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REVIEW ARTICLE

Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases

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Curcumin, a yellow pigment in the Indian spice Turmeric (*Curcuma longa*), which is chemically known as diferuloylmethane, was first isolated exactly two centuries ago in 1815 by two German Scientists, Vogel and Pelletier. However, according to the pubmed database, the first study on its biological activity as an antibacterial agent was published in 1949 in *Nature* and the first clinical trial was reported in *The Lancet* in 1937. Although the current database indicates almost 9000 publications on curcumin, until 1990 there were less than 100 papers published on this nutraceutical. At the molecular level, this multitargeted agent has been shown to exhibit anti-inflammatory activity through the suppression of numerous cell signalling pathways including NF-κB, STAT3, Nrf2, ROS and COX-2. Numerous studies have indicated that curcumin is a highly potent antimicrobial agent and has been shown to be active against various chronic diseases including various types of cancers, diabetes, obesity, cardiovascular, pulmonary, neurological and autoimmune diseases. Furthermore, this compound has also been shown to be synergistic with other nutraceuticals such as resveratrol, piperine, catechins, quercetin and genistein. To date, over 100 different clinical trials have been completed with curcumin, which clearly show its safety, tolerability and its effectiveness against various chronic diseases in humans. However, more clinical trials in different populations are necessary to prove its potential against different chronic diseases in humans. This review's primary focus is on lessons learnt about curcumin from clinical trials.

LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviation

MCP, monocyte chemoattractant protein

DOI:10.1111/bph.13621

Tables of Links

TARGETS	
Enzymes[a]	**G protein-coupled receptors**[b]
5-LOX	CXCR4
COX-2	MCP-1 receptor (CCR2)
Cytosolic PLA2	**Nuclear hormone receptors**[c]
DNMTs	AR
ERK	ER-α
FAK	PPAR-γ
HATs	**Other protein targets**[d]
HDACs	Bcl-2
iNOS	Bcl-xL
JAK	IAP
JNK	TNF-α
ODC	XIAP
p38 MAPK	**Catalytic receptors**[e]
PKA (Akt)	EGFR
PKC	ROS receptors
uPA	

LIGANDS	
EGF	IL-6
ICAM-1	IL-12
IL-1β	Nrf2
IL-2	VCAM-1
IL-5	β-catenin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016) and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

Despite the substantial advances in the treatment of complex, multigenic and chronic human diseases, their occurrence rate has increased significantly in recent times (Gupta *et al.*, 2012). A number of mono-targeted therapies, also referred to as 'smart drugs', have been designed over the past few years for the treatment of these chronic diseases. However, complex diseases like cardiovascular, metabolic, cancer and neurological diseases occur due to perturbations of multiple signalling pathways. Therefore, targeting a single pathway among many of the pathways involved is not likely to be effective for the prevention and treatment of these diseases (Bordoloi *et al.*, 2016). Besides, high cost and adverse side effects are the other major disadvantages associated with these smart drugs. These limitations necessitate the urge to develop multi-targeted, cost-effective, readily available, non-toxic and highly potent agents for the management of different human diseases (Gupta *et al.*, 2012).

Among the numerous natural remedies, turmeric has gained considerable attention due to its profound medicinal values (Prasad *et al.*, 2014a). This agent possesses antioxidant, anti-inflammatory, anticancer, antigrowth, antiarthritic, antiatherosclerotic, antidepressant, antiaging, antidiabetic, antimicrobial, wound healing and memory-enhancing activities (Aggarwal *et al.*, 2013a). Moreover, it exerts chemopreventive, chemosensitization and radiosensitization effects as well (Goel and Aggarwal, 2010; Gupta *et al.*, 2011a). In traditional Indian medicine, this spice has been also used to treat different ailments such as gynecological problems, gastric problems, hepatic disorders, infectious diseases, blood disorders, acne, psoriasis, dermatitis, rash and other chronic ailments (Gupta *et al.*, 2013a). Diverse *in vivo* studies have also indicated its potential against pro-inflammatory diseases, cancers, neurodegenerative diseases, depression, diabetes, obesity and atherosclerosis (Gupta *et al.*, 2013c). Among the huge number of compounds isolated from turmeric (Tyagi *et al.*, 2015), curcumin (a diferuloylmethane) was found to be the most widely studied compound as evinced by more than 9000 citations in the literature. It was first discovered by Vogel and Pelletier from the rhizomes of turmeric (*Curcuma longa*) (Prasad *et al.*, 2014b). Structurally, it can exist in at least two tautomeric forms, keto and enol and they possess antioxidant, anti-inflammatory, anticancer, antiviral, antibacterial and antidiabetic properties (Aggarwal *et al.*, 2008; Goel *et al.*, 2008; Gupta *et al.*, 2010; Gupta *et al.*, 2012; Aggarwal *et al.*, 2013b; Rainey *et al.*, 2015). These traits can possibly be attributed to the methoxy, hydroxyl, α, β-unsaturated carbonyl moiety or diketone groups present in curcumin (Aggarwal *et al.*, 2015). Besides its safety and tolerability, cost-effectiveness is an added advantage of this compound (Shoba *et al.*, 1998; Rasyid and Lelo, 1999; Rasyid *et al.*, 2002; Lao *et al.*, 2006; Tuntipopipat *et al.*, 2006; Juan *et al.*, 2007; Vareed *et al.*, 2008; Shimouchi *et al.*, 2009; Dominiak *et al.*, 2010; Cuomo *et al.*, 2011; Pungcharoenkul and Thongnopnua, 2011; Sasaki *et al.*, 2011; DiSilvestro *et al.*, 2012; Kusuhara *et al.*, 2012; Sugawara *et al.*, 2012; Vitaglione *et al.*, 2012; Aggarwal *et al.*, 2013a; Jager *et al.*,

