmeric extract combined with galactomannosides providing 200–300 mg/day of curcuminoids is likely to easily achieve the bioavailability provided by doses of 1–1.2 g/day of curcuminoid phosphatidylcholine complex containing curcuminoids (about 200–240 mg/day))
- clinical studies of the complex at this dose range:
  - were beneficial for osteoarthritis, diabetics (improved microangiopathy and aspects of retinopathy), recurrent anterior uveitis, chorioretinopathy, meibomian gland dysfunction (including reduced eyelid inflammation), nonalcoholic fatty liver, benign prostatic hyperplasia, osteopaenia (preliminary data)
- improved general fitness in the elderly and decreased muscle pain during intense exercise

Turmeric (*Curcuma longa*) rhizome has been used widely as a food and traditional medicine. Some traditional uses of the rhizome include:

- rheumatic pains, traumatic swellings, masses in the abdomen, dysmenorrhoea, amenorrhoea and for health promotion;[1,2,3]
- as a blood purifier; internally and externally for skin diseases;[4]
- dyspeptic complaints and digestive disorders of hepatic origin.[5]

The main constituents of *Curcuma longa* rhizome are yellow pigments (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and an essential oil containing sesquiterpenes.[6] 'Curcumin' is often used as shorthand for the total curcuminoids, namely curcumin, demethoxycurcumin and bisdemethoxycurcumin – usually curcumin is the majority component. For example, commercially available 'curcumin' often consists of curcumin (60–80%), demethoxycurcumin (15–30%) and bisdemethoxycurcumin (2–6%).[7]

Curcumin: Key Mechanisms of Action

The main properties of curcumin are antioxidant, anti-inflammatory and anticancer. The underlying mechanisms of its effects elucidated via thousands of studies, are diverse and involve the regulation of many molecular targets, including:[8]

- transcription factors (such as nuclear factor-kB (NF-kB), signal transducer and activator of transcription (STAT) proteins, nuclear factor erythroid 2-related factor 2 (Nrf2)),
- growth factors (such as vascular endothelial cell growth factor),
- inflammatory cytokines (such as tumour necrosis factor (TNF)-alpha, interleukin 1 (IL-1) and IL-6),
- protein kinases (such as mitogen-activated protein kinases (MAPKs) and Akt),
- other enzymes closely associated with anti-inflammatory and chemopreventive effects (such as cyclooxygenase-2 (COX-2), hemeoxygenase-1 (HO-1, which is induced via Nrf2 activation), NAD(P)H:quinone oxidoreductase 1 (NQO1)).

By inhibiting NF-kB activation, curcumin suppresses the expression of various cell survival and proliferative genes, including Bcl-2, Bcl-xL, cyclin D1, IL-6, COX-2 and matrix metallopeptidase (MMP)-9, and subsequently arrests the cell cycle, inhibits proliferation and induces apoptosis. Modulating the expression activity of growth factors and protein kinases, enables antiproliferative, anti-invasive and antiangiogenic effects. Anti-inflammatory activity occurs by curcumin modulating the production of inflammatory cytokines and regulating NF-kB.[8]

Phase II enzymes assist the body, particularly the liver, to detoxify toxic substances. The induction of antioxidant defense mechanisms and phase II enzymes by curcumin is achieved by induction of Nrf2 signalling pathways.[9]

Curcumin: Bioavailability Challenges

Curcumin has poor absorption and low systemic bioavailability – this is evidenced by very low serum levels after oral doses. It has limited tissue distribution, apparent rapid metabolism and a short half-life. Methods to improve the bioavailability have been suggested, for example:[10-12]

- combining with oily preparations or adjuvants such as piperine,
- use of curcumin derivatives/analogues,
- preparation of novel formulations such as curcumin combined with galactomannosides, phospholipid complexes, nanoparticles.

Curcumin galactomannosides (CGM) consists of soluble fibre (galactomannans) derived from debitterised Fenugreek seed (a spice) impregnated with curcumin/curcuminoids. The soluble dietary fibre forms a non-digestible gel which undergoes fermentation in the colon by the action of the enzyme beta-mannanase.[13]

CGM showed increased solubility in solutions of pH 1.2 and 6.8 (which mimics the pH of the stomach and colon) in comparison with unformulated curcumin.[13] Following this *in vitro* work, a study in rats confirmed the increased bioavailability of CGM formulation in comparison to unformulated curcumin. There was increased distribution of free (unmetabolised) curcuminoids to heart, liver, kidney, spleen, and in particular, to the brain. The maximum level of free curcuminoids after administration of CGM in brain tissues was 343 ng/g at 2 hours. In comparison, unformulated curcumin produced a maximum curcumin level of 1.4 ng/g. It is thought that CGM provided substantial plasma levels of curcuminoids for sufficiently longer duration to allow passage across the blood-brain-barrier for substantial uptake by the brain tissues. The ratio of curcuminoid in brain to plasma after CGM administration was 1.0 which suggests that the formulation provided stability (and decreased metabolism) of the curcuminoids.[14]

Curcumin Galactomannosides Formulation: Increased Curcumin Bioavailability in Humans

The improved bioavailability been demonstrated in several studies with healthy volunteers.

