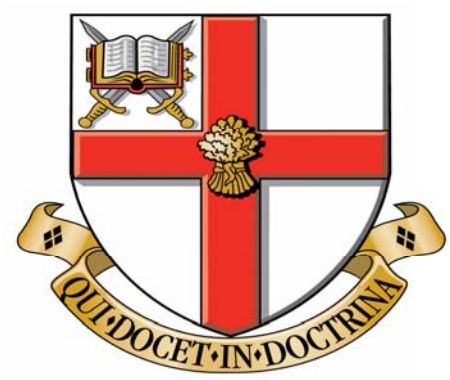

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Declaration

'This work is original and has not been submitted previously in support of a degree qualification or another course'.

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Portfolio Contents

Curcumin and its role in autoimmune disease

Literature review

Abstract

Autoimmune disease is responsible for a considerable disease burden worldwide. There is an increasing interest in the development of nutritional supplements that contain naturally-occurring plant compounds able to alleviate the symptoms associated with autoimmune disease. One such compound is curcumin, the main active component of turmeric (*Curcuma longa*), which has been shown to possess anti-oxidant and anti-inflammatory properties.

This paper reviews evidence for the positive effects of curcumin on the symptoms of five autoimmune diseases: scleroderma, multiple sclerosis, psoriasis, inflammatory bowel disease and diabetes mellitus, including evidence from in-vitro, animal and human clinical studies.

Evidence supports curcumin as being able to positively influence the symptoms of these five autoimmune diseases, although there are relatively few published human clinical trials to provide clear evidence for its effects and studies taking a nutritional standpoint are even fewer. Considerable variation exists in trial design, including but not limited to the use of blinding, randomisation and controls, highlighting the need for a systematic review approach to be implemented in future. Such an approach would critically select and assess published and unpublished evidence and enable more concrete conclusions to be established about the efficacy of curcumin as a nutritional supplement for treating autoimmune disease.

Introduction

Segen's Medical Dictionary defines autoimmune disease as: "The reaction of a host organism's immune system to self-antigens as if they were foreign. It is characterised by T-cell activation, clonal expansion and antibody production against tissues, cells and antigens, which results in autoimmune disease" (Segen, 2006, p.765).

One phytonutrient rapidly gaining interest amongst the nutritional community as a therapeutic agent in autoimmune disease is curcumin, the primary curcuminoid found in turmeric (*Curcuma longa*) giving this popular spice its golden colour. Evidence continues to grow about the positive impact curcumin can have on chronic inflammatory processes, owing to its anti-oxidant (Srinivasan, 2012) and anti-inflammatory properties (Jurenka, 2009). Mechanistic studies have revealed its effects on several important molecular targets (Shishodia, Sethi, & Aggarwal, 2005), including:

- Transcription factors, such as NF-κB - a protein responsible for cytokine production and cell survival, the incorrect regulation of which has been linked to inflammatory and autoimmune diseases
- Enzymes involved in the inflammatory cascade such as COX-2, 5-LOX, and iNOS
- Inflammatory cytokines (e.g., Tumour necrosis factor (TNF), Interleukin (IL)-1, IL-6, and chemokines)
- Cell surface adhesion molecules, they allow immune cells to infiltrate tissue and are therefore involved in initiation and propagation of autoimmune diseases.

This paper investigates the evidence for the link between supplementation with curcumin (or its derivatives) and a reduction in inflammatory processes and oxidative damage in relation to five important autoimmune diseases: scleroderma, multiple sclerosis, psoriasis, inflammatory bowel disease and diabetes mellitus. To this end, this review brings together evidence from human trials, in-vivo and ex-vivo animal models and in-vitro studies to provide a complete picture of the mechanisms by which curcumin can aid in the treatment of autoimmune disease.

Scleroderma

Scleroderma is an autoimmune disease associated with a hardening of the skin, typically affecting the face, arms and hands and characterised by increased synthesis of collagen leading to blood vessel damage and connective tissue complications. Scleroderma may also affect internal organ function in severe cases (Gabrielli, Avvedimento, & Krieg, 2009).

An in-vitro study by Song, Peng, Sun, Li, and Yang (2011) investigated the effect of curcumin on TGF-β signalling, a key factor in the fibrotic process. Curcumin was shown to counteract TGF-β-induced phosphorylation of Smad2. This was related to the up-regulation of fibroblast activity, which potentiates scleroderma. Further study revealed curcumin works by inducing up-regulation of TGF-β-induced factor (TGIF), a protein responsible for the down-regulation of TGF-β.

In addition, cell line work by Tourkina et al. (2004) showed that normal lung fibroblasts have a protective pathway against curcumin-induced apoptosis whereas curcumin causes apoptosis in scleroderma lung fibroblasts (SLF). This was linked to SLF

having reduced levels of the phase 2 detoxification enzyme GST P1 and its regulator protein kinase C. This suggests that curcumin could be useful therapeutically for limiting the progression of fibrosis in scleroderma, but in-vivo studies are needed to clarify this effect.

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated disease in which T-cells become sensitised to attack and damage certain cellular structures within the central nervous system (CNS) (Poser et al., 1983). Cellular structures targeted include myelin, oligodendrocytes, and the underlying nerve fibres (Steinman, 2001). Research suggests that turmeric has neuroprotective and anti-inflammatory properties and this has led to interest in whether curcumin could help to block the progression of MS (Xie, Li, & Takahara, 2011).

In laboratory tests, mice were bred with an experimental autoimmune encephalomyelitis (EAE), a syndrome with symptoms closely resembling those of MS. By combining in-vivo and in-vitro experimentation, Natarajan and Bright (2002) demonstrated that curcumin inhibited EAE symptoms in mice. In vivo curcumin inhibited EAE, detected by a decrease in IL-12 production from macrophage/microglial cells and differentiation of neural Th1 cells. In-vitro curcumin inhibited IL-12-induced tyrosine phosphorylation of Janus kinase 2, tyrosine kinase 2, and STAT3 and STAT4 transcription factors. The inhibition of the Janus kinase-STAT pathway by curcumin resulted in a decrease in IL-12-induced T cell proliferation and Th1 differentiation.

Mice with EAE have also been shown to have increased expression of Toll-like receptors (TLRs) in their T-cells, and in-vivo work by Chearwae and Bright (2008)

demonstrated that curcumin administration significantly decreases TLR expression on these cells and improved EAE symptoms.

Although EAE was previously considered to be mediated by Th1 cells, a number of recent studies provided strong evidence that T helper cells that produce IL-17 may play a dominant role. Xie et al. (2009) looked at the mechanism for curcumin activity against EAE in rats. They found curcumin significantly reduced the clinical severity of EAE in-vivo, the number of inflammatory cells infiltrating the spinal cord and the proliferation of the MBP-reaction lymphocytes. There was also a dramatic decrease in mRNA expression of IL-17, TGF-β, IL-6, IL-21, STAT3, and RORgammaT expression, factors involved with the inflammatory process. They suggested that a key pathway in the curcumin amelioration of EAE was its ability to inhibit differentiation and development of Th17 cells by down-regulating the expression of IL-6, IL-21, RORgammaT signaling and inhibiting STAT3-phosphorylation. The authors therefore proposed curcumin may have therapeutic benefit in the treatment of MS and other Th17 cell-mediated inflammatory diseases.

More recently, Kanakasabai et al. (2012) showed that EAE mice had elevated levels of interferon (IFN) γ and IL-17 in their CNS and lymphoid organs and also higher levels of IL-12 and IL-23. Curcumin administration resulted in decreased secretion of IFN-γ, IL-17, IL-12 and IL-23 in culture. Curcumin also up-regulated IL-10, peroxisome proliferator-activated receptor γ and CD4(+), CD25(+-), Foxp3(+) Treg cells in the CNS and lymphoid organs. This once again demonstrated the anti-inflammatory properties of curcumin and provides support for further research into its use as a nutritional therapeutic supplement for treating MS autoimmune symptoms.

Although the above studies provide in-vivo evidence for the potential therapeutic actions of curcumin, animals disease differs from human disease both physiologically and biochemically, and therefore evidence obtained from non-human trials may have limited clinical applicability. To date there have not been any randomised controlled studies in humans with MS, although some studies using human cell line cultures have been performed. Lian et al. (2013) looked at how curcumin is able to inhibit proliferation and proinflammatory cytokine secretion of effector memory T-cells (T(EM) cells) isolated from human samples. Their results showed that the pathway for this inhibition was through the direct blockage of human Kv1.3 channels, potassium channels involved in T-cell activation and proliferation. It was suggested that this pathway could be one of the pharmacological mechanisms by which curcumin could be used to treat autoimmune disease.

