Nutritional Medicine Journal

Curcumin: A Review of Clinical Use and Efficacy

Karin Elgar

Abstract

Turmeric has a long tradition of use in Ayurvedic medicine for a variety of indications, including digestive and liver support, in mood-related disorders and inflammatory conditions. Modern research has confirmed anti-inflammatory, antioxidant, anti-microbial and anti-tumour activities of compounds isolated from turmeric, including curcumin and other curcuminoids. Curcumin has poor bioavailability and various formulations have therefore been developed to overcome this issue. Clinical trials have shown benefits of curcuminoids in a wide range of conditions, including cardiometabolic, inflammatory and mood disorders. Turmeric extracts have been found to be safe in humans with only mild adverse events being observed in clinical trials, mostly gastrointestinal disturbances, but due to its physiological actions, some drug interactions are possible.

Cite as (AMA): Elgar K. (2022) Curcumin: A Review of Clinical Use and Efficacy. Nutr Med J., 1 (1): 10-31.
Affiliation: K. Elgar is with the Nutritional Medicine Institute, London, UK.
Corresponding author: Karin Elgar **(email info@karinelgar.com)**
Article history: Received 10 March 2021. Peer-reviewed and received in revised form 12 July 2021. Accepted 15 July 2021. Available online 6 October 2021
Published by: The Nutritional Medicine Institute

Introduction

Turmeric (*Curcuma longa*) is a member of the ginger family and has a long tradition of use not only as a culinary spice, but also in Chinese and Ayurvedic medicine for a variety of clinical uses, including digestive and liver support, in mood-related disorders and inflammatory conditions.[1] Curcumin is a yellow polyphenolic compound that gives turmeric its characteristic colour and, alongside other curcumoids including bisdemethoxycurcumin and demethoxycurcumin, is also one of the main active components thought to mediate its medicinal properties, which include anti-inflammatory, antioxidant, anti-microbial and anti-tumour activities.[2]

The bioavailability of curcumin is limited due to poor absorption and rapid metabolism through the liver, and various techniques have therefore been employed to increase bioavailability through different delivery systems.[3] Despite this, turmeric extracts seem to have good clinical efficacy, even without such enhancements (unformulated products), and it has been postulated that this may be due to the fact that some of the metabolites of curcumin also possess beneficial biological activities, some of which appear to have stronger antioxidant effects than curcumin itself.[4]

Piperine, a compound from black pepper, has been shown to enhance bioavailability by 20 times, and is therefore commonly added to curcumin supplements.[5] Other methodologies that have been used to increase the bioavailability of curcumin include hydrophilic nanoparticles and solid lipid particles.[6] Being lipid soluble, the solubility and absorption of curcumin is enhanced by the presence of lipids, either through a lipid-containing formulation such as solid lipid particles, or by taking it with a meal.[6] This is also the way that turmeric has been consumed, either as part of a meal or, in Ayurvedic tradition, in a milky drink.

The issues of bioavailability and the large variety of formulations on the market that claim to have enhanced bioavailability make it difficult to compare the dosages used in studies and suggest dose recommendations for specific indications. Where dosages have been suggested, they generally refer to non-enhanced formulations.

General Functions

Inflammation/inflammatory markers

Inflammation is a main driver for chronic degenerative disease, including cardiovascular disease (CVD), cancer, neurodegenerative conditions like Alzheimer's disease (AD), metabolic disorders, such as diabetes and obesity, and autoimmune conditions. As such, safe and effective anti-inflammatory compounds play an important role in the prevention and management of these conditions, and curcumin has shown promising anti-inflammatory effects in animal studies.[7] Its anti-inflammatory properties appear to be due to a number of mechanisms, including effects on cellular signalling, and modulating expression and release of pro- and anti-inflammatory cytokines (messenger molecules of the immune system that regulate inflammation).[7] Nuclear factor kappa B (NF-κB) is a key upregulator of the expression of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8, and curcumin has been shown to have an inhibitory effect on NF-κB.[8] Curcumin also appears to exert a positive effect on the microbiome, which may contribute to its anti-inflammatory potential.[9,10]

The effects of curcumin on a large range of conditions associated with inflammation have therefore been studied in many human clinical trials, and many of these studies have assessed inflammatory markers to elucidate specific mechanisms by which curcumin works.

Two recent meta-analyses looked at studies evaluating inflammatory markers and, although they included largely the same studies,

came to differing results. In one review, improvements in C-reactive protein (CRP), high-sensitivity CRP (hsCRP), IL-1 beta, IL-6 and TNF-α failed to reach statistical significance;[7] however, the other review found statistically significant improvements in IL-6 and hsCRP but not TNF-α.[11] These contradictory results may be due to the high heterogeneity of trial results observed in both meta-analyses.

Two meta-analyses looked at individual markers. One, which included nine randomised-controlled trials (RCTs) with 609 participants, found that curcumin significantly decreased IL-6.[12] A subgroup analysis suggested that taking curcumin for more than 8 weeks is more beneficial, whilst dosages lower than 1000 mg per day and unformulated supplements were more effective than higher dosages and formulated products. The reasons for these findings are unclear, and are not further discussed by the authors. The other review, which included eight RCTs and 549 participants, looked at TNF-α, and found a significant lowering of TNF-α in those taking curcumin compared with placebo.[13] There appeared to be no association with duration or dosage but, again, unformulated products appeared to be more effective. This may be due to compounds other than curcumin that have also been shown to have biological activities.[2]

Many more studies, not included in the above meta-analyses, have looked at inflammatory markers as part of the evaluation of curcumin for particular disorders. On the whole, those that included several markers found significant decreases in at least some of them in patients with a variety of underlying health conditions, including metabolic syndrome (metS),[14] non-alcoholic fatty liver disease (NAFLD),[15,16,17] kidney disease with haemodialysis,[18] ulcerative colitis,[19] obesity,[20,21] diabetes[22] and schizophrenia.[23] On the other hand, a number of studies that only included one or two markers found no benefits or the benefits failed to reach statistical significance versus placebo.[24,25,26,27]

Supplementation regimes varied widely in all of these studies in terms of formulations (including both turmeric and curcumin/curcuminoid supplements, with or without enhanced bioavailability), dosage (46–4000 mg curcumin) and duration (4–36 weeks), as well as in the study populations, for example, patients with inflammatory or metabolic disorders.

Although the evidence is mixed, overall it suggests that curcumin has anti-inflammatory effects in humans, which may depend on dose and duration of supplementation as well as study population. The clinical findings from a variety of inflammatory conditions (see 'Clinical uses') also support an anti-inflammatory effect.

Oxidative stress

Oxidative stress is characterised by an imbalance between the production and elimination of reactive oxygen species or 'free radicals'. Oxidative stress plays an important role in inflammation, and has been associated with aging and chronic disease. Malondialdehyde (MDA), an end-product of lipid peroxidation, and the two antioxidant enzymes glutathione peroxidase (GPX) and superoxide dismutase (SOD) are commonly used markers of oxidative stress, and numerous preclinical studies, including *in vitro* and animal studies, have shown that curcumin can increase these markers.[28]

Two recent meta-analyses looked at the effects of curcumin on oxidative stress markers in humans. Both found that curcumin significantly reduced MDA levels.[11,28] One found that curcumin also significantly increased SOD,[28] whilst in the other this failed to reach statistical significance versus placebo.[11] The former review also evaluated GPX and found no significant benefit, although this was based on only two studies.

Since then, some further studies have found contradictory results, with some showing significant benefits in some antioxidant markers,[29,30] and some showing no benefits,[24,26] using a variety of markers.

Dosages varied widely, from 46 to 1500 mg per day for 4–24 weeks. Dosages of above

800 mg per day and formulations including piperine were found to be more effective in lowering MDA than lower dosages and formulations without piperine.[28]

The reasons for the contradictory results are unclear, but may be due to the heterogeneity of the studies, with regards to dose, formulation, duration and study population. Where there is clear evidence in a particular indication, this will be discussed below in 'Clinical uses'.

Clinical Uses

Alzheimer's disease (AD) /cognitive function

The most common neurodegenerative disease is AD, affecting more than 35 million people worldwide, and is characterised by memory loss and cognitive impairment. The main histopathological feature of AD is amyloid-β plaques, and preclinical research suggests that curcumin can directly affect the processes involved.[31] A human study in non-demented adults has also shown that cognitive and behavioural benefits (from curcumin intervention) are associated with decreases in plaques and accumulation of tau tangles (clumps of the protein tau, which is essential for brain cells to work properly) in brain regions that regulate mood and behaviour, a hallmark of AD.[32]

A series of three cases with AD in 2012 reported benefits in cognitive function with curcumin (764 g turmeric providing 100 mg curcumin per day) after 12 months of supplementation.[33] All three patients took curcumin for at least 1 year, and did not experience any deterioration. However, two double-blind, placebo-controlled trials did not confirm such benefits of curcumin at doses of up to 4000 mg per day for 6 months on clinical parameters and/or biomarkers.[34,35]

Despite promising preclinical evidence on the effectiveness of curcumin in AD, so far clinical research has failed to demonstrate statistically significant effects.[31] It is important though to bear in mind that AD is a complex condition and, in view of the anti-inflammatory, antioxidant and possibly anti-amyloid properties of curcumin, one could consider including it in a more comprehensive programme, although at present there is no evidence for this from RCTs.

A study in people at high risk of developing type 2 diabetes mellitus (T2DM) found that curcumin reduced circulating levels of islet amyloid polypeptide and glycogen synthase kinase-3, compounds that may link T2DM and AD, suggesting that curcumin may help reduce the risk of developing AD as well as T2DM.[36]

A number of RCTs have also been carried out on cognitive function in healthy, middle-aged and elderly people, as well as in people with schizophrenia. Some studies have found curcumin to be significantly better than placebo in improving cognitive function (including memory) in middle-aged and elderly people without dementia,[32,37,38,39] whilst other studies found no significant benefit.[32,40,41] Dosages ranged from 80 to 1500 mg curcumin per day, and study durations ranged from 4 weeks to 18 months, with positive and nil studies amongst both shorter- and longer-term studies. Positive effects on cognitive function have even been seen with acute single-dose administration.[39] The somewhat contradictory results may be explained by the variety of formulations used that are likely to have different bioavailabilities.