Eight healthy volunteers received a single dose of unformulated curcumin, followed after one week, with a dose of CGM, and one week later with another, lower dose of CGM. The C_{max} and AUC results indicate that at 10 times lower than the equivalent dose of curcumin, CGM formulation produced 13 times greater plasma concentration and exposure of tissues to curcumin and its metabolites, compared to unformulated curcumin. At 1.6

times lower than the equivalent dose of curcumin, CGM formulation produced 16 times greater plasma concentration and exposure of tissues to curcumin/curcuminoids, compared to unformulated curcumin.[13]

A randomised, double-blind, crossover study also investigated the absorption of CGM formulation compared to 'curcumin' with 50 healthy volunteers. They received a single dose of unformulated curcuminoids or a dose of CGM. After a minimum of 10 days they received the other treatment. The same protocol was used to investigate a lower dose of CGM. At a dose of 1000 mg, the CGM formulation had 45.6 times the bioavailability of an equivalent amount of unformulated curcuminoids (391 mg). (AUC for CGM formulation was 2.274 µg/mL h, AUC for unformulated curcuminoids was 0.04987 µg/mL h.) At a dose of 250 mg, the CGM formulation had 24.8 times the bioavailability of an equivalent amount of unformulated curcuminoids (97.7 mg). Additional testing found that the concentration of curcumin conjugates in plasma was less than the concentration of free (unconjugated) curcuminoids, suggesting the CGM formulation inhibits the initial metabolism.[15]

Healthy volunteers participated in a study investigating the absorption and pharmacokinetics of a single dose and of daily dosing for 30 days, of CGM formulation compared to unformulated 'curcumin'. For ongoing administration at 2.4 times lower than the equivalent dose of curcuminoids, CGM formulation produced 24 times greater plasma concentration and 39 times greater exposure of tissues to curcuminoids, compared to unformulated 'curcumin'. The single-dose results also reflect the superior absorption of the CGM formulation.[16]

Refer to Table 1.

Clinical Studies of Curcumin Galactomannosides Formulation

Curcumin galactomannosides formulation has been evaluated in several clinical studies.

Forty-six healthy volunteers completed a clinical trial in India that assessed the efficacy of CGM formulation on occupational stress. In this double-blind, pilot study, participants were randomised to receive CGM (1000 mg/day, containing 391 mg of total curcuminoids), unformulated curcumin (1000 mg/day, containing 951 mg of total curcuminoids) or placebo for 30 days. Both products contained similar proportions of individual curcuminoids. Volunteers were asked not to consume Turmeric or caffeine in their diet, and to maintain their usual dietary and exercise practices. There was significant improvement in the general quality of life for the CGM group, as indicated by reduced physical/mental fatigue and better concentration. The improvement in overall stress, fatigue and anxiety was significantly greater than occurred in the group taking unformulated curcumin. No significant changes were observed in the placebo group. *See Table 2 for results.*

Compound	Dose of compound administered (mg)	Dose of curcumin/total curcuminoids* administered (mg)	Plasma level of curcumin/ curcuminoids‡ (C_{max})§	AUC†	Relative Increase in Bioavailability¦
Study 1: single dose[13]					
unformulated curcumin	1000	1000	0.022	510	
CGM formulation	250	100	0.29	6587	
CGM formulation	1500	600	0.37	8100	
Study 2: single dose[15]					
unformulated curcumin	411	391	0.0134	0.04987	1
CGM formulation	1000	391	0.440	2.274	45.6
unformulated curcumin	102.7	97.7	0.0091	0.0388	1
CGM formulation	250	97.7	0.3419	0.963	24.8
Study 3a: single dose[16]					
unformulated curcumin	500	475	0.016	0.03	
CGM formulation	500	195	0.31	0.89	
Study 3b: ongoing administration[Δ16]					
unformulated curcumin	1000	951	0.02	0.031	
CGM formulation	1000	391	0.48	1.197	

Table 1. Superior absorption of curcumin galactomannosides formulation demonstrated in healthy volunteers.[13,15,16]

Abbreviations: AUC: area under the plasma concentration-time curve; C_{max}: maximum plasma concentration

Notes: * Study 1: unformulated curcumin and CGM formulation described as providing curcumin, but likely to be curcuminoids; Studies 2 and 3: total curcuminoids and both products had similar proportions of individual curcuminoids. ‡ Study 1 measured curcumin and its metabolites; Studies 2 and 3 measured total free (unconjugated/unmetabolised) curcuminoids. § Study 1 measured as µg/g; Studies 2 and 3 measured as µg/mL. † Study 1 measured as µg/g h; Studies 2 and 3 measured as µg/mL h. ¦ Relative bioavailability can be accurately quantified because this study compared the same dose of curcuminoids. Δ Dose taken daily for 30 days; both products had similar proportions of individual curcuminoids.