Axon degeneration is another key feature of MS (Steinman, 2001). Autoimmune activity leading to the destruction of the insulating myelin sheath is considered to be the primary cause of MS pathology, but there is increasing evidence for axonal degeneration independent of autoimmune demyelination processes (as reviewed by Haines, Inglese, and Casaccia (2011)). In-vitro work by Tegenge et al. (2014) demonstrated that neuroinflammation induced by the stimulation of human microglia with lipopolysaccharide (LPS; a major component of the cell wall of Gram-negative bacteria) resulted in axonal degeneration via the activation of MyD88 and the p38MAPK signalling pathways, the production of nitric oxide and involved c-Jun N-terminal kinase (JNK) phosphorylation. Since curcumin acts as both an antioxidant and a JNK inhibitor the authors proposed that curcumin may have a role in protecting against such axon degeneration, but clinical trials in

human cohorts are needed to establish whether curcumin supplementation can result in these positive effects in MS patients.

Psoriasis

Psoriasis is a common skin condition caused by an accelerated skin cell (keratinocyte) turnover and defects in skin cell apoptosis, which together result in an accumulation of skin cells and the formation of the psoriatic plaques characteristic of the most common form, Psoriasis vulgaris (Lowes, Bowcock, & Krueger, 2007). Psoriasis is frequently referred to as a T-cell-mediated disease since it is the excessive production of inflammatory mediators and growth factors by T-cells that initiate and propagate the disease, and the disease is responsible for a considerable health burden worldwide (Rapp, Feldman, Exum, Fleischer, & Reboussin, 1999).

Sun, Han, Zhao, Zhu, and Hu (2012) recently investigated the effect of curcumin on the induction of apoptosis in TNF-α-treated immortal keratinocyte cells. They concluded that curcumin has the ability to reverse the defective apoptosis function in this in-vitro model of psoriasis. More recently, the same authors reported that topical use of a curcumin gel formulation strongly inhibited imiquimod -induced psoriasis-like inflammation in mice (Sun, Zhao, & Hu, 2013). These beneficial changes were related to changes in the IL-23/IL-17A cytokine axis, which plays a critical role in the pathogenesis of psoriasis. Results showed that epidermal hyperplasia and inflammation in the ears of affected mice was inhibited following treatment with curcumin gel, whilst cellular examination showed that the expression of the inflammatory mediator cytokines IL-17A, IL-17F, IL-22, IL-1β, IL-6 and TNF-α was decreased.

Topical treatment has however not yet progressed to the clinical trial stage in humans and as a means of application differs significantly from supplementation via the oral route. In terms of oral curcumin application, the only human clinical trial for psoriasis showed limited results due to a poor design. Kurd et al. (2008) conducted a phase II, open-label, Simon's two-stage trial of 4.5 g/day of oral curcuminoid C3 complex in patients with plaque psoriasis. The intention-to-treat analysis response rate was 16.7% (95% confidence interval: 2%, 48%), but the small cohort of just eight subjects and the wide confidence interval meant that observed improvements in the symptoms of study subjects could have resulted from a placebo effect or the natural resolution of psoriasis rather than as a result of the activity of the curcumin. Therefore larger, preferably placebo-controlled clinical trials are needed before the efficacy of curcumin supplementation for psoriasis can be confirmed.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an umbrella term used to describe a group of autoimmune inflammatory conditions of the colon and small intestine (Hanauer, 2006). The two most common diseases in this category are Crohn's disease (CD) and Ulcerative Colitis (UC). IBD appears to be driven by inflammatory cytokines such as TNF-α, a major target for conventional therapies (Peyrin-Biroulet, 2010), and thus there is a strong interest in agents such as curcumin that can block the generation or actions of such pro-inflammatory cytokines.

In a 2009 study, Arafa, Hemeida, El-Bahrawy, and Hamada (2009) induced ulcerative colitis in rats by the administration of dextran sulfate sodium. Biochemically this was seen as elevated levels of serum TNF-α, increased colonic activity of myeloperoxidase, increased levels of lipid peroxidation and total nitric oxide, whilst colonic glutathione-S-transferase

activity and the concentration of its substrate glutathione were reduced. Rats that were given curcumin orally at 100mg/kg for seven days prior to DSS administration did not demonstrate these biochemical changes.

Curcumin has also been shown to have a protective role in mouse models of IBD and in human cell lines. In a recent study by Larmonier et al. (2011) curcumin was shown to specifically weaken LPS-stimulated expression and secretion of macrophage inflammatory protein (MIP)-2, IL-1β, keratinocyte chemoattractant and MIP-1α in colonic epithelial cells and in macrophages. Curcumin was also shown to significantly inhibit neutrophil chemotaxis. This inhibition of neutrophil motility was attributed to a down-regulation of PI3K activity, AKT phosphorylation, and F-actin polymerisation.

Ex-vivo, curcumin has also been shown to suppress p38 mitogen-activated protein kinase activation, reduce IL-1β and matrix metalloproteinase-3 and enhance IL-10 in mucosal cells from children and adults with inflammatory bowel disease (Epstein, Docena, MacDonald, & Sanderson, 2010).

Similarly, Motawi, Rizk, and Shehata (2012) carried out experiments on rats which demonstrated that curcumin led to reduced levels of inflammation. This was determined by looking at myeloperoxidase, matrix metalloproteinase activity, metalloproteinase-1 inhibitor, nitric oxide, hydroxyproline, TNFα, ceruloplasmin, and histopathological scoring. These measured parameters were all lower in the treated group than in the IBD rats.

In a 2005 trial, Holt, Katz, and Kirshoff studied five CD and five ulcerative proctitis patients. All the participants were given a pure curcumin preparation in an open label trial. The severity of symptoms was reduced in all the proctitis participants and four out of five

were able to reduce their intake of medication. Using the Crohn's Disease Activity Index as a benchmark, four out of five CD patients had lower scores after the curcumin treatment, while blood test results indicated reductions in inflammation.

Later studies have adopted the more robust randomised double-blind trial methodology with work showing that curcumin can uphold remission in patients with quiescent UC (Hanai et al., 2006). Eighty-nine UC sufferers in remission participated: one group of 45 patients received 2g of curcumin daily as a split dose, in addition to their normal anti-inflammatory medication that was either sulfasalazine or mesalamine. In the other group, 44 patients received a placebo treatment in addition to their normal medication. The trial ran for six months. The outcomes measured included clinical activity index (CAI) and endoscopic index (EI) at entry and every two months up to the end of the trial. Overall, seven people dropped out of the trial and 4.65% relapsed in the curcumin group compared to 20.51% in the placebo group. Intention-to-treat analysis showed the difference between the active and placebo groups to be statistically significant (P=0.049). Curcumin was also shown to statistically significantly improve both CAI (P=0.038) and EI (P=0.0001) scores.

Similarly, in a small contemporary pilot study by Suskind et al. (2013), eleven paediatric patients, six with CD and five with UC, were recruited in order to determine the benefits of curcumin on measures of disease activity. All patients received curcumin in addition to their usual drug regime. The starting dose of curcumin was 500mg twice per day for three weeks; from weeks three-six the dose increased to 1g twice a day, and then at week six the dose increased to 2g twice per day. Disease activity was assessed at weeks three, six and nine using the Paediatric Ulcerative Colitis Activity Index (PUCAI), the Paediatric Crohn's Disease Activity Index (PCDAI) and the Monitoring of Side effects system

score. The only adverse symptom reported was gassiness; two patients only reported this. Three patients saw improvements in their disease activity scores.

Curcumin enemas have also been investigated in a double-blind, single-centre pilot trial by Singla et al. (2014). Forty-five patients with mild to moderate UC were randomised to either receive a standardised curcumin enema plus their normal mesalazine anti-inflammatory, or a placebo enema plus the mesalazine. Improvements were seen in 56.5% of the curcumin group compared to 36.4% in the control group. By week eight, remission was observed in 43.4% of participants in the curcumin group in comparison to 22.7% in the placebo group. Similarly, 52.2% of participants in the curcumin group showed endoscopic improvements compared to 36.4% of patients in placebo group. Per protocol analysis revealed significantly better clinical response outcomes in the curcumin group (92.9% vs. 50%, p=0.01), clinical remission (71.4% vs. 31.3%, p=0.03), and improvement on endoscopy (85.7% vs. 50%, p=0.04).

However, curcumin is known to have poor bioavailability (Anand, Kunnumakkara, Newman, & Aggarwal, 2007). This has led to interest in novel delivery systems such as solid lipid micro particles (SLM) for curcumin in the treatment of diseases. A 2009 trial by Yadav, Suresh, Devi, and Yadav measured the effectiveness of different formulations for curcumin delivery and monitored anti-angiogenic and anti-inflammatory activity using chick embryo and rat colitis models. The particle with the best delivery contained one part stearic acid and 0.5% surfactant, with the smallest diameter of 108 micrometers. This SLM proved to be a potent angio-inhibitory compound. In addition, rats treated with the curcumin SLM complex showed a faster weight gain compared with control rats and increases in whole colon length appeared to be significantly greater in SLM-treated rats when compared with pure curcumin

and control rats. The results also highlighted that rats treated with either curcumin or the SLM had fewer mast cells in the colonic mucosa.

Recently Claramunt et al. (2009) studied the effects of seven N-unsubstituted curcuminoid pyrazoles on the activity of matrix metalloprotease 9 (MMP-9). Their in-vitro study revealed that these compounds beneficially down-regulated MMP-9 activity in inflamed intestinal cells. This suggests that n-pyrazole curcumin derivatives should be further investigated for the treatment of IBD.

