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Curcuminoid Phospholipid Complex

Key Points at a Glance

Curcuminoids

- yellow pigments, major components of Turmeric rhizome
- 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 and involves the regulation of many molecular targets including NF-kB and Nrf2
- known, however, to have low bioavailability

More Bioavailable Curcumin: Phospholipid Complex

- bioavailability of curcumin/curcuminoids increased substantially by combining with the phospholipid phosphatidylcholine
- verified in healthy volunteers
  - the increase in the average absorption of curcuminoids from a proprietary phosphatidylcholine complex containing about 380 mg of curcuminoids ranges from around 10 to 30 times higher than from curcuminoids alone; absorption at the higher end of the range possibly achieved by consuming with food containing fat
  - rectal tissue concentrations of curcumin were 5-fold higher when curcuminoid phosphatidylcholine complex was taken

Safety

- Curcumin (up to 8 g/day) showed low toxicity in trials, but some minor gastrointestinal adverse effects were reported.
- Due to increased bioavailability, caution is advised in pregnancy, women wishing to conceive, patients taking drugs, particularly those with a narrow therapeutic window. Monitor anti-inflammatory and/or analgesic drugs. Curcuminoid phosphatidylcholine complex has been shown in a pilot study, not to interact with antiplatelet and anticoagulant drugs, thyroxine or metformin.
- May not be suitable to take 48 hours either side of each chemotherapy or radiotherapy treatment.
- Caution in gallstones, contraindicated in obstruction of the biliary tract.

Phospholipid Complex: Clinical Results

- proprietary complex containing curcuminoids (20%; 75% curcumin, 15% demethoxycurcumin and 10% bisdemethoxycurcumin), phosphatidylcholine (40%) and microcrystalline cellulose (40%)
- clinical studies
  - anti-inflammatory and antioxidant activity: osteoarthritis, diabetic microangiopathy, macular oedema (diabetic retinopathy), recurrent uveitis, retinopathy, meibomian gland dysfunction (causes dry eye syndrome), advanced cancer with cachexia
  - other activity: cancer (treatment and symptom relief), reduce exercise-induced muscle soreness and risk of heat stroke, muscular strength and physical performance in the elderly, acute pain relief, nonalcoholic fatty liver disease, benign prostatic hyperplasia, psoriasis, temporary kidney dysfunction, osteopaenia (preliminary results); some benefit in prediabetes and chronic fatigue syndrome
  - most common dose: 1 g/day of the complex providing about 200 mg/day curcuminoids; higher dose for cancer, analgesic and exercise-related applications

Potential Uses: Curcumin Trials

- clinical trials using curcumin may provide applications for curcuminoid phosphatidylcholine complex
- extensively clinically-evaluated, usually at high doses
- major activities and conditions include:
  - inflammation generally, and arthritis specifically
  - cancer, including difficult to treat types; precancerous conditions
  - reducing physiologically-relevant oxidation
  - diabetes; benefit in some cardiovascular conditions
  - ulcerative colitis (although may be dose dependent)
- also benefit in:
  - irritable bowel syndrome, systemic lupus erythematosus patients with hypovitaminosis D, premenstrual syndrome, reflux, oral lichen planus (dose dependent), allergic rhinitis, serious kidney conditions (combined with Boswellia or quercetin)

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

- rheumatic pains, traumatic swellings, masses in the abdomen, dysmenorrhoea, amenorrhoea and for health promotion;[1-3]
- 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 (COX2), 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] The induction of antioxidant defense mechanisms and phase II enzymes 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:[10,11]

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

Phospholipids, including phosphatidylcholine, are essential components of cell membranes. Common sources of phosphatidylcholine include egg yolk, sunflower seed, wheat germ, soy bean. Phosphatidylcholine is also formed in the body from choline.

The lipophilic (fat soluble) nature of the combination of curcumin and phospholipid may facilitate the diffusion of curcumin across the gastrointestinal tract wall, resulting in improved absorption. The formation of a phospholipid monolayer on the mucosal surface, increasingly allows curcumin to move from the hydrophilic (water soluble) gut contents across the lipophilic membranes into cells. The increase in bioavailability of curcuminoids combined with phosphatidylcholine was confirmed in rats.[12]

Bioavailability in Humans

A study with healthy volunteers published in 2011, compared the absorption of curcuminoids to two doses of curcuminoid phosphatidylcholine complex.[13] The randomised, double-blind, crossover study measured the plasma concentration of curcumin, demethoxycurcumin and bisdemethoxycurcumin after dosing with the formulations. After an overnight fast, participants received a single dose of test substance and then ate a breakfast consisting of a bagel (99 g) with cream cheese (25 g). Free curcumin could not be detected in any plasma sample, consequently the plasma samples were enzymatically hydrolysed to enable the phase 2 metabolites (glucuronide and sulfate conjugates) to be measured. The main results are listed here – *refer also to Table 1*.

1. Combining curcuminoids with phosphatidylcholine resulted in a much higher level of curcuminoid conjugates in the blood than that achieved when curcuminoids were taken alone.
    - Taken as the phosphatidylcholine complex at the low dose, the increase in the average absorption of curcuminoids was just over 27 times higher than from curcuminoids alone. This means, taking the phosphatidylcholine complex containing 209 mg of curcuminoids provided similar absorption to that achieved from taking 5.7 g of curcuminoids alone.

Table 1. Superior absorption of a proprietary complex of curcuminoids with phosphatidylcholine in healthy volunteers.

Formulation	Dose* (mg)	Plasma Level of Total Curcuminoids^ (Cmax; ng/mL)	Relative Absorption§	Equivalent Dose of Total Curcuminoids Alone† (g)
curcuminoids + phospholipid: low dose	209	68.9	27.2	5.7
curcuminoids + phospholipid: high dose	376	206.9	31.5	11.8
reference curcuminoids	1799	14.4	1	–

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

Notes: * The composition of the curcuminoids in the phospholipid complex and the reference were similar: 78.6% curcumin, 19.0% demethoxycurcumin and 2.4% bisdemethoxycurcumin for the complex; 71.9% curcumin, 22.0% demethoxycurcumin and 6.1% bisdemethoxycurcumin for the reference. The complex contained curcuminoids (20%), phosphatidylcholine (40%) and microcrystalline cellulose (40%). ^ As phase 2 conjugates (glucuronides and sulfates). § Obtained by comparing the AUC of the curcuminoid phosphatidylcholine complex to the AUC of the reference, after both AUC values had been normalised (i.e. adjusted for dosage). † i.e. without phosphatidylcholine

- A higher dose of the complex produced even greater absorption: the absorption of curcuminoids from the complex was 31.5 times higher than from curcuminoids alone. Taking the phosphatidylcholine complex containing 376 mg of curcuminoids provided similar absorption to that achieved from taking 11.8 g of curcuminoids alone.