Significant increases in plasma antioxidants (catalase, superoxide dismutase, glutathione peroxidase, glutathione) occurred in both unformulated curcumin and CGM groups, however, the increases were greater for CGM formulation. Lipid peroxidation was inhibited by 53.6% in the CGM group and by 25.2% in the unformulated curcumin group.[16]

A placebo-controlled, pilot study found that treatment with CGM (500 mg/day, containing 193 mg of total curcuminoids) for 12 weeks may have reduced the stiffness of arteries in a subset of young, healthy, obese men. Aortic stiffness was determined by carotid-femoral pulse wave velocity (cfPWV). Brachial pulse pressure (subtraction of diastolic blood pressure from systolic blood pressure) which gives an indication of aortic stiffness, was significantly reduced in the CGM group compared to placebo. For the cfPWV results, of the 11 participants treated with CGM, 5 did not respond to treatment. Those that did respond (i.e. had a reduction of cfPWV) had higher baseline cfPWV values. Concentrations of the anti-inflammatory cytokine interleukin-13 were significantly increased in the blood of responders at the completion of treatment.[17]

Major Clinical Studies of Oral Curcumin

Other applications for formulations of concentrated, standardised Turmeric extract combined with galactomannosides can be considered from clinical trials that have evaluated curcuminoids alone, especially those involving higher doses. Given that curcumin galactomannosides formulation containing about 200 mg/day of curcuminoids is likely to have a bioavailability similar to at least 5 g/day of curcuminoids alone, the results of clinical trials of curcuminoids up to, and even higher than, this dosage may be considered relevant.

Anti-inflammatory Activity

Anti-inflammatory activity has been demonstrated in several conditions. (*Other inflammatory conditions, and settings where inflammatory cytokines and inflammatory markers have been measured, are detailed in other sections below*.)

- Curcumin (1.2 g/day) was similar to phenylbutazone and better than placebo in relieving symptoms of postoperative inflammation.[18]
- C-reactive protein (CRP) levels on day 3 after surgery were significantly lower in patients undergoing coronary artery bypass grafting who received curcuminoids (4 g/day, containing 52.6% curcumin, taken 3 days before surgery and for 5 days after) compared to the placebo group.[19] CRP levels were significantly reduced by 300 mg/day of curcuminoids in type 2 diabetics (placebo-controlled trial of 3 months' duration).[20] There was no significant effect on high sensitive CRP found in coronary artery patients treated with curcuminoids (2 g/day) for 2 months compared to placebo.[21]
- IκB, an inhibitory protein on inflammatory signalling, in patient's lymphocytes was increased in type 2 diabetics after curcumin administration (500 mg/day) for 15-30 days.[22]
- Blood levels of interleukin-6 and tumour necrosis factor-alpha were significantly reduced in patients with type 2 diabetes after treatment with curcuminoids (containing 600 mg/day of curcumin; placebo-controlled trial of 8 weeks' duration;[23] 300 mg/day curcuminoids; placebo-controlled trial of 3 months' duration).[20]

Arthritis & Exercise

A prospective study found that after 4 weeks of treatment with curcuminoids (90 mg/day) cyclooxygenase-2 secretion by monocytes in the synovial fluid of patients with osteoarthritis was significantly reduced. The activity was similar to that of the diclofenac sodium group.[24]

Curcumin (1.2 g/day) significantly relieved symptoms in patients with rheumatoid arthritis (such as morning stiffness and walking time), although was inferior to that achieved with phenylbutazone.[25]

Taking 5 g/day of curcuminoids, 2 days prior to, and 3 days after heavy exercise lowered the pain associated with delayed onset muscle soreness in healthy men. A blood marker of muscle damage (creatine kinase) was lowered to a small extent. A consistent effect on inflammation, measured by interleukin-6 and tumour necrosis factor-alpha, was not demonstrated in this randomised, placebo-controlled, crossover trial.[26]

	CGM Formulation		Unformulated Curcumin		Placebo	
	Before	After	Before	After	Before	After
stress§	60.95	49.29	57.86	51.79	64.52	65.48
anxiety‡	23.62	13.62	25.61	18.48	21.57	24.52
quality of life†	66.41	75.14	57.61	63.82	61.70	58.78

Table 2. Improvement in healthy volunteers experiencing occupational stress after treatment with curcumin galactomannosides (CGM) formulation.

