Therapeutic application and recent advances of curcumin in human health

TABLE OF CONTENTS

Curcumin bioavailability 2

Curcumin and antioxidant activity 3

Curcumin and inflammation 3

Clinical indications 3

Autoimmune diseases 3
- Osteoarthritis and rheumatoid arthritis 4
- Inflammatory bowel disease 4
- Multiple sclerosis 4
- Psoriasis 5
- Oral lichen planus 5

Metabolic health 5
- Obesity 5
- Metabolic syndrome 6
- Type 2 diabetes mellitus 6

Cardiovascular disease 6
- Dyslipidaemia 7
- Atherosclerosis and coronary artery disease 7

Hepatic disease 7

Neuropsychiatric disorders 7
- Mood disorders 8
- Schizophrenia 8

Cognition and neurodegeneration 8

Gastrointestinal health 9
- GIT microbiome 9
- Irritable bowel syndrome 9
- Peptic ulcer/*Helicobacter pylori* 9

Reproductive health 10

Ophthalmology 10

Allergy and atopy 10

Genetic disorders 10

Cancer 11

Clinical summary 12

Dosage, safety and clinical tips 12

Introduction

Turmeric (*Curcuma longa*), a plant species belonging to the Zingiberaceae (ginger) family, is a popular spice and food additive widely used in South Asian and Middle Eastern countries. The rhizome has been used in Ayurvedic medicine for nearly 4000 years for the treatment of a wide variety of conditions such as respiratory, gastrointestinal and liver disorders, inflammatory diseases, menstrual problems, and skin conditions.[1,2] Turmeric is also an essential component of traditional Chinese medicine, used for the treatment of inflammatory and digestive disorders, and to manage stress, depression, and other mood disorders.[3]

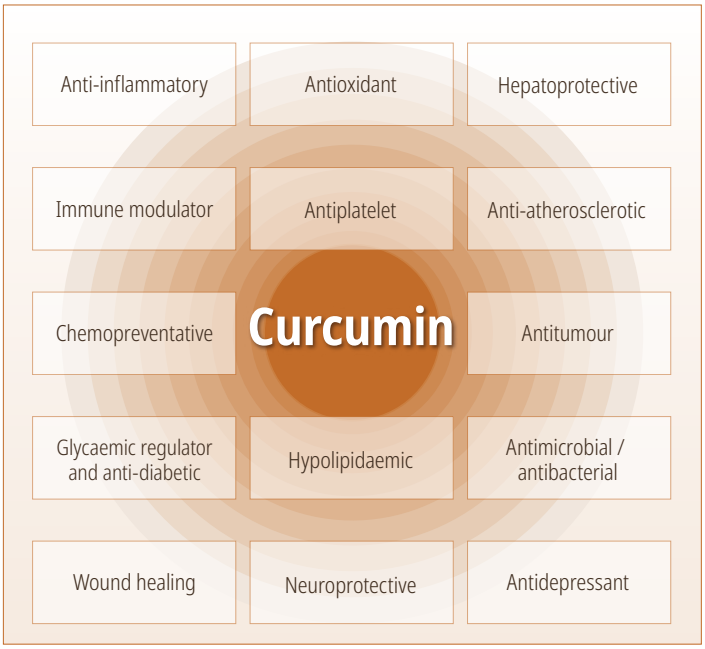
The bioactive constituents of this herb, collectively known as curcuminoids, are now the focus of an unprecedented number of clinical trials. Curcumin (diferuloylmethane) is the primary curcuminoid, followed by demethoxycurcumin and bisdemethoxycurcumin, respectively.[4] 'Curcumin' is often used to refer to the total curcuminoids. Most currently available preparations contain all three curcuminoids in varying ratios.

Curcumin is a highly pleiotropic molecule that was first isolated from the rhizomes of turmeric in 1815.[5] Since this time, thousands of clinical trials have revealed the therapeutic potential of curcumin as an antioxidant, anti-inflammatory, anti-cancer, and antimicrobial agent.[1,2] Curcumin has become the target of human clinical trials due to its diverse biological and pharmacological activities (see Figure 1). These investigations indicate curcumin's therapeutic potential in inflammatory, cardiovascular, neoplastic, neurodegenerative and metabolic diseases.[4]

This technical sheet (V.10/22) is intended for the further education of practitioners. Any statements made do not intend to claim a cure for any condition mentioned.

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Figure 1: Curcumin possesses varied biological activity, indicating potential for diverse therapeutic applications.



Bioavailability

Curcumin is one of the most widely researched herbal medicines and has demonstrated therapeutic benefits for a broad range of conditions. However, the major obstacle for the clinical application of curcumin is poor bioavailability. Low aqueous solubility, poor absorption, and rapid metabolism and elimination are the three primary causes.[6] Low oral bioavailability is evidenced in clinical trials showing negligible or undetectable serum plasma curcumin levels after oral consumption.[7,8] Various formulations and delivery systems have been developed to enhance the stability and bioavailability of curcumin. These include the use of adjuvants such as piperine, formulating liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complexes, and the use of structural analogs of curcumin such as turmeric oil.[9]

A significant focus within the existing body of turmeric research has been on measuring serum plasma curcumin levels due to the known poor bioavailability. Many industry initiatives focus on bioavailability over efficacy, claiming an increase in plasma curcuminoid concentrations indicates superior efficacy, and numerous technologies have been employed to bypass gastrointestinal metabolism and increase delivery of curcumin to the tissues. Despite this focus, numerous studies utilising concentrated curcuminoid extracts, including Curcumin C3 Complex®, have found clinical benefits and positive effects on relevant biomarkers at doses deemed insufficient to impact plasma curcumin levels.

Based on this emerging clinical data, the efficacy of curcumin may not be entirely due to the parent molecule but due to its metabolites and degradation products, as well as the other primary curcuminoids.[10-12] It is also likely that a significant proportion of curcumin's clinical efficacy arises from its action within the gastrointestinal tract, which elicits beneficial effects in peripheral body systems.[8]

The clinical efficacy of curcumin relates to delivery mechanisms, dosage and raw material. The clinical efficacy of curcumin is thought to be enhanced when administered with the primary curcuminoids, bisdemethoxycurcumin and demethoxycurcumin, exerting a synergistic effect. These curcumin analogs are more stable in physiological conditions, and some research indicates that they display increased potency and antineoplastic activity compared with curcumin.[13] In particular, bisdemethoxycurcumin has been shown to exert potent anti-inflammatory, antioxidant, and anti-cancer properties.[13-16] From a clinical perspective, when selecting a curcumin extract, it is therefore important to choose a curcumin preparation which maximally increases these curcuminoids.

Curcumin C3 Complex® is a highly purified extract of turmeric with demonstrated biological activity in over 100 published studies. It is standardised to a specific compositional ratio of the three primary curcuminoids: curcumin (75–81%), bisdemethoxycurcumin (2.2–6.5%) and demethoxycurcumin (15–19%)

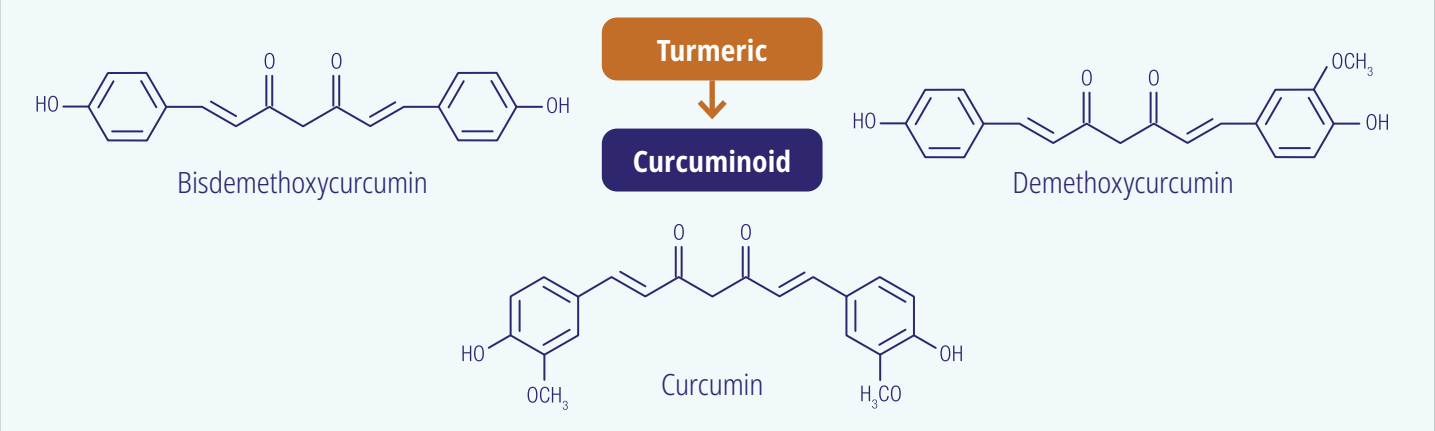
A comparison between clinically relevant doses of Curcumin C3 Complex® and a commercially available curcumin phospholipid complex demonstrated that there are significant pharmacokinetic differences between the two formulations.[17] While serum curcumin concentrations reached similar levels between the two interventions,

Table 1: Comparison between pharmacokinetic parameters of parent curcuminoids between clinically relevant doses of Curcumin C3 Complex® and a curcumin phospholipid complex.