(Referring to Table 1, the higher absorption is suggested qualitatively from the maximum plasma levels – for the low dose, C_{max} of total curcuminoids were 68.9 ng/mL (complex) and 14.4 ng/mL (alone/reference). To compare the results quantitatively, the relative absorption is calculated, using the AUC (measures extent of absorption) adjusted for dosage.)

2. The demethoxylated forms of curcumin (demethoxycurcumin and bisdemethoxycurcumin) had greater relative absorption than curcumin, and the phospholipid complex increased these differences in bioavailability (*data not shown in Table*). For example, at the low dose, absorption of curcumin was 17.5 times higher when taken as the complex compared to taking the curcuminoids alone, but the absorption of both demethoxycurcumin and bisdemethoxycurcumin were over 50 times higher.

Two more recent studies[14,15] have also found improved absorption for curcuminoid phosphatidylcholine complex compared to curcuminoids alone. For a dose of phosphatidylcholine complex providing about 380 mg of curcuminoids, the average absorption of total curcuminoids was 8.5 times higher than from curcuminoids alone.[14] The improvements in the relative absorption of demethoxycurcumin and bisdemethoxycurcumin were 11.9 and 7.1, respectively in one trial,[14] and 2.9 and 3.0, respectively in the other.[15]

The results cannot really be directly compared because there were differences in the design of the trials, for example, the curcuminoid profile of the products, although the same methodology for measuring curcumin in the plasma was used: enzymatic hydrolysis of the phase 2 conjugates. The curcumin products were administered to healthy volunteers in the fasted state as a single dose[14] or on an empty stomach provided as a powder mixed in apple sauce for 7 days.[15] In comparison, in the 2011 study, the curcumin products were taken in a meal containing some fat.[13]

It is not known if this is the deciding factor affecting the higher absorption, but it may be advisable to take the curcuminoid phosphatidylcholine complex with meals.

The concentration of curcuminoids was also evaluated in rectal tissue. In the 7-day study,[15] after adjusting for curcumin dose, the tissue concentration of deconjugated curcumin was 5-fold greater for the phosphatidylcholine extract, and the tissue concentration of parent (unconjugated) curcumin was about 4-fold greater. Because the primary metabolites of curcumin (tetrahydrocurcumin and hexahydrocurcumin) were found in high concentrations in plasma but absent from the rectal mucosa, the increase in curcumin tissue concentration is likely to be the result of absorption across the intestine rather than disposition via the plasma.

Refer to the Appendix for a glossary providing additional explanation of terms relating to the metabolism of curcuminoids.[13,15,16]

Clinical Studies: Curcuminoid Phospholipid Complex

The curcuminoid phosphatidylcholine complex has been evaluated in many clinical studies, particularly for anti-inflammatory activity. The complex usually contains curcuminoids (20%), phosphatidylcholine (40%) and microcrystalline cellulose (40%), with a curcuminoid profile of about 75% curcumin, 15% demethoxycurcumin and 10% bisdemethoxycurcumin.[17]

Inflammation & Cancer

Major results of studies of inflammation and cancer are outlined in Tables 2 and 3. Several of the cancer studies involved very small numbers of patients.

Table 2. Clinical studies of a proprietary complex of curcuminoids with phosphatidylcholine investigating inflammation.

Details	Results	Ref
knee osteoarthritis 2 controlled trials§ dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	3-month trial	18
	▪ significant decrease from baseline in global WOMAC scores at 2 months and at 3 months ($p < 0.05$): from 83.4 to 41.1 and 34.8 respectively; very little change in the control group ▪ walking distance in the treadmill test‡ was increased from baseline of 76 m to 332 m at 3 months ($p < 0.05$); walking distance in the control group increased from 82 m to 129 m ▪ significantly greater reduction in lower limb oedema in the treatment group compared to controls at 3 months ($p < 0.05$), with a decrease in distal oedema of 65% compared to 5% in the control group ($p < 0.05$) ▪ in a subgroup of patients with elevated CRP values at baseline, a significantly greater decrease was observed in the treatment group (168 to 11 mg/L compared to 175 to 112 mg/L at 3 months) ▪ significant decrease in the use of NSAIDs and painkillers, the use of other drugs or treatments (including physiotherapy) and gastrointestinal complications in the curcumin group	
	8-month trial	19
	Results were similar to the 3-month trial with significant improvements in the group treated with the complex for global WOMAC scores, increase in walking distance, distal oedema and the use of drugs/treatments and gastrointestinal complications†. There were also significant changes ($p < 0.05$) in the following: ▪ improvement in Karnofsky scale** (from 73.3 to 92.2); no significant improvement in control group ▪ decreases noted for the pain, stiffness and physical function scores of WOMAC and for well-being for the treatment group ▪ reduction in all inflammatory markers (IL-1beta, IL-6, sCD40L, sVCAM-1, ESR) from baseline by the complex, with little change in these parameters in the control group	
knee osteoarthritis observational study, 4 months dose: 0.5 g/day of complex containing curcuminoids (about 100 mg/day)	▪ compared curcuminoid complex + glucosamine with chondroitin sulfate + glucosamine ▪ curcuminoid complex + glucosamine provided better improvement in symptoms and functionality, as evidenced by significantly higher Karnofsky Index and WOMAC scores (both in physical and emotional functioning), compared to those in the chondroitin + glucosamine group ▪ walking distance at the treadmill test after one month was also significantly higher in the curcuminoid complex + glucosamine group, and was sustained until the end of the study	20
diabetic microangiopathy 2 pilot studies§ – retinopathy also assessed (1 study), 4 weeks dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	Unlike the experiences in the control group, treatment with the complex resulted in significant ($p < 0.05$): ▪ decrease in skin flux at the surface of the foot (indicates an improvement in microangiopathy) ▪ decrease in oedema score and improvement in the venoarteriolar response (these measurements are closely linked and indicates reduced oedema (below the knee)) ▪ increased transcutaneous PO_2, a result which was expected from better oxygen diffusion into the skin due to the decreased oedema	21
	▪ decrease in peripheral oedema and improvement in the venoarteriolar response ▪ improvement in retinal blood flow, retinal oedema and visual acuity ▪ no effect observed in control patients	22
macular oedema (diabetic retinopathy) uncontrolled study, 90 days dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ 83% of eyes showed improvement in visual acuity ($p = 0.0072$), and 17% were stabilised ▪ 92% of eyes had a reduction in macular oedema and 8% were stabilised ▪ mean macular thickness was also significantly decreased	23
recurrent anterior uveitis^ uncontrolled trial, 12–18 months dose: 1.2 g/day of complex containing curcuminoids (about 240 mg/day)	▪ 90% of patients completed the 12-month follow up ▪ signs and symptoms of eye discomfort reduced after a few weeks in more than 80% of patients ▪ the number of patients with relapses in one year was reduced from 106 to 19 after treatment ($p < 0.001$), and the number of relapses decreased from 275 to 36 ($p < 0.001$)	24