Notes: § Measured using the Perceived Stress Scale (PSS-14). ‡ Measured using the Beck Anxiety Inventory (BAI). † Measured using the SF-36 health survey scales.

Antioxidant Activity

Treatment with curcuminoids (4 g/day, containing 52.6% curcumin) significantly lowered plasma malondialdehyde (MDA) in patients undergoing cardiopulmonary bypass surgery. MDA increased in the placebo group.[19] MDA was also significantly reduced in patients with type 2 diabetes (curcuminoids, containing 600 mg/day of curcumin; placebo-controlled trial of 8 weeks' duration).[23] Serum superoxide dismutase was increased in type 2 diabetics after treatment with curcuminoids (300 mg/day, containing 36% curcumin) taken for 3 months compared to placebo. There were no significant effects on serum glutathione peroxidase or MDA concentration.[20]

Curcumin (500 mg/day, for 15-30 days) reduced plasma MDA level in type 2 diabetics. In addition, the Nrf2 system specifically regulated protein, NAD(P)H quinone oxidoreductase 1 (NQO-1) together with other antioxidative enzymes in patients' blood lymphocytes were enhanced.[22]

In obese men, curcumin (500 mg/day) decreased lipid peroxidation, oxidised LDL and oxidised protein in serum from baseline, although the effect not observed at 750 mg/day except for oxidised protein (randomised, single-blind; 12 weeks). Placebo had no effect.[27]

Curcuminoids (90 mg/day) taken for one week by healthy volunteers significantly lowered plasma MDA levels when measured immediately after intensive exercise, compared to placebo.[28]

Uncontrolled trials have found that curcuminoids (500 mg/day, containing 71.4% curcumin for 12 months) improved markers of oxidative stress (MDA, superoxide dismutase, glutathione peroxidase and reduced glutathione in red blood cells, serum non-transferrin bound iron)[29,30] and reduced the oxidative damage caused by coagulation factors and proteins involved in iron homeostasis[30] in those with beta-thalassaemia/haemoglobin E. Serum ferritin did not change.[29,30]

In healthy volunteers, treatment reduced serum lipid peroxides (uncontrolled trial; 500 mg/day, curcumin)[31] and prevented the increase in MDA, 8-hydroxydeoxyguanosine and prevented the decrease in vitamins C and E in blood and saliva after experiencing microgravity stress (weightlessness simulation, controlled trial; 1 g/day of curcuminoids, containing 90% curcumin).[32]

Treatment with curcuminoids (1–4 g/day) raised plasma vitamin E levels in patients with Alzheimer's disease, although there was no effect on isoprostanes (placebo-controlled trial).[33]

In uncontrolled trials, treatment with curcuminoids had no effect on glutathione S-transferase activity or levels of M_1G in leukocytes (4 g/day curcuminoids; colorectal cancer patients),[49] no effect of levels of M_1G in liver tissue (doses up to 4 g/day; healthy volunteers and colorectal cancer patients with liver metastases),[34] but significantly decreased M_1G levels in malignant colorectal tissue (4 g/day; colorectal cancer patients).[35] In each study the curcuminoids consisted of 90% curcumin. M_1G (malondialdehyde-DNA adduct) is indicative of oxidative DNA damage.

Diabetes

In a randomised, double-blind trial, treatment with curcuminoids (1.5 g/day, containing 50% curcumin) prevented the development of type 2 diabetes in prediabetic individuals (0% vs 16.4% (placebo), after 9 months; $p < 0.001$). The overall functioning of beta cells was improved in the treated group.[36]

A placebo-controlled trial found that curcuminoids (300 mg/day, containing 36% curcumin) taken for 3 months, significantly lowered blood glucose, glycosylated haemoglobin A1c (HbA1c), insulin resistance index and triglycerides in type 2 diabetics. The effect may have been at least partly due to a decrease in serum fatty acids,[37] and/or a decrease in serum adipocyte-fatty acid binding protein.[20]

Six months' treatment with curcuminoids (1.5 g/day) significantly reduced pulse wave velocity, increased serum adiponectin, decreased leptin, insulin resistance, triglycerides, as well as visceral fat and total body fat in type 2 diabetics compared to placebo.[38]

Intake of the curcuminoids (1.85 g/day) for 12 weeks resulted in significant increase in HDL-cholesterol compared to placebo, but did not improve weight or glucose homeostasis in patients with metabolic syndrome.[39]

Curcuminoids (containing 600 mg/day of curcumin) had a significant beneficial effect, comparable to that of atorvastatin, on endothelial function in type 2 diabetics (placebo-controlled trial).[23]

Treatment with curcumin (500 mg/day, for 15-30 days) markedly reduced excretion of urinary micro-albumin in type 2 diabetics. The effect was stronger in those with diabetic kidney disease compared to those with normal albuminuria. The beneficial effect of curcumin was not due to alteration of metabolic control, as fasting blood glucose, insulin and all lipids except LDL-cholesterol were unaltered.[22]