2014; Klickovic *et al.*, 2014). Because of its amazing properties, curcumin is being marketed in several countries of the world in various forms (Prasad *et al.*, 2014b).

However, the utility of curcumin is greatly hindered by its colour, lack of water solubility and low bioavailability (Anand *et al.*, 2008). Prime factors contributing towards the low bioavailability of curcumin in both plasma and tissue might be associated with its poor absorption, rapid metabolism and rapid systemic elimination. Therefore, to enhance these, various approaches have been sought that include the use of adjuvants, liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complexes, curcumin reformulated with various oils and with inhibitors of metabolism, conjugation of curcumin prodrugs and linking curcumin with polyethylene glycol (Anand *et al.*, 2007; 2008; Goel *et al.*, 2008; Nair *et al.*, 2010). The use of structural analogues of curcumin and synthesis of 'man-made' curcumin analogues also play a role in the enhancement of its bioavailability. For instance, the natural analogues of curcumin such as demethoxycurcumin and bidemethoxycurcumin were reported to have a similar biological activity to curcumin (Kocaadam and Şanlier, 2015). Furthermore, it has been proposed that the presence of an active methylene group and β-diketone moiety causes curcumin to be unstable under physiological conditions together with its poor absorption and rapid metabolism. Supporting this proposal, more recently, different structural modifications were performed and many of the active methylene and carbonyl substituted curcumin derivatives/analogues were found to exert much improved antioxidant activity when compared with curcumin (Sahu *et al.*, 2016). Thus, diverse synthetic derivatives of curcumin can be obtained with various chemical modifications including phenolic hydroxyl groups, acylation, alkylation, glycosylation and amino acylation to improve its bioavailability (Kocaadam and Şanlier, 2015).

Molecular targets of curcumin

Curcumin can impact a diverse range of molecular targets and signalling pathways, which augment the efficacy of existing chemotherapeutic agents (Figure 1). It can interact with a huge number of different proteins such as nuclear factor E2-related factor 2 (Nrf2), β-catenin, NF-κB, p38 MAPK, DNA (cytosine-5)-methyltransferase-1, COX-2, 5-lipoxygenase, PGE_2, FOXO3, inducible NOS, ROS, cyclin D1, VEGF, glutathione, cytosolic PLA2, p-Tau (p-τ) and TNF-α. This ability of curcumin facilitiates selective modulation of multiple cell signalling pathways linked to different chronic diseases, which strongly suggest that it is a potent multi-targeted polyphenol (Anand *et al.*, 2008; Kunnumakkara *et al.*, 2008; Ravindran *et al.*, 2009; Goel and Aggarwal, 2010; Hasima and Aggarwal, 2012; Aggarwal *et al.*, 2015; Rainey *et al.*, 2015). The common molecular targets of curcumin include transcription factors, inflammatory mediators, protein kinases and enzymes like protein reductases and histone acetyltransferase (Goel *et al.*, 2008; Yadav and Aggarwal, 2011; Gupta *et al.*, 2011b; 2012). A plausible mechanism through which curcumin exerts its manifold effects might be via epigenetic regulation (Tuorkey, 2014). Many recent studies have reported curcumin as a potent epigenetic regulator in different diseases, such as neurological disorders, inflammation, diabetes and different cancer types. The epigenetic regulatory roles of curcumin primarily include inhibition of DNA methyltransferases, regulation of histone modifications via effects on histone acetyltransferases and histone deacetylases and regulation of micro RNAs (Reuter *et al.*, 2011; Boyanapalli and Tony Kong, 2015; Remely *et al.*, 2015). Curcumin also modulates various proteosomal pathways (Hasima and Aggarwal, 2014) and impairs glycogen metabolism through selective inhibition of phosphorylase kinase (Reddy and Aggarwal, 1994). Nonetheless, it has been shown to exhibit anti-inflammatory effects by down-regulating various cytokines, such as TNF-α, IL-1, IL-6, IL-8, IL-12, monocyte chemoattractant protein (MCP)-1 (also known as CCL2) and IL-1β, and various inflammatory enzymes and transcription factors (Bharti *et al.*, 2004; Davis *et al.*, 2007; Aggarwal and Sung, 2009; Gupta *et al.*, 2011a; 2014).