Details	Results	Ref
central serous chorioretinopathy[Δ] uncontrolled trials, 6-12 months dose: 1.2 g/day of complex containing curcuminoids (about 240 mg/day)	After 6 months of treatment: ▪ 18 eyes from 12 patients were assessed; visual acuity improved in 61% of eyes, 39% stabilised and none showed reduction in visual acuity (results approached statistical significance (p = 0.08)) ▪ neuroretinal or retinal pigment epithelium detachment was reduced in 78% of eyes, 11% stabilised and 11% showed an increase, although the results did not reach statistical significance After 12 months of treatment: ▪ no eyes showed further reduction in visual acuity, 39% showed stabilisation, and 61% showed statistically significant improvement ▪ 95% of eyes showed reduction in neuroretinal or retinal pigment epithelium detachment, 5% showed stabilisation ▪ difference in retinal thickness after 12 months was statistically significant	25, 26
meibomian gland dysfunction case series, 3 months dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ tear instability, quality of life, interpalpebral corneal dye staining and lid margin inflammation improved from baseline values	27

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-1beta: interleukin-1beta; IL-6: interleukin-6; NSAIDs: nonsteroidal anti-inflammatory drugs; PO_2: partial pressure of oxygen; sCD40L: soluble CD40 ligand; sVCAM-1: soluble vascular cell adhesion molecule; WOMAC: questionnaire developed by the Western Ontario and McMaster Universities which rates the symptoms of osteoarthritis into pain, stiffness and difficulty in performing physical functions, and a total (global) score

Notes: § Best available medical treatment versus best available medical treatment plus the complex. ‡ At a speed of 3 km/hour and an inclination of 10%, total pain-free distance covered was recorded. † Presumably due to decreased use of NSAIDs and possibly due to a gastroprotective effect of curcumin. ** Karnofsky Performance Scale Index: classifies patients as to their functional impairment (e.g. in terms of their ability to carry on normal activity and work, whether special care is needed) – the lower the score the worse the functional impairment. ^ Inflammation of the middle layer of the eye; of these patients aetiology was mainly of autoimmune origin followed by herpetic origin, then different or unknown aetiology; all patients received standard treatment (systemic drugs or eye drops). Δ Disease that causes fluid to collect under the retina, affecting the macula resulting in visual impairment.

Table 3. Clinical studies of a proprietary complex of curcuminoids with phosphatidylcholine investigating cancer.

Details	Results	Ref
patients with solid tumours receiving chemotherapy controlled trial, 8 weeks dose: 0.9 g/day of complex containing curcuminoids (about 180 mg/day)	▪ significantly greater improvement in quality of life occurred in the curcuminoid complex group compared to the placebo group ▪ the magnitude of reductions in mediators of systemic inflammation including TNF-alpha, TGF-beta, IL-6 and hs-CRP were all significantly greater in the curcumin versus placebo group ▪ curcumin produced a significant antioxidant effect, evidenced by an increase of serum SOD, catalase and GSH	28,29
advanced cancer with cachexia uncontrolled trial, 10 days dose: 1.2 g/day of complex containing curcuminoids (about 240 mg/day)	▪ significant reduction of reactive oxygen species in blood ($p < 0.001$) ▪ significant improvement in circulating levels of glutathione peroxidase and total blood antioxidant status ($p < 0.05$), but results for SOD not significant	30
metastatic or locally advanced pancreatic cancer prospective, phase II trial dose: 2 g/day of complex containing curcuminoids (about 400 mg/day)	▪ curcuminoid complex administered with gemcitabine until progression, chemotherapy delay of more than 2 weeks, unacceptable toxicities or patient refusal ▪ response rate was 27.3% (all partial responses), stable disease was reported in 34.1% of cases with a disease control rate of 61.4% ▪ at the 26-month mark, the overall survival was 10.2 months (16 months in those with locally advanced disease, and 8.5 months in patients with metastatic disease),§ and the progression free survival was 8.4 months ▪ patients who did not respond to treatment had significantly higher baseline levels of IL-6, CRP and sCD40L ▪ there was no decrease in quality of life ▪ grade 3/4 haematological toxicities included neutropaenia (38.6%), thrombocytopaenia (6.8%) and anaemia (6.8%)	31
cancer patients undergoing chemotherapy or radiotherapy pilot, controlled trial, 60 days dose: 1.5 g/day of complex containing curcuminoids (about 300 mg/day) starting from the day after the first cycle	▪ treatment with curcuminoid complex resulted in lower incidence of signs and symptoms; differences between the groups were significant for a majority of signs and symptoms ▪ severity of all side effects† (e.g. fatigue, cognitive function, weight loss) decreased in those treated with the complex, but did not change in the placebo group; difference in results between groups was significant; severity of local pain/swellings at site of radiotherapy was reduced from 6 to 2.7 in those who received the complex	32
breast cancer patients who had completed chemotherapy and radiotherapy controlled trial, 6 weeks dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ curcuminoid complex group had a greater decrease in fatigue and the increase in NF-kappa B activity was alleviated more than that of the placebo group – not known yet if the results are statistically significant (preliminary results)	33
chronic lymphocytic leukaemia uncontrolled trial, 6 months dose: 2 g/day of complex containing curcuminoids (about 400 mg/day)	▪ four patients (20%) demonstrated a positive response (more than 20% decrease in ALC, three had lower ALC at the end of the study as compared to baseline ▪ decrease in ALC was accompanied by an increase in CD4, CD8 and natural killer cells ▪ no demonstrable response was seen in seventeen patients (80%) who exhibited stable, fluctuating or increasing ALC during the study	34