One double-blind, placebo-controlled trial in people with schizophrenia found that 8 weeks of curcumin supplementation improved cognitive function.[23] Another 8-week RCT in schizophrenia found no significant improvements in cognitive function but noted an increase in brain-derived neurotrophic factor, which is generally lower in people with schizophrenia, in the curcumin but not in the placebo group.[42] Whilst limited, the results in schizophrenia are promising, and may suggest that a longer duration of curcumin administration may be needed to see benefits in cognitive function.

Arthritis

Osteoarthritis

Osteoarthritis is a common degenerative joint disease that is characterised by progressive loss of cartilage in the joints. This is thought to be due to 'wear and tear', but inflammatory processes have also been shown to be involved, and standard treatment is usually with non-steroidal anti-inflammatory drugs (NSAIDs).[43,44]

Due to its anti-inflammatory action, curcumin has become a popular natural alternative to NSAIDs, which can have significant side-effects, in particular in terms of the digestive system. There is an overwhelmingly positive body of clinical and preclinical research into the use of curcumin and curcuminoids in osteoarthritis.

Three recent meta-analyses[43,44,45] of 10 studies altogether have come to the conclusion that curcumin is significantly better than placebo and as effective as some NSAIDs in relieving pain and improving function and quality of life, and reducing the use of rescue medication such as paracetamol (acetaminophen). A variety of curcumin preparations have been used in the included studies at dosages of 180–2000 mg per day for 4–16 weeks.

Since then, in 2019 and 2020, several more RCTs have been published, all showing significant improvements in pain and other outcomes measured.[46,47,48,49,50,51] Many of the studies showed a halving in pain score with curcumin supplements,[49,50,51] and curcumin was not only found to be superior to placebo but also as effective as NSAIDs in relieving symptoms.[50,51]

Studies have lasted from 4 weeks to 6 months, and dosages have varied considerably, depending on the formulation used, with as low as 80 mg per day for reportedly highly bioavailable formulations to 1500 mg per day. One study evaluated short-term benefits (3 days and 1 week), and found that whilst both curcumin and placebo relieved symptoms to a similar extent in that short time-frame, the curcumin group saw a significantly greater reduction in hsCRP.[52] It would therefore be advisable to supplement for at least 4 weeks (3 months would be better) to see significant beneficial effects.

The anti-inflammatory and antioxidant properties of curcumin are thought to mediate its benefits in osteoarthritis, and a number of studies have found reductions in various markers of inflammation[48,52,53] and oxidative stress in patients with osteoarthritis.[54] Reductions in markers of cartilage matrix degradation have also been reported.[55]

Rheumatoid arthritis

RA is an autoimmune disease with inflammation of the joints, leading to their progressive destruction. As many of the conventional disease-modifying anti-rheumatic drugs can have severe side-effects, there has been increasing interest in natural anti-inflammatory treatments.

Four RCTs (three double-blind, one single-blind) have studied the potential benefits of curcumin in RA. Two of them showed statistically significantly better improvements than placebo in disease activity and clinical symptoms,[56,57] whilst one showed curcumin to be better than diclofenac (an NSAID) with fewer side-effects.[58] In all three studies, disease activity and/or symptoms scores approximately halved. The fourth study found significant improvements in disease activity and symptoms in both the curcumin and the placebo groups, and although the curcumin group improved more, this failed to reach statistical significance.[59]

Dosages ranged from 120 to 500 mg per day for 8 weeks to 3 months. The study with the non-significant results only used 120 mg per day,[59] and one study compared 250 mg with 500 mg and found both dosages to be equally efficacious.[57]

Overall, curcumin appears to be beneficial in RA at dosages of 250–500 mg for 3 months.

All four studies cited above also reported significant improvements in inflammatory markers, suggesting the anti-inflammatory

properties of curcumin to be an important mechanism of action.

Asthma

Curcumin has been used for asthma in India and China for centuries, and preclinical research has confirmed its potential for alleviating asthma, through its anti-inflammatory action, in particular with respect to inflammation of the smooth muscles of the airways, which are affected in asthma.[60]

Two RCTs in adults found no clinical benefits, although one RCT using 1000 mg per day for 1 month[61] found significant improvements in FEV1 (a measure of airway obstruction), whereas the other study used 2000 mg per day for 6 months and found no such improvement.[60] The latter study was double-blind whilst the former was an open-label RCT, therefore a placebo effect may explain the difference. A more recent double-blind, placebo-controlled trial in 34 children and adolescents with asthma found that turmeric powder improved night-time awakening, use of rescue medication and overall disease control significantly more in the turmeric group compared with the placebo group.[62] Both groups saw significant improvements in frequency of symptoms and interference of activity, with no statistically significant difference between the groups.

Whilst turmeric powder appears to be promising for children and adolescents, there is no evidence for a benefit of curcumin in adults with asthma.

Cancer

According to the National Cancer Institute, almost 40% of people in the USA will be diagnosed with cancer at some point in their lives and about a third will die from the disease.[63] Cancer treatments are expensive and are often accompanied by serious side-effects. A plethora of preclinical research studies have shown benefits of curcumin in both cancer initiation and progression.[64]

A recent review of 22 human clinical studies[64] found benefits of curcumin, as an adjunct to standard treatment, in a variety of common cancers, such as breast, prostate, pancreatic and colorectal. These benefits, some of which have been confirmed by further studies, have included:

- Reduced side-effects of chemo- or radiotherapy;[65,66]
- Increased survival rate;
- Improved quality of life;
- Reductions in pre-cancerous lesions;
- Increased effectiveness of treatment;[65,67]
- Decrease in tumour markers.[66]

A meta-analysis looking at six trials of curcumin, four with topical and two with oral application, on treatment-induced oral mucositis (an inflammation of the lining of the mouth, a common side-effect of both chemo- and radiotherapy) in patients with head and neck cancers found curcumin to reduce the severity of oral mucositis and weight loss, which is often caused by the treatment (chemo- and/or radiotherapy).[68]

Formulations, and with that potential differences in bioavailability, dosages and duration of curcumin supplementation have varied significantly, with doses of up to 8 g per day for 11 months being reported to be safe and well tolerated.[69] Evaluated outcome measures, concomitant chemo-/radiotherapy regimes and study designs have also differed from trial to trial, making it difficult to suggest a particular dose for a particular cancer.

A number of mechanisms are thought to be involved in the anti-cancer effects of curcumin, including anti-angiogenic effects (interfering with the blood supply to the tumour), induction of apoptosis (programmed cell death), interfering with the cell proliferation cycle of tumour cells, and inhibition of the tumour's invasion of healthy tissues. There is also a strong relationship between inflammation and cancer, so the anti-inflammatory properties of curcumin are also thought to play a role in its anti-tumour effects.[64]

Cardiometabolic conditions and risk factors

Dyslipidaemia

Dyslipidaemia is characterised by increased triglycerides (TGs), total cholesterol (TC) and/or low-density lipoprotein (LDL) cholesterol, and/or decreased high-density lipoprotein (HDL) cholesterol, and is considered an important risk factor for CVD. It is commonly associated with overweight/obesity, metabolic disturbances such as T2DM and NAFLD.[70]

A 2019 review and meta-analysis of the effects of curcumin on blood lipids in patients with metabolic disorders found statistically and clinically significant beneficial effects on TGs, TC, LDL and HDL cholesterol, although there was considerable heterogeneity amongst the included studies.[70] Results were generally better with higher dosages, longer duration and in patients with T2DM.

These findings have been confirmed by further double-blind, placebo-controlled trials in a range of patient populations, including women with polycystic ovary syndrome (PCOS),[71] in overweight women together with exercise,[72] patients with NAFLD,[16,73,74] young obese men,[75] patients at high risk of T2DM,[76] patients with T2DM[22,26] and patients with elevated CVD risk,[21] although not necessarily all lipid parameters were significantly improved in all studies. In a few RCTs, however, lipid profiles were not significantly improved.[18,25,77,78]

Dosages reported were generally in the range of 40–1800 mg per day, the lower dosages often being nano-formulations, and the duration of supplementation was 4 weeks to 6 months. A common dose range that showed benefits was 1000–1500 mg per day for at least 8 weeks.

A number of mechanisms for the lipid-lowering potential of curcumin have been discussed, including its modulation of the expression of factors involved in regulating lipid metabolism, such as adiponectin, resistin and leptin.[22,70,79,80]

Endothelial dysfunction

The endothelium is the inner layer of blood vessels, and it controls vascular relaxation and contraction. In endothelial dysfunction (ED), there is an imbalance between vasodilating substances (that widen the blood vessels) and vasoconstricting substances (that narrow the blood vessels). ED is involved in the development of atherosclerosis and, as such, is a risk factor for CVD. High blood pressure, smoking and diabetes are thought to contribute to ED.[81] The most commonly used method to evaluate ED is a flow-mediated dilation (FMD) test.[82]

A couple of recent meta-analyses, 1 of 5 and 1 of 10 studies, found that curcumin is effective in improving FMD, although improvements in other ED measurements failed to reach statistical significance.[83,84] Since publication of the above reviews, a further long-term[85] and an acute curcumin supplementation trial[86] have reported beneficial effects, whilst another long-term trial reported no improvement in ED.[75]

Depending on formulation, dosages ranged from 25 mg to 2000 mg per day, for 4–24 weeks. Neither dose nor duration appeared to explain the heterogeneity of the results.

Although not all trials report benefits, the overall evidence suggests that curcumin can help improve endothelial function. Turmeric at a dose of 1200 mg per day for 12 weeks has shown benefits.[85]

It is thought that the benefits of curcumin for endothelial function are due to its anti-inflammatory and antioxidant properties,[84] a lower dose may suffice with a more concentrated or bioavailable formulation.

Hypertension

Hypertension is the largest known risk factor for heart disease and, globally, hypertension is the second biggest risk factor for overall mortality and morbidity after poor diet.[87] In 2015, one in four men and one in five women worldwide had high blood pressure.[86,87,88]

A 2019 meta-analysis of 11 RCTs on the effects of curcumin on blood pressure found a significant benefit for lowering systolic but not diastolic blood pressure, but only in studies with a duration of 12 weeks or longer.[89] Subgroup analysis did not show any effect of the participants' condition or the type of formulation of curcumin used. Results from some more recent RCTs are also mixed.[73,90]

Although the evidence for the use of curcumin in hypertension is weak, the fact that hypertension is commonly associated with other cardiovascular or metabolic risk factors for which curcumin has been shown to be beneficial suggests that curcumin may still be worth considering for patients with hypertension.