Another area of research has focused on combining curcumin in nanoparticles with medication. Gugulothu et al. (2014) formulated pH-sensitive nanoparticles of curcumin-celecoxib combination as a potential therapy for UC. Trials in a rat model of UC showed that the curcmuin-drug combination was more efficacious than nanoparticles of either component separately or in suspension. Sareen, Jain, Rajkumari, and Dhar (2014) build on this delivery system technology with their work on pH-triggered Eudragit-coated chitosan microspheres of curcumin. These were tested in a mouse model of colitis, where reduction in severity and extent of colonic damage with curcumin-loaded microspheres as compared to pure curcumin was confirmed by histopathological study. Further trials are now needed in humans to confirm these effects.

Diabetes

Diabetes mellitus (DM) is a metabolic condition affecting blood sugar levels and whose progression is associated with detrimental vascular changes, increased risk of cardiovascular disease and many other complications, which makes its increasing global prevalence a serious cause for concern (Freeman, 2010). DM is classically separated into

two forms, Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) (Alberti & Zimmet, 1998). T1DM is a T cell-mediated autoimmune disease that selectively destroys pancreatic β cells, requiring as treatment frequent injections with insulin; the only possible cure is to control autoimmunity against β cell-specific antigens (Daneman, 2006). In contrast T2DM involves insulin insensitivity, often associated with lifestyle factors such as a poor diet and obesity and may be controlled by careful dietary and exercise management without the need for insulin injections (Olokoba, Obateru, & Olokoba, 2012; Tuomilehto et al., 2001). Despite this split in classification between the two forms of DM, recent evidence has indicated that autoimmunity may play a significant role in T2DM as well (Velloso, Eizirik, & Cnop, 2013). Thus researchers have become interested in the therapeutic value of curcumin as a potential nutritional supplement for the treatment for the autoimmune pathology associated with DM in both forms of the disease.

Initial studies focused on the effects of curcumin on conventionally monitored diabetes parameters such as blood sugar and insulin levels. Gutierres et al. (2012) used a rat model of diabetes to investigate the effects of a curcumin supplement in yogurt. Diabetic rats were subdivided into three groups and administered curcumin and yogurt by gavage at three doses of curcumin: 30, 60 and 90 mg/kg bodyweight for 31 days. The authors also established a number of control groups. One group of non-diabetic rats was also treated with 90 mg/kg bodyweight per day curcumin. Three control groups of diabetic animals received water, yoghurt or insulin at 27·78 μmol/day by subcutaneous injection. Two groups of non-diabetic animals received water or yoghurt. Insulin treated rats and the diabetic rats receiving 90mg of curcumin per day exhibited falls in food and water intake, urine volume, blood sugar, urinary glucose, proteinuria, triglycerides and higher hepatic glycogen and body

weight relative to the diabetic rats receiving just water or yogurt. There were also improvements in liver enzyme results. The improvements were greater in the insulin-treated diabetic rats compared to the curcumin-treated ones. No differences were observed in the serum levels of total cholesterol, high-density lipoprotein (HDL)-cholesterol, or in the masses of fat and muscular tissues between curcumin-treated diabetic rats and the diabetic rats fed just water or yogurt. Nonetheless, the improvements in curcumin-treated rats, relative to the diabetic rats given just water or yogurt, were significant and dose-dependent.

Similar studies have looked at how curcumin might protect against detrimental diabetes-induced changes in the vascular system and brain. Rungseesantivanon et al. (2010) tested the effects of curcumin on diabetes-induced endothelial dysfunction in the streptozotocin (STZ) treated rat model of diabetes. Oral doses of daily curcumin were started six weeks after the STZ injection. Six-weeks later arteriole responses were recorded in the mesenteric arteries of the rats and levels of superoxide and vascular protein kinase C (PKC-βII) were also examined. Arteriole dilation significantly decreased in the diabetic rats compared to the control rats and was significantly improved by both low and high doses (30 and 300 mg/kg, respectively) of curcumin. In addition superoxide production, which was significantly higher in the diabetic rats than in the control rats, was reduced by both the low and high doses of curcumin. Lastly, the higher dose of curcumin also diminished diabetes-induced PKC-βII expression. This enzyme is involved in endothelial cell proliferation and therefore the progression of atherosclerosis.

More recently, Wongeakin, Bhattarakosol, and Patumraj (2014) performed a similar study looking at diabetes-induced vascular dysfunction, this time looking at the effects of curcumin on Txnip, ICAM-1, and NOX2 enzymes. They used male Wistar rats for their

experiments and divided them into four groups. One group was kept as a control, one group was induced with diabetes, one group was treated with curcumin and the final group was induced with diabetes and treated with curcumin. After 12 weeks, iris blood perfusion, leukocyte adhesion, Txnip, p47phox, and malondialdehyde (MDA) levels were determined. The iris blood perfusion of both groups of diabetic rats, untreated and curcumin treated, was decreased significantly compared to the two control groups ($P < 0.001$). Plasma glucose and HbA1c were also significantly raised in the diabetic rats compared to the controls ($P < 0.001$). However, white blood cell adhesion, ICAM-1, p47phox expression, and MDA levels were increased in just the diabetic control rats compared to the healthy rats and the diabetic rats treated with curcumin ($P < 0.05$). Txnip expression in both groups of diabetic rats was significantly higher than the control groups ($P < 0.05$). A Pearson's analysis was used to confirm a correlation between the plasma MDA level and leukocyte adhesion ($r=0.705$), p47phox ($r=0.729$) and Txnip ($r=0.636$). The authors suggest that curcumin could reduce diabetic vascular inflammation by decreasing ROS overproduction, reducing leukocyte-endothelium interaction, and inhibiting ICAM-1 and NOX2 expression.

Franco-Robles et al. (2014) recently investigated the effects of curcumin on the following markers: protein oxidation (PO), lipid peroxidation (LP) and brain-derived neurotrophic factor (BDNF). These markers were tested in the brains of diabetic mice and in the blood of obese humans. Results showed decreased levels of BDNF compared to non-diabetic untreated mice. Curcumin also improved or restored BDNF levels to normal levels in diabetic mice, but hyperglycaemia and curcumin did not have an effect on LP levels in the mice brains. With respect to PO, hyperglycaemia increased PO levels in mice brains, whereas curcumin decreased this effect, specifically in the hippocampus. For the human

part of the study blood samples were taken at weeks 0, 2, 6, and 12. Curcumin did not have any effect on BDNF levels in the sera of obese humans. However, at a 500-mg dose, LP levels in weeks 6 and 12 were decreased when compared with basal levels, but the 750-mg dose of curcumin did not have any effect. However, both doses of curcumin decreased PO levels in weeks 2, 6 and 12 of treatment.

Chuengsamarn et al. (2012) performed a randomised, double-blind, placebo-controlled trial to ascertain the efficacy of curcumin in slowing down T2DM onset in a pre-diabetic cohort. The 240 human subjects were randomly assigned to receive either three capsules of curcumin or a placebo for nine months. Progression to T2DM was assessed by monitoring changes in beta-cell function, insulin resistance, C-peptide, adiponectin levels and other markers, three, six and nine months into the study. After nine months of treatment 16.4% of the placebo cohorts were diagnosed with type 2 diabetes compared with no diagnoses in the curcumin group. The curcumin treated cohort also showed better overall beta-cell function ($P < 0.01$) combined with lower C-peptide levels suggesting improved insulin sensitivity. The curcumin-treated group showed a lower level of insulin resistance measured as HOMA-IR ($P < 0.001$) and higher adiponectin ($P < 0.05$) when compared with the placebo group.

More recently, Chuengsamarn, Rattanamongkolgul, Phonrat, Tungtrongchitr and Jirawatnotai (2014) evaluated the effects of a curcuminoid on risk factors for atherosclerosis in T2DM patients. The participants were instructed to take three capsules containing either 250 mg of the curcuminoid or a placebo twice per day. Curcuminoid intervention significantly reduced pulse wave velocity (an atherosclerosis indicator), increased levels of serum adiponectin, and decreased levels of leptin, indicating a reduced risk of

atherosclerosis in patients with T2DM. At the last follow-up visit, the authors also noticed reductions in insulin resistance, triglycerides, uric acid, visceral fat and total body fat. Overall, this suggests that the curcumin intervention not only decreased atherogenic risk but also positively influenced the subjects' metabolic profiles.

A similar study by Na et al. (2012) assessed whether curcuminoids positively affect body weight, markers of glycemic control and blood lipid levels in diabetics. One hundred overweight or obese T2DM subjects were randomly assigned to receive either 300mg/day of curcuminoids or placebo for 3 months. Bodyweight, glycosylated hemoglobin A1c (HbA1c), serum fasting glucose, free fatty acids (FFAs), lipids, and lipoprotein lipase (LPL) were recorded. Curcuminoid supplementation significantly decreased fasting blood glucose levels ($p < 0.01$), HbA1c ($p = 0.031$), and insulin resistance index ($p < 0.01$). Curcuminoids also led to a significant decrease in serum total FFAs ($p < 0.01$) and triglycerides ($P = 0.018$), and increased LPL activity ($p < 0.01$). The authors commented that their findings suggest "a glucose-lowering effect of curcuminoids in type 2 diabetesT2DM, which is partially due to decrease in serum FFAs, which may result from promoting fatty acid oxidation and utilization".