Abbreviations: ALC: absolute lymphocyte count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GSH: reduced glutathione; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; sCD40L: soluble CD40 ligand; SOD: superoxide dismutase; TGF-beta: transforming growth factor-beta; TNF-alpha: tumour necrosis factor-alpha

Notes: § New treatments aim to improve the performance of chemotherapy by increasing overall survival (OS) whilst limiting toxicities. OS of patients treated with gemcitabine (GEM) alone is 5.7 months, and the recently-introduced combination of nanoparticle albumin-bound paclitaxel and GEM increases the OS to rates ranging from 8.5 to 10.7 months. In this regard, curcuminoid complex had a similar beneficial effect as the standard of care combination with a better toxicity profile (the absence of neurotoxicity and lower haematological toxicity). † Measured using a visual analogue scale.

An uncontrolled study investigated the effect of curcuminoid phosphatidylcholine complex on levels of inflammatory markers in 7 patients with endometrial cancer. They received 2 g/day of complex containing curcuminoids (about 400 mg/day) for 2 weeks. Minor immunological effects were observed: downregulation of the expression of major histocompatibility complex (MHC) by leukocytes, decreased percentage of CD14+ monocytes, decreased expression of ICOS by CD8+ T cells and upregulation of CD69 on CD16-NK cells. There were no significant changes in inflammatory biomarker levels, frequencies of other immune cell types, T cell activation and COX-2 expression. Patients experienced a non-significant trend to improved quality of life.[35]

Prediabetes & Metabolic Syndrome

In a randomised controlled trial conducted in Australia, curcuminoid phosphatidylcholine complex lowered serum insulin levels and improved insulin sensitivity in patients at high risk of developing type 2 diabetes. The changes were statistically significant compared to the placebo group. Despite this there was no beneficial effect on fasting blood glucose or HbA1c. Although the curcuminoid complex also decreased serum triglycerides and the atherogenic index of plasma (an independent indicator of coronary artery disease and atherosclerosis), the effect was not as great as that achieved by fish oil. Curcuminoid phosphatidylcholine complex (1 g, providing 180 mg/day of curcuminoids) or fish oil (2 g, providing 1.2 g/day of DHA + EPA), were taken for 12 weeks. There were no significant differences between the groups for diet and physical activity levels, at baseline and after treatment.[36]

A placebo-controlled clinical trial conducted in Iran did not find beneficial effects on blood lipids, blood pressure or fasting blood glucose in patients with metabolic syndrome, after administration of curcuminoid phosphatidylcholine complex (1 g, providing 200 mg/day of curcuminoids) for 6 weeks. Serum total cholesterol was significantly reduced from baseline in the group who received the curcuminoid complex, but the reduction was greater in the placebo group. The trial also administered unformulated curcumin (1 g/day), and the decrease in serum total cholesterol from baseline was the least of all the groups. Participants were given advice about maintaining an isocaloric diet and analysis found no significant differences between the groups in terms of calorie intake and all macronutrients, except saturated fatty acid, which decreased in the curcuminoid complex and placebo groups and increased in the curcumin group. Serum levels of high-sensitivity C-reactive protein and heat shock protein 27 antibodies were not affected.[37,38]

Effects during Exercise

Moderately active, healthy volunteers participated in a randomised, single-blind trial. They took 2 g/day of curcuminoid phosphatidylcholine complex containing curcuminoids (about 400 mg/day) or placebo, 48 hours prior to a downhill running test and continuing for 24 hours after the test (4 days in total). Nineteen volunteers completed the study.[39]

- Those in the curcuminoid complex group reported less pain in the lower limb as compared with the placebo group, although significant differences were observed only for the right and left anterior thighs.
- Significantly fewer volunteers in the curcuminoid complex group had magnetic resonance imaging evidence of muscle injury in the posterior or medial compartment of both thighs.
- With the exception of IL-8, which was reduced, there was no significant effect found on markers of inflammation, oxidative stress or muscle injury.

A crossover, placebo-controlled study involving 11 recreational athletes did not find a significant effect for intake of curcumin on cytokine and inflammatory markers. Whilst on a low carbohydrate diet, they underwent 2 hours of mild-intensity cycling. Placebo or curcuminoid phosphatidylcholine complex containing about 500 mg/day of curcuminoids was taken for 3 days prior to the exercise.[40]

The translocation of bacterial lipopolysaccharide from the gastrointestinal tract into circulation is an important factor in the development of exertional heat stroke. The effect of curcuminoid phosphatidylcholine complex (2.5 g/day containing about 500 mg/day of curcuminoids) or placebo taken for 3 days, was investigated in 8 healthy volunteers who were challenged with a single bout of exercise (60 minutes) under hot and dry conditions.[41]

- The increase in core temperature and heart rate were significantly lower in the curcuminoid complex group compared to the placebo. Physiological strain index, which is indicative of risk of heat stroke, was also increased significantly less under the action of the curcuminoid complex.
- Curcumin may have reduced GI barrier damage and the associated cytokine responses, as indicated by lower, postexercise circulating levels of I-FABP (intestinal fatty acid-binding protein) and IL-1RA (interleukin-1 receptor antagonist), compared to placebo at the same point in time (e.g. immediately after exercise). I-FABP is a sensitive measure of GI barrier damage. IL-1RA inhibits the proinflammatory effect of IL-1beta, and the reduced GI barrier damage may have decreased the need for producing this anti-inflammatory response.
- Other cytokines, including TNF-alpha, were not significantly changed.