Metabolic syndrome

MetS is not a disease as such but a cluster of cardiovascular risk factors, and is defined as a combination of at least three of the following metabolic abnormalities: elevated TGs, decreased HDL cholesterol, hypertension, elevated blood sugar, and central obesity [increased waist circumference (WC)].[91] The risk of developing metS increases with age, and it is estimated to affect 40% of those over 50 years old in the USA and nearly 30% in Europe, and insulin resistance is thought to play an important part in the development of metS.[92]

A meta-analysis of 7 RCTs including 503 participants with metS found that curcumin supplementation led to significant improvements in fasting blood glucose, TGs, HDL cholesterol and diastolic blood pressure, but failed to reach statistical significance for WC and systolic blood pressure.[93] The findings regarding the effect on hypertension are contradictory to the findings in another meta-analysis, discussed in the 'Hypertension' section, which found a significant decrease with systolic but not diastolic blood pressure.[89] The reasons for these contradictory results are not clear, but may be due to different study populations. Dosages used ranged from 800 to 2400 mg per day for 4–12 weeks.

Another meta-analysis looked more specifically at obesity-related parameters in patients with either metS or related metabolic disorders, including T2DM and NAFLD.[94] The pooled data showed that curcumin had benefits in terms of reduced body mass index (BMI), weight and WC, as well as improved leptin and adiponectin levels, two important metabolic messenger molecules.

Curcumin has also been shown to decrease markers of inflammation and oxidative stress in patients with metS,[14] although another study showed no benefits of curcumin on pro-oxidant antioxidant balance.[30]

Overall, curcumin appears to be beneficial for people with metS, and could be suggested at a dose of at least 800 mg for at least 8 weeks.

Possible mechanisms for the benefits of curcumin in metS include reduced oxidative stress and modulation of genes involved in glucose and lipid metabolism.[93]

Type 2 diabetes mellitus

T2DM is caused by impaired insulin secretion and insulin resistance, and is an important risk factor for CVD. T2DM, especially when poorly controlled, can also lead to a number of complications, such as diabetic nephropathy, retinopathy and neuropathy.[95]

There has been a significant increase in T2DM over the past decades, and it was estimated that in 2018/2019, 4.8 million people in the UK had diabetes, with about a fifth not being aware that they had the disease, and a further 13.6 million at risk of developing T2DM.[96] As such, T2DM poses an enormous public health risk and burden.

Improving glycaemic (blood sugar) control is key in the management of T2DM and reducing the associated longer-term risks. A 2018 meta-analysis, including 11 studies and 1144 participants, looked at the effects of curcumin on glycaemic control in both diabetic and non-diabetic patients and found that, in people with diabetes and prediabetes, curcumin had a positive

effect on fasting blood sugar and HbA1c (a marker of blood glucose levels over the past 2–3 months), but not HOMA-IR (a method used to estimate insulin resistance and function of the beta-cells that secrete insulin).[97] Improvements in glycaemic control have also been seen in women with PCOS.[71] Formulations varied widely in the studies, and effects were seen with curcumin and curcuminoids but not turmeric; curcumin dosages ranged from 70 to 4000 mg per day, and durations from 4 to 36 weeks.

People with diabetes also commonly have other cardiovascular risk factors, and studies have shown that curcumin can improve lipid profiles,[22,26,90,98,99] endothelial function,[85] inflammatory markers[22] and obesity[26,27,90,100] in diabetics.

A number of small pilot studies have also found beneficial effects on a number of diabetic complications, including diabetic sensorimotor polyneuropathy,[101] eye conditions,[102,103] kidney disease[104,105] and microangiopathy (a disease of the small blood vessels that leads to other complications).[102,106]

Curcumin has also been shown to be beneficial in the prevention of T2DM. A double-blind, placebo-controlled study of 240 people with prediabetes found that none of the patients on curcumin progressed to T2DM over the study duration of 9 months, whilst 16.4% of the placebo group did.[107] Indicators of glycaemic control and beta-cell function were also significantly better in the curcumin group at the end of the study. The dosage of curcumin in this study was 1500 mg per day for 9 months.

Based on the available data, the benefits of supplementation with curcumin for patients with diabetes or prediabetes are well demonstrated. Dosages varied widely in the clinical trials, and may depend on the specific formulation. Using a dosage of at least 500 mg per day for at least 8 weeks could be suggested, with a lower dose for formulations with particularly high bioavailability.

A number of possible mechanisms have been suggested, including the antioxidant and anti-inflammatory properties of curcumin, and its ability to modulate the functions of various cell signalling molecules.[97] Curcumin can modulate the gut microbiota in diabetics and with that the concentration of lipo-polysaccharides in the blood, which may contribute to the anti-inflammatory action of curcumin.[104] Curcumin has also been shown to reduce free fatty acids, which are thought to mediate insulin resistance.[108]

Digestive conditions

Gallbladder function

Turmeric is considered a cholagogue, a substance triggering contraction of the gallbladder to promote bile flow, and is commonly used as such in naturopathic tradition to support fat digestion and detoxification.

Two early ultrasound studies indeed showed that curcumin led to gallbladder contraction, with 40 mg triggering a 51% decrease in gallbladder volume and 80 mg a reduction of 72%.[109,110] A more recent study in healthy volunteers also showed beneficial effects of a turmeric-based drink on bile acid metabolism when taken before a medium- or high-fat breakfast.[111]

Clinical research into gallbladder disease is scarce. One small, open-label pilot study in patients with primary sclerosing cholangitis, a chronic disease in which the bile ducts inside and outside the liver become inflamed and scarred, potentially leading to narrowing and blockage, found no benefit of curcumin (1500 mg per day for 12 weeks).[112]

Whilst curcumin has been shown to stimulate bile flow, research of its benefits in gallbladder disease is lacking.

Gastric ulcer/*Helicobacter pylori*

Turmeric has a long tradition of use for gastric ulcers and gastritis, in particular in Thailand.[113]

Some early studies from Thailand investigated the use of turmeric in gastric or duodenal ulcers. An open-label pilot study involving

25 patients with endoscopically confirmed ulcers found a significant benefit of 3000 mg of turmeric powder per day, with 48% of ulcers healed after 4 weeks and 76% after 12 weeks.[114] A double-blind, placebo-controlled study of 118 patients with duodenal ulcers, on the other hand, found no benefits of 6000 mg of turmeric for 8 weeks.[115] A double-blind study from 1989 found turmeric to be more beneficial than placebo in patients with dyspepsia syndrome, which may not be ulcer-related, with 87% and 53% of patients, respectively, reporting improvements.[113]

More recently, curcumin has been investigated for gastritis, gastric or duodenal ulcers associated with *Helicobacter pylori (H. pylori).* An open-label study found that 7 days of a combination of 60 mg of curcumin with lactoferrin, N-acetylcysteine and a proton pump inhibitor (PPI) led to a significant improvement in dyspeptic symptoms despite not eradicating *H. pylori.*[116] Whilst turmeric on its own has been shown to be ineffective in eradicating *H. pylori* or decreasing inflammatory markers in patients with chronic gastritis,[117] 2 RCTs showed that used alongside standard triple therapy (two antibiotics plus a PPI), curcumin led to a statistically significant improvement of the efficacy of treatment.[118,119]

Based on the results of the above studies, curcumin at a dose of 500 mg per day for 4 weeks would be a worthwhile add-on to triple therapy in *H. pylori*-related gastritis or ulcers, and turmeric may be beneficial for dyspeptic symptoms where no further diagnosis has been made.

Curcumin is well known for its anti-inflammatory properties. In this context it is thought that IL-8, an inflammatory cytokine that is involved in *H. pylori*-related inflammation, can be suppressed by curcumin.[119] The study by Judaki *et al.* also showed that curcumin decreased oxidative stress and oxidative DNA damage in the gastric mucosa.[120]

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is characterised by chronic inflammation of the digestive tract. It includes ulcerative colitis, which affects the colon and rectum only, and Crohn's disease, which can affect any part of the digestive tract, from mouth to anus.

Several meta-analyses over the past few years have evaluated the same six original studies on ulcerative colitis, and found curcumin to be beneficial in inducing clinical and endoscopic remission and response.[121,122,123] Depending on statistical methodology and studies included, curcumin was found to be two to more than five times more effective than placebo. In one meta-analysis that included only three of the original studies in their meta-analysis, a different methodology was used and benefits failed to reach statistical significance.[124]

As with studies in other conditions, formulations and dosages varied widely. Whilst evidence as to the best dosage and duration is lacking, higher dosages (e.g. 3000 mg per day) or products with higher bioavailability and longer duration of supplementation (at least 3 months) appear to be of more benefit.[122]

There are fewer studies in patients with Crohn's disease. An early pilot study[125] involving 5 patients with Crohn's disease taking 1080 mg of curcumin for 1 month and then 1440 mg for another 2 months saw improvements in 4 patients, with an average decrease of disease activity of 20.8%. The fifth patient did not complete the study due to worsening of symptoms. 2 more studies were published in 2020. One double-blind, placebo-controlled trial in patients with mild to moderate disease found clinical remission rates of 35%, 40% and 40% at weeks 4, 8 and 12, respectively, which were significantly higher than those in the placebo group, and 15% endoscopic remission in the curcumin group versus 0% in the placebo group.[126] This study used 360 mg of Theracurmin per day. The second double-blind, placebo-controlled trial evaluated the effects of 3000 mg of curcumin per day for 6 months in 62 consecutive

patients with Crohn's disease undergoing bowel resection, and found no benefits of curcumin on post-operative recurrence; in fact, in patients on curcumin who had a recurrence it tended to be more severe, although this was not statistically significantly different from placebo.[127]

Curcumin has also been studied in paediatric IBD. In an open-label, dose-escalation study involving 9 children, aged 11–19 years, over 9 weeks with a maximum dose of 4000 mg per day, none of the children had a worsening of symptoms, whilst 2 with ulcerative colitis and one with Crohn's disease saw improvements.[128]

Whilst the evidence is strongly in favour of the use of curcumin for ulcerative colitis, whether there are benefits in Crohn's disease is unclear. A suggested dose for ulcerative colitis would be 3000 mg per day for at least 3 months.

The anti-inflammatory actions of curcumin, including its effects on IL-1, TNF-α and other cytokines, are thought to mediate its benefits in IBD.[121]

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, characterised by symptoms such as abdominal pain, altered bowel habits and changes in stool frequency, which can significantly impact on quality of life. The causes are unclear and are likely to be multi-factorial, with disturbances in the microbiome often playing an important role.[129]

Only 2 studies looked at curcumin on its own in patients with IBS. A double-blind, placebo-controlled study reported no benefits,[130] whilst an open-label, uncontrolled trial reported significant benefits.[129] In neither of these studies was the actual dose of curcumin clearly reported.