In a small, pharmacokinetic investigation, coadministration of curcumin (475 mg/day) and glyburide (glibenclamide)

over 11 days to type 2 diabetics resulted in significantly decreased blood glucose and improved lipid levels. No patient experienced hypoglycaemia. It is possible the pharmacodynamics of the drug may have been affected by curcumin. (Although the mean serum glyburide level was 12% higher at 2 hours, C_{max} was unchanged and the changes in the area under the curve parameters (indicating overall absorption) were not indicative of a pharmacokinetic interaction.) More robust results are required.[40]

Bowel Conditions

There was a lower rate of relapse in patients with ulcerative colitis treated with 2 g/day of curcumin at 6 months ($p = 0.06$) compared to those treated with placebo, but no difference at 12 months. All patients received treatment with sulphasalazine or mesalamine.[41] In a later, randomised, double-blind study of 50 mesalamine-treated patients with active mild to moderate ulcerative colitis, curcumin (3 g/day) produced significantly better results in terms of clinical remission, clinical response and endoscopic remission compared to placebo.[42-44] A lower dose of curcumin (450 mg/day) did not induce remission in patients with mild to moderate ulcerative colitis. The randomised, double-blind trial compared curcumin plus mesalamine to placebo plus mesalamine for a period of 8 weeks.[45] *See also Safety section below.*

An uncontrolled trial found that curcumin (1–3 g/day; mean: 1.84 g/day) relieved symptoms associated with irritable bowel syndrome. Stool frequency and consistency improved in those with diarrhoea.[46]

Cardiovascular Disorders

Treatment with curcuminoids (4 g/day, containing 52.6% curcumin) significantly decreased myocardial infarction associated with coronary artery bypass grafting. Incidence of myocardial infarction decreased from 30.0% in the placebo group to 13.1% in the curcuminoid group (adjusted hazard ratio: 0.35, $p = 0.038$). In addition to standard therapy, treatment began 3 days before surgery and continued for 5 days after surgery.[19]

Tetralogy of Fallot patients who received curcumin (45 mg/day) for 14 days prior to corrective surgery had lower temperature and better ventricular functions than the placebo group. Blood test results suggest the cardioprotective effect may include inhibition of the c-Jun N-terminal kinase pathway and caspase-3 in cardiomyocytes, particularly in the ischaemic phase.[47]

Curcumin (300 mg/day) was clinically effective for patients with Takayasu arteritis (a chronic inflammation that affects the aorta and its main branches). This was evident from the significant reduction in disease activity (Birmingham Vascular Activity Scores) after 4 weeks for the curcumin group compared to patients taking placebo. In addition, erythrocyte sedimentation rate and plasma levels of C-reactive protein and tumour necrosis factor-alpha were significantly reduced in the curcumin group compared to the results for the placebo-treated group. Tumour necrosis factor-alpha was found to be significantly correlated with BVAS.[48]

Cancer

The chemopreventive and antitumour activities of curcumin have been extensively studied *in vitro* and in animal models. Clinical studies began to investigate the activity in humans in 2001, although there was concern about the poor bioavailability. Published data on the potential benefit in cancer patients is *outlined in Table 3*. In some cases, patients ceased treatment with curcumin due to the inability to take the volume of tablets required. What is of interest, is the benefit in advanced pancreatic cancer (although only assessed in small numbers of patients), a condition that is very difficult to treat and almost always lethal.

Immediately after surgery, 40 patients with advanced colon cancer were treated with curcumin (3 g/day) or placebo for one month. Analysis of blood samples taken after treatment found that curcumin significantly increased the population of T helper 1 cells (antitumour effector cells), and reduced the population of immunosuppressive regulatory T cells. (Tregs may play a role in tumour tolerance.)[49]

Curcumin has also been evaluated in precancerous conditions.

A phase I study investigated increasing doses of synthetic curcumin in patients with high-risk or premalignant lesions (including oral leukoplakia and cervical intraepithelial neoplasm (CIN)). Doses from 0.5 g to 12 g/day were proposed although the dose was not extended beyond 8 g/day due to problems with tolerability. Seven of 25 patients demonstrated histological improvement and a dose-dependent effect was not observed as improvement was seen at almost all dose levels. Histologic improvement of precancerous lesions was seen in 2 of 7 patients with oral leukoplakia, and one of 4 patients with CIN.[50]

Significant improvement was observed in the clinical signs and symptoms (such as burning sensation, pain, extent of mouth opening) of patients with oral submucous fibrosis who were treated with curcumin (1 g/day, for 3 months) compared to those treated with a control tablet. Beneficial changes were also observed in biopsies after treatment, although these changes were greater in a group of patients who received Turmeric oil, which suggested the oil provides an additional topical effect.[51]