Numerous preclinical and clinical studies have shown the effectiveness of curcumin in the prevention and treatment of various human diseases; however, the main focus of this review is the lessons learnt from clinical trials.

Clinical studies with curcumin

Encouraging outcomes of preclinical studies have engendered ample clinical trials of curcumin to evaluate its safety and efficacy against a diverse range of human diseases (Figure 2; Tables 1 and 2). Approximately 120 clinical trials have been successfully carried out so far, involving more than 6000 human participants. In addition, there are several systematic reviews/meta-analyses based on the clinical trials of curcumin for human data (Table 2).

Safety and adequate daily intake (ADI) value of curcumin as well as its derivatives

In general the consumption of curcumin is considered to be safe. As per JECFA (The Joint FAO/WHO Expert Committee on Food Additives) and EFSA (European Food Safety Authority) reports, the ADI value of curcumin is 0–3 $mg \cdot kg^{-1}$ (Kocaadam and Şanlier, 2015). In addition, the safety and efficacy of curcumin was evaluated in several clinical trials involving healthy human subjects. For instance, in one such study in healthy human volunteers, the effect of curcumin combined with piperine was measured; this increased the bioavailabilty of curcumin by approximately 2000% without causing any adverse effects (Shoba *et al.*, 1998). Furthermore, curcumin was found to exhibit positive cholekinetic effect as it induced a significant contraction of the human gall-bladder (Rasyid and Lelo, 1999). At the dosage of 40 mg, curcumin evoked a 50% contraction of the gall bladder (Rasyid *et al.*, 2002). A dose-response study was undertaken to detect the maximum tolerated dose and safety of a single dose of standardized powder extract; uniformly-milled curcumin was administered to healthy volunteers at doses ranging from 500 to 12 000 mg and it was found to be profoundly well tolerated (Lao *et al.*, 2006). Concomitant administration of curcumin and talinolol reduced the bioavailability of talinolol possibly due to the low intraluminal curcumin concentration or an up-regulation of further