A review lists 3 clinical trials that used curcumin in combination with other herbs and/or nutrients, and reports positive results in 2 of the studies.[131] A combination with fennel essential oil appears to be particularly beneficial, with improvements in the severity and symptoms of IBS, as well as quality of life.[120,132]

At this point, there is insufficient evidence to suggest that curcumin on its own is effective in relieving IBS symptoms.

Exercise recovery/performance

Due to its anti-inflammatory and antioxidant effects, curcumin has received considerable attention for its potential benefits in sports nutrition.

2 recent reviews of 11 studies[10,133] and 1 meta-analysis[134] of 9 RCTs found significant effects of curcumin in reducing muscle soreness and creatine kinase (a marker of muscle damage). 2 studies published in 2020 further corrobarated these conclusions.[135,136] Subgroup analysis of the meta-analysis suggested that statistically significant effects were seen at follow-up durations of more than 1 day and with higher dosages. It also suggested that untrained individuals benefit more than trained ones.

Beneficial effects have also been observed in terms of reduced inflammation and oxidative stress, superior recovery and muscle performance, better psychological and physiological responses (thermal and cardiovascular) during training, and improved gastrointestinal function.[10]

Dosages used in trials have varied widely, from 90 to 6000 mg per day. Most studies looked at the effects of acute, short-term supplementation (1–7 days), whilst some looked at longer durations (up to 3 months). Both short- and longer-term studies reported benefits. Longer-term studies have used 600–1500 mg per day for 4–8 weeks.

The known anti-inflammatory and antioxidant effects of curcumin are thought to confer the observed benefits at least in part. The negative effect of prolonged exercise on gastrointestinal function and the immune system may be ameliorated by curcumin through its positive effects on the microbiome, which plays an important role in modulating inflammation.[10]

Non-alcoholic fatty liver disease

NAFLD is a common disorder caused by a build-up of fat within liver cells. Risk factors include obesity/overweight, metS and T2DM.[137]

5 recent meta-analyses looked into the effects of curcumin on NAFLD, looking at different parameters. 2 found that curcumin significantly reduced liver enzymes,[138,139] 1 saw improvements in glucose and lipid metabolism,[140] and 1 found that curcumin reduced BMI and WC,[141] whilst another did not find benefits for weight/body composition.[142]

Since then, more RCTs have been published, with some not showing any benefits in decreasing liver enzymes,[143,144,145] whilst others found benefits in a number of biochemical markers,[73] inflammatory markers[15] and NAFLD severity (as per ultrasound).[15,144] The reasons for these discrepancies are unclear.

Overall, curcumin, but not turmeric, appears to offer benefits to patients with NAFLD, although studies sometimes arrive at contradictory results and conclusions. This may be due to the fact that the studies have used a wide range of formulations, dosages and durations, making it difficult to establish general recommendations. Higher dosages (at least 1000 mg per day) for at least 8 weeks may offer the best benefits.

Overweight/obesity

Overweight and obesity are closely associated with inflammation and metabolic abnormalities, and body weight, BMI and/or WC have been measured and reported in a number of studies looking at curcumin and cardiometabolic risk factors and conditions, such as metS and NAFLD.

Two recent meta-analyses pooled data from such studies, and found a significant effect of curcumin on decreasing weight, BMI and WC.[94,146] Dosages have varied from 200 to 2800 mg per day, and durations from 4 to 36 weeks, with generally better results with dosages of 1000 mg or over and duration of 8 weeks or longer.[146]

A number of additional RCTs since the publication of the reviews have come up with contradictory results, with some showing a benefit in terms of obesity,[72] and others not.[73,90,147] The reasons for the differing results are not clear and do not appear to be due to dosage or duration, but may be due to different patient groups, in that patients were considered healthy in the study that showed benefits, whilst patients in the other studies had metS,[147] T2DM[90] and suboptimal blood glucose, respectively.[73]

1 RCT evaluated curcumin, 500 mg per day for 10 weeks, alongside a diet, in obese adolescent girls and found no significant benefits over placebo on BMI, WC and hip circumference.[77]

Overall, the evidence suggests that curcumin is beneficial for weight loss in overweight or obese individuals, at doses of at least 1000 mg and for at least 8 weeks.

Psychiatric disorders

Depression/anxiety

In Ayurvedic medicine, curcumin has been used for centuries for depression and anxiety.[148] Inflammation can play an important role in depression[149] and, as such, curcumin has been investigated in depressive disorders.

2 meta-analyses, including 7 clinical trials on people with major depressive disorder, found significant effects of curcumin, alongside treatment with conventional anti-depressants, in improving both depression and anxiety.[150,151] A number of trials have also investigated the effects of curcumin on mood and anxiety in patients with other disorders and healthy elderly people with mixed results. Some studies showed significant improvements in mood and/or anxiety over placebo,[39,152,153] whilst a study combining curcumin with vitamin E found no benefit in reducing anxiety but significantly reduced hot flushes in post-menopausal women.[154]

Dosages ranged from 150 to 1500 mg per day and duration of trials was 4–12 weeks, with neither dose nor duration appearing to affect outcomes.[150]

Overall, there is good evidence for the use of curcumin in people with depression alongside anti-depressant medication, whilst the effects on mood and anxiety in people without diagnosed depression are less clear. Most studies showing beneficial effects were at a dose of 1000 mg per day for at least 6 weeks.

A number of mechanisms appear to be involved in the benefits of curcumin, including modulation of neurotransmitter concentrations, inflammation, excitotoxicity, neuroplasticity, hypothalamic–pituitary–adrenal imbalances, insulin resistance, oxidative stress and the endocannabinoid system.[148]

Schizophrenia

3 double-blind, placebo-controlled clinical trials have looked at curcumin as an add-on to the usual treatment in patients with schizophrenia. The one with the highest dose (3000 mg curcumin) and longest duration (24 weeks) saw significant improvements in some but not all schizophrenia assessment scores.[155] The other 2, using 360 mg and 180 mg, respectively, for 8 weeks, did not see any improvement in schizophrenia symptom scores; however, one saw an increase in levels of brain-derived neurotrophic factor,[42] whilst the other saw improvements in memory and reduced levels of the pro-inflammatory marker IL-6.[23]

Whilst evidence is scarce, in view of the excellent safety profile of curcumin, supplementation with curcumin, at 3000 mg for at least 24 weeks, could be suggested to patients with schizophrenia.

The antioxidant, anti-inflammatory and neuroprotective actions of curcumin are thought to mediate the observed benefits,[155] which the latter two studies appear to confirm.

Skin conditions

Oral lichen planus

OLP is an autoimmune disease affecting the mucous membranes of the mouth, leading to lesions and open sores. Conventional treatment is usually with topical or systemic corticosteroids, which carry the risk of potentially serious side-effects, especially with long-term use. Natural anti-inflammatory compounds, like curcumin, are therefore of interest.

4 RCTs have been published on the use of oral curcumin and OLP. 2 of them used 2000 mg per day for 4 and 7 weeks, respectively, and found no benefit.[156,157] A study using a much higher dose, 6000 mg per day, found significant improvements over placebo within the study period of 2 weeks.[158] A recent study compared nano-curcumin, 80 mg per day, with standard treatment with prednisone, 10 mg per day, for 1 month in a double-blind fashion and found the nano-curcumin to be as effective as prednisone, with both treatments resulting in significant improvements of symptoms.[159]

Although evidence is limited, curcumin seems to be promising for people with OLP, although it seems that high dosages or highly bioavailable formulations, rather than longer-term treatment, are required to see benefits.

The observed benefits are thought to be due to the anti-inflammatory potential of curcumin, although changes of CRP and IL-6 were measured in one trial and failed to reach statistically significant results.[158]

Psoriasis

Psoriasis is another autoimmune skin disorder, and is characterised by an increased production of skin cells, leading to red, flaky, crusty patches of skin that can be itchy or sore.

A number of RCTs have evaluated the efficacy of curcumin in psoriasis, and found that curcumin is beneficial in relieving symptoms on its own[160] as well as in combination with topical steroids,[161] acitretin (a vitamin A analogue commonly used to treat psoriasis)[162] and light therapy.[163,164] Formulations have varied widely, from curcumin nano-particles to a turmeric tonic, as have dosages, and trials lasted for 9–12 weeks.

Overall, curcumin is a promising natural compound to either use alone or alongside other treatments. A dose of 400 mg per day has been used successfully.[161]

The observed benefits are thought to be due to the anti-inflammatory, anti-angiogenic, antioxidant and anti-proliferative effects of curcumin, and a reduction in the pro-inflammatory marker IL-22, which is involved in the development of psoriasis, has been observed.[161]

Safety

In 2018, a review of preclinical as well as human clinical trials concluded that standardised powders and extracts of turmeric and curcumin were safe and non-toxic in humans.[165] This review suggested that formulations with higher bioavailability or nano-formulations may also be safe, although there were few studies on such supplements. The most commonly reported side-effects are gastrointestinal disturbances, including constipation, diarrhoea, flatulence, nausea and vomiting.[166,167] An overview of systematic reviews concluded that adverse events reported in clinical trials were generally mild and similar to placebo, and also lists the most common adverse events as abdominal pain, nausea and dyspepsia.[168]

However, there have been some concerns over hepatotoxic effects (toxic effects on the liver). A review of the Italian Phytovigilance system showed that between April 2002 and July 2019, 76 reports of suspected adverse reactions to turmeric-containing products were received, of which 39 referred to possible liver damage.[169] These included a cluster of 28 cases of hepatotoxicity, which were reported from the Tuscany region of Italy within 6 months in 2018/2019. A recent article evaluated 7 cases of hepatotoxicity suspected to be due to turmeric or curcumin supplementation, the dosages used in all cases were well within the range used in clinical trials.[166] These cases appear to be limited to a specific period and region, and the wider relevance of this is as yet unclear, bearing in mind that The European Food Safety Agency, the US Food and Drug Administration and the European Medicines Agency all have considered turmeric extracts with high curcumin concentrations as safe.[170]

Another potential safety issue of turmeric or its extracts is contamination with toxic substances, including lead[171,172] and metanil yellow (an illegal food dye),[172] therefore choosing a product from a reputable company is important.

Drug interactions

A number of potential drug interactions are listed on the Natural Medicines Database.[167] It should be noted that many of them are based on *in vitro* or animal experiments or theoretical considerations.