Condition	Study Details & Results	Ref
advanced colorectal cancer refractory to standard chemotherapies	• phase I (uncontrolled) trial • treatment with 500 mg/day to 4 g/day of curcuminoids (containing 90% curcumin) for up to 4 months • two of 15 patients exhibited stable disease by radiological criteria after 2 months of treatment with 1 g/day and 2 g/day of curcuminoids	52
colorectal cancer	• randomised controlled trial investigating mechanism of action • treatment with curcumin (1.08 g/day or placebo for 10–30 days prior to surgery) • curcumin significantly improved the body weight of patients compared to the control group (calorie intake, diarrhoea and the presence of bowel obstruction did not differ between the groups)	53
locally advanced rectal cancer	• randomised, double-blind, placebo controlled trial • curcumin 8 g/day for 6 weeks; patients also received capecitabine and radiation therapy • curcumin did not improve clinical outcomes	54
advanced and metastatic breast cancer	• phase I (uncontrolled), dose escalation study • curcuminoids from 0.5 g to 8 g/day (containing 90% curcumin); patients also received standard dose of docetaxel • of the 14 patients enrolled, progressive disease was not observed • nine patients were evaluable for tumour response – based on the observations, a response rate up to 50% treated with docetaxel plus curcumin could be expected	55
breast cancer	• randomised, double-blind, placebo controlled trial • curcuminoids 5.7 g/day (containing 82% curcumin), during radiotherapy • reduced severity of radiation dermatitis compared to placebo ($p = 0.008$), although not effective in those who had undergone total mastectomy • significantly fewer curcumin-treated patients had moist desquamation	56
advanced pancreatic cancer	• phase II (uncontrolled) study • curcuminoids 8 g/day (containing 90% curcumin) • significant clinical activity was observed in 2 of the 21 patients: one experienced ongoing stable disease for more than 18 months and the other had a brief but marked tumour regression (73%) accompanied by significant increases in serum cytokine levels • a later retrospective analysis found these patients (treated with curcumin) had significantly greater loss of subcutaneous fat and muscle than matched untreated control patients[57]	58
advanced pancreatic cancer	• phase II (uncontrolled) study • initial dose: curcuminoids 8 g/day (containing 90% curcumin); dose dropped to 4 g/day for 2 patients; patients also received gemcitabine • of 11 evaluable patients, one had partial response and 4 had stable disease	59
advanced pancreatic cancer	• preliminary (small) controlled study • curcuminoids 8 g/day + celecoxib versus placebo; all patients received gemcitabine • stabilisation of the disease was achieved in 50% of patients receiving curcuminoids; the disease progressed in all those receiving placebo	60
hormone-resistant prostate cancer	• prospective, phase II (uncontrolled) study • preliminary results suggested that treatment with curcuminoids (6 g/day, for 7 days of the cycle) improved the response rate to docetaxel • full results indicated a response in serum prostate specific antigen, defined as a reduction of at least 50%, occurred in 59% of patients and was achieved within the first three cycles for 88% of responders; 14% reached PSA normalisation; among the 15 patients with measurable or evaluable lesions, partial response occurred for 40% and 60% had stable disease	61,62

Table 3. Clinical studies of curcumin in support of patients with cancer.

Other Conditions

A randomised, double-blind trial conducted in Indonesia, found adding curcumin (60 mg/day) to vitamin D supplementation (1200 IU/day) produced greater and significant benefits in systemic lupus erythematosus patients with hypovitamin D, compared to those who received placebo and vitamin D. Treatment with curcumin for 3 months decreased disease activity, fatigue severity, proteinuria and serum levels of anti-double-stranded DNA, and the ratios of the following cytokines: interferon-gamma/interleukin-4, interleukin-17/transforming growth factor-beta.[63-65]

Treatment with curcuminoids (1 g/day, containing 70% curcumin) for 6 weeks resulted in a decrease in depression scores compared to the placebo group. Patients were also taking the SSRI drug escitalopram. Curcumin significantly increased plasma brain-derived neurotrophic factor levels, decreased the inflammatory cytokines interleukin-1beta and tumour necrosis factor-alpha and decreased salivary morning cortisol concentrations compared with placebo.[66]

In a small trial, those treated with curcuminoids (6 g/day, containing about 75% curcumin) showed a greater reduction in clinical signs and symptoms of oral lichen planus compared with the placebo group.[67] In two randomised, placebo-controlled, double-blind trials,

treatment with 2 g/day of curcumin/curcuminoids was not efficacious for this autoimmune condition.[68,69]

Curcumin (2 g/day) was completely successful as a replacement for proton pump inhibitor and H2-receptor antagonist drugs in 11 of 14 patients with gastroesophageal reflux (these patients became asymptomatic).[70]