Other Conditions

Other conditions and applications are outlined in Table 4.

Table 4. Clinical studies of a proprietary complex of curcuminoids with phosphatidylcholine investigating a variety of conditions.

Details	Results	Ref
healthy, elderly volunteers with tiredness and apparent loss of strength controlled study, 3 months dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ hand grip, lifting weights, walking, climbing stairs and general fitness significantly improved from baseline for those taking curcuminoid complex in addition to standardised diet and exercise plan ▪ control group (on standardised diet and exercise plan) did not improve; results for the curcumin group were significant in comparison with control group	42
patients with acute pain‡ pilot, comparative study, single days dose: 1.5-2 g of complex containing curcuminoids (about 300-400 mg)	▪ at dose of 2 g curcuminoid complex showed analgesic activity, comparable with that of a standard dose (1 g) of paracetamol, but lower than that of a therapeutic (100 mg) dose of the NSAID nimesulide ▪ analgesic activity of the lower dose of the complex (1.5 g) was less satisfactory, and the onset of activity for both doses of the complex took longer than that of nimesulide ** ▪ gastric tolerability was significantly better than that of nimesulide and comparable with that of paracetamol	43
nonalcoholic fatty liver disease randomised, placebo-controlled trial†, 8 weeks dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ significant reduction in blood levels of uric acid and many lipids in the curcuminoid complex group ▪ findings of liver ultrasonography improved in 75% of the curcuminoid complex group, but only 4.7% of the placebo group ▪ serum levels of AST and ALT were reduced at the end of the trial in those treated with curcuminoid complex but were elevated in the placebo group	44,45
benign prostatic hyperplasia pilot, controlled study, 24 weeks dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ symptoms (feeling of incomplete bladder emptying, urination frequency, intermittency, urgency, weak stream, straining, nocturia) significantly improved compared to the control group (standard management only) ▪ quality of life improved in both groups, but was significantly better in the curcuminoid complex group ▪ clinical and subclinical episodes of urinary infections and urinary block, as well as PSA, significantly decreased in the curcumin group	46
mild to moderate plaque psoriasis randomised, double-blind trial, 12 weeks dose: 2 g/day of complex containing curcuminoids (about 400 mg/day)	▪ significant reduction in psoriasis severity was observed, with greater reduction in those treated with both topical steroids and oral curcuminoid complex than in patients treated with topical steroids and placebo ▪ IL-22 serum levels were significantly reduced in patients treated with the complex	47
temporary kidney dysfunction^ controlled study, 4 weeks dose: 1.5 g/day of complex containing curcuminoids (about 300 mg/day)	▪ albuminuria improved to a greater and significant extent than for the control group (standard management only)	48
healthy volunteers with osteopaenia pilot, controlled* study, 6 months dose: 1 g/day of complex containing curcuminoids (about 200 mg/day)	▪ significant improvement in bone densities of heel, small finger and upper jaw from baseline values (as assessed by the less precise, ultrasound method) in those treated with curcuminoid complex whereas there were no changes in the control group	49
patients with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) uncontrolled study, 8 weeks dose: 1 g/day of complex containing curcuminoids (about 180 mg/day)	▪ CFS symptom score was significantly reduced§ ▪ the score for less specific symptoms was not significantly reduced ▪ of the 52 patients enrolled, 9 dropped out due to side effects; of the remaining patients, all met the criteria for CFS, and 72% met the criteria for ME	50

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; IL: interleukin; NSAID: nonsteroidal anti-inflammatory drug; PSA: prostate specific antigen

Notes: ‡ Patients were experiencing osteoarthritic pain of the shoulder and/or knee (3), neuropathic pain (neuralgia, low back pain; 6), recurrent headache (3), muscular pain (contractions, sport injuries; 2), dental pulpitis pain (and on antibiotic therapy; 1).

** Reduced pain perception after 1-3 hours (nimesulide), 2-4 hours (paracetamol), 2 hours (2 g of complex), 3 hours (1.5 g of complex). † All patients received diet and lifestyle advice. ^ Condition occurred after drug consumption, a clinical event or dehydration. * Standard management: diet providing adequate vitamins C and D and calcium as well as regular exercise program (20 mins at least 4 times/week including light weightlifting and walking or running); volunteers undertook standard management with or without curcuminoid phosphatidylcholine complex. § CFS symptom score included post-exertional fatigue, unrefreshing sleep, problems remembering and concentrating, muscle aches and pains, joint pain, sore throat, tender lymph nodes and swollen glands, and headaches; 10 less specific symptoms, including for example, diarrhoea, fever, sleeping problems, abdominal pain, depression were also scored.

Major Clinical Studies of Oral Curcumin

Other applications for curcuminoid phosphatidylcholine complex can be considered from clinical trials that have evaluated curcuminoids alone, especially those involving higher doses. Presented here are trials investigating the major activities of curcumin and a selection of the some of the more frequently-researched areas.

Anti-inflammatory Activity

Anti-inflammatory activity has been demonstrated in several conditions. (*Other inflammatory conditions, and settings where inflammatory markers and cytokines 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.[51]

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.[52] There was no significant effect on high-sensitivity CRP (hs-CRP) found in coronary artery patients treated with curcuminoids (2 g/day) for 2 months compared to placebo.[53] Curcumin did not have a beneficial effect on markers of tissue injury or inflammation (including hs-CRP) in patients who underwent elective repair of an unruptured abdominal aortic aneurysm. The large, randomised, placebo-controlled trial was conducted in Canada, and those assigned to curcumin received 2-gram doses 8 times over 4 days (i.e. 4 g/day).[54]

CRP levels were significantly reduced by 300 mg/day of curcuminoids in type 2 diabetics (placebo-controlled trial of 3 months' duration).[55] Levels of IκB, an inhibitory protein on inflammatory signalling, in blood lymphocytes were increased in type 2 diabetics after curcumin administration (500 mg/day) for 15-30 days.[56] Blood levels of IL-6 and TNF-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;[57] 300 mg/day curcuminoids; placebo-controlled trial of 3 months' duration).[55]