Since curcumin has demonstrated lipid-lowering effects, there has been interest in investigating the safety of combining curcumin supplementation with standard diabetic drug regimes. Neerati, Devde, and Gangi (2014) combined curcumin with the sulfonylurea drug glyburide, which works by stimulating pancreatic insulin secretion. The aim was to investigate whether the curcumin would affect the pharmacokinetic and pharmacodynamics of glyburide and influence blood lipid levels. The open-label trial included eight T2DM subjects who were taking 5mg of glyburide daily. On the first day of the study, the subjects

took their glyburide medication as normal and blood samples were collected at various time intervals through the day to establish baseline markers for drug bioavailability and blood lipid levels. For the next 10 days the subjects were asked to take curcumin capsules in addition to their glyburide medication and blood sampling was repeated on day 11. Glyburide concentrations were shown to be changed at the second hour, but the maximum drug concentration was unchanged. Overall glucose levels were decreased, Area Under first Movement Curve (AUMC) was increased, but none of the patients experienced hypoglycaemia symptoms. Low-density lipoprotein, very-low-density lipoprotein and triglycerides were decreased significantly, and the high-density lipoprotein content increased. These results suggested that co-administration of curcumin capsules with glyburide may be beneficial to the patients in improving their glycaemic control. The lipid lowering and anti-diabetic properties of the curcumin demonstrate its potential as a drug to treat T2DM.

Curcumin may also inhibit processes involved in the initiation of autoimmune diabetes. Castro et al. (2014) investigated whether curcumin, via its antioxidant and anti-inflammatory properties, could down-regulate the T-cell response associated with destruction of B-cells in autoimmune diabetes. The authors used two different autoimmune diabetes models: (i) cyclophosphamide (CYP) administration to non-obese diabetic (NOD) mice and (ii) adoptive transfer of diabetogenic splenocytes into NODscid mice. Overall, their work highlighted that the administration of curcumin led to a marked delay in the onset of diabetes and in some cases stopped T1DM developing entirely by stopping pancreatic leukocyte infiltration, thus maintaining the presence of insulin-expressing cells. Investigation into underlying mechanisms revealed that curcumin: (1) modulates the T-lymphocyte

response impairing proliferation, (2) reduces nuclear factor (NF)-κB activation, (3) impairs the T-cell stimulatory function of dendritic cells and lowers surface expression of co-stimulatory molecules, leading to an overall diminished antigen-presenting cell activity and (4) reduces secretion of pro-inflammatory cytokines and nitric oxide. These effects correlated with ex-vivo analysis of cells obtained from curcumin-treated mice during the course of T1DM and the authors state that "these findings reveal an effective therapeutic effect of curcumin in autoimmune diabetes by its actions on key immune cells responsible for beta-cell death".

To address the issue of the bioavailability and therapeutic effectiveness of curcumin its natural form, Abdel Aziz et al. (2012) developed a water-soluble form of curcumin and tested its effects in rat models of diabetes. In particular, they were interested in investigating the role curcumin plays in the induction of heme-oxygenase-1 activity. They used a standard rat model of diabetes and key outcome measures including diabetes-induced reactive oxygen species and lipid peroxidation. The curcumin derivative was given orally for a 45-day period. Rats were divided into five groups: control, control plus curcumin, diabetic, diabetic plus curcumin and finally diabetic plus curcumin plus heme-oxygenase-1 inhibitor. After 45 days, fasting blood samples were taken before the animals were sacrificed so their pancreas, liver and aorta could be accessed. The curcumin derivative had a significant positive impact on blood sugar levels in the diabetic rats: plasma glucose dropped 27.5% and plasma insulin increased by 66.67%. The curcumin derivative was also found to increase insulin levels in the control rats without affecting plasma glucose, decrease lipid peroxides in all the organs studied and improve blood lipid profiles.

More recently Abdel Aziz et al. (2013) tested the effects of their novel curcumin derivative on pancreatic islet function in rat model of diabetes over 10 months. The diabetic rats given the novel curcumin derivative showed markedly lower plasma glucose and increased plasma insulin and C-peptide levels compared to the control rats. These built up to more significant improvements by month two. In fact, the plasma insulin and C-peptide continued to increase for ten months, reaching levels significantly higher than the baseline level. Curcumin-treated rats also showed improvement in beta-cell function with the appearance of primitive cell collections, large insulin positive cells and endoglin-positive cells in the adipose tissue infiltrating the pancreatic tissues. This was followed by the gradual appearance of insulin positive cells in the pancreas. However, there was a tendency to spontaneous recovery in the control group around four months into the study which means the effect of curcumin was less clear.

In terms of human studies, Steigerwalt et al. (2012) recently conducted a controlled trial in 38 diabetic subjects to determine whether Meriva®, a curcumin and soy lecithin adduct designed to improve bioavailability, could improve diabetic microangiopathy and retinopathy. Two tablets per day of Meriva® were administered (each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) for a period of at least four weeks in addition to the standard management plan, while a comparable group of 39 subjects followed the standard management plan alone. After four weeks, microcirculatory and clinical evaluations indicated an improvement in microangiopathy, a significant improvement in the venoarteriolar response ($p<0.05$) and a decrease in the score of peripheral oedema ($p<0.05$), a sign typically associated with the failure of the venoarteriolar response. Improvements were also seen in retinal blood flow, retinal oedema and visual

acuity in the Meriva treated patients, while no clinical or microcirculatory effects were observed in controls.

Conclusion

There is a considerable body of published evidence from in-vivo, ex-vivo, animal models and limited human studies showing that curcumin is able to have immunomodulatory effects that can lead to improvements in the symptoms associated with autoimmune conditions. However there are still considerable gaps in the current understanding of this area.

1.

No published studies have assessed how much curcumin, in its natural form as turmeric, is generally used for culinary purposes in different parts of the world, and whether curcumin at these levels is able to have positive effects on autoimmune disease.

2.

Is supplementation with curcumin (or its derivatives) more beneficial as a stand-alone nutritional aid or is it more effective when taken in conjunction with other naturally occurring compounds within the turmeric root? Another naturally occurring compound, ascorbic acid (a form of vitamin C), was found to be 35% more bioavailable when given as an extract which included the proteins, carbohydrates and bioflavonoids found naturally in citrus fruits, than when administered by itself to human subjects (Vinson & Bose, 1988).

3.

There is no literature addressing the effect of processing, storage and preparation of turmeric on the bioavailability and activity of curcumin; it is known, for example, that they can play a role in reducing the content of vitamins and minerals in food (Reddy & Love, 1999).India is the world's largest producer of turmeric and after the various processing techniques are completed, considerable time has passed before the spice reaches the tables of consumers in the West (Azam-Ali, 2008).

Overall, there is a need for more extensive, ideally randomised, controlled and blinded human clinical trials to confirm whether curcumin supplementation, at both high, therapeutic doses, and low culinary doses, can mitigate the symptoms associated with autoimmune diseases. Finally, as interest in curcumin continues to grow and more human clinical studies emerge, it is essential that systematic reviews are periodically conducted to critically assess the available evidence for the therapeutic benefits of curcumin supplementation.

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The role of curcumin supplementation in mitigating the autoimmune symptoms of Diabetes Mellitus

A Systematic Review

"Dissertation submitted in accordance with requirements of University of Chester for the degree of Master of Science"

Systematic Review Contents

Abstract

Background

Curcumin is the main component of the widely-used cooking spice turmeric (*Curcuma longa*). This curcuminoid has been shown to have immunomodulatory effects which may have therapeutic benefit for patients suffering from autoimmune conditions such as Type 1 and Type 2 diabetes mellitus (T1DM/T2DM) when given as an oral supplement. The objective of this study was to evaluate the evidence for therapeutic curcumin supplementation on the symptoms associated with T1DM and T2DM.

Methods

Five electronic database literature searches were conducted (Science Direct, PubMed, Web of Science, Wiley online library and Ingenta Connect) in order to identify studies investigating the effect of curcumin supplementation on autoimmune symptoms associated with T1DM and T2DM. A key-word search strategy restricted to English-language publications published after 2008 was refined and implemented. Randomised and non-randomised controlled and non-controlled trials that utilised oral application of curcumin or its derivatives on subjects exhibiting autoimmune-related symptoms were included. Data was extracted from the selected studies using a standard data extraction sheet and studies were assessed for quality using the Jadad scale.

Results

Five studies were identified that fulfilled the selection criteria. Threes studies were randomised with two of these studies using double blinding, whilst one study did not use

either. Studies reported positive outcomes for autoimmune-associated measures including; the anti-atherosclerosis impact of treatment, enhanced low-density lipoprotein levels, the insulin resistance index and the levels of serum free fatty acids. One study indicated that curcumin supplementation could prevent the onset of T2DM. The studies all used trialled curcumin via the oral route although each study used a different dosage.