Treatment with curcumin (1–3 g/day; mean: 1.86 g/day) was associated with rapid and complete resolution of diarrhoea, substantial weight gain, improvement in the reduction of bloating and abdominal pain in HIV patients.[71]

Curcumin (200 mg/day) for seven days before and three days after menstruation for three successive cycles reduced the severity of symptoms of premenstrual syndrome in Iranian women.[72] In addition, serum levels of brain-derived neurotrophic factor were significantly higher than in the placebo group.[73]

Four patients experienced complete recovery, and one patient partial recovery, after treatment with curcumin (1125 mg/day, for 6-22 months) for idiopathic inflammatory orbital pseudo-tumours (an inflammatory condition of the eye).[74]

A randomised, double-blind trial found that curcumin (500 mg/day) taken for 2 months significantly relieved nasal symptoms in patients with seasonal allergic rhinitis. Unlike placebo, curcumin significantly reduced sneezing, itching, rhinorrhoea and obstruction. Curcumin treatment also significantly reduced nasal congestion as measured by increased nasal airflow. [75]

Curcumin (2 g/day) was not beneficial for atopic asthma in a small controlled trial.[76] Although there was significant improvement in the pulmonary function test measure FEV1, there was no improvement in clinical symptoms of asthma in those treated with curcumin (1 g/day) for 30 days.[77]

Combinations

Boswellia

Sixteen patients with stage 2 and stage 3 chronic kidney disease completed 8 weeks of treatment with a combination of curcuminoids (783 mg/day) and *Boswellia serrata* extract in a placebo-controlled trial. Plasma levels of interleukin-6 and prostaglandin E2 significantly decreased in the treatment group. Other parameters (C-reactive protein, tumour necrosis factor-alpha, glutathione peroxidase) were unchanged.[78,79]

Quercetin

Curcumin combined with quercetin has been clinically evaluated. Quercetin is a flavonoid found in a variety of plant foods. The mean daily intake of quercetin in a usual Western diet is in the range of less than 5 mg to about 40 mg, although much higher intakes can be achieved from high consumption of quercetin-rich fruits and vegetables.[80] Examples of foods high in quercetin (mean values, mg/100 g) include:[81]

- brown onion, raw: 21.4
- watercress, raw: 29.9
- coriander leaf, raw: 52.9
- apple skin: 19.0
- green peas, raw: 14.2

A randomised, placebo-controlled trial found that treatment with a combination of curcumin and quercetin improved early renal function and decreased tacrolimus-induced tremor in dialysis-dependent kidney transplant recipients. The improvement may have been influenced by induction of HO-1 (hemeoxygenase-1). Two doses were administered, starting within 24 hours of surgery and continuing for one month: 480 mg/day curcumin + 20 mg/day quercetin; 960 mg/day curcumin + 40 mg/day quercetin. The best results occurred for the higher dose.[82]

A decrease in the number and size of ileal and rectal adenomas in 5 patients with familial adenomatous polyposis was observed after treatment with 1440 mg/day curcumin + 60 mg/day quercetin for 3–9 months.[83]

Clinical Studies of Another Bioavailability-Enhanced Product

Other applications for formulations of concentrated, standardised Turmeric extract combined with galactomannosides can be considered from clinical trials that have evaluated other products in which the bioavailability of curcumin has been enhanced – providing, that is, that the resulting levels of curcumin in the body tissues, such as the blood, is similar. An example is the proprietary curcumin phospholipid complex, in which curcumin/curcuminoids and phosphatidylcholine-enriched soy lecithin are combined in a complex with non-covalent bonds.

Curcumin phospholipid complex has demonstrated increased bioavailability, compared to curcuminoids alone, in healthy volunteers.[84]

- The relative absorption obtained for a 209-mg dose of curcuminoids was found to be 27.2, and 31.5 for a 376-mg dose of curcuminoids. Most clinical trials have utilised 1-1.2 g/day of the complex containing curcuminoids (about 200-240 mg/day), which, using the lower relative absorption factor, corresponds to an approximate equivalent of 5.5-6.5 g/day of standard curcumin.

Curcumin galactomannosides formulation was found to have relative absorption factors of 24.8 (obtained for a 97.7-mg dose of curcuminoids) and 45.6 (for a 391-mg dose of curcuminoids). Taking an average of these relative absorption factors, for a formulation of concentrated, standardised Turmeric extract combined with galactomannosides providing 200-300 mg of curcuminoids, this suggests an approximate equivalent of 7-10.5 g/day of standard curcumin, which is likely to be a sufficient dose to potentially replicate the clinical results of the curcumin phospholipid complex trials.