	Curcumin C3 Complex®	Curcumin Phospholipid Complex
Curcumin		
C_{max} ng/mL	57	71
C_{24} ng/mL	14	11
AUC_{0-24} ng/mL	731.6	669.4
AUC_{0-48} ng/mL	929	785
Demethoxycurcumin		
C_{max} ng/mL	180	55
C_{24} ng/mL	9	Below level of quantification
AUC_{0-24} ng/mL	**674.5**	**152.5**
AUC_{0-48} ng/mL	**801**	**178**
Bisdemethoxycurcumin		
C_{max} ng/mL	58	24
C_{24} ng/mL	9	Below level of quantification
AUC_{0-24} ng/mL	**593.8**	**124.5**
AUC_{0-48} ng/mL	**706**	**132**

C_{max} Maximum serum concentration; C_{24} Serum concentration at 24 hours; AUC_{0-24} Area under the curve (0–24hours); AUC_{0-48} Area under the curve (0–48hours)

Figure 2: The three major curcuminoids in turmeric and their chemical structure[9]



the level of the other primary curcuminoids were significantly higher in the Curcumin C3 Complex® group. These results suggest that the curcuminoids are either poorly absorbed or more rapidly metabolised when consumed as a phospholipid complex[17] (see Table 1). As a result, the half-life of curcumin and its active metabolites was also longer for Curcumin C3 Complex® compared to the phospholipid complex, potentially providing a longer therapeutic effect.[17] Furthermore, gastrointestinal tissue concentrations of the three primary curcuminoids were significantly higher after supplementation with Curcumin C3 Complex®. Therefore, considering the important therapeutic role of curcumin in the gastrointestinal tract (GIT), Curcumin C3 Complex® has the advantage of not only maximally enhancing GIT curcuminoid concentration but also demonstrates superior systemic bioavailability compared with the curcumin phospholipid complex.

Curcumin and antioxidant activity

Antioxidant and anti-inflammatory activities are the two primary mechanisms that explain the majority of the therapeutic effects of curcumin. Both *in vitro* and *in vivo* studies have revealed that curcumin has significant antioxidant activity and improves systemic markers of oxidative stress.[9] The research on the chemical structure of curcumin shows that electron-donating groups of curcumin, particularly the phenolic hydroxyl and β-diketone groups, are the main contributors to its antioxidant activity.[18,19]

Curcumin exerts direct free radical scavenging activity and can scavenge different forms of free radicals, including reactive oxygen and nitrogen species, as well as preventing reactive oxygen species (ROS) production.[20,21] In addition to direct antioxidant activity, curcumin can enhance activities of antioxidant enzymes, such as catalase, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione-S-transferase (GST).[9]

Curcumin also exerts indirect antioxidant activity by inducing the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, which is essential in cellular antioxidant defence systems.[22,23] Under normal physiological conditions, Nrf2 is inactive due to its combination with the cytosolic protein Kelch-like ECH associated protein 1 (Keap1).[24] In response to oxidative stress, Nrf2 moves into the nucleus where it binds to antioxidant response elements and induces antioxidant enzymes.[24] Curcumin can activate Nrf2 and thereby increase the expression of enzymes involved in detoxification and antioxidant defences.[24-26]

Accumulating evidence from human clinical trials demonstrates the antioxidant activity of curcumin. In a recent meta-analysis of human clinical trials, curcumin significantly improved oxidative stress parameters, including serum SOD and catalase activities, GSH concentrations, and serum lipid peroxides.[27]

Curcumin and inflammation

Curcumin is a potent anti-inflammatory due to its pleiotropic effects on several critical pro-inflammatory enzymes and transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[28,29] NF-κB regulates a broad array of genes involved in different processes of immune and inflammatory responses, as well as cellular proliferation and transformation.[4,29]

By interacting with multiple receptors and signalling pathways, curcumin inhibits the production of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), and interleukin (IL) 1, 6, 8 and 12.[4,5,29] Curcumin is a dual inhibitor of the arachidonic cascade and it exerts anti-inflammatory effects by downregulating multiple enzymes in this cascade, including cyclooxygenases (COX), 5-lipoxygenase and inducible nitrogen oxide synthase (iNOS).[4,30] Oxidative stress can exacerbate the inflammatory process by activating redox-sensitive transcription factor, such as NF-κB. Through its antioxidant activity, curcumin can modulate cellular redox status and oxidative stress response, and subsequently, the inflammatory response through the Nrf2 pathway.[31,32]

Curcumin in autoimmune diseases

Autoimmune diseases (AIDs) are chronic inflammatory diseases characterised by deregulated immune function and a loss of tolerance to self-(auto) antigens. Pro-inflammatory cytokines and other inflammatory mediators are now recognised to drive tissue damage in AIDs. Researchers have studied curcumin in a wide variety of inflammatory autoimmune conditions,[33] and it has been shown to exert therapeutic benefits on these inflammatory diseases by

attenuating oxidative stress and regulating inflammatory cytokines and pro-inflammatory signalling pathways in immune cells.

Osteoarthritis and rheumatoid arthritis

In osteoarthritis (OA), unresolved inflammation in joints not only leads to the development of symptoms, including pain and stiffness, but also the progressive destruction of articular cartilage and remodelling of joint tissues. The overproduction of ROS and inflammatory mediators in the synovial fluid induces matrix metalloproteinases and other hydrolytic enzymes resulting in cartilage breakdown secondary to proteoglycan and collagen destruction.[34,35] In rheumatoid arthritis (RA), complex autoimmune and inflammatory processes that involve the innate and adaptive immune system contributes to synovitis, swelling and joint destruction.[36] Curcumin can inhibit inflammatory cytokines and matrix metalloproteinases by blocking NF-κB mediated IL-1β/TNF-α catabolic signalling pathways in articular chondrocytes, suggesting curcumin has specific therapeutic benefits in the management of RA and OA.[37-40]

In an eight week randomised, open-label study, curcumin supplementation (500mg daily) was as effective as diclofenac (50mg daily) in reducing measures of disease activity, tenderness and swelling joints in patients with RA.[41] In a more recent randomised, double-blind, three-arm parallel-group trial, curcumin administration (250 or 500mg twice daily) for 90 days produced significant improvements in clinical symptoms in patients with active RA and was well tolerated. Curcumin demonstrated significant anti-inflammatory effects with significant changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and RA factor values in both curcumin treatment groups.[42]

Several human clinical trials have demonstrated curcumin's efficacy for reducing symptoms associated with OA. A meta-analysis of seven clinical trials (n=797) using between 180mg to 2g of curcumin daily and ranging from four to 16 weeks demonstrated that curcumin supplementation significantly reduced knee pain and improved quality of life in patients with knee OA. The use of rescue medication was also significantly reduced in the curcumin group.[43] A more recent, 28-day randomised controlled trial (RCT) found curcumin supplementation (500mg, three times daily) was as effective as diclofenac (50mg, twice daily) at reducing pain scores and improving stiffness, functions of daily living and quality of life. Adverse effects were significantly less in the curcumin group (13% versus 38% in the diclofenac group; P <0.01). None of the patients in the curcumin group required H2 blockers, compared to 28% in the diclofenac group.[44]

Several trials show that clinical improvement in OA symptoms are associated with improved inflammatory markers and antioxidant status. Curcumin supplementation decreased pain scores (WOMAC) by more than 50%, increased treadmill-walking performance more than threefold, and significantly decreased inflammatory markers (IL-1β, IL-6, soluble vascular cell adhesion molecule-1 and ESR) in OA patients.[45]