Due to its own therapeutic potential, curcumin may have an accumulative effect with certain medications, and should therefore be used with caution alongside:

- Anti-diabetic drugs;
- Blood-thinning drugs.

Due to its antioxidant effects, curcumin may interact with certain chemotherapy drugs:

- Alkylating agents;
- Anti-tumour antibiotics;
- Topoisomerase I inhibitors.

Curcumin may increase levels of the following drugs:

- Amlodipine;
- Docetaxel;
- Norfloxacin;
- P-glycoprotein substrates;
- Paclitaxel;
- Sulfasalazine;
- Tacrolimus.

Curcumin may reduce levels of the following drug:

- Talinolol.

Curcumin may interfere with certain Cytochrome P450 pathways, and may therefore affect the efficacy and safety of drugs that are metabolised through the same Cytochrome P450 enzymes.[165]

Due to the possible hepatotoxicity of curcumin, care should be taken alongside hepatotoxic drugs.[169]

Pregnancy and breastfeeding

In amounts commonly found in foods, turmeric and curcumin are considered to be 'likely safe' during pregnancy and breastfeeding.[173]

However, there are no data from human clinical trials on the use of turmeric extracts as dietary supplements during pregnancy. Whilst *in vitro* and animal research suggests that the anti-inflammatory effects of curcumin may be of benefit for a number of pregnancy-related complications, curcumin has also shown harmful effects in oocyte maturation, fertilisation and development of the blastocyst in animal studies.[174]

Not enough is known about using turmeric or curcumin as a dietary supplement during breastfeeding, and should therefore not be recommended.[173]

One double-blind, placebo-controlled study compared a herbal supplement containing fenugreek, ginger and turmeric with placebo for 4 weeks in breastfeeding mothers, and found that the herbal supplement led to an increase in milk production that was significantly greater than in the placebo group.[175] No differences in milk nutrient content or adverse effects in the infants were observed. Adverse events in the mothers, including excessive gas, were no more frequent than in the placebo group. The daily dose of turmeric in the supplement was 900 mg.

Children and adolescents

A number of clinical studies have been conducted in children and adolescents. 1 RCT in asthmatic children and adolescents, aged 7–18 years, saw no adverse reactions with powdered turmeric root, 30 mg per kg body weight (mg kg^{-1}) per day for 6 months, and found benefits in some symptoms.[62] An RCT in obese pubescent girls, taking 500 mg of curcumin daily for 10 weeks, reported mild headaches and nausea, which resolved through continual use of curcumin capsules.[29,77]

A dose-escalation study in children and adolescents, aged 11–18 years, with IBD went up to a maximum dose of 4000 mg of curcumin per day for 3 weeks with no serious reactions.[128] 2 patients experienced increased gassiness during 3 visits. Inconsistent reports of symptoms that occurred only once or resolved on their own were reported in the majority of patients but were not considered to be related to curcumin; they were mild and did not require a lowering of the dose. Laboratory values remained within normal range for the duration of the study.

Although clinical research using curcumin in children and adolescents is limited, the available evidence suggests that curcumin is safe at a daily dose of 30 mg kg^{-1} turmeric powder for up to 6 months in children from 7 years old, or 500 mg of curcumin per day for 10 weeks in adolescents.

Conclusion

The research reviewed in this paper suggests that curcumin is safe and effective in a range of disorders, in particular conditions associated with inflammation and/or increased oxidative stress. Various formulations and a large range of dosages have shown benefits in clinical trials, making it difficult to make specific recommendations. Concerns have been raised over possible hepatotoxic effects, although the relevance of such reports is unclear, and agencies in both the US and Europe consider turmeric extracts to be safe.

Acknowledgements

Author contributions: K. Elgar carried out the literature review and formulated the manuscript.

Peer-reviewers and editors: the Nutritional Medicine Institute thanks the peer-reviewers and editors for their important contributions.

Funding: Open Access publication was supported by an unrestricted donation from Pure Encapsulations, Sudbury, MA, USA. No other funding or sponsorship has been received for this work.

Declaration of interest: K. Elgar has received consultancy fees from Pure Encapsulations, Sudbury, MA, USA. This article is the independent work of the author and Pure Encapsulations was not involved in the decision to publish this research.

References

[1] Ross, S. M. (2018) *Curcuma longa* (Theracumin®): A bioavailable form of curcumin and its cognitive benefits. *Holist. Nurs. Pract.,* **32**, 217–220.

[2] Ahmad, R. S. *et al*. (2020) Biochemistry, safety, pharmacological activities, and clinical applications of turmeric: A mechanistic review. Evid. Based. Complement. *Alternat. Med.,* 2020, 7656919.

[3] Schiborr, C. *et al*. (2014) The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. *Mol. Nutr. Food Res.,* **58**, 516–527.

[4] Shen, L., Liu, C.-C., An, C.-Y. & Ji, H.-F. (2016) How does curcumin work with poor bioavailability? Clues from experimental and theoretical studies. *Sci. Rep.,* **6**, 20 872.

[5] Shoba, G. *et al*. (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.*, **64**, 353–356.

[6] Dei Cas, M. & Ghidoni, R. (2019) Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients*, **11**, 2147.

[7] White, C. M., Pasupuleti, V., Roman, Y. M., Li, Y. & Hernandez, A. V. (2019) Oral turmeric/curcumin effects on inflammatory markers in chronic inflammatory diseases: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.,* **146**, 104 280.

[8] Wang, Y., Tang, Q., Duan, P. & Yang, L. (2018) Curcumin as a therapeutic agent for blocking NF-κB activation in ulcerative colitis. Immunopharmacol. *Immunotoxicol.,* **40**, 476–482.

[9] Zam, W. (2018) Gut microbiota as a prospective therapeutic target for curcumin: A review of mutual influence. *J. Nutr. Metab.,* **2018**, 1 367 984.

[10] Suhett, L. G. *et al*. (2020) Effects of curcumin supplementation on sport and physical exercise: A systematic review. *Crit. Rev. Food Sci. Nutr.,* **1–13** doi:10.1080/10408398.2020.1749025.

[11] Tabrizi, R. *et al*. (2019) The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.*, **33**, 253–262.

[12] Derosa, G., Maffioli, P., Simental-Mendía, L. E., Bo, S. & Sahebkar, A. (2016) Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.,* **111**, 394–404.

[13] Sahebkar, A., Cicero, A. F. G., Simental-Mendía, L. E., Aggarwal, B. B. & Gupta, S. C. (2016) Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res*., **107**, 234–242.

[14] Osali, A. (2020) Aerobic exercise and nano-curcumin supplementation improve inflammation in elderly females with metabolic syndrome. *Diabetol. Metab. Syndr.*, **12**, 26.

[15] Saberi-Karimian, M. *et al*. (2020) Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: A randomized controlled trial. *Complement. Ther. Med.,* **49**, 102 322.

[16] Jazayeri-Tehrani, S. A. *et al*. (2019) Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): A double-blind randomized placebo-controlled clinical trial. *Nutr. Metab. (Lond).,* **16**, 8.

[17] Saadati, S. *et al*. (2019) Curcumin and inflammation in non-alcoholic fatty liver disease: A randomized, placebo controlled clinical trial. *BMC Gastroenterol.,* **19**, 133.

[18] Vafadar Afshar, G. *et al*. (2020) The effects of nano-curcumin supplementation on serum level of hs-CRP, adhesion molecules, and lipid profiles in hemodialysis patients, a randomized controlled clinical trial. Iran. *J. Kidney Dis.*, **14**, 52–61.

[19] Sadeghi, N., Mansoori, A., Shayesteh, A. & Hashemi, S. J. (2020) The effect of curcumin supplementation on clinical outcomes and inflammatory markers in patients with ulcerative colitis. *Phytother. Res.,* **34**, 1123–1133.

[20] Saraf-Bank, S., Ahmadi, A., Paknahad, Z., Maracy, M. & Nourian, M. (2019) Effects of curcumin supplementation on markers of inflammation and oxidative stress among healthy overweight and obese girl adolescents: A randomized placebo-controlled clinical trial. *Phytother. Res.,* **33**, 2015–2022.

[21] Uchio, R. *et al*. (2019) Hot water extract of *Curcuma longa L*. improves serum inflammatory markers and general health in subjects with overweight or prehypertension/mild hypertension: A randomized, double-blind, placebo-controlled trial. *Nutrients,* **11**, 1822.

[22] Adibian, M. *et al*. (2019) The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Phytother. Res.*, **33**, 1374–1383.

[23] Kucukgoncu, S., Guloksuz, S. & Tek, C. (2019) Effects of curcumin on cognitive functioning and inflammatory state in

schizophrenia: A double-blind, placebo-controlled pilot trial. *J. Clin. Psychopharm*., **39**, 182–184.

[24] da Silva, T. A. L. *et al*. (2020) Influence of curcumin on glycemic profile, inflammatory markers, and oxidative stress in HIV-infected individuals: A randomized controlled trial. *Phytother. Res*., **34**, 2323–2330.

[25] Sohaei, S., Amani, R., Tarrahi, M. J. & Ghasemi-Tehrani, H. (2019) The effects of curcumin supplementation on glycemic status, lipid profile and hs-CRP levels in overweight/obese women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled clinical trial. *Complement. Ther. Med.*, **47**, 102 201.

[26] Adab, Z. *et al*. (2019) Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients. *Phytother. Res.,* **33**, 1173–1181.

[27] Panahi, Y. *et al*. (2018) Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled trial. *Drug Res. (Stuttg).,* **68**, 403–409.

[28] Qin, S. *et al*. (2018) Meta-analysis of randomized controlled trials of 4 weeks or longer suggest that curcumin may afford some protection against oxidative stress. *Nutr. Res.*, **60**, 1–12.

[29] Saraf-Bank, S., Ahmadi, A., Paknahad, Z., Maracy, M. & Nourian, M. (2019) Effects of curcumin supplementation on markers of inflammation and oxidative stress among healthy overweight and obese girl adolescents: A randomized placebo-controlled clinical trial. *Phytother. Res.,* **33**, 2015–2022.

[30] Ghazimoradi, M. *et al*. (2017) The effects of curcumin and curcumin-phospholipid complex on the serum pro-oxidant-antioxidant balance in subjects with metabolic syndrome. *Phytother. Res.*, **31**, 1715–1721.

[31] Voulgaropoulou, S. D., van Amelsvoort, T. A. M. J., Prickaerts, J. & Vingerhoets, C. (2019) The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Res.*, **1725,** 146 476.