In addition to treatment of cancer patients, curcuminoid phosphatidylcholine complex, in doses of 1-1.2 g/day containing curcuminoids (about 200-240 mg/day) has:

- decreased symptoms (including pain and stiffness), lower limb oedema and use of painkillers, and increased walking distance in patients with knee osteoarthritis; it also decreased C-reactive protein in those with high baseline levels (3-month and 8-month controlled trials);[85,86]
- improved a measure of microangiopathy (skin flux), retinal blood flow and visual acuity, and decreased retinal oedema in diabetic patients (two pilot, controlled studies);[87,88]
- decreased eye discomfort and relapse in patients with recurrent anterior uveitis (uncontrolled trial);[89]
- improved visual acuity and retinal thickness in patients with central serous chorioretinopathy (6-month and 12-month uncontrolled trials);[90,91]
- decreased eyelid margin inflammation and improved tear stability in patients with meibomian gland dysfunction (case series);[92]
- reduced blood levels of uric acid and many lipids, and improved liver enzymes and liver ultrasonography findings in patients with nonalcoholic fatty liver disease (randomised, placebo-controlled trial);[93,94]
- improved symptoms, episodes of urinary infections and PSA levels in patients with benign prostatic hyperplasia (pilot, controlled study);[95]
- provided preliminary data suggesting improvement in bone densities of the heel, small finger and upper jaw in those with osteopaenia (pilot, controlled study);[96]
- improved general fitness in healthy elderly volunteers (controlled study; all participants undertook a diet and exercise program);[97]
- decreased pain in the thigh muscles in moderately active volunteers (randomised, single-blind trial using downhill running test).[98]

Safety

The safety of curcumin galactomannosides formulation was demonstrated in toxicity studies in rats for the acute dose of 5 g/kg body weight and subchronic oral administration at 2 g/kg body weight. The no observable adverse effect level was found to be 2 g/kg/day. No mutagenicity was found in the Ames test when CGM was tested up to a concentration of 5 mg per plate.[99] There were no significant changes noted in haematology parameters or liver enzymes in healthy volunteers who took CGM (1000 mg/day, containing 391 mg of total curcuminoids) for 30 days.[16]

Despite Turmeric and curcumin having low toxicity (and no increase in adverse effects in patients undergoing surgery, *see below*), caution is advised for the use of curcumin galactomannosides formulation (due to the increased bioavailability) in pregnancy, women wishing to conceive and patients taking prescribed medications, such as those with a narrow therapeutic window and/or antiplatelet or anticoagulant drugs. Monitoring is advised for patients taking anti-inflammatory and/or analgesic drugs, as reduced dosage of the drug may be possible.

A randomised, double-blind trial found no increase in adverse events, including severe postoperative haemorrhage, in patients undergoing coronary artery bypass grafting who received curcuminoids (4 g/day, containing 52.6% curcumin) compared to the placebo group.[19]

Curcumin is known to activate Nrf2.[8] Nrf2 and its downstream genes are overexpressed in many cancer cell lines and human cancer tissues, giving cancer cells an advantage for survival and growth. Also, Nrf2 is upregulated in cancer cells resistant to chemotherapy and is thought to be responsible for acquired chemoresistance. Therefore, it may be necessary to inhibit the Nrf2 pathway during chemotherapy.[100] So until more information is available curcumin should not be taken at least 48 hours either side of each chemotherapy or radiotherapy treatment.

In healthy volunteers, plasma levels of talinolol decreased when taken together with curcuminoids (300 mg/day),[101] but increased when taken at a higher dosage of curcuminoids (1 g/day),[102] although was influenced by genotype.[102] A pharmacokinetic study found 2 g/day of curcumin increased the absorption of sulphasalazine. The increase was large although no adverse effects were identified in the healthy volunteers, who were carrying a particular genotype.[103] It is not known if the extent of the interaction would occur across the entire population.

Contraindicated in obstruction of the biliary tract and caution is advised in gallstones. (Curcumin (20 mg, single dose) stimulated gallbladder contraction in healthy volunteers.[104])

There have been a few cases of diarrhoea, nausea or abdominal fullness/pain reported from cancer trials that often used high doses of curcumin.

Actions

Anti-inflammatory, antioxidant and potentially cancer preventive and antitumour.

Indications

Primary:

- Diabetes, prediabetes, insulin resistance, diabetic complications.
- Supportive therapy for cardiovascular disease.
- Pain management linked to inflammation, exercise-induced muscle soreness.
- Depression.
- Cancer and precancerous conditions. Supportive therapy for preventing cancer recurrence, although not during chemotherapy or radiotherapy.

Secondary:

- Other inflammatory conditions, including osteoarthritis, ulcerative colitis, irritable bowel syndrome, benign prostatic hyperplasia, nonalcoholic fatty liver disease, reflux, gastrointestinal symptoms of HIV, premenstrual syndrome, allergic rhinitis.
- Stress.
- Conditions requiring antioxidant and liver detoxification support.

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