Curcumin C3 Complex® (1500mg daily) for six weeks produced a significant reduction in pain scale scores in patients with knee OA compared to placebo, with significant improvements in both pain and physical function.[46] Improvements in pain scores correlated with significant enhancements in antioxidant status (increased serum SOD activities and GSH concentrations) and reduced lipid peroxidation (reduced serum levels of malondialdehyde (MDA)).[46] Serum concentrations of inflammatory markers (IL-4, IL-6 and high-sensitivity CRP (Hs-CRP)) were significantly reduced in the curcumin group compared to baseline. However, changes were not significantly different to placebo, which the authors concluded was due to a localised anti-inflammatory effect in the osteocartilaginous tissue rather than a systemic effect.[47]

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic condition that affects the GIT, with periods of exacerbation and remission. Its primary forms of presentation are ulcerative colitis (UC) and Crohn's disease (CD). Pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β, play the central role in initiating and sustaining inflammation in the intestinal mucosa, resulting in tissue damage. Curcumin has been shown to attenuate intestinal inflammation by modulating different anti-inflammatory and immunoregulatory mechanisms in experimental colitis.[48,49] In an immune-mediated model, curcumin reduced oxidative stress, the neutrophil influx, and ROS-related cellular damage. It also attenuated colon epithelial apoptosis, suggesting its potential benefit in ameliorating oxidative bowel inflammation in IBD.[50]

Curcumin supplementation as an adjunct to conventional treatment has improved treatment outcomes in patients with IBD in several clinical trials. In a recent meta-analysis of five randomised controlled trials (RCTs), ranging in duration from four weeks to 12 months, oral curcumin supplementation (240mg up to 3g per day) in combination with mesalamine (5-ASA), produced significant clinical responses.[51] In four of the five studies included, there was a significant improvement in the clinical response with curcumin, allied with no serious adverse events. Five studies reported that curcumin was able to reduce the symptoms of the disease, achieve clinical remission, and prevent relapse when used as a complementary therapy to mesalamine.[52-56]

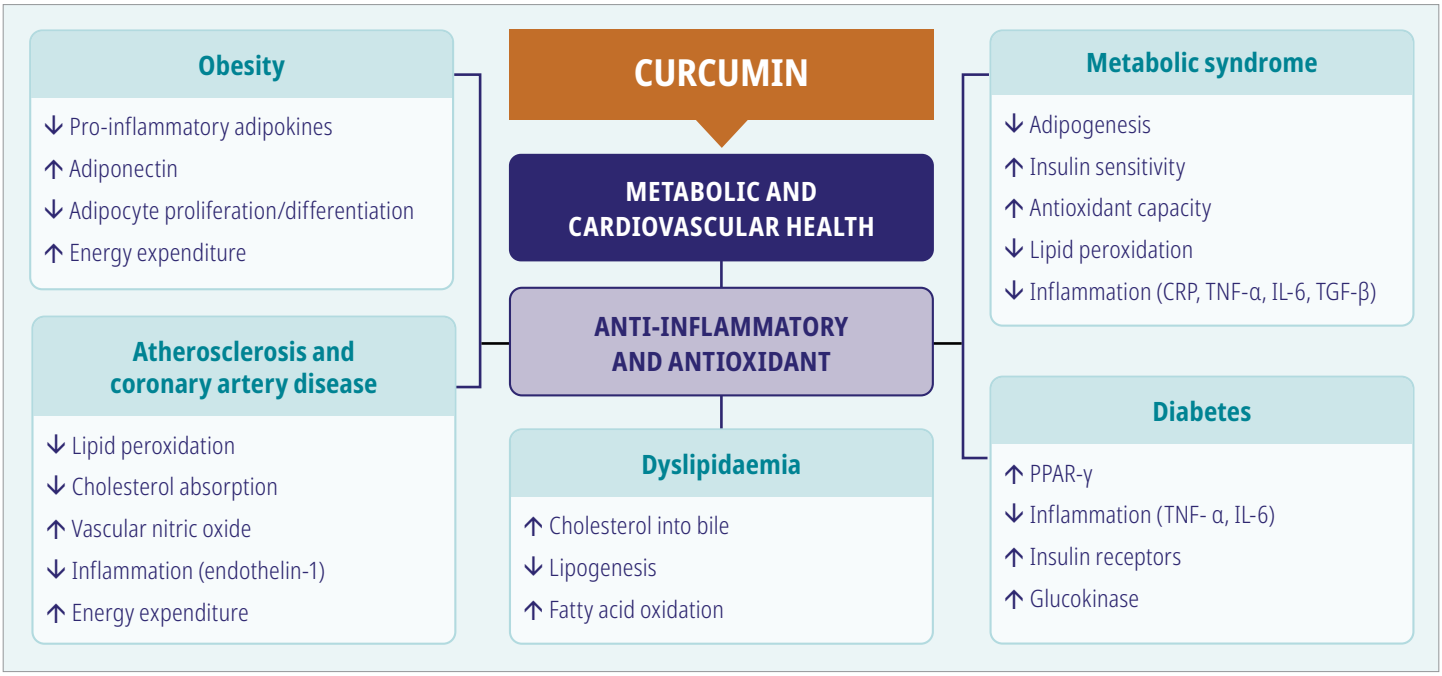
Sagehdi et al. (2018) conducted the first RCT investigating the effect of curcumin on inflammatory markers in patients with mild-to-moderate UC.[56] In this eight week trial, supplementation with curcumin (1500mg daily) in combination with conventional therapy significantly improved clinical outcomes, disease activity scores, and quality of life, and decreased the levels of the inflammatory markers hs-CRP and ESR compared to placebo. Furthermore, 83.9% of curcumin patients achieved clinical remission, compared to 43.8% of the placebo group.

In a prospective tolerability study, curcumin supplementation was assessed in a paediatric population with CD or UC. Curcumin supplementation was titrated up from 500mg twice daily to 2g twice daily over nine weeks. Curcumin was generally well-tolerated, and three out of nine patients showed improvement in disease activity scale scores.[57]

Multiple sclerosis

Curcumin is also being investigated as a therapy for multiple sclerosis (MS), a demyelinating inflammatory disorder of the central nervous system.[58] T helper 17 (Th17) cells are IL-17-producing effector cells

Figure 3: The metabolic and cardiovascular effects of curcumin



that mediate significant inflammatory events in the pathophysiology of MS.[59] In a six month clinical study, supplementation with 80mg daily of nano-curcumin significantly decreased Th17 associated parameters such as Th17 frequency, expression levels of retinoic acid-related orphan receptor gamma (RORγt) (a Th17 corresponding specific transcription factor) and secretion levels of IL-17, suggesting curcumin may be effective on the inflammatory features of MS.[59]

Psoriasis

Psoriasis is an autoimmune inflammatory condition, in which aberrant T-cell activation and subsequent production of arachidonic acid and other pro-inflammatory mediators cause abnormal keratinocyte proliferation. Oral and topical administration of curcumin has been investigated for psoriasis treatment.[60-64] Oral curcumin administration (2g daily) as an adjunct to topical steroids was more effective than steroid treatment alone for improving psoriasis lesions and downregulating T-cell-mediated inflammation, in particular, the Th22 pathway.[60]

In the RCT conducted by Bilia et al. (2018) oral curcumin (3g daily) in combination with acitretin (0.4mg/kg/d) for 12 weeks produced a significantly higher reduction in Psoriasis Area Severity Index (PASI) values than acitretin alone in patients with moderate-to-severe psoriasis.[61] Furthermore, serum total cholesterol levels increased in the acitretin group (a known side effect of treatment); however, no changes in serum lipid profile occurred in the curcumin group. In a third study,[63] the safety and efficacy of oral Curcumin C3 Complex® (4.5g daily) was evaluated. Only eight of the 12 participants completed the study, and the efficacy of the study drug was low, with an intention-to-treat response rate of 16.7%. However, those who responded had excellent responses: 83% and 88% improvement in PASI scores at week 12.