Conclusions

Evidence supports the effectiveness of curcumin, applied orally as a supplement, to reduce the severity of autoimmune symptoms associated with DM. However it is evident that considerable further research into the dose dependency and bioavailability of curcumin when given as an oral supplement is required, together with a standardisation of research methodology. This may help establish a more reliable link between curcumin and its therapeutic effects.

1. Background

1.1 The global burden of diabetes mellitus

Diabetes mellitus (DM) is regarded as one of the world's oldest diseases; the first reference to it was in Egyptian manuscripts dated at 3000 years old (Ahmed, 2002). T2DM is the most commonly occurring form of diabetes and is characterised by the occurrence of hyperglycemia, insulin resistance and a comparative deficiency in insulin levels (Alberti & Zimmet, 1998). T2DM is caused by an interaction between genetics, environmental and lifestyle (Olokoba, Obateru, & Olokoba, 2012) and its prevalence continues to grow on a global scale. In the year 2000 there was estimated to be approximately 171 million people with diabetes and that number is projected to grow to 366 million by 2030 (Freeman, 2010). With careful management of lifestyle factors including diet and weight T2DM can be prevented (Tuomilehto et al., 2001) and after its onset, often controlled without the need for insulin injections (European Diabetes Policy Group, 1999). In contrast, T1DM usually occurs in people under thirty years of age and is sometimes referred to as juvenile-onset diabetes and can only be controlled with injection of insulin (Daneman, 2006). T1DM is a chronic autoimmune disorder that occurs in individuals who are genetically susceptible. It also tends to be driven by environmental factors (van Belle, Coppieters, & von Herrath, 2011).

Although the classification and separation of T1DM and T2DM has remained largely unchanged since the 1980s (Alberti & Zimmet, 1998), there is increasing evidence of the role of autoimmunity in both types of the disease, as recently reviewed by Velloso, Eizirik, & Cnop (2013). For example, chronic inflammation has been identified as a risk factor for the

development of T2DM in a pre-diabetic population (Festa, D'Agostino, Tracy, & Haffner, 2002), and there is evidence of autoimmune involvement in both children (Dahlquist et al., 1989) and the elderly (Pietropaolo, Barinas-Mitchell, Pietropaolo, Kuller, & Trucco, 2000).

1.2 Curcumin and autoimmune disease

Curcumin is the main component of the widely-used cooking spice turmeric (*Curcuma longa*), used extensively in Asian cuisine (Ammon & Wahl, 1991). Considerable in-vitro work has been followed up by a growing body of evidence from in- and ex-vivo animal models and limited human trials about the potential of oral curcumin supplementation as a treatment for several autoimmune conditions including Scleroderma (Tourkina et al., 2004), Multiple Sclerosis (Xie, Li, & Takahara, 2011), Psoriasis (Kurd et al., 2008), Inflammatory Bowel Disease (Holt, Katz, & Kirshoff, 2005) and DM (Meng, Li, & Cao, 2013). The beneficial effects of curcumin on these autoimmune conditions is considered to be as a result of its cellular anti-oxidant properties (Srinivasan, 2012) and anti-inflammatory effects (Jurenka, 2009). Curcumin has been demonstrated to be safe for human use at high doses (Chainani-Wu, 2003) which means there is potential for its therapeutic use by patients without the supervision of a clinician. This gives it a considerable advantage over drugs-based diabetes mitigation methods (Rapaka & Coates, 2006).

2. Objective of this systematic review

This systematic review aims to critically evaluate the available literature to determine whether curcumin supplementation is able to mitigate the effects of autoimmune symptoms associated with both T1DM and T2DM. The focus on the autoimmune symptoms of DM sets this study aside from earlier reviews concerning the role

of curcumin in disease mitigation (for example Pari, et al. (2008)). The critical, systematic approach applied here utilising the structure of the Cochrane reviews methodology, adds a robust evaluation of the literature, more so than the recent systematic review by Zhang, Fu, Gao, and Liu (2013). Finally, this review aims to identify gaps in the current understanding of this area and make suggestions with regards to future potential areas of interest and research.

3. Methods

3.1 Format and layout of this systematic review

This systematic review follows the guidelines of the Systematic Reviews Journal (http://www.systematicreviewsjournal.com/authors/instructions/research). This journal publishes systematic reviews on a wide range of topics including human nutrition and exercise physiology. The exception to this is the referencing structure as it follows the American Psychological Association (APA) guidelines, as required by the MSc submission guidelines. Additional structural guidance for this systematic review was obtained from the Cochrane Review methodology (Higgins & Green, 2011). Performing a full Cochrane Review was beyond the scope of this review due to the limitations of the MSc word count and the fact that only one author produced this work; standard Cochrane methodology requires at least two authors (Higgins & Green, 2011).

3.2 Structure of the systematic review

Figure 1 details the seven-step structure of this systematic review, based on the standard Cochrane methodology (Higgins & Green, 2011).

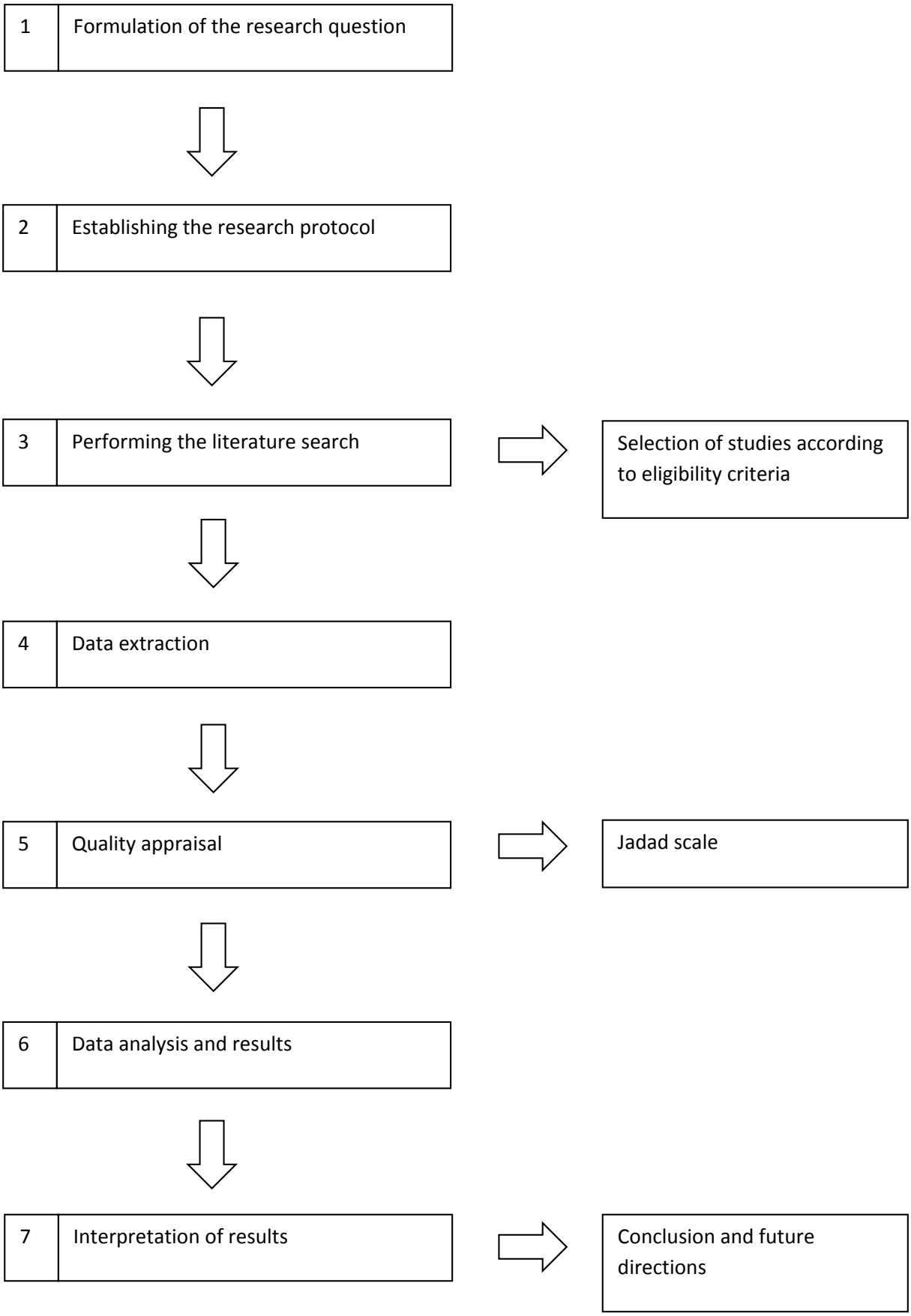

Figure 1 - Flow chart illustrating the stepwise methodology of this systematic review

3.2.1 Formulation of the research question

Preliminary key word searches from five online databases were made to aid in the formulation of the research question (Table A1). Subsequent searches to investigate the availability of literature for curcumin, DM and the link between the two were made using key word searches from six online databases (Table 1). The keywords used were "curcumin", "diabetes" and "curcumin" AND "diabetes". The results of these preliminary literature searches are laid in out in Table 2.