[32] Small, G. W. *et al*. (2018) Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: A double-blind, placebo-controlled 18-month trial. *Am. J. Geriatr. Psychiatry*, **26**, 266–277.

[33] Hishikawa, N. *et al*. (2012) Effects of turmeric on Alzheimer's disease with behavioral and psychological symptoms of dementia. *Ayu*, **33**, 499–504.

[34] Ringman, J. M. *et al*. (2012) Oral curcumin for Alzheimer's disease: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. *Alzheimers Res. Ther.,* **4**, 43.

[35] Baum, L. *et al*. (2008) Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J. Clin. Psychopharmacol*., **28**, 110–113.

[36] Thota, R. N. *et al*. (2020) Dietary supplementation with curcumin reduce circulating levels of glycogen synthase kinase-3β and islet amyloid polypeptide in adults with high risk of type 2 diabetes and Alzheimer's disease. *Nutrients,* **12**, 1032.

[37] Kuszewski, J. C., Howe, P. R. C. & Wong, R. H. X. (2020) Evaluation of cognitive performance following fish-oil and curcumin supplementation in middle-aged and older adults with overweight or obesity. *J. Nutr.,* **150,** 3190–3199.

[38] Cox, K. H. M., White, D. J., Pipingas, A., Poorun, K. & Scholey, A. (2020) Further evidence of benefits to mood and working memory from lipidated curcumin in healthy older people: A 12-week, double-blind, placebo-controlled, partial replication study. *Nutrients,* **12**, 1678.

[39] Cox, K. H. M., Pipingas, A. & Scholey, A. B. (2015) Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. *J. Psychopharmacol.*, **29**, 642–651.

[40] Santos-Parker, J. R. *et al*. (2018) Curcumin supplementation and motor-cognitive function in healthy middle-aged and older adults. *Nutr. Heal. Aging*, **4**, 323–333.

[41] Rainey-Smith, S. R. *et al*. (2016) Curcumin and cognition: A randomised, placebo-controlled, double-blind study of community-dwelling older adults. *Br. J. Nutr.,* **115**, 2106–2113.

[42] Wynn, J. K. *et al*. (2018) The effects of curcumin on brain-derived neurotrophic factor and cognition in schizophrenia: A randomized controlled study. *Schizophrenia Res.,* **195**, 572–573.

[43] Onakpoya, I. J., Spencer, E. A., Perera, R. & Heneghan, C. J. (2017) Effectiveness of curcuminoids in the treatment of knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. *Int. J. Rheum. Dis.,* **20**, 420–433.

[44] Bannuru, R. R., Osani, M. C., Al-Eid, F. & Wang, C. (2018) Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin. Arthritis Rheum.,* **48**, 416–429.

[45] Wu, J., Lv, M. & Zhou, Y. (2019) Efficacy and side effect of curcumin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials. *Pak. J. Pharm. Sci.*, **32**, 43–51

[46] Wang, Z. *et al*. (2020) Effectiveness of *Curcuma longa* extract for the treatment of symptoms and effusion-synovitis of knee osteoarthritis: A randomized trial. *Ann. Intern. Med.*, **173**, 861–869.

[47] Nakagawa, Y. *et al*. (2020) The efficacy and safety of highly-bioavailable curcumin for treating knee osteoarthritis: A 6-month open-labeled prospective study. *Clin. Med. Insights Arthritis Musculoskelet. Disord.,* **13**, 1179544120948471.

[48] Atabaki, M., Shariati-Sarabi, Z., Tavakkol-Afshari, J. & Mohammadi, M. (2020) Significant immunomodulatory properties of curcumin in patients with osteoarthritis; a successful clinical trial in Iran. *Int. Immunopharmacol.*, **85**, 106 607.

[49] Henrotin, Y. *et al*. (2019) Bio-optimized *Curcuma longa* extract is efficient on knee osteoarthritis pain: A double-

blind multicenter randomized placebo controlled three-arm study. *Arthritis Res. Ther.,* **21**, 179.

[50] Gupte, P. A. *et al*. (2019) Evaluation of the efficacy and safety of Capsule Longvida((R)) Optimized Curcumin (solid lipid curcumin particles) in knee osteoarthritis: A pilot clinical study. *J. Inflamm. Res.*, **12**, 145–152.

[51] Shep, D., Khanwelkar, C., Gade, P. & Karad, S. (2019) Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: A randomized open-label parallel-arm study. *Trials,* **20**, 214 .

[52] Calderón-Pérez, L. *et al*. (2020) Acute effects of turmeric extracts on knee joint pain: A pilot, randomized controlled trial. *J. Med. Food,* doi:10.1089/jmf.2020.0074.

[53] Belcaro, G. *et al*. (2010) Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Altern. Med. Rev.,* **15**, 337–344.

[54] Panahi, Y., Alishiri, G. H., Parvin, S. & Sahebkar, A. (2016) Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: Results of a randomized controlled trial. *J. Diet. Suppl.,* **13**, 209–220.

[55] Henrotin, Y. *et al*. (2014) Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial. *BMC Complement. Altern. Med*., **14**, 159.

[56] Amalraj, A. *et al*. (2017) A novel highly bioavailable curcumin formulation improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, double-blind, placebo-controlled, two-dose, three-arm, and parallel-group study. *J. Med. Food*, **20**, 1022–1030.

[57] Jacob, J. *et al*. (2019) A novel bioavailable hydrogenated curcuminoids formulation (CuroWhiteTM) improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, double blind and placebo controlled study. *J. Tradit. Complement. Med.,* **9**, 346–352.

[58] Chandran, B. & Goel, A. (2012) A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother. Res*., **26**, 1719–1725.

[59] Javadi, M., Khadem Haghighian, H., Goodarzy, S., Abbasi, M. & Nassiri-Asl, M. (2019) Effect of curcumin nanomicelle on the clinical symptoms of patients with rheumatoid arthritis: A randomized, double-blind, controlled trial. *Int. J. Rheum. Dis*., **22**, 1857–1862.

[60] Kim, D. H., Phillips, J. F. & Lockey, R. F. (2011) Oral curcumin supplementation in patients with atopic asthma. *Allergy Rhinol. (Providence)*, **2**, e51-e53.

[61] Abidi, A., Gupta, S., Agarwal, M., Bhalla, H. L. & Saluja, M. (2014) Evaluation of efficacy of curcumin as an add-on therapy in patients of bronchial asthma. *J. Clin. Diagn. Res.*, **8**, HC19–HC24.

[62] Manarin, G. *et al*. (2019) *Curcuma longa L*. ameliorates asthma control in children and adolescents: A randomized, double-blind, controlled trial. *J. Ethnopharmacol.*, **238,** 111 882.

[63] National Cancer Institute (US). (2020) Cancer statistics. https://www.cancer.gov/about-cancer/understanding/statistics.

[64] Mansouri, K. *et al*. (2020) Clinical effects of curcumin in enhancing cancer therapy: A systematic review. *BMC Cancer,* **20**, 791.

[65] Saghatelyan, T. *et al*. (2020) Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer: A comparative, randomized, double-blind, placebo-controlled clinical trial. *Phytomedicine,* **70**, 153 218.

[66] Choi, Y. H. *et al*. (2019) A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation. *Prostate,* **79**, 614–621.

[67] Howells, L. M. *et al*. (2019) Curcumin combined with FOLFOX chemotherapy Is safe and tolerable in patients with metastatic colorectal cancer in a randomized phase IIa trial. *J. Nutr.*, **149**, 1133–1139.

[68] Zhang, L., Tang, G. & Wei, Z. (2020) Prophylactic and therapeutic effects of curcumin on treatment-induced oral mucositis in patients with head and neck cancer: A meta-analysis of randomized controlled trials. *Nutr. Cancer,* **1–10,** doi:10.1080/01635581.2020.1776884.

[69] Kanai, M. *et al*. (2011) A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother. Pharmacol.,* **68**, 157–164.

[70] Yuan, F. *et al*. (2019) A systematic review and meta-analysis of randomized controlled trials on the effects of turmeric and curcuminoids on blood lipids in adults with metabolic diseases. *Adv. Nutr.*, **10**, 791–802.

[71] Jamilian, M. *et al*. (2020) Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. *Clin. Nutr. ESPEN,* **36**, 128–133.

[72] Dolati, S. *et al*. (2020) The effect of curcumin supplementation and aerobic training on anthropometric indices, serum lipid profiles, C-reactive protein and insulin resistance in overweight women: A randomized, double-blind, placebo-controlled trial. *J. Obes. Metab. Syndr.*, **29**, 47–57.

[73] Cicero, A. F. G. *et al*. (2020) Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: A double-blind, placebo-controlled clinical trial. *Eur. J. Nutr.,* **59**, 477–483.

[74] Ghaffari, A. *et al*. (2019) Turmeric and chicory seed have beneficial effects on obesity markers and lipid profile in non-alcoholic fatty liver disease (NAFLD). *Int. J. Vitam. Nutr. Res*., **89**, 293–302.

[75] Campbell, M. S. *et al*. (2019) Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: A double-blinded, randomized, controlled trial. *Nutrition,* **62**, 135–139.

[76] Thota, R. N., Acharya, S. H. & Garg, M. L. (2019) Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: A randomised controlled trial. *Lipids Health Dis.*, **18**, 31.

[77] Saraf-Bank, S., Ahmadi, A., Paknahad, Z., Maracy, M. & Nourian, M. (2019) Effects of curcumin on cardiovascular risk factors in obese and overweight adolescent girls: A randomized clinical trial. *Sao Paulo Med. J.,* **137**, 414–422.

[78] Saadati, S. *et al*. (2019) The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease. *Eur. J. Clin. Nutr.*, **73**, 441–449.

[79] Panahi, Y. *et al*. (2017) Curcuminoids plus piperine modulate adipokines in type 2 diabetes mellitus. *Curr. Clin. Pharmacol.*, **12**, 253–258.

[80] Clark, C. C. T., Ghaedi, E., Arab, A., Pourmasoumi, M. & Hadi, A. (2019) The effect of curcumin supplementation on circulating adiponectin: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab. Syndr.,* **13**, 2819–2825.

[81] (2019) Endothelial dysfunction. *diabetes.co.uk* https://www.diabetes.co.uk/diabetes-complications/endothelial-dysfunction.html.

[82] Harris, R. A., Nishiyama, S. K., Wray, D. W. & Richardson, R. S. (2010) Ultrasound assessment of flow-mediated dilation. *Hypertens. (Dallas, Tex. 1979)*, **55**, 1075–1085.