Oral lichen planus

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the mucous membrane of the oral cavity. It is a T-cell mediated autoimmune disease in which the cytotoxic $CD8^+$ T-cells trigger apoptosis of the basal cells in the oral epithelium.[65] In a study by Chainani-Wu et al. (2012), 20 patients were randomised to receive 6g daily of Curcumin C3 Complex® or placebo for 12 days.[66] The curcuminoid group showed a greater reduction in clinical signs and symptoms compared to the placebo group, in addition to an improvement in the Modified Oral Mucositis Index (MOMI) score, which used to measure OLP signs. A recent meta-analysis investigating oral and topical curcumin for the treatment of OLP concluded that seven studies showed statistically significant differences in pain severity and clinical appearance of lesions after treatment with curcumin compared to baseline.[67] Three controlled clinical trials compared the efficacy of curcumin to corticosteroids; two of these studies found the topical application of curcumin was as effective as topical corticosteroids when used at a higher concentration of curcumin.[67]

Curcumin in metabolic health

The growing number of experimental studies and human clinical trials demonstrate curcumin's beneficial effects on glycaemic control and lipid parameters.[68-70] In addition to its antioxidant and anti-inflammatory activity, the lipid-lowering and anti-glycaemic effects make curcumin a promising therapeutic for preventing and treating metabolic disorders and their related vascular complications. Curcumin administration has also demonstrated positive effects on body weight and waist circumference, which are risk factors for metabolic diseases.

Obesity

Obesity is an inflammatory condition associated with white adipose tissue expansion, increased levels of pro-inflammatory cytokines and impaired antioxidant status. The most important source of pro-inflammatory cytokines in obesity is macrophages that

infiltrate adipose tissue in response to adipocyte growth. These macrophages suppress the production and secretion of protective anti-inflammatory factors such as adiponectin.[71,72] These changes contribute to insulin resistance and disrupted glucose homeostasis, thus making obesity a risk factor for type 2 diabetes mellitus (T2DM).[72]

In human adipose tissue, curcumin reduces the expression of pro-inflammatory adipokines (IL-6 and TNF-α), and induces the expression of adiponectin, an essential anti-inflammatory agent secreted by adipocytes.[73,74] Curcumin can inhibit adipocyte proliferation and differentiation, suggesting enhanced catabolism in adipose tissue is a relevant mode of action.[75] Moreover, curcumin has been shown to promote browning of white adipose tissue in diet-induced obese mice, which indicates increased energy expenditure as another mechanism by which curcumin reduces fat mass deposition.[76]

Two recent meta-analyses have found that curcumin intake among patients with metabolic syndrome (MetS) and related disorders (T2DM, non-alcoholic fatty liver disease (NAFLD)) has positive effects on body weight and body mass index (BMI).[77,78] Curcumin doses varied from 70 to 2400mg daily, and duration of intervention was between one and six months.[77] Both studies found positive effects on body waist circumference, which is an indicator of central adiposity; however, in the study by Mousavi et al. (2018), this was only found in studies that used curcumin doses ≥1000mg per day and ≥eight weeks.[77] In the most recent meta-analysis, curcumin supplementation also produced a significant decrease in leptin and a significant increase in adiponectin levels.[78]

Several human clinical trials demonstrate curcumin's antioxidant and anti-inflammatory effects in obese individuals. In a randomised clinical trial, Curcumin C3 Complex® (1g daily) modulated the immune response in obese individuals by altering the circulating concentrations of IL-1β, IL-4, and vascular endothelial growth factor (VEGF).[71] Oxidation associated with obesity was attenuated within 12 weeks of curcumin supplementation, as demonstrated by reduced lipid peroxidation, oxidised low-density lipoprotein cholesterol (LDL-c) and protein oxidation levels.[79] Curcumin supplementation (500mg daily) in overweight and obese adolescent girls had beneficial effects on inflammation (hs-CRP and IL-6) and oxidative stress (total antioxdant capacity) markers but did not significantly decrease anthropometric measurements after 10 weeks.[80]

Metabolic syndrome

Curcumin has been shown to attenuate several aspects of MetS by improving insulin sensitivity,[81,82] suppressing adipogenesis,[74] and reducing elevated blood pressure,[83] inflammation,[84] and oxidative stress.[85] A recent meta-analysis of several clinical trials using between 800-2400mg daily of curcumin or turmeric powder, and ranging from four to 12 weeks, demonstrated that curcumin supplementation significantly improved fasting blood glucose, triglycerides, high-density lipoprotein cholesterol (HDL-c) and diastolic blood pressure in individuals with MetS.[70] The administration of Curcumin C3 Complex® (1g daily) produced a significant improvement in biomarkers of systemic antioxidant capacity (SOD), lipid peroxidation (MDA) and inflammation (CRP, TNF-α, IL-6, TGF-β and MCP-1). Supplementation also improved all lipid profile indices[86-90]

Type 2 diabetes mellitus

Continued oxidative stress and inflammation disturbs the insulin signalling pathway and can promote the development of β-cell dysfunction and insulin resistance, which eventually leads to diabetes. Current clinical evidence suggests the benefits of curcumin/curcuminoids in diabetes mellitus is mediated mainly by its hypoglycaemic, antioxidant, and anti-inflammatory properties.[91]

Curcumin can induce activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ), which regulates genes involved in glucose and lipid metabolism, and thus improves insulin secretion, fat metabolism, and insulin sensitivity.[92-94] Additionally, curcumin attenuates TNF-α, which has been shown to inhibit insulin transduction and affect glucose metabolism.[94,95] Curcumin also improves insulin resistance through the activation of the insulin receptor and its downstream pathways[96] and promotes glucose homeostasis by triggering glucokinase activity in the liver.[68]

A recent meta-analysis of RCTs confirms that curcumin has a positive effect on lipid and glycaemic profiles in T2DM subjects.[68] The meta-analysis included eight trials, with doses ranging from 80-1500mg daily curcumin or turmeric, and trial lengths ranging from eight weeks to six months. Curcumin or combined curcuminoid supplementation effectively lowered the level of fasting blood glucose in individuals with some degree of dysglycaemia. Also, isolated curcumin supplementation significantly decreased haemoglobin A1c (HbA1c) compared to placebo.[68] Curcumin supplementation (1500mg daily) prevented T2DM development in a pre-diabetic population, and improved pancreatic β-cell function, insulin resistance, and adiponectin levels.[82]

There is some evidence to suggest that curcumin may reduce cardiovascular complications associated with T2DM. T2DM patients are especially prone to develop atherosclerosis due to elevated levels of inflammation, increased ROS generation and abnormal metabolic profiles.[97] Curcumin given daily for six months improved endothelial function, insulin sensitivity, and metabolic markers associated with atherosclerosis (plasma triglycerides, and visceral and total body fat) in T2DM subjects.[97] Curcumin administration was as effective as the lipid-lowering drug atorvastatin in reducing circulating markers of oxidative stress (MDA) and inflammation (endothelin-1, TNF-α, IL-6) and in improving endothelial function in T2DM subjects.[98] Curcumin may also slow the progression of diabetic-related kidney damage, with short term curcumin administration significantly reducing proteinuria and inflammatory markers in patients with diabetic nephropathy.[99]

Curcumin and cardiovascular disease

Dyslipidaemia, hypertension, and insulin resistance promote vascular inflammation and endothelial dysfunction, leading to atherosclerosis, the primary cause of cardiovascular disease (CVD).[23,100] Various clinical trials have demonstrated that curcumin exerts cardioprotective effects, which are due to its antioxidant, anti-inflammatory, hypolipidaemic and anti-atherosclerotic activities.[23,101]

Dyslipidaemia

In preclinical studies, curcumin has been shown to ameliorate almost all lipid parameters in both genetically and dietary-induced animal models of dyslipidaemia.[102] Several molecular and cellular mechanisms are proposed for the lipid-modifying effects of curcumin. Curcumin may stimulate the conversion of cholesterol into bile acids, and therefore increase the excretion of cholesterol.[103] Curcumin may inhibit *de novo* lipogenesis by downregulating key lipogenic transcription factors.[104] It also upregulates LDL receptor and stimulates fatty acid oxidation.[70,105]

In a randomised, double-blind, placebo-controlled trial, 1g daily of Curcumin C3 Complex® for eight weeks significantly improved serum lipid concentrations (triglycerides, non-HDL-c, total cholesterol) and lipoprotein(a) (Lp(a)) (a marker of cardiovascular risk) compared to standard care only in patients with MetS.[86] Similarly, Curcumin C3 Complex® at 1g daily for 12 week significantly reduced atherogenic lipid indices, including total cholesterol, non-HDL-c and Lp(a), and significantly increased HDL-c compared to standard care in T2DM patients.[88]