These initial search results from this search showed that several thousand published articles are available using the keywords "curcumin" and "diabetes", although considerably fewer studies contain both search terms in their title. This initial search also showed that there is no literature concerning the effect of curcumin on DM in the grey literature from Europe via Open Grey. Therefore for the final search strategy Open Grey searches were omitted.

As a result of initial literature searches and background reading the research question was constructed: "is there evidence for a therapeutic benefit of curcumin supplementation on autoimmune symptoms related to T1DM and T2DM?"

3.2.2 Establishing the research protocol and search strategy

The methods for carrying out the literature searches and data extraction were established at this stage in order to avoid bias during these later stages. Eligibility criteria were established which ensured only studies which addressed the research question were included for analysis (Table 3). It became clear during preliminary searches that an

additional search term with two variations, “autoimmune” and “autoimmunity”, was required to ensure only those studies with direct relevance to the research question were included according to the eligibility criteria. Trial type was not used as an eligibility criterion in order to include as many human trials. This was also a key quality appraisal factor in the Jadad Scale (see section 3.2.5). Therefore randomised and non-randomised and controlled and non-controlled trials were included in the search results.

3.2.3 Performing the literature search

A total of five online databases were selected for the final literature search in this study. These databases were: Science Direct, PubMed, Web of Science, Wiley online library and Ingenta Connect, all of which search published literature (See Table 1 for a summary of each database). The final search terms were “curcumin” AND “diabetes” OR “autoimmune”/”autoimmunity”. Tables showing the search process broken down into sequential selection steps can be found in Tables A2-A5.

3.2.4 Data extraction

A standardised data extraction sheet was used to ensure consistency in analysis between each paper selected (Table 4). This included assessment of whether the study fulfilled the eligibility criteria shown in Table 3. The individual results for the data extractions can be seen in Tables A6-A10.

3.2.5 Quality appraisal

The quality of selected studies was evaluated using the Jadad scale. The Jadad scale is a questionnaire which can used to evaluate the methodological quality that was utilised in

the studies. The Jadad scale uses randomisation, blindness, and the reporting of drop outs as assessment criteria (Jadad et al., 1996).

Randomisation is important as it removes any influence on the results caused by the manner in which participants are selected. This prevents systematic differences that occur between different interventions affecting the outcome of any experiments (Sibbald & Roland, 1998). Double blinding refers to studies where both the test subject and the investigator are not aware of the true nature of the treatment or intervention, that is, neither is aware whether an individual test subject is receiving the Placebo treatment or not. The use of double blinding eliminates the possibility of potential researcher bias and the obvious impact it may have on the results (Misra, 2012).

The third criterion is concerning drop outs. Recording dropout rates is important as these individuals tend to be the subjects that have not experienced positive results from the intervention. Their removal often tends to skew the results inaccurately towards the positive direction (Olivo et al., 2008).

There are three main advantages of using the Jadad scale. Firstly its small number of questions makes it easier to use compared in more complex scales like Downs and Black. Secondly its criteria has been shown to empirically correlate with sources of bias. Lastly it possesses a proven reliability and external validity (Halpern & Douglas, 2005).

3.2.6 Data analysis and results

A critical appraisal of the reviews having identified the key papers was conducted. The criteria for assessment were:

1. Appropriateness of the sample group used
2. How robust the methodology was
3. How valid the study is in the context of nutritional science
4. The statistical significance of the results

3.2.7 Interpretation of results and conclusions

The quality assessment and critical appraisal results were together used to draw conclusions for this systematic review and in doing so identify gaps in the current understanding, and to recommend future research priorities.

4. Results

4.1 Studies selected for inclusion

Five studies fulfilled the eligibility criteria for inclusion. These studies were, in order of analysis below (Chuengsamarn, Rattanamongkolgul, Luechapudiporn, Phisalaphong, & Jirawatnotai, 2012; Neerati, Devde, & Gangi, 2014; Steigerwalt et al., 2012; Na et al., 2012; Chuengsamarn, Rattanamongkolgul, Phonrat, Tungtrongchitr, & Jirawatnotai, 2014). Data was extracted, summarised and critically appraised; see section 4.2.

4.2 Description and critical appraisal of included studies

1. Chuengsamarn et al. (2014). Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial.

Description

This clinical trial investigated the antiatherosclerotic effect of curcumin in subjects with diabetes by assessing their risk factors for arterial damage. It involved a 6-month randomized, double-blinded, placebo controlled parallel design. In total 240 T2DM patients, aged 35 or over, were selected for this nine month trial period. Subjects consuming medication were excluded. The purpose of this study was to assess the safety and efficacy of curcumin extract intervention as a means of reducing atherogenesis (the formation of abnormal fatty plaques in arterial walls) in T2DM.

Participants consumed 3 x 2 capsules daily of either curcumin, or a starch placebo capsule at 250mg per capsule. Pulse wave velocity (PWV) was assessed both in the curcumin and placebo groups. Any shift in the anti-inflammatory adipocytokines levels was noted.

Curcumin ill effects were monitored. Elevated levels of creatinine and aspartate aminotransferase beyond an acceptable value range were recorded as an indicator of ill effects. Body weight, kidney function, liver function and blood pressure were monitored for curcumin intervention adverse effects. Vital sign status including abdominal weight, body weight and waist circumference were periodically measured. Plasma assay samples for insulin were taken for hormone analysis. A power calculation was performed for statistical validity purposes.

Study results

Curcumin treatment enhanced glucose regulation (adiponectin) and reduced leptin, the satiety hormone. Triglycerides and abdominal obesity levels were lower than in the placebo group. Lower levels of LDL cholesterol and raised levels of HDL cholesterol were noted in the curcumin treated group, a key marker for atherosclerosis. Curcumin intervention in this study therefore appeared to improve many of the metabolic syndrome indicators for arterial damage. These inflammatory responses play a significant role in arterial plaque formation.

Critical appraisal

The participating subjects in this study came from a small provincial region in central Thailand sharing virtually an identical ethnic and cultural heritage. Clearly this cohort, sharing many similarities, potentiates greater accuracy in the report findings. However, a lack of intervariability also has the potential to skew results and flag health issues that may in part be as a result of other factors such as genetic predisposition to illness. Otherwise this

study shows solid methodology, and utilises randomisation in its selection and double blinding.

2. Neerati et al. (2014). Evaluation of the Effect of Curcumin Capsules on Glyburide Therapy in Patients with Type-2 Diabetes Mellitus.

Description

This study aimed to evaluate the effect of curcumin supplementation in relation to its lipid lowering impact in subjects with type 2 diabetes mellitus in conjunction with Glyburide, a diabetic drug. Curcumin was shown to increase the action and duration of glyburide when taken in therapeutic doses. As reported by the American Diabetes Association (ADA), curcumin regulates the expression of inflammatory mediators such as tumour necrosis factor and COX-2, two markers strongly associated with insulin resistance and type 2 diabetes mellitus. The purpose of this study was to assess whether curcumin could influence the pharmacodynamic (PD) and pharmacokinetic (PK) impact of glyburide.

Eight type 2 diabetic patients taking Daonil, Glyburide's trade name, were treated with 475mg of curcumin daily for 10 days. Subjects were aged between 32 and 38. Mean weight, height and body mass index was recorded. A standardized diet was applied both before and during the trial. Periodic blood samples were collected throughout the trial including the pre and post curcumin treatment period.

Study results

Curcumin application in conjunction with glyburide had a greater lowering effect on LDL, VLDL and triglycerides than with glyburide application alone. Blood glucose levels were

significantly altered with the combination of curcumin and glyburide. Results also highlighted blood glucose levels reduced post breakfast, lunch and dinner on the supplement glyburide combination. Clearly, with insulin sensitivity being an issue in type 2 diabetic patients, the PD impact of curcumin ingestion could be telling.

Critical appraisal

The authors noted in a similar study conducted by Soni & Kuttan (1992), subjects were given curcumin for seven consecutive days at 500mg/day. Likewise, with a decrease in total serum cholesterol and an increase in HDL cholesterol, one could point to the significant period between both studies and reference the fact this information was clearly in the public domain having produced similar results. There was no reporting of double blinding in this experiment that could result in inherent bias resulting in deceptively positive results. There is also no mention of drop outs which further calls into question the results, although it is possible there were simply no drop outs.

3. Steigerwalt et al. (2012). Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy.

Description

The purpose of this study was to assess the impact Meriva, a lecithin based curcumin delivery system, had upon the diabetic condition of 38 patients suffering from retinopathy and microangiopathy. The group consisted of a mean age of 55, 21 male and 17 female in the Meriva group, and a mean age of 54, 22 male and 17 female in the control group. One

tablet was taken twice daily prior to food for a four-week period; the capsule composed of 500mg Meriva and 100mg curcumin. Subjects were not dependent upon insulin nor were they using other health related medications. A comparable group of subjects, total thirty-nine, followed a standard treatment plan including exercise, diet and antidiabetics taken orally. Following the trial period, clinical evaluations indicated microangiopathy improvements. Retinal flow measures were obtained highlighting improvements in those subjects using Meriva and a Mann-Whitney U-test for significant statistical differences was applied.