[83] Changal, K. H., Khan, M. S., Bashir, R. & Sheikh, M. A. (2020) Curcumin preparations can improve flow-mediated dilation and endothelial function: A meta-analysis. *Complement. Med. Res.*, **27**, 272–281.

[84] Hallajzadeh, J. *et al*. (2019) The effects of curcumin supplementation on endothelial function: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.*, **33**, 2989–2995.

[85] Srinivasan, A. *et al*. (2019) Effect of *Curcuma longa* on vascular function in native Tamilians with type 2 diabetes mellitus: A randomized, double-blind, parallel arm, placebo-controlled trial. *Phytother. Res.*, **33**, 1898–1911.

[86] Choi, Y., Tanabe, Y., Akazawa, N., Zempo-Miyaki, A. & Maeda, S. (2019) Curcumin supplementation attenuates the decrease in endothelial function following eccentric exercise. *J. Exerc. Nutr. Biochem*., **23**, 7–12.

[87] Forouzanfar, M. H. *et al*. (2015) Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, **386**, 2287–2323.

[88] World Health Organization. (2019) Hypertension. https://www.who.int/news-room/fact-sheets/detail/hypertension.

[89] Hadi, A., Pourmasoumi, M., Ghaedi, E. & Sahebkar, A. (2019) The effect of Curcumin/Turmeric on blood pressure modulation: A systematic review and meta-analysis. *Pharmacol. Res.*, **150**, 104 505.

[90] Ebrahimkhani, S., Ghavamzadeh, S. & Mehdizadeh, A. (2020) The effects of vitamin D and curcuminoids supplementation on anthropometric measurements and blood pressure in type 2 diabetic patients with coexisting hypovitaminosis D: A double-blind, placebo-controlled randomized clinical trial. *Clin. Nutr. ESPEN,* **37**, 178–186.

[91] Alberti, K. G. M. M. *et al*. (2009) Harmonizing the metabolic syndrome. *Circulation,* **120**, 1640–1645.

[92] Tidy, C. (2016) Metabolic syndrome. patient.info https://patient.info/doctor/metabolic-syndrome#ref-10.

[93] Azhdari, M., Karandish, M. & Mansoori, A. (2019) Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.*, **33**, 1289–1301.

[94] Akbari, M. *et al*. (2019) The effects of curcumin on weight loss among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Front. Pharmacol*., **10**, 649.

[95] Tidy, C. (2016) Diabetes mellitus. patient.info professional articles https://patient.info/doctor/diabetes-mellitus-pro#.

[96] (2020) *Diabetes.co.uk.* Diabetes Prevalence 2019. https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2019.

[97] de Melo, I. S. V., Dos Santos, A. F. & Bueno, N. B. (2018) Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: Systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.,* **128**, 137–144.

[98] Panahi, Y. *et al*. (2017) Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. *Complement. Ther. Med.*, **33**, 1–5.

[99] Neerati, P., Devde, R. & Gangi, A. K. (2014) Evaluation of the effect of curcumin capsules on glyburide therapy in patients with type-2 diabetes mellitus. *Phytother. Res.*, **28**, 1796–1800.

[100] Rahimi, H. R. *et al*. (2016) The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: A randomized clinical trial. *Avicenna J. Phytomedicine,* **6**, 567–577.

[101] Asadi, S. *et al*. (2019) Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial. *Complement. Ther. Med*., **43**, 253–260.

[102] Steigerwalt, R. *et al*. (2012) Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. *Panminerva Med*., **54**, 11–16.

[103] Mazzolani, F., Togni, S., Giacomelli, L., Eggenhoffner, R. & Franceschi, F. (2018) Oral administration of a curcumin-phospholipid formulation (Meriva®) for treatment of chronic diabetic macular edema: A pilot study. *Eur. Rev. Med. Pharmacol. Sci*., **22**, 3617–3625.

[104] Yang, H. *et al*. (2015) Curcumin attenuates urinary excretion of albumin in type II diabetic patients with enhancing nuclear factor erythroid-derived 2-like 2 (Nrf2)

system and repressing inflammatory signaling efficacies. Exp. Clin. Endocrinol. *Diabetes,* **123**, 360–367.

[105] Khajehdehi, P. *et al*. (2011) Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: A randomized, double-blind and placebo-controlled study. *Scand. J. Urol. Nephrol.*, **45**, 365–370.

[106] Appendino, G. *et al.* (2011) Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. *Panminerva Med.,* **53**, 43–49.

[107] Chuengsamarn, S., Rattanamongkolgul, S., Luechapudiporn, R., Phisalaphong, C. & Jirawatnotai, S. (2012) Curcumin extract for prevention of type 2 diabetes. *Diabetes Care*, **35**, 2121–2127.

[108] Na, L.-X. *et al*. (2013) Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. *Mol. Nutr. Food Res.*, **57**, 1569–1577.

[109] Rasyid, A., Rahman, A. R. A., Jaalam, K. & Lelo, A. (2002) Effect of different curcumin dosages on human gall bladder. *Asia Pac. J. Clin. Nutr.,* **11**, 314–318.

[110] Rasyid, A. & Lelo, A. (1999) The effect of curcumin and placebo on human gall-bladder function: An ultrasound study. *Aliment. Pharmacol. Ther.*, **13**, 245–249.

[111] Ghaffarzadegan, T. *et al*. (2019) Postprandial responses of serum bile acids in healthy humans after ingestion of turmeric before medium/high-fat breakfasts. *Mol. Nutr. Food Res.*, **63**, e1900672.

[112] Eaton, J. E. *et al*. (2019) Efficacy and safety of curcumin in primary sclerosing cholangitis: An open label pilot study. *Scand. J. Gastroenterol.*, **54**, 633–639.

[113] Thamlikitkul, V. *et al*. (1989) Randomized double blind study of *Curcuma domestica* Val. for dyspepsia. *J. Med. Assoc. Thai.,* **72**, 613–620.

[114] Prucksunand, C., Indrasukhsri, B., Leethochawalit, M. & Hungspreugs, K. (2001) Phase II clinical trial on effect of the long turmeric *(Curcuma longa Linn)* on healing of peptic ulcer. *Southeast Asian J. Trop. Med. Public Health,* **32**, 208–215.

[115] Van Dau, N. *et al*. (1998) The effects of a traditional drug, turmeric *(Curcuma longa),* and placebo on the healing of duodenal ulcer. *Phytomedicine*, **5**, 29–34.

[116] Di Mario, F. *et al*. (2007) A curcumin-based 1-week triple therapy for eradication of *Helicobacter pylori* infection: something to learn from failure? *Helicobacter*, **12**, 238–243.

[117] Koosirirat, C., Linpisarn, S., Changsom, D., Chawansuntati, K. & Wipasa, J. (2010) Investigation of the anti-inflammatory effect of *Curcuma longa* in *Helicobacter pylori*-infected patients. *Int. Immunopharmacol.*, **10**, 815–818.

[118] Judaki, A., Rahmani, A., Feizi, J., Asadollahi, K. & Hafezi Ahmadi, M. R. (2017) Curcumin in combination with triple therapy regimes ameliorates oxidative stress and histopathologic changes in chronic gastritis-associated *Helicobacter pylori* infection. *Arq. Gastroenterol.*, **54**, 177–182.

[119] Khonche, A. *et al*. (2016) Adjunctive therapy with curcumin for peptic ulcer: A randomized controlled trial. *Drug Res. (Stuttg).*, **66**, 444–448.

[120] Di Ciaula, A., Portincasa, P., Maes, N. & Albert, A. (2018) Efficacy of bio-optimized extracts of turmeric and essential fennel oil on the quality of life in patients with irritable bowel syndrome. *Ann. Gastroenterol.*, **31**, 685–691.

[121] Chandan, S. *et al*. (2020) Curcumin use in ulcerative colitis: Is it ready for prime time? A systematic review and meta-analysis of clinical trials. *Ann. Gastroenterol.*, **33**, 53–58.

[122] Zheng, T. *et al*. (2020) Efficacy of adjuvant curcumin therapy in ulcerative colitis: A meta-analysis of randomized controlled trials. *J. Gastroenterol. Hepatol.*, **35**, 722–729.

[123] Iqbal, U., Anwar, H. & Quadri, A. A. (2018) Use of curcumin in achieving clinical and endoscopic remission in ulcerative colitis: A systematic review and meta-analysis. *Am. J. Med. Sci.,* **356**, 350–356.

[124] Grammatikopoulou, M. G. *et al*. (2018) Oral adjuvant curcumin therapy for attaining clinical remission in ulcerative colitis: A systematic review and meta-analysis of randomized controlled trials. *Nutrients*, **10**, 1737.

[125] Holt, P. R., Katz, S. & Kirshoff, R. (2005) Curcumin therapy in inflammatory bowel disease: A pilot study. *Dig. Dis. Sci.*, **50**, 2191–2193.

[126] Sugimoto, K. *et al*. (2020) Highly bioavailable curcumin derivative ameliorates Crohn's disease symptoms: A randomized, double-blind, multicenter study. *J. Crohns Colitis,* doi:10.1093/ecco-jcc/jjaa097.

[127] Bommelaer, G. *et al*. (2020) Oral curcumin no more effective than placebo in preventing recurrence of Crohn's disease after surgery in a randomized controlled trial. *Clin. Gastroenterol. Hepatol.*, **18**, 1553-1560.e1.

[128] Suskind, D. L. *et al*. (2013) Tolerability of curcumin in pediatric inflammatory bowel disease: A forced-dose titration study. *J. Pediatr. Gastroenterol. Nutr.,* **56**, 277–279.

[129] Bundy, R., Walker, A. F., Middleton, R. W. & Booth, J. (2004) Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: A pilot study. *J. Altern. Complement. Med.*, **10**, 1015–1018.

[130] Brinkhaus, B. *et al*. (2005) Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: A randomized, placebo-controlled, double-blind clinical trial. *Scand. J. Gastroenterol.*, **40**, 936–943.

[131] Ng, Q. X. *et al*. (2018) A meta-analysis of the clinical use of curcumin for irritable bowel syndrome (IBS). *J. Clin. Med.,* **7**, 298.

[132] Portincasa, P. *et al*. (2016) Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. *J. Gastrointestin. Liver Dis.*, **25**, 151–157.

[133] Fernández-Lázaro, D. *et al*. (2020) Modulation of exercise-induced muscle damage, inflammation, and oxidative markers by curcumin supplementation in a physically active population: A systematic review. *Nutrients,* **12**, 501.