After adjusting for confounders, curcumin had a significant effect on hs-CRP and IL-6, compared to placebo in overweight and obese adolescents. In addition to a weight-loss diet, curcumin (500 mg/day) was taken 10 weeks.[58]

A randomised trial in Indonesia found curcumin was more effective than the NSAID mefenamic acid in reducing pain after surgical removal of impacted molars. Comparison was made between those who received mefenamic acid (1.5 g/day) plus amoxicillin and curcumin (600 mg/day) plus amoxicillin, which were taken for 3 days after surgery. Participants were asked about their pain level immediately after the anaesthesia had worn off, and three times for the next 24 hours, one hour after taking their medications.[59]

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.[60]

Curcumin (1.2 g/day, for 4 days) significantly relieved symptoms in patients with rheumatoid arthritis (such as morning stiffness and walking time), although was inferior to that achieved with phenylbutazone.[61]

Taking curcuminoids (5 g/day) 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 IL-6 and TNF-alpha, was not demonstrated in this randomised, placebo-controlled, crossover trial.[62]

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 5.* 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.

Table 5. Clinical studies of curcumin in support of patients with cancer.

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	63
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)	64
metastatic colorectal cancer	▪ phase IIa, open-label, randomised controlled trial investigating mainly safety ▪ curcuminoids 2 g/day (containing 80% curcumin, 20% demethoxycurcumin and bisdemethoxycurcumin) + FOLFOX versus FOLFOX; chemotherapy given once every 2 weeks for up to 12 cycles ▪ similar adverse event (AE) profiles were observed; AEs where causality was reported as possibly or probably related to curcumin were primarily gastrointestinal, with the most common being diarrhoea ▪ of the efficacy measures, significant difference was found for overall survival (OS) e.g. in the intention-to-treat population, median OS was 502 and 200 days for curcumin and control, respectively; other measures (such as the number of patients exhibiting stable disease) were not significantly improved ▪ no significant differences were found for quality or life or neurotoxicity	65
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	66,67
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	68
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	69
breast cancer	▪ large randomised, double-blind, placebo-controlled trial ▪ curcuminoids 6 g/day (containing 90% curcumin, 8% demethoxycurcumin and 2% bisdemethoxycurcumin), during and for one week after radiotherapy ▪ radiation dermatitis severity was not significantly reduced compared to placebo ▪ no difference in the number of patients experiencing moist desquamation ▪ inclusion of women with breast reconstructions may have caused a variation in the results*	70
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	71
	▪ a later retrospective analysis found these patients (treated with curcumin) had significantly greater loss of subcutaneous fat and muscle than matched untreated control patients	72
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	73
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	74

Condition	Study Details & Results	Ref
gemcitabine-resistant pancreatic cancer	▪ phase I/II (uncontrolled) study; preliminary results from a small sample ▪ curcuminoids 8 g/day (containing 90% curcumin); patients also received gemcitabine ▪ no patients experienced a partial or complete response, but curcumin increased the median survival time (161 days; compared to the expected 70 days)	75
	▪ several patients reported an improvement of cancer- or chemotherapy-related symptoms	
locally advanced cervical cancer	▪ randomised controlled trial ▪ curcumin 4 g/day + chemoradiation versus chemoradiation; 7–9 weeks of treatment ▪ a better response occurred for the curcumin group in terms of tumour response, disease-free survival and overall survival (at 2-yr follow up), but the difference was not statistically significant compared to the control group ▪ occurrence of severe acute radiation toxicity to skin and mucosa was significantly lower in the curcumin group e.g. grade 3 skin reactions occurred in 3.3% and 20% of patients in the curcumin and control groups, respectively and this contributed to less delay of radiotherapy	76
prostate cancer managed with IAD	▪ randomised, double-blind, placebo-controlled trial ▪ curcumin 1.44 g/day, during the off-treatment (androgen deprivation) period i.e. for 6 months ▪ although curcumin lowered PSA levels, it did not contribute to changes in clinical outcomes e.g. curcumin did not significantly affect overall off-treatment duration of IAD ▪ curcumin group had significantly fewer overall adverse events (AEs; 15.6% vs 34.8%)	77
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 PSA, 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	78,79
multiple myeloma	▪ randomised, placebo-controlled study ▪ curcumin 8 g/day for 28 days; all patients received melphalan and prednisone for 7 days ▪ improved remission (significant compared to placebo)† ▪ significant decrease of NF-kB, VEGF, TNF-alpha compared to placebo; significant correlation between TNF-alpha and remission status	80

Abbreviations: FOLFOX: folinic acid, 5-fluorouracil, oxaliplatin chemotherapy; IAD: intermittent androgen deprivation; NF-kB: nuclear factor-kB; PSA: prostate specific antigen; TNF-alpha: tumour necrosis factor-alpha; VEGF: vascular endothelial growth factor

Notes: * Skin on a reconstructed breast reacts differently – it is more likely to burn due to its inability to dissipate heat. † Remission status was evaluated after 4 cycles of treatment.

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; Th1), and reduced the population of immunosuppressive regulatory T cells (Tregs). (Tregs may play a role in tumour tolerance.)[81] Another clinical study in China investigated the regulation of curcumin on Tregs and Th1 in lung cancer patients. Patients with non-small cell lung cancer were treated with curcumin (3 g/day) for 2 weeks. Blood samples were taken, and immune cells were isolated from the peripheral blood mononuclear cells. Compared with healthy volunteers, the frequency of Tregs was higher, and the frequency of Th1 cells was lower, in lung cancer patients before the curcumin therapy. After taking curcumin, the frequency of Tregs was suppressed and the frequency of Th1 cells was increased in the patients.[82]

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.[83]

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.[84]

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic disorders that can progress to multiple myeloma. Treatment with curcumin (4 and 8 g/day) decreased paraprotein load, bone turnover, free light chains and the percentage of plasma cells in the bone marrow of some MGUS and SMM patients.[85]

Curcumin (3 g/day, for 12 months) had no effect on the number or size of intestinal adenomas in patients with familial adenomatous polyposis who participated in a placebo-controlled trial.[86]