A recent meta-analysis and systematic review of seven RCTs, ranging from four weeks to six months, found that both turmeric and curcumin had beneficial effects on serum triglycerides and LDL-c levels in MetS and T2DM patients at risk of CVD.[100] Low doses of 15, 30, or 60mg per day of curcumin were a useful adjunct therapy for inpatients suffering from acute coronary syndrome due to its effect on total cholesterol and LDL-c[106]

Atherosclerosis and coronary artery disease

In models of atherosclerosis, curcumin can prevent lipid peroxidation, a critical process in the development of atherosclerosis, while inhibiting cholesterol absorption and attenuating atherosclerosis progression.[107] In several human clinical trials with healthy volunteers, curcumin or turmeric supplementation decreased serum lipid peroxides, suggesting curcumin may be beneficial for preventing and treating atherosclerosis.[108-110] Curcumin (500mg daily) administration for seven days produced a significant decrease in the level of serum lipid peroxides (33%) and total cholesterol (11.63%) and an increase in HDL-c (29%) in healthy volunteers.[108]

Vascular endothelial dysfunction and increased arterial stiffness increases the risk of CVD. Curcumin supplementation for 12 weeks improved artery endothelial function via increasing vascular nitric oxide bioavailability and reducing oxidative stress in healthy middle-aged and older adults.[111] In a postmenopausal population, curcumin administration improved flow-mediated dilation and decreased systolic blood pressure, potentially improving the age-related decline in endothelial function and reducing the risk of CVD.[112]

Curcumin supplementation for three days prior and five days post-surgery reduced frequency of acute myocardial infarction (MI) after coronary artery bypass grafting.[113] The incidence of in-hospital MI decreased from 30.0% in the placebo group to 13.1% in the curcumin group. Postoperative CRP, MDA, and N-terminal proB-type natriuretic peptide levels were also lower in the curcumin group than in the placebo group, indicating the antioxidant and anti-inflammatory effects of curcumin may account for their cardioprotective effects.[113]

Curcumin and hepatic disease

Experimental and clinical studies have demonstrated curcumin's potential benefit for attenuating markers of inflammation and oxidative stress in hepatic damage. Curcumin has been shown to prevent lipoperoxidation of liver mitochondria and subcellular membranes due to its antioxidant action.[114] Curcumin also blocks endotoxin-mediated activation of NF-κB and suppresses the expression of cytokines, and inflammatory mediators in Kupffer cells (COX-2 and iNOS), and may be useful for preventing hepatic fibrosis.[115,116] Curcumin is also able to reduce heavy metal-induced hepatic damage due to its scavenging and chelating properties, and ability to induce the Nrf2 pathway.[117]

There is growing interest in curcumin's hepatoprotective activity for the prevention and treatment of NAFLD with two recent systemic reviews and meta-analyses demonstrating its ability to ameliorate liver damage characterised by elevated liver aminotransferases.[118,119] Administration of curcumin for eight weeks was associated with significant reductions in BMI, waist circumference and liver aminotransferases (ALT and AST). Liver sonography was improved in 75% of the curcumin group, and curcumin decreased the NAFLD severity by reducing fat content in the liver.[120]

In another eight week study, curcumin supplementation improved glycaemic (HbA1c and glucose) and lipid (total cholesterol, LDL-c and triglyceride) profiles, aminotransferase levels (ALT and AST) and anthropometric indices (BMI and weight) in NAFLD patients.[121] Compared with placebo, curcumin was associated with a significant reduction in liver fat content (78.9% improvement in the curcumin vs 27.5% improvement in the placebo group). This study demonstrated the ability of curcumin to improve insulin sensitivity and correct dyslipidaemia, two of the significant risk factors for NAFLD.[121]

In a recent 12 week RCT, effects of curcumin supplementation on inflammatory indices and hepatic features in NAFLD patients were evaluated.[122] Fifty patients were randomised to receive lifestyle modification advice plus 1500mg curcumin or placebo for 12 weeks. Curcumin supplementation was associated with a significant decrease in hepatic fibrosis ($p < 0.001$), and NF-κB ($p < 0.05$) compared with baseline. Hepatic steatosis, serum liver enzymes and TNF-α significantly reduced in both groups ($p < 0.05$).

Curcumin and neuropsychiatric disorders

Curcumin as a neuropsychiatric treatment holds promise due to its potential to attenuate neuroinflammation and oxidative stress. Several human clinical trials have examined the therapeutic benefits of curcumin for depression, anxiety and schizophrenia. Positive results from animal studies for bipolar disorder,[123] obsessive-compulsive disorder,[124] and autism spectrum disorders[125] indicate further research is warranted.

Mood disorders

Until recently, treatment of mood disorders including major depression and bipolar disorder were based mainly on the monoamine theory; however, cumulative research also implicates oxidative stress, neuroinflammation, and immune dysregulation in the pathogenesis, which has prompted the exploration of curcumin as a therapeutic option.

Curcumin has been shown to exert antioxidant, anti-inflammatory and neuroprotective effects in animal models and human studies of depression,[126] with similar effect sizes compared to conventional antidepressants.[127] Oral supplementation with curcumin (1000mg daily) as an adjunct to escitalopram reduced plasma levels of inflammatory cytokines (IL-1β and TNF-α) and salivary cortisol, and increased brain-derived neurotrophic factor (BDNF) compared with placebo in depressed patients. The results of the study suggest curcumin's antidepressant activity is mediated via the hypothalamus-pituitary-adrenal (HPA)-axis and BDNF signalling pathway, which are often dysregulated in mood disorders.[128]

RCTs ranging from four to 12 weeks, have assessed the efficacy of curcumin (500-1500mg daily) for the treatment of depression as either a monotherapy or as an adjunct to conventional antidepressants.[127,129,130] Two RCTs found curcumin (500-1000mg daily) to have greater antidepressant efficacy than placebo,[126,129] while a third study demonstrated curcumin supplementation (1g daily) was more effective than placebo in reducing anxiety symptoms but not depression. However, the results of this study were limited by the use of a non-clinical sample population and short trial duration.[131] Enhanced antidepressant efficacy has been demonstrated in several clinical trials when curcumin was used as an adjunct to antidepressant medication.[128-130,132] Administering Curcumin C3 Complex® alongside antidepressants. antidepressants was found to be more effective at reducing both depression and anxiety symptoms in patients with major depressive disorder than antidepressant medication alone.[132]

Schizophrenia

Multiple pathological processes converge in schizophrenia to produce its associated positive symptoms (e.g. abnormal perceptions and beliefs) and negative symptoms (e.g. social and cognitive deficits). Alterations in cellular homeostasis due to oxidative stress, inflammation and immune dysfunction are believed to result in dysfunctional microglia-mediated pruning and disruption of N-methyl-D-aspartate (NMDA) receptor function.[133] The antioxidant, anti-inflammatory and neuroprotective activities of curcumin make it a potential candidate for the treatment of schizophrenia.[134]

Emerging evidence suggests that curcumin can regulate expression of genes involved in inflammation and NMDA-glutamate systems, which are associated with both positive and negative symptoms and cognitive deficits in schizophrenia.[135,136]

Several human clinical studies have explored the potential benefits of curcumin as an adjunct to antipsychotic medication in patients with schizophrenia.[134,137-140] In two of the studies, 1g and 4g daily of Curcumin C3 Complex® improved negative symptoms of schizophrenia.[138,139] While in an eight week trial, curcumin supplementation did not produce significant changes in clinical symptoms and cognitive functioning. However, it improved BDNF levels compared with placebo, suggesting possible long-term benefits of curcumin in cognition and clinical symptoms.[140] Two recent double-blind, placebo-controlled, clinical trials have demonstrated positive effects of curcumin as an adjunct therapy, with one demonstrating improvements in working memory and inflammatory markers (IL-6)[137] and the other demonstrating improvements in negative symptoms.[134]