Results

At four weeks clinical evaluations were gathered. Oedema, an indicator of diabetic microangiopathy and prevalent in diabetic patients, was decreased when measured against the control group. Visual acuity in the Meriva group was also noteworthy compared to the control group using the Snellen scale. Other retinal markers for improved visual performance increased in the Meriva subjects. No noticeable observational changes were evident in the control group as per the applied testing methods.

Critical appraisal

This paper uses a methodology that is closer to how someone would take a supplement rather than mimicking the structure of a drug based intervention. This therefore demonstrates how curcuminoids can be used without input from clinicians, and more accurately, models how curcuminoids would be utilised outside of clinical trials. However this paper records no utilisation of either double blinding of the assessors, or the participants, nor any randomisation in the selection procedure. This could lead to systematic

problems in the trial and could have skewed the results due to the addition of subconscious bias on behalf of the researchers. Additionally, this study did not include a control group that were given curcumin without Meriva. Therefore it is not possible to assess whether the drug delivery system in fact enhanced the effect of the selected dosage of curcumin.

4. Na et al. (2012). Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial.

Description

The scope of this study was to evaluate the impact curcumin exerted on diabetic patients with elevated free fatty acids (FFAs). Subjects were prescribed oral hypoglycemic drugs, insulin or both throughout this three-month trial. Notable exclusions applied; history of type 1 diabetes, endocrine disease, diabetic ketoacidosis and previous infection within the last three months. Randomized, double-blind, placebo controlled criteria applied. Homogeneity of outcome variables was applied at baseline between the placebo and curcumin subjects. The curcumin subjects consumed curcumin capsules at 150mg twice daily post mealtime. The placebo group followed this same protocol ingesting starch capsules at 150mg per capsule. Subject compliance was monitored and blood samples were collected at baseline and end of study period. Anthropometric measures were taken. Lifestyle matters such as exercise, leisure time and sedentary time were recorded. Nutritional intake was calculated.

Results

Fasting glucose decreases were observed in the curcumin group. Total FFAs and triglycerides compared to the placebo group were also noted; this included both saturated

fatty acids and unsaturated fatty acids. Decreasing FFAs have been acknowledged therapeutically in helping arrest insulin resistance. These findings suggest the decrease in serum FFAs via curcumin application may promote the oxidation of free fatty acids in tissue.

Critical appraisal

The methodology of this study was robust in that a randomised, double-blind approach was undertaken. The timeframe for the study was three months, possibly a limited amount of time for a condition such as T2DM that may remain with the patient indefinitely. The results can be viewed as promising however future trials, based from this line of enquiry, are required over longer time periods in order to determine the long term outcomes of this treatment.

5. Chuengsamarn et al. (2012). Curcumin Extract for Prevention of Type 2 Diabetes.

Description

This study was designed to determine the efficacy of curcumin use on a prediabetic population in helping delay the onset of T2DM. 240 patients, subject to certain inclusion and exclusion criteria, were chosen to participate in this 12-month trial, all aged thirty-five or over. Height, body weight and vital signs were recorded pre-treatment and every three months thereafter. Standard lifestyle recommendations were issued to all participants in this double-blinded, randomized, placebo-controlled study. No other medications were permitted throughout the trial. Certain health related criteria was applicable in order for subjects to be deemed suitable for participation. Candidates currently regarded as diabetic according to specific guidelines were excluded. Other specific health issues and conditions rendered subject participation ineligible. There was a random selection process for the

curcumin treated group and the placebo treated group. All participants consumed six capsules daily for nine months, with blinded labels of either curcumin, or the placebo. Each curcumin capsule comprised 250mg.

Results

Primary health outcomes according to specific guidelines were assessed in relation to those considered type 2 diabetic, both in the curcumin, and placebo treated groups. Adverse effects of curcumin supplementation were also noted. Certain secondary health trial outcomes were measured as a means to assess the wider impact of this trial. They were conducted every three, six and nine months. The anti-inflammatory cytokine adiponectin, a glucose and fatty acid regulator, was elevated in the curcumin treated group. This study demonstrated curcumin was shown to reduce inflammation and inflammatory molecules, a primary B-cell antagonist shown to promote diabetic tendencies. Significantly, some subjects in the placebo treated group developed T2DM as observed during the three, six and nine month trial visits. During this same period, no subjects within the curcumin treated group developed this condition. Nor were there hypoglycaemic symptoms or blood sugar dysregulation reported in this same group.

Critical appraisal

This study shows promising results and utilises sound methodology in relation to limiting bias. It clearly shows that over the trial period of nine months curcumin can significantly reduce the probability of developing diabetes. It would be advisable to conduct further long-term studies using this methodology in order to assess the limitations of curcumin and its ability to prevent diabetes. This trial highlights the value of curcumin as a

supplement on its own without any other treatment. This would suggest the conditions of this trial most closely replicate how curcumin could be consumed outside a clinical setting. This makes it the most relevant study out of the five from a nutritional science perspective.

4.3 Critical Appraisal Summary

Table 5 summarises the selected papers in terms of the four key criteria as outlined in section 3.2.6.

4.4 Jadad scale quality assessment

The result of the Jadad quality assessment for each of the five papers is laid out in Table 6.5.

Discussion

The systematic review highlighted a number of studies that showed positive outcomes for DM patients and prediabetic patients who have taken a curcumin based treatment. For the diabetic patients, a number of parameters were examined including how much of an anti-atherosclerotic affect the treatment had, impact on low-density lipoprotein levels, the insulin resistance index, and the levels of serum free fatty acids. The patients that had received an administration of a curcumin-based treatment were observed to have more positive results than those on placebo. This lends credence to the idea that curcumin could be used to manage the symptoms of diabetes.

In pre-diabetic populations curcumin was shown to reduce the numbers of people developing diabetes down to zero over a nine month period. These promising results suggest the curcumin could be used to prevent the development of diabetes and means

that it would be advisable for at risk population to take a supplement. The study took place over a nine month period, a relatively short period of time in a person's life. Further investigation would be advised in order to examine how significantly curcumin may reduce the risk of diabetes over longer periods. The disparity between different study timeframes also makes comparison between them more difficult. Conclusions about the efficacy of curcumin over time are therefore harder to make. Establishing cross-group standardised time periods for monitoring DM outcomes in nutritional interventions would help to overcome this issue with different timeframes.

This review also brings up the importance of standardisation of measurement outcomes when performing clinical trials in order for trials to be fully comparable; this review included studies that each recorded a range of different outcomes although all pertained to T2DM development or the autoimmune-related symptoms of DM. Furthermore, each study used a different oral dosage of curcumin that makes it difficult to draw conclusions regarding the appropriate dosage as a supplement.

Finally, one study Steigerwalt et al. (2012) utilised a drug delivery system to administer the curcumin. The positive results gained from this study indicate the potential for drug delivery systems in administering natural compounds such as curcumin to the body. However their lack of a standalone curcumin control group meant that the ability to assess the effect of the drug delivery system on curcumin delivery is minimal. This highlights the importance of thorough, thoughtful trial design to ensure that major, potentially confounding factors, are accounted and controlled for.

6. Conclusion

Curcumin has the ability to both positively influence the autoimmune-associated symptoms of DM and to prevent its development, at least within the short term. Further investigations using properly controlled and blinded human trials are needed to determine optimum dosing and administration methodologies. Further investigations into its efficacy over longer periods of time will also help determine the development period and progression of the disease. In doing so medical support structures within our communities may be more ably equipped to cope with the burgeoning global issue that is diabetes.

7. Tables

Database	Description
Science Direct	A database that archives 25% of the world's peer reviewed scientific, technical and medical content, boasting 15 million global subscribers. It has access to approximately 2,200 journals and 26,000 book titles (ScienceDirect, 2014).
Pubmed	A database that contains over 24 million citations for biomedical literature contained in MEDLINE, books and life science journals, and covers a wide range of different sciences (Pubmed, 2014).
Web of Science	A scientific citation service with access to several cross-disciplinary academic and scientific databases. It forms links between publications, researchers, and the utilisation of controlled indexing and is actively curated (Reuters, 2014).

Wiley Online	Contains approximately 1500 peer reviewed journals and over 15,000 online books including hundreds of multi-volume referenced works. It also houses over 4 million articles (Wiley, 2014).
Ingenta Connect	An online database offering a comprehensive collection of 4.5 million research articles spanning 13,500 publications (Ingenta, 2014).
Open Grey	An open-access database containing 700,000 references of unpublished (grey) literature produced in Europe, which includes but is not limited to theses and conference reports (Open Grey, 2014).