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.[52] 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).[57] 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.[55]

Curcumin (500 mg/day, for 15-30 days) reduced plasma MDA level in type 2 diabetics. In addition, NAD(P)H quinone oxidoreductase 1 (NQO-1, which is specifically regulated by the Nrf2 system) together with other antioxidative enzymes, were enhanced in patients' blood lymphocytes.[56]

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.[87]

Uncontrolled trials have found that curcuminoids (500 mg/day, containing 71.4% curcumin for 12 months) improved markers of oxidative stress (lowered MDA, superoxide dismutase, glutathione peroxidase and increased GSH (reduced glutathione) in red blood cells and lowered serum nontransferrin-bound iron)[88,89] and reduced the oxidative damage caused by coagulation factors and proteins involved in iron homeostasis[89] in those with beta-thalassaemia/haemoglobin E. Serum ferritin did not change.[88,89] More recently, a randomised, double-blind trial found that curcumin (1 g/day) taken for 12 weeks, significantly decreased serum MDA compared to placebo in patients with beta-thalassaemia major. Haemoglobin, serum iron, ferritin, catalase and vitamin E were not substantially changed. A significant decrease was also observed in levels of nontransferrin-bound iron, ALT and AST in the curcumin group in comparison with placebo group. All patients were also controlled with deferoxamine.[90,91]

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.[92]

In healthy volunteers, treatment reduced serum lipid peroxides (uncontrolled trial; 500 mg/day, curcumin)[93] 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).[94]

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).[95]

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),[63] 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),[96] but significantly decreased M_1G levels in malignant colorectal tissue (4 g/day; colorectal cancer patients).[97] 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.[98]

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,[99] and/or a decrease in serum adipocyte-fatty acid binding protein.[55]

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.[100]

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).[57]

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.[56] Similarly, curcumin (1.5 g/day) taken for 16 weeks, significantly reduced macroscopic proteinuria in type 2 diabetic patients with overt albuminuria, compared to placebo. There was no effect on lipids or glycaemia.[101]

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.[102]

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.[52] Treatment with curcuminoids (4 g/day, containing 52.6% curcumin) did not reduce the incidence of myocardial injury in patients undergoing percutaneous coronary intervention, compared with placebo. The duration of curcuminoid treatment was relatively short: one day before, and continued until one day after the procedure.[103]

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 ischaemia phase.[104]

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, measured using the Birmingham vascular activity score, after 4 weeks for the curcumin group compared to patients taking placebo. In addition, erythrocyte sedimentation rate and plasma levels of CRP and TNF-alpha were significantly reduced in the curcumin group compared to the results for the placebo group. TNF-alpha was found to be significantly correlated with BVAS.[105]

Bowel Conditions

There was a lower rate of relapse in patients with ulcerative colitis treated with 2 g/day of curcumin at 6 months compared to those treated with placebo (p = 0.06), but no difference at 12 months. All patients received treatment with sulphasalazine or mesalamine.[106] 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.[107-109] 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.[110] *See also pharmacokinetic study of sulphasalazine in Safety section below.*

In a randomised controlled trial of patients who underwent surgery for Crohn's disease and received thiopurine treatment, curcumin was no more effective than placebo in preventing recurrence of the disease. Curcumin (3 g/day) was taken for 6 months.[111]

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.[112]

Selected 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 hypovitaminosis 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/IL-4, IL-17/transforming growth factor-beta.[113-115]

Treatment with curcuminoids (1 g/day, containing 70% curcumin) for 6 weeks resulted in a decrease in depression scores compared to those who received placebo. Patients were also taking the SSRI drug escitalopram. Curcumin significantly increased plasma brain-derived neurotrophic factor levels, decreased the inflammatory cytokines IL-1beta and TNF-alpha and decreased salivary morning cortisol concentrations compared with placebo.[116] A randomised, double-blind, 12-week trial conducted in Thailand investigated the efficacy of curcumin versus placebo as an add-on treatment for major depression. All participants were stable, being treated with: fluoxetine, other SSRIs (mainly sertraline), other antidepressants combined or not with psychotherapy, and mood stabilisers.

The dose of curcuminoids (containing 77% curcumin, 17% demethoxycurcumin and 6% bisdemethoxycurcumin) increased every week from 500 mg/day in the first week to 1.5 g/day after 4 weeks. A follow-up visit was conducted at week 16. Depression was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS). Curcumin was more efficacious than placebo in improving MADRS scores with significant differences between curcumin and placebo emerging at weeks 12 and 16. The effects of curcumin were more pronounced in men than in women.[117]

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.[118] In two randomised, placebo-controlled, double-blind trials, treatment with 2 g/day of curcumin/curcuminoids was not efficacious for this autoimmune condition.[119,120]

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).[121]

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. In addition, serum levels of brain-derived neurotrophic factor were significantly higher after curcumin treatment compared to the results for the placebo group.[122,123]

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. In addition, curcumin treatment significantly reduced nasal congestion as measured by increased nasal airflow.[124]

Curcumin (2 g/day) was not beneficial for atopic asthma in a small controlled trial.[125] 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.[126]

Curcumin, in combination with other substances, may provide therapeutic activity in kidney disease.

- 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 IL-6 and prostaglandin E2 significantly decreased in the treatment group. Other parameters (CRP, TNF-alpha, glutathione peroxidase) were unchanged. The Boswellia extract was standardised for 3-acetyl-11-keto-β-boswellic acid, providing 51 mg/day of this constituent.[127,128]
- 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). The best results occurred for the following dose: 960 mg/day curcumin + 40 mg/day quercetin.[129] Quercetin is found in a variety of plant foods. Examples of foods high in quercetin (mean values, mg/100 g) include:[130] coriander leaf, raw: 52.9; apple skin: 19.0; green peas, raw: 14.2.

Safety

Despite Turmeric and curcumin having low toxicity, caution is advised for the use of curcuminoid phosphatidylcholine complex (due to the increased bioavailability) in pregnancy, women wishing to conceive and patients taking prescribed medications, especially those with a narrow therapeutic window. Monitoring is advised for patients taking anti-inflammatory and/or analgesic drugs, as reduced dosage of the drug may be possible.