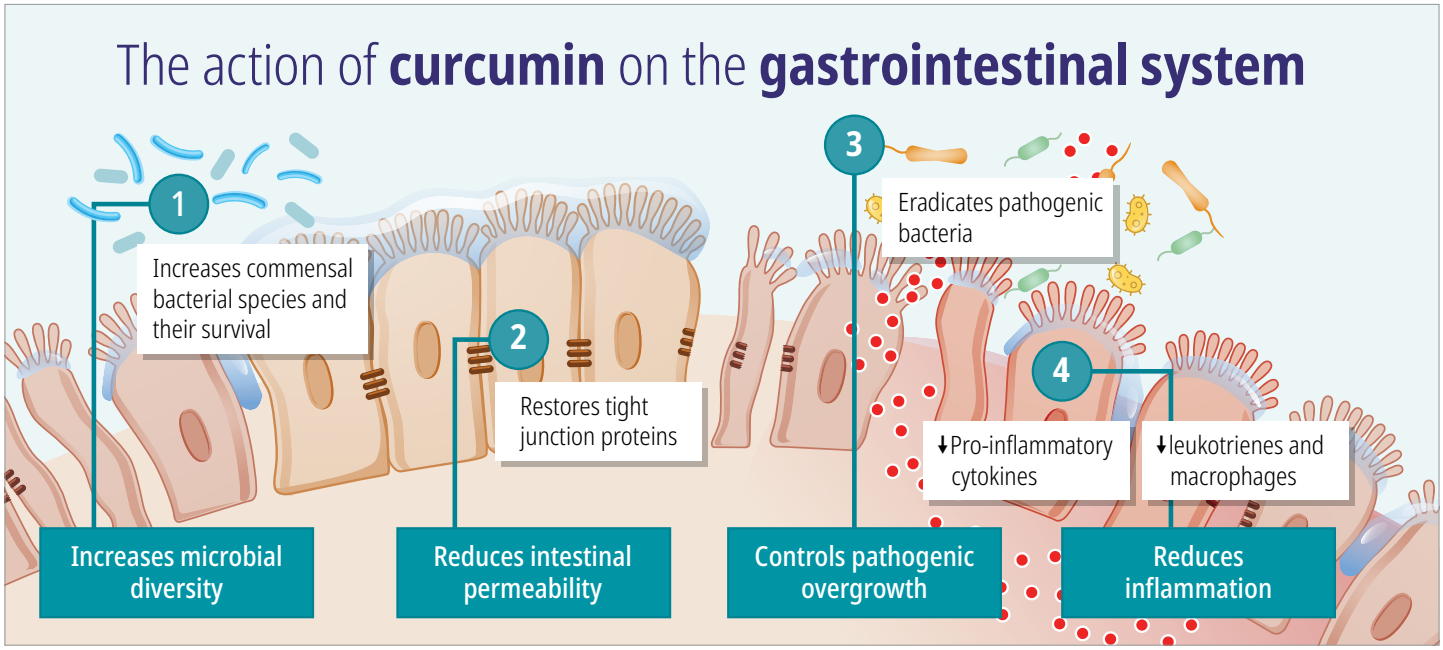
Curcumin, cognition and neurodegeneration

Mitochondrial dysfunction, resulting in oxidative stress and neuroinflammation, is tied to the development of neurodegenerative diseases, such as Alzheimer's disease. Increased generation of ROS, either alone or in conjunction with inflammation, can contribute to the aberrant accumulation of proteins. These proteins trigger an immune response resulting in neuronal death and progressive cognitive decline.[58,141,142] Curcumin's antioxidant and anti-inflammatory effects, as well as its ability to cross the blood-brain barrier, provide a promising avenue for neuroprotection.[141] Perhaps the most promising application of curcumin in neurodegenerative disease is its anti-amyloid properties. There has been some evidence that curcumin possesses the ability to bind amyloid plaques and enhance immune clearance of amyloids from the brain, thus reducing the plaque burden and slowing the progression of Alzheimer's disease.[143-146]

Although curcumin is a promising treatment for neurodegenerative diseases and age-associated cognitive decline due to its pleiotropic actions on the central nervous system, human clinical evidence is limited and has been inconsistent. Early clinical trials investigating the effect on Alzheimer's disease patients showed no difference between curcumin and placebo group after six and 12 months on cognitive measures.[147,148] However, in the study by Baum et al. (2008) a combination of curcumin (1g or 4g daily) with ginkgo increased serum Aβ40 levels, suggesting that curcumin can disaggregate Aβ-deposits in the brain, leading to their release into the circulation.[147] A 12-month, randomised, placebo-controlled, double-blind study investigated the ability of a curcumin formulation (1500mg daily) to prevent cognitive decline in a population of community-dwelling older adults aged 40-90 years. The results showed cognitive decline after six months in the placebo group on the Montreal cognitive assessment that is used to assess general cognitive functioning; however, cognitive performance in the curcumin group remained stable. The authors concluded that curcumin attenuates cognitive decline over time.[149]

Recent trials in healthy subjects demonstrated positive effects of novel curcumin formulations on cognitive function.[150,151] A single dose of curcumin improved sustained attention and working memory tasks, while a four-week administration produced enhanced memory, mood, alertness and contentedness in healthy subjects.[150] In an 18 month RCT, daily supplementation with a bioavailable form of curcumin (90mg daily) improved visual and verbal short-term memory as well as attention in adults compared to the placebo group.[151] Additionally, data derived from PET scans indicate a reduction in amyloid and tau

Figure 4: The mode of action of curcumin on the gastrointestinal tract[152,153,154,156]



accumulation in the amygdala and stable levels in the hypothalamus of the curcumin-treated group compared to elevated levels in the placebo group.

Curcumin and gastrointestinal health

Curcumin's potential as a therapeutic agent may not solely rely on its bioavailability, but also from its positive influence on gastrointestinal health and function. Evidence suggests that a significant proportion of curcumin's therapeutic potential may arise from its effect on the GIT specifically through its ability to modulate the microbiome, reduce intestinal permeability and gut inflammation and control pathogenic microbial overgrowth.[8] Curcumin has been examined as a therapeutic intervention in human clinical trials for IBD, peptic ulcers, pancreatitis, irritable bowel syndrome (IBS), and *Helicobacter pylori* infection. Its effects on the GIT microbiome have also been studied.[101,152]

GIT microbiome

Curcumin has poor bioavailability, indicating after ingestion, curcumin reaches the gut almost unaltered and could potentially exert beneficial effects on gut microbiota and intestinal permeability. Several animal studies suggest that curcumin can favourably alter the gut microbiota community, including microbial richness, diversity and composition.[8,153,154] For example, in an animal model of NAFLD, curcumin dietary supplementation shifted the gut microbiota population structure toward the lean phenotype in rats fed a high-fat diet, and ameliorated diet-induced metabolic endotoxaemia and intestinal inflammation.[155]

The beneficial effects of curcumin administration have also been reported to act through improving intestinal barrier function. Preclinical studies have demonstrated that curcumin can have a positive effect on intestinal barrier permeability by reducing gene expression of pro-inflammatory cytokines and reducing cell disruption by LPS-induced secretion of leukotrienes and macrophages.[156] In rats fed a high-fat diet, curcumin supplementation restored intestinal barrier function and expression of tight junction proteins.[155]

Results from a human clinical trial suggest that curcuminoids found in turmeric modulate the composition and population of the gut microbiota, potentially offering health benefits to the host. Curcumin C3 Complex® (1g daily) and turmeric supplementation increased bacterial species diversity in healthy subjects by 69% and 7%, respectively, compared to placebo, which had a 15% reduction. The authors concluded that turmeric exerted a prebiotic effect due to catabolism of polysaccharides present in the plant's root. However, curcumin cannot serve as a direct energy source for commensal microbiota and thus does not fully meet the definition of prebiotic. Therefore, its prebiotic-like effects are expected to be primarily driven by indirect effects based on alterations in host physiology, which may include changes in barrier function or through selective survival of local gut bacteria.[152]

Irritable bowel syndrome

The aetiology of IBS is multifactorial, involving low-grade inflammation, intestinal dysbiosis, HPA-axis dysregulation, neuroendocrine alterations, and visceral hypersensitivity. These factors result in the hallmark symptoms of abdominal pain and disordered gut motility.[157] With its antioxidant and anti-inflammatory activities and ability to modulate gut microbiota, curcumin is emerging as a potential therapeutic agent for the treatment of IBS. Furthermore, in a rat model of IBS, curcumin was able to exert beneficial effects via the gut-brain axis. Curcumin administration increased serotonin (5-HT), BDNF and phosphorylation of cAMP response element-binding protein (pCREB) expression in the hippocampus and colon.[158] A recent meta-analysis based on three studies and 326 patients found curcumin to have a beneficial, albeit not statistically significant effect on IBS symptoms.[159]

Peptic ulcer / *Helicobacter pylori*

Helicobacter pylori is a common cause of inflammation of the

gastric mucosa, otherwise known as gastritis and peptic ulcers. The inability of the host to clear infection results in a chronic inflammatory state with continued oxidative stress within gastric tissue. ROS produced by the immune system and epithelial cells cause lipid peroxidation and DNA damage, which can eventually lead to gastric cancer.[160]

Evidence from *in vitro* and animal studies has demonstrated the inhibitory effect of curcumin on *H. pylori*, due to its potent antioxidant, anti-inflammatory, antibacterial, biofilm-disrupting and immunomodulatory properties.[161-164] However, results from human clinical trials are mixed.