[134] Fang, W. & Nasir, Y. (2020) The effect of curcumin supplementation on recovery following exercise-induced muscle damage and delayed-onset muscle soreness: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.,* doi:10.1002/ptr.6912.

[135] Amalraj, A., Divya, C. & Gopi, S. (2020) The effects of bioavailable curcumin (Cureit) on delayed onset muscle soreness induced by eccentric continuous exercise: A randomized, placebo-controlled, double-blind clinical study. *J. Med. Food*, **23**, 545–553.

[136] Basham, S. A. *et al*. (2020) Effect of curcumin supplementation on exercise-induced oxidative stress, inflammation, muscle damage, and muscle soreness. *J. Diet. Suppl*., **17**, 401–414.

[137] *NHS*. (2018) Non-alcoholic fatty liver disease (NAFLD). https://www.nhs.uk/conditions/non-alcoholic-fatty-liver-disease/.

[138] Mansour-Ghanaei, F., Pourmasoumi, M., Hadi, A. & Joukar, F. (2019) Efficacy of curcumin/turmeric on liver enzymes in patients with non-alcoholic fatty liver disease: A systematic review of randomized controlled trials. *Integr. Med. Res.,* **8**, 57–61.

[139] Goodarzi, R., Sabzian, K., Shishehbor, F. & Mansoori, A. (2019) Does turmeric/curcumin supplementation improve serum alanine aminotransferase and aspartate aminotransferase levels in patients with nonalcoholic fatty liver disease? A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res*., **33**, 561–570.

[140] Jalali, M. *et al*. (2020) The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials. *Complement. Ther. Med.,* **48**, 102 283.

[141] Baziar, N. & Parohan, M. (2020) The effects of curcumin supplementation on body mass index, body weight, and waist circumference in patients with nonalcoholic fatty liver disease: A systematic review and dose-response meta-analysis of randomized controlled trials. *Phytother. Res.,* **34**, 464–474.

[142] Jafarirad, S. *et al*. (2019) Does turmeric/curcumin supplementation change anthropometric indices in patients with non-alcoholic fatty liver disease? A systematic review and meta-analysis of randomized controlled trials. *Clin. Nutr. Res.*, **8**, 196–208.

[143] Moradi Kelardeh, B., Rahmati-Ahmadabad, S., Farzanegi, P., Helalizadeh, M. & Azarbayjani, M.-A. (2020) Effects of non-linear resistance training and curcumin supplementation on the liver biochemical markers levels and structure in older women with non-alcoholic fatty liver disease. *J. Bodyw. Mov. Ther*., **24**, 154–160.

[144] Panahi, Y. *et al*. (2019) Curcuminoids plus piperine improve nonalcoholic fatty liver disease: A clinical trial. *J. Cell. Biochem.*, **120**, 15 989–15 996.

[145] Hariri, M., Gholami, A., Mirhafez, S. R., Bidkhori, M. & Sahebkar, A. (2020) A pilot study of the effect of curcumin on epigenetic changes and DNA damage among patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled, clinical trial. *Complement. Ther. Med.,* **51**, 102 447.

[146] Mousavi, S. M., Milajerdi, A., Varkaneh, H. K., Gorjipour, M. M. & Esmaillzadeh, A. (2020) The effects of curcumin supplementation on body weight, body mass index and waist circumference: A systematic review and dose-response meta-analysis of randomized controlled trials. *Crit. Rev. Food Sci. Nutr.*, **60**, 171–180.

[147] Shirmohammadi, L. *et al*. (2020) Effect of curcumin on serum cathepsin D in patients with metabolic syndrome. Cardiovasc. *Hematol. Disord. Drug Targets*, **20**, 116–121.

[148] Ramaholimihaso, T., Bouazzaoui, F. & Kaladjian, A. (2020) Curcumin in depression: Potential mechanisms of action and current evidence−a narrative review. *Front. Psychiatry,* **11**, 572 533.

[149] Malhi, G. S. & Mann, J. J. (2018) Depression. *Lancet (London, England),* **392**, 2299–2312 .

[150] Fusar-Poli, L. *et al*. (2020) Curcumin for depression: A meta-analysis. *Crit. Rev. Food Sci. Nutr.*, **60**, 2643–2653.

[151] Ng, Q. X., Koh, S. S. H., Chan, H. W. & Ho, C. Y. X. (2017) Clinical use of curcumin in depression: A meta-analysis. *J. Am. Med. Dir. Assoc.*, **18**, 503–508.

[152] Latif, R., Mumtaz, S., Al Sheikh, M. H., Chathoth, S. & Nasser Al Naimi, S. (2020) Effects of turmeric on cardiovascular risk factors, mental health, and serum homocysteine in overweight, obese females. *Altern. Ther. Health Med.*

[153] Asadi, S., Gholami, M. S., Siassi, F., Qorbani, M. & Sotoudeh, G. (2020) Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial. *Phytother. Res.*, **34**, 896–903.

[154] Ataei-Almanghadim, K., Farshbaf-Khalili, A., Ostadrahimi, A. R., Shaseb, E. & Mirghafourvand, M. (2020) The effect of oral capsule of curcumin and vitamin E on the hot flashes and anxiety in postmenopausal women: A triple blind randomised controlled trial. *Complement. Ther. Med.*, **48**, 102 267.

[155] Miodownik, C. *et al*. (2019) Curcumin as add-on to antipsychotic treatment in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *Clin. Neuropharmacol.,* **42**, 117–122.

[156] Amirchaghmaghi, M., Pakfetrat, A., Delavarian, Z., Ghalavani, H. & Ghazi, A. (2016) Evaluation of the efficacy of curcumin in the treatment of oral lichen planus: A randomized controlled trial. *J. Clin. Diagn. Res*., **10**, ZC134–ZC137.

[157] Chainani-Wu, N. *et al*. (2007) A randomized, placebo-controlled, double-blind clinical trial of curcuminoids in oral lichen planus. *Phytomedicine*, **14**, 437–446.

[158] Chainani-Wu, N., Madden, E., Lozada-Nur, F. & Silverman, S. (2012) High-dose curcuminoids are efficacious in the reduction in symptoms and signs of oral lichen planus. *J. Am. Acad. Dermatol.*, **66**, 752–760.

[159] Kia, S. J., Basirat, M., Mortezaie, T. & Moosavi, M.-S. (2020) Comparison of oral nano-curcumin with oral prednisolone on oral lichen planus: A randomized double-blinded clinical trial. BMC *Complement. Med. Ther.*, **20**, 328.

[160] Bahraini, P. *et al*. (2018) Turmeric tonic as a treatment in scalp psoriasis: A randomized placebo-control clinical trial. *J. Cosmet. Dermatol.*, **17**, 461–466.

[161] Antiga, E., Bonciolini, V., Volpi, W., Del Bianco, E. & Caproni, M. (2015) Oral curcumin (Meriva) is effective as an adjuvant treatment and is able to reduce IL-22 serum levels in patients with psoriasis vulgaris. *Biomed Res. Int.,* **2015**, 283 634.

[162] Bilia, A. R., Bergonzi, M. C., Isacchi, B., Antiga, E. & Caproni, M. (2018) Curcumin nanoparticles potentiate therapeutic effectiveness of acitrein in moderate-to-severe psoriasis patients and control serum cholesterol levels. *J. Pharm. Pharmacol.,* **70**, 919–928.

[163] Ramírez-Boscá, A. *et al*. (2017) Efficiency and safety of a Curcuma extract combined with visible blue light phototherapy on adults with plaque psoriasis: A phase IV, randomized, open pilot clinical trial. *J. Dermatol.,* **44**, 1177–1178.

[164] Carrion-Gutierrez, M. *et al*. (2015) Effects of Curcuma extract and visible light on adults with plaque psoriasis. *Eur. J. Dermatol.*, **25**, 240–246.

[165] Soleimani, V., Sahebkar, A. & Hosseinzadeh, H. (2018) Turmeric *(Curcuma longa)* and its major constituent (curcumin) as nontoxic and safe substances: Review. *Phytother. Res.,* **32**, 985–995.

[166] Lombardi, N. *et al*. (2020) Acute liver injury following turmeric use in Tuscany: An analysis of the Italian Phytovigilance database and systematic review of case reports. *Br. J. Clin. Pharmacol.,* doi:10.1111/bcp.14460.

[167] Turmeric (curcumin). naturalmedicines.*therapeuticresearch.com* https://naturalmedicines.therapeuticresearch.com/databases/commercial-products/commercial-product.aspx?cpid=150165.

[168] Pagano, E., Romano, B., Izzo, A. A. & Borrelli, F. (2018) The clinical efficacy of curcumin-containing nutraceuticals: An overview of systematic reviews. *Pharmacol. Res.,* **134**, 79–91 .

[169] Menniti-Ippolito, F. *et al*. (2020) Turmeric *(Curcuma longa L.)* food supplements and hepatotoxicity: An integrated evaluation approach. *Ann. Ist. Super. Sanita,* **56**, 462–469 .

[170] Donelli, D., Antonelli, M. & Firenzuoli, F. (2020) Considerations about turmeric-associated hepatotoxicity following a series of cases occurred in Italy: Is turmeric really a new hepatotoxic substance? *Intern. Emerg. Med*., **15**, 725–726.

[171] Cowell, W., Ireland, T., Vorhees, D. & Heiger-Bernays, W. (2017) Ground turmeric as a source of lead exposure in the United States. *Public Health Rep.*, **132**, 289–293.

[172] Gleason, K. *et al*. (2014) Contaminated turmeric is a potential source of lead exposure for children in rural Bangladesh. *J. Environ. Public Health,* **2014**, 730 636.

[173] National Centre for Complementary and Integrative Medicine. (2020) Turmeric. *National Institutes of Health* https://www.nccih.nih.gov/health/turmeric.

[174] Tossetta, G., Fantone, S., Giannubilo, S. R. & Marzioni, D. (2021) The multifaced actions of curcumin in pregnancy outcome. *Antioxidants (Basel, Switzerland),* **10**, 126.

[175] Bumrungpert, A., Somboonpanyakul, P., Pavadhgul, P. & Thaninthranon, S. (2018) Effects of fenugreek, ginger, and turmeric supplementation on human milk volume and nutrient content in breastfeeding mothers: A randomized double-blind controlled trial. *Breastfeed. Med.,* doi:10.1089/bfm.2018.0159.