In a randomised, placebo-controlled study, after consumption of Turmeric extract, 5 of 24 healthy volunteers showed an inhibitory effect on arachidonic acid-induced platelet aggregation. These volunteers did not demonstrate a reduction in platelet aggregation to the other agonists. No bleeding events were reported. Concomitant consumption with aspirin did not further suppress platelet function inhibited by aspirin alone (including when arachidonic acid was used as the agonist). Prothrombin time was not impaired. Participants were administered a product made from two concentrated Turmeric extracts (50:1 and 25-30:1) which provided 475 mg/day of curcuminoids for 3 days.[131]

A pilot study evaluated the potential for curcuminoid phosphatidylcholine complex to cause interactions in 4 groups of patients taking medications: antiplatelet (aspirin or ticlopidine or clopidogrel; taken for at least 2 years), anticoagulant (warfarin or dabigatran), thyroxine and metformin. This was done by assessing the pharmacodynamics (not the pharmacokinetics). Blood samples were taken before and after 10-15 days of supplementation with 1 g/day of complex (containing about 200 mg/day of curcuminoids). Interactions were not observed based on a lack of change in:[132]

- bleeding time (for antiplatelet drugs),
- international normalised ratio (for anticoagulant drugs),
- thyroid function tests,
- fasting blood glucose test.

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.[52]

In a randomised trial of 608 patients who underwent elective repair of an unruptured abdominal aortic aneurysm, there was a higher risk of acute kidney injury among patients who received curcumin (17%) than among those who received placebo (10%; p = 0.01). There was no statistically significant difference in the likelihood of the risk of clinically-important bleeding (2% vs 3%). Those assigned to the curcumin group received 2-gram doses 8 times over 4 days.[54]

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.[133] So until more information is available, and despite documented concomitant administration in clinical studies, curcumin should not be taken at least 48 hours either side of each chemotherapy or radiotherapy treatment.

A randomised, crossover study conducted in Thailand with healthy volunteers found that administration of curcuminoids did not substantially affect the extent of absorption (AUC) or the maximum plasma concentration (C_{max}) of digoxin. Curcuminoids (1 g/day) were taken for four days prior and three days after a single dose of digoxin. Turmeric extract providing 1 g/day of curcuminoids were taken for four days prior and three days after a single dose of digoxin. However, a breakdown of the individual results showed variation. Considering a change of 25% in C_{max} to be of clinical relevance, three categories of interaction between curcuminoids and digoxin were observed: C_{max} of digoxin increased, remained unchanged, and decreased in six, four, and two volunteers, respectively. Although in this individual breakdown, the AUC was not measured. Four participants had non-pathological ECG changes following administration of digoxin alone (n = 1), with curcuminoids (n = 1), or in both phases of the study (n = 2). ECG changes in these volunteers returned to normal within 24 hours.[134]

In healthy volunteers, plasma levels of talinolol decreased when taken together with curcuminoids (300 mg/day),[135] but increased when taken at a higher dosage of curcuminoids (1 g/day),[136] although was influenced by genotype.[136]

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.[137] It is not known if the extent of the interaction would occur across the entire population.

High doses of Turmeric taken in food were suspected of increasing drug levels of tacrolimus in transplant patients (2 case reports).[138,139]

Contraindicated in obstruction of the biliary tract and caution is advised in gallstones. (Curcumin (20 mg, single dose) stimulated gallbladder contraction in healthy volunteers.[140])

There have been a few cases of diarrhoea, nausea or abdominal fullness/pain reported from cancer trials.

A patient undergoing low-density lipoprotein-apheresis experienced three episodes of anaphylactoid-like reactions after beginning intake of Turmeric ("several spoonfuls" dissolved in water, each morning). Prior to commencing Turmeric the patient had not experienced the reaction.[141]

Major Actions

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

Indications

- Inflammatory and autoimmune conditions, including osteoarthritis, uveitis, arteritis, ulcerative colitis, systemic lupus erythematosus.
- Cancer and precancerous conditions.
- Management of pain, particularly when linked to inflammation or after surgery.
- Diabetes, prediabetes, insulin resistance, diabetic complications.
- Support during exercise, including decreasing muscle soreness, better performance in hot conditions and reduced risk of heat stroke.
- Muscular strength in the elderly.
- Support for kidney function.
- Nonalcoholic fatty liver disease, benign prostatic hyperplasia, psoriasis, depression, premenstrual syndrome, irritable bowel syndrome, reflux, allergic rhinitis.
- Conditions requiring antioxidant support.
- Supportive therapy for preventing cancer recurrence, although not during chemotherapy or radiotherapy.
- Possibly for oral lichen planus (results may be dependent on dose).

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Appendix

Glossary	
major curcuminoids of Turmeric rhizome	▪ curcumin, demethoxycurcumin and bisdemethoxycurcumin
demethoxylated forms of curcumin	▪ demethoxycurcumin and bisdemethoxycurcumin
phase 1 metabolites	▪ also known as primary metabolites, formed via reduction ▪ e.g. for curcumin: predominantly tetrahydrocurcumin and hexahydrocurcumin
phase 2 metabolites	▪ metabolites formed via conjugation with glucuronide and sulfate, producing conjugates ▪ e.g. for curcumin: curcumin glucuronide and curcumin sulfate ▪ parent curcuminoids and primary metabolites are subjected to phase 2 metabolism
enzymatic hydrolysis of the phase 2 conjugates	▪ also known as enzymatic deconjugation ▪ in pharmacokinetic studies incubation of samples with glucuronidase and sulfatase converts the conjugates (then known as deconjugated forms) ▪ e.g. for curcumin: curcumin glucuronide and curcumin sulfate are deconjugated and the results are reported as total curcumin (or curcumin)
free curcumin	▪ unconjugated curcumin
parent curcuminoid	▪ the curcuminoid in original form e.g. curcumin, demethoxycurcumin and bisdemethoxycurcumin ▪ in pharmacokinetic studies also refers to the free form e.g. parent curcumin is free curcumin in plasma or tissue
total curcumin	▪ in pharmacokinetic studies: sum of free/parent curcumin and conjugated curcumin (the latter measured as deconjugated curcumin)