As a monotherapy, curcumin for four weeks at 2100mg daily, caused very low eradication rate and had a limited effect on the production of inflammatory cytokines compared to triple antibiotic therapy in *H.pylori*-infected patients.[165] Curcumin C3 Complex® (500mg daily) as an adjunct to the standard anti-*helicobacter* regimen in patients with peptic ulcer improved dyspepsia symptoms but did not enhance the eradication rate of *H.pylori* infection.[166] In an RCT, administration of curcumin as an adjunct to triple therapy for four weeks reduced the level of MDA, DNA oxidative damage, endoscopic and chronic inflammation scores and glutathione peroxides in gastritis patients. Curcumin additionally increased the eradication rate compared to triple therapy alone.[167] Curcumin (1-3g per day) administration for up to 12 weeks, reduced or even eradicated ulcers and erosions, and markedly decreased abdominal pain and discomfort.[168,169]

Curcumin and reproductive health

The wide variety of premenstrual syndrome (PMS) presentations suggests that multiple causative factors play a role, consisting of an overlapping and complex interplay of hormonal, endogenous opioid peptides, neurotransmitters and prostaglandins in the circadian, peripheral, autonomic and endocrine systems. Some studies have also found a correlation between circulating serum BDNF levels and PMS symptoms.[170,171]

Daily supplementation of 200mg curcumin for 10 days during three consecutive menstrual cycles significantly reduced overall PMS severity as assessed by a composite measure of emotional, behavioural and physical symptoms. Serum BDNF levels in the curcumin group were also significantly higher than placebo in all cycles.[172,173] The therapeutic benefit of curcumin supplementation on PMS symptoms is, therefore, possibly mediated via the modulation of neurotransmitters and BDNF, and its anti-inflammatory effects.[172,173]

In vitro and animal studies have shown that curcumin has potential benefit for the prevention and treatment of endometriosis through its ability to suppress inflammatory cytokine expression, and inhibit invasion, attachment and angiogenesis of endometrial lesions. In women with endometriosis, the apoptosis of the eutopic and ectopic endometriotic cells is lower; thus, curcumin can exert a positive effect due to its ability to induce cell cycle arrest and apoptosis.[174]

Curcumin and ophthalmology

Due to its angiogenesis-modulating and anti-inflammatory properties, curcumin has potential in the treatment of inflammatory and neovascular proliferative diseases of the retina.[175] Experimental data has demonstrated a potential therapeutic role in eye disorders such as allergic conjunctivitis, glaucoma, macular degeneration and diabetic retinopathy.[176] Three clinical studies have investigated the anti-inflammatory effects of curcumin in chronic anterior uveitis and inflammatory orbital pseudotumour.[177-179]

Studies on patients with chronic anterior uveitis demonstrated marked symptom improvements in all treated patients[178] and reduced eye discomfort and number of relapses[179] after oral curcumin intake for 12 weeks and 18 months, respectively. Also, five patients with idiopathic inflammatory orbital pseudotumour, treated orally with curcumin (375mg, three times a day) for six–22 months, showed regression of inflammatory signs at subsequent follow-ups performed every three months for two years. Five patients completed the study, out of which four recovered completely.[177]

Allergy and atopy

Curcumin exerts anti-allergic effects by modulating mast cell release of histamine and inhibiting the release of pro-inflammatory mediators that affect IgE synthesis and eosinophil function.[180] In a randomised, double-blind, placebo-controlled, clinical trial of 241 patients with perennial allergic rhinitis, 500mg daily of curcumin for two months was found to relieve nasal symptoms, including sneezing, itching, rhinorrhoea and obstruction, and significantly increased nasal airflow from baseline. Curcumin was found to modulate the immune response by suppressing of inflammatory cytokine production.[181]

In animal studies, turmeric and curcumin have been shown to attenuate airway inflammation and hyper-responsiveness; however, there have been few human clinical studies in asthma.[182,183] Curcumin (2g per day) for six months was not beneficial for atopic asthma in a small controlled trial.[184] However, in a larger clinical trial, 1000mg of curcumin daily for 30 days as an adjunct therapy in subjects with mild to moderate bronchial asthma produced significant improvements in the pulmonary function test measure FEV1.[185]

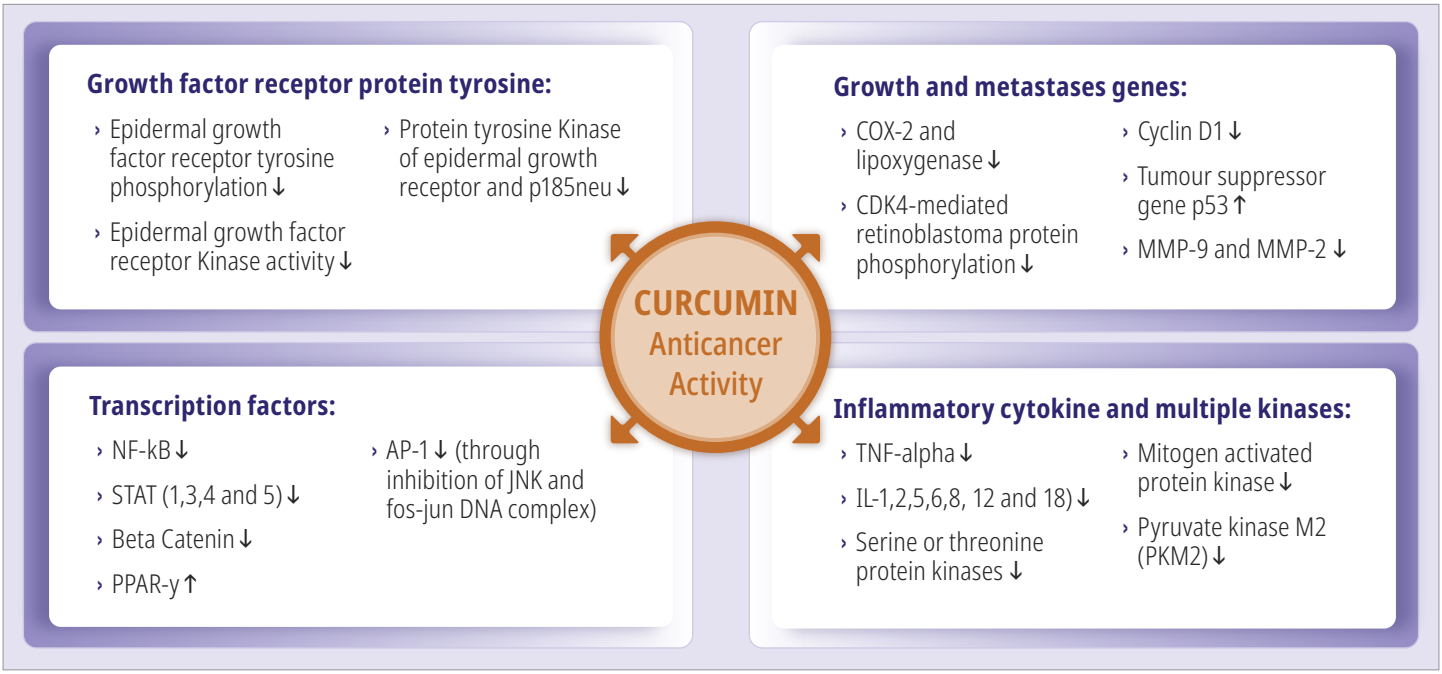
In a recent randomised, double-blind, placebo-controlled trial of children and adolescent asthmatics, 30mg/kg/day powdered turmeric root for six months reduced the frequency of nighttime awakenings, and use of short-acting β-adrenergic agonists. Supplementation also produced better disease control after three and six months when compared to placebo.[186]

Genetic disorders

Beta-thalassemia

Beta-thalassemia (β-thalassemia) is the most common hereditary anaemia, characterised by a genetic deficiency in the synthesis of haemoglobin β-globin chains. Iron overload, the main complication of