Table 1 - Details of the online scientific databases used for literature searches in this systematic review

Database Searched	**Results for "curcumin"**	**Results for "diabetes"**	**Results for "curcumin" AND "diabetes"**
Science Direct	15 159	612 331	3 328
Pubmed	6978	484,902	282
Web of Science	29024	1 277 553	397
Wiley online library	6072	279 986	1614
Ingenta Connect	909	35 527	36
Open Grey	280	20,100	0

Table 2 - Results of preliminary keyword searches to establish the availability of the data

Number	Eligibility criteria	Explanation and rationale
1	English language studies	Only papers in English were included, as other languages could not be interpreted by the author
2	Primary research article	Only primary research articles were considered. This excluded reviews and books from the search process
3	Articles published after 2008	A 2008 review (Pari et al., 2008) included literature published up until 2008. This study therefore was designed to evaluate only studies published since the publication of their review
4	Studies on human subjects	Research using animal models was not included. Whilst animal studies can be both accurate and

		informative regarding treatments, dosages and other research outcomes, the purpose of this review was to focus on human clinical trials from a nutritional perspective.
5	Key word search relevance	Only studies containing the search terms in the title or abstract were considered. This removed research papers that did not include data linking curcumin to DM
6	Intervention: oral administration of curcumin	This review focuses on the benefit of curcumin supplementation on DM and therefore the oral route is the most appropriate method of administration
7	Study outcome: evaluated an effect of curcumin on alleviating autoimmune-related symptoms of either T1DM or T2DM or on the development of T2DM	Only studies that assessed the effect of curcumin on DM-related autoimmune conditions were included to maintain focus on the research question. This excluded studies focusing on other DM-related conditions

Table 3 - The Eligibility Criteria for this systematic review, with explanation and rationale for their use

Research Summary	
Sample	
Treatment Details	
Jadad Score	
Results	

Table 4 - blank data extraction sheet used for analysis of selected papers

Study	Appropriateness of the sample group used	How robust the methodology was	How valid the study is in the context of nutritional science	Statistical significance of the results
1. Chuengsamarn et al., (2014)	Used appropriate selection of diabetic patients	Used randomisation and double blinding. Make use of a starch based placebo as the control	Used capsules for administration, relevant for nutritional supplementation	Reduction in level of ALT p = 0.26
2. Neerati et al., (2014)	Used appropriate selection of diabetic patients	Lack of double blinding and reporting of drop outs may be causes of bias	Used capsules for administration, relevant for nutritional supplementation	Decrease in LDL, VLDL and triglyceride p = 0.001
3. Steigerwalt et al., (2012)	Uses appropriate selection of selection of	Lack of randomisation and double	Did not use curcumin alone, instead uses a	Improvement in visual acuity

	patients suffering from retinopathy and microangiopathy	blinding may be causes of bias.	drug base delivery system (500mg Meriva, 100mg curcumin per capsule). It approaches the subject from a clinical perspective rather than a nutritional one.	$p < 0.025$ Improvement in retinal oedema $p < 0.05$
4. Na et al., (2012)	Stringent criteria for inclusion may limit the range of people these results can be confidently applied to	Used randomisation, double blinding and states withdrawals, an overall robust methodology	Used capsules for administration, relevant for nutritional supplementation	A decrease in fasting blood glucose $p < 0.01$ HbA1c $p = 0.031$ Insulin resistance index $p < 0.01$

5. Chuengsamarn et al., (2012)	Used appropriate selection of pre-diabetic patients	Used randomisation, double blinding and states withdrawals, an overall robust methodology	Used capsules for administration, relevant for nutritional supplementation. Shows how curcumin when used as a nutritional supplement could possibly prevent the onset of T2DM.	Increase in HOMA-β *P* < 0.01 Lower C-peptide *P* < 0.05 Reduction in level of HOMA- *P* < 0.001 Higher level of adiponectin *P* < 0.05

Table 5 - Critical appraisal summary for the five selected papers.

Paper	Was the study described as randomised	Was the study described as double blind	Was there a description of withdrawals and dropouts	The method of randomisation was described in the paper, and that method was appropriate	he method of blinding was described, and it was appropriate	The method of randomisation was described, but was inappropriate	The method of blinding was described, but was inappropriate
1	yes	yes	yes	yes	yes	no	no
2	yes	no	no	yes	no	no	no
3	no	no	yes	no	no	no	no
4	yes	yes	yes	yes	yes	no	no
5	yes	yes	yes	yes	yes	no	no

Table 6 - Jadad quality scale assessment of selected studies

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9. Appendix

Keywords Used	Science direct	PubMed	Wiley Online	Web of Science	Ingenta Connect
Curcumin	15 159	6860	6072	29 024	909
Diabetes	612,331	481 256	279 986	1 277 553	35 527
Auto-immune	53 380	2652	10 920	12 978	490
Inflammation	59 550	451 898	269 505	1 659 396	27 986
Curcumin and Diabetes	3,328	279	1614	397	36
Curcumin and Auto-immune	492	1	110	2	0
Curcumin and Inflammation	6389	730	2820	1250	85
Diabetes and Auto-immune	11 137	211	3432	508	26
Diabetes and Inflammation	122 613	18 131	58 401	54 518	1395
Inflammation and Auto-immune	18,462	240	4206	3036	26
Curcumin and Diabetes and Auto-immune	224	0	96	3036	0

Table A1 - Initial Keyword searches across the different databases

Database Searched	**Results for curcumin and Diabetes**
Science Direct	1,912
Pubmed	176
Web of Science	238
Wiley online library	176

Table A2 - Studies that match the search criteria that were published after 2008.

Preliminary searches with the purpose of developing new search criteria for use in stage three of the literature review.

Database Searched	Results for curcumin and Diabetes
Science Direct	49
Pubmed	146
Web of Science	32
Wiley online library	37

Table A3 - review articles, book and magazines removed

Database Searched	**Results for curcumin and Diabetes**
Science Direct	10
Pubmed	7
Web of Science	8
Wiley online library	4

Table A4 - Sources that contain both the keywords in either the title or the abstract

Paper	Number of citations found
Chuengsamarn et al., (2014)	0
Neerati et al., (2014)	Not found on Web of Science
Steigerwalt et al., (2012)	6
Na et al., (2013)	2
Chuengsamarn et al., (2012)	21

Table A5 - Sources relevant to the research question; citation update

Research Summary	Assesses effect of Curcumin on atherosclerosis by examining the pulse wave velocity
Sample	200 Patients with Type 2 diabetes
Treatment Details	The participants consumed 3 x 2 capsules daily of either curcumin, or a starch placebo capsule at 250mg per capsule.
Jadad Score	5
Results	Curcumin treatment enhanced glucose regulation (adiponectin) and reduced leptin, the satiety hormone. Triglycerides and abdominal obesity levels were lower than in the placebo group

Table A6 - Data extraction table for selected studies number 1: Chuengsamarn et al. (2014). Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial

Research Summary	How Curcumin inliuences the symptoms of Type-2 Diabetes Mellitus
Sample	Eight type 2 diabetic patients receiving Glyburide treatment
Treatment Details	475mg of curcumin daily for ten days
Jadad Score	2
Results	Curcumin application in conjunction with glyburide had a greater lowering effect on LDL, VLDL and triglycerides than with glyburide application alone. Blood glucose levels were significantly altered with the combination of curcumin and glyburide. Results also highlighted blood glucose levels reduced post breakfast, lunch and dinner on the supplement glyburide combination.

Table A7 - Data extraction table for selected paper number 2: Neerati et al. (2014). Evaluation of the Effect of Curcumin Capsules on Glyburide Therapy in Patients with Type-2 Diabetes Mellitus.

Research Summary	Effect of Meriva on the syptoms of diabetes focusing on the eyes
Sample	Mean age of 55, 21 male and 17 female in the Meriva group, and a mean age of 54, 22 male and 17 female in the control group.
Treatment Details	One tablet taken twice daily prior to food for a four-week period, the capsule composed of 500mg Meriva and 100mg curcumin
Jadad Score	1
Results	Oedema, an indicator of diabetic microangiopathy and prevalent in diabetic patients, was decreased when measured against the control group. Visual acuity in the Meriva group was also noteworthy compared to the control group using the Snellen scale. Other retinal markers for improved visual performance increased in the Meriva subjects

Table A8 - Data extraction table for selected paper number 3: Steigerwalt et al. (2012). Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy.

Research Summary	Relationship between curcumin and the lowering of glucose levels in type-2 diabetes patients.
Sample	100 subjects, aged between 18 – 65, registered overweight/obese and with type 2 diabetes.
Treatment Details	The curcumin subjects consumed curcumin capsules at 150mg twice daily post mealtime.
Jadad Score	5
Results	Fasting glucose decreases in the curcumin group were observed.

Table A9 - Data extraction table for selected paper number 4: Na et al. (2013). Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial.

Research Summary	Study into how curcumin can be used to prevent the development of diabetes in pre-diabetic patients
Sample	240 patients aged 35 and over
Treatment Details	All participants consumed six capsules daily for nine months, with blinded labels of either curcumin, or the placebo. Each curcumin capsule comprised 250mg
Jadad Score	5
Results	This study demonstrated curcumin was shown to reduce inflammation and inflammatory molecules, a primary B-cell antagonist shown to promote diabetic tendencies. Significantly, some subjects in the placebo treated group developed T2DM as observed during the three, six and nine month trial visits. During this same period, no subjects within the curcumin treated group developed this condition.

Table A10 - Data extraction table for selected paper number 5: Chuengsamarn et al. (2012). Curcumin Extract for Prevention of Type 2 Diabetes.