Figure 5: The main molecular targets of curcumin in cancer cells (↑) Increase; (↓) Decrease; MMP Matrix metalloproteinase; AP-1: Activation protein-1[201]



β-thalassemia major, results from ineffective erythropoiesis leading to a compensatory decrease in hepcidin expression and the resulting increase in intestinal iron absorption.[187] Iron overload and oxidative stress also arises when repeated blood transfusions are required. Due to its antioxidant and potential iron-chelating properties, curcumin has been researched as an adjunct therapy in β-thalassemia major.[96,187,188]

In a 12 month pilot study, 500mg of curcumin daily was shown to reduce oxidative stress in β-thalassemia/Haemoglobin E patients as indicated by decreased methemoglobin (MHb), SOD, red blood cell MDA, glutathione peroxidase (GSH-Px), serum ferritin and serum non-transferrin bound iron (NTBI), and increased glutathione (GSH) levels. However, curcumin did not have any effect on haematological parameters, liver and kidney function tests and lipid profiles.[189]

In a subsequent study, 12 weeks supplementation with 1000mg daily of curcumin with deferoxamine significantly reduced total and direct bilirubin, and improved antioxidant status in β-thalassemia major patients as indicated by reduced serum MDA levels, and increased total antioxidant capacity.[188] A recent investigation of curcumin's effect on iron overload, hepcidin level and liver function in β-thalassemia major patients, demonstrated that 12 weeks curcumin supplementation (1000mg daily) was able to alleviate iron burden and liver dysfunction by reducing nontransferrin-bound iron, ALT and AST levels.[187]

Cancer

Normal cellular behaviour is controlled by a complex network of signalling pathways, which ensures that the proliferation of cells occurs only when physiologically required, such as in wound repair or growth and development. Cancer occurs when normal growth regulation breaks down, usually due to defects in signalling mechanisms and is a state of unusual, uncontrolled cell growth.[190]

Conventional treatments for cancer, including surgery, chemotherapy, and radiotherapy, are associated with numerous limitations including drug resistance, drug availability and expense, poor outcomes and high risk of relapse. In light of these limitations, research has focused on the molecular mechanisms underpinning cancer initiation and progression and the presence of genetic alterations in the cell cycle. Numerous molecular abnormalities have been found in malignant conditions and targeting such aspects presents a novel approach to cancer treatment.[191]

Curcumin represents a promising candidate as an effective anticancer drug to be used alone or in combination with other medications. It affects different signalling pathways and molecular targets involved in the development of several cancers (see Figure 5). It suppresses transformation, proliferation, inhibits metastasis of tumours and induces apoptosis through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes.[192] The chemoprotective and anti-tumour activities of curcumin have been extensively studied *in vitro* and animal models since 1985.[192] There have been several clinical studies carried out in human subjects to evaluate the efficacy and safety of curcumin treatment in different types of cancer, either alone or in combination with other chemotherapy agents.

The efficacy of curcumin in the treatment of pancreatic cancer was investigated in a non-randomised, open-label, phase II clinical trial.[193] In this study, 25 patients with histologically confirmed pancreatic adenocarcinoma were treated with Curcumin C3 Complex® at 8g daily for eight weeks. The patients did not receive any chemotherapy or radiotherapy from four weeks before commencing the trial and also during the trial. Only two patients showed a clinical, biological response to curcumin therapy; however, curcumin down-regulated the expression of NF-κB, COX-2, and pSTAT3 (a molecule implicated in tumorigenesis and chemoresistance) in peripheral blood mononuclear cells obtained from patients.

In a randomised, double-blind, placebo-controlled trial, colorectal patients receiving curcumin (360mg twice daily) showed a significant reduction in the serum levels of TNF-α. In contrast, no such effect was observed in the placebo group.[194] The number of apoptotic cells was increased after treatment with curcumin compared to baseline values, whereas no significant change was observed in the placebo group. Furthermore, curcumin supplementation upregulated expression of p53 molecule in tumour tissue and modulated apoptosis-related Bax and Bcl2 molecules in cancer cells.

Carroll et al. (2011) carried out a non-randomised, open-label clinical trial to assess the effects of oral curcumin in the prevention of colorectal cancer in smokers with aberrant crypt foci (ACF).[195] Participants were given either 2g or 4g daily of curcumin for 30 days, and the levels of PGE2 and 5-hydroxyeicosatetraenoic acid (5-HETE) within ACF were assessed, as well as the reduction in the number and/or proliferation of ACF. ACF reduction is used to determine the chemopreventative potency of compounds. Curcumin at either 4g or 2g per day for 30 days did not reduce concentrations of PGE2 (the primary endpoint) or 5-HETE in ACF or normal flat mucosa. However, a daily dose of 4g curcumin resulted in a significant 40% reduction in ACF formation. Serum curcumin was measured although it was not detected. However, the ACF reduction in the 4g group was associated with a significant, five-fold increase in post-treatment plasma conjugate levels from baseline. The treatment-related increase in conjugate concentrations in plasma suggests that the ACF reduction resulted from systemic rather than local delivery of conjugates.

A phase I study investigated increasing doses of curcumin in patients with metastatic or locoregionally recurrent advanced breast cancer.[196] Docetaxel (100mg/m2) was administered intravenously every three weeks for six cycles. Oral curcumin was given from 500mg daily for seven consecutive days by cycle (from five days before to two days after administration of docetaxel) and escalated until dose-limiting toxicity occurred (8000mg daily). In terms of clinical responses, some degree of improvement was observed in most patients, with five patients showing partial response to treatment and three patients having stable disease at least six weeks after the last cycle of treatment. No disease progression was observed in any of the patients. Moreover, curcumin/docetaxel combination significantly decreased the levels of VEGF after three cycles of treatment.[196]

Radiation dermatitis occurs in approximately 95% of patients receiving radiotherapy for breast cancer. Oral supplementation with 6g of Curcumin C3 Complex® daily during radiotherapy was shown to reduce the severity of radiation dermatitis as indicated by Radiation Dermatitis Severity (RDS) score, and fewer curcumin-treated patients (28.6%) had moist desquamation compared to placebo (87.5%). Erythema was not improved in either arm.[197]

Curcumin has been investigated in two clinical trials for monoclonal gammopathy of undetermined significance (MGUS)[198] and smouldering myeloma (SMM),[99] which can progress to multiple myeloma. Serum paraprotein (PP) levels have been associated with an increased risk of MGUS progression.

Oral supplementation with 4g daily of Curcumin C3 Complex® decreased paraprotein load, whereas PP levels remained steady or increased in the placebo arm.[198] Curcumin patients also had a decrease in their urinary cross-linked N-telopeptide of type I collagen (uNTx) levels, a highly specific marker of osteolysis. In a second study, 4g and 8g of Curcumin C3 Complex® decreased bone resorption markers and serum creatinine, suggesting that curcumin might have the potential to slow the disease process in patients with MGUS and SMM.[199]

Clinical summary

Curcumin represents a core consideration for practitioners seeking supplemental support for the management of chronic health conditions associated with inflammation and oxidative stress, particularly given its high safety and tolerability profile.

For reliability of clinical outcomes, primary consideration should be given to the evidence that supports a particular material over absorption alone. Increased 'bioavailability' does not directly translate to increased clinical efficacy.

Dosage, safety and clinical tips

Dosing: The daily dosage of oral curcumin in clinical trials has ranged from 0.2g - 12g daily. High doses have proven safe in a number of clinical trials with limited side effects (such as transient gastrointestinal discomfort). Most commonly, studies reporting positive results have employed doses between 100mg and 4g of either curcumin or mixed curcuminoids.

Timing: There is no clear indication from the literature to date that curcumin needs to be given with or away from food. Theoretically as a fat soluble compound, absorption may be enhanced with a fat containing meal.

Adverse effects: Clinical studies indicate that curcumin is well tolerated with no serious side effects. In a dose escalation trial, single oral doses of 12g were safe, and minor adverse effects including diarrhoea and headache were not related to dose.[7] In another Phase I trial in patients with precancerous conditions or noninvasive cancer, 8g of curcumin daily for three months was well tolerated.[200] Some individuals may experience gastrointestinal upset, such as nausea, abdominal pain and diarrhoea, and require lower doses of curcumin.

Contraindications: Curcumin is contraindicated in bile duct obstruction and caution is advised in gallstones, as a single dose of curcumin (20mg) stimulated gallbladder contraction in healthy volunteers.[201]

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