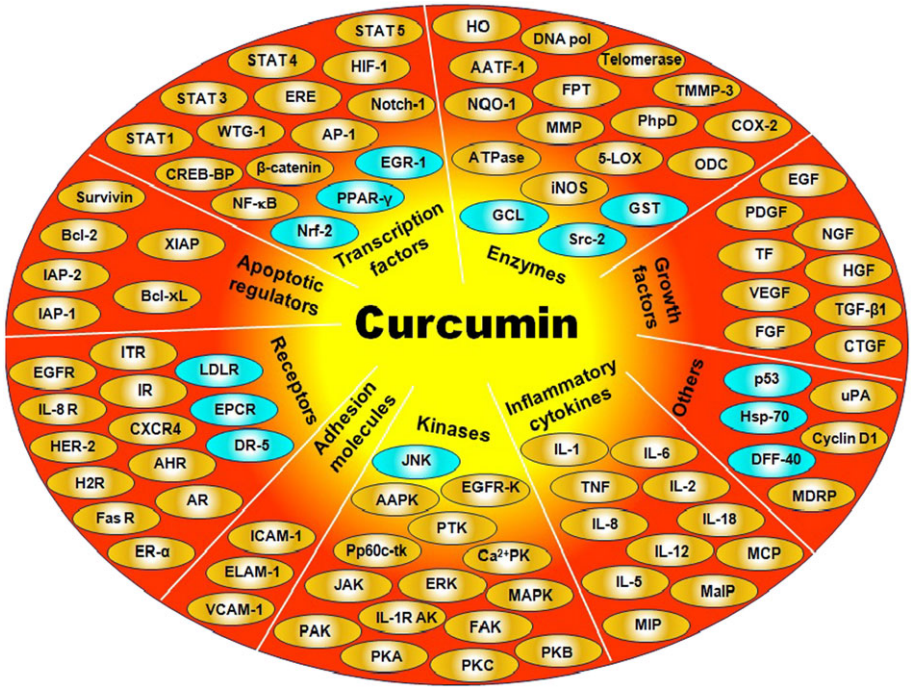

Figure 1

Molecular targets of curcumin. 5-LOX, 5-lipoxygenase; AAPK, autophosphorylation-activated protein kinase; AATF-1, arylamine N-acetyltransferases-1; AHR, aryl hydrocarbon receptor; AP-1, activating protein-1; AR, androgen receptor; Bcl-2, beta-cell lymphoma protein 2; Bcl-xL, beta-cell lymphoma extra large; Ca2+PK, Ca2+-dependent protein kinase; CXCR4, chemokine (C-X-C motif) receptor 4; CREB-BP, CREB-binding protein; CTGF, connective tissue growth factor; DFF-40, DNA fragmentation factor 40-kd subunit; DR5, death receptor-5; ELAM-1, endothelial leukocyte adhesion molecule-1; EPCR, endothelial protein C-receptor; ERE, electrophile response element; ER-α, estrogen receptor-alpha; FAK, focal adhesion kinase; FPT, farnesyl protein transferase; FR, Fas receptor; GCL, glutamyl cysteine ligase; GST, gluthathione-S-transferase; H2R, histamine (2)-receptor; HER-2, human epidermal growth factor receptor-2; HGF, hepatocyte growth factor; HIF-1, hypoxia inducible factor-1; HO, haem oxygenase 1; HSP-70, heat-shock protein 70; IAP-1, inhibitory apoptosis protein-1; ICAM-1, intracellular adhesion molecule-1; iNOS, inducible NOS; IR, integrin receptor; MaIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; MDRP, multi-drug resistance protein; MIP, migration inhibition protein; NGF, nerve growth factor; NQO-1, NAD(P)H:quinoneoxidoreductase-1; Nrf, nuclear factor 2-related factor; ODC, ornithine decarboxylase; PAK, protamine kinase; PhpD, phospholipase D; Pp60c-tk, pp60c-src tyrosine kinase; PTK, protein tyrosine kinase; Src-2, Src homology 2 domain-containing tyrosine phosphatase 2; STAT, signal transducer and activator of transcription; TF, tissue factor; TMMP-3, tissue inhibitor of metalloproteinase-3; uPA, urokinase-type plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; WTG-1, Wilms' tumour gene 1.

ATP-binding cassette transporters in different tissues (Juan *et al.,* 2007). Another study was attempted to evaluate the pharmacokinetics of a curcumin preparation in healthy human volunteers for up to 72 h following a single oral dose of curcumin. It was found to be absorbed after oral dosing in humans and was detected in plasma as glucuronide and sulfate conjugates (Vareed *et al.,* 2008). Moreover, dietary turmeric was shown to activate bowel motility as well as carbohydrate colonic fermentation (Shimouchi *et al.,* 2009). In addition, the ingestion of a capsule containing curcumin (30%), resveratrol (15%), EGCG (30%) and soybean extract (25%) was found to exert a protective effect against oxidative stress in normal healthy adults (Dominiak *et al.,* 2010). Treatment with curcumin (500 mg·day^{-1}) also markedly lowers serum cholesterol and triglyceride levels in healthy human subjects (Pungcharoenkul and Thongnopnua, 2011). The efficacy of curcumin dispersed with colloidal nano-particles, known as Theracurmin was also investigated in terms of absorption and was compared with that of curcumin powder. However, the former showed a much higher bioavailability and thus may be of immense use with ample clinical benefits in humans even at a very low dose (Sasaki *et al.,* 2011). Meriva, the lecithin formulation of a standardized curcuminoid mixture also exhibited a much improved absorption and plasma curcuminoid profile at significantly lower doses (Cuomo *et al.,* 2011). Another trial in healthy middle aged people showed that treatment with curcumin caused a marked reduction in plasma triglyceride values, salivary amylase levels, plasma β amyloid protein concentrations, plasma sICAM readings, plasma alanine amino transferase activities and increased salivary radical scavenging capacities, plasma catalase activities, plasma myeloperoxidase without increasing C-reactive protein (CRP) levels or plasma nitric oxide (DiSilvestro *et al.,* 2012). Regular endurance exercise together with daily curcumin administration caused a marked reduction in left ventricular afterload (Sugawara *et al.,* 2012). A formulation of curcumin in combination with a hydrophilic carrier, cellulosic derivatives and natural antioxidants was shown to enhance the bioavailability of curcumin in blood (Jager *et al.,* 2014). On the other hand, another study indicated that the short term use of a piperine-enhanced curcuminoid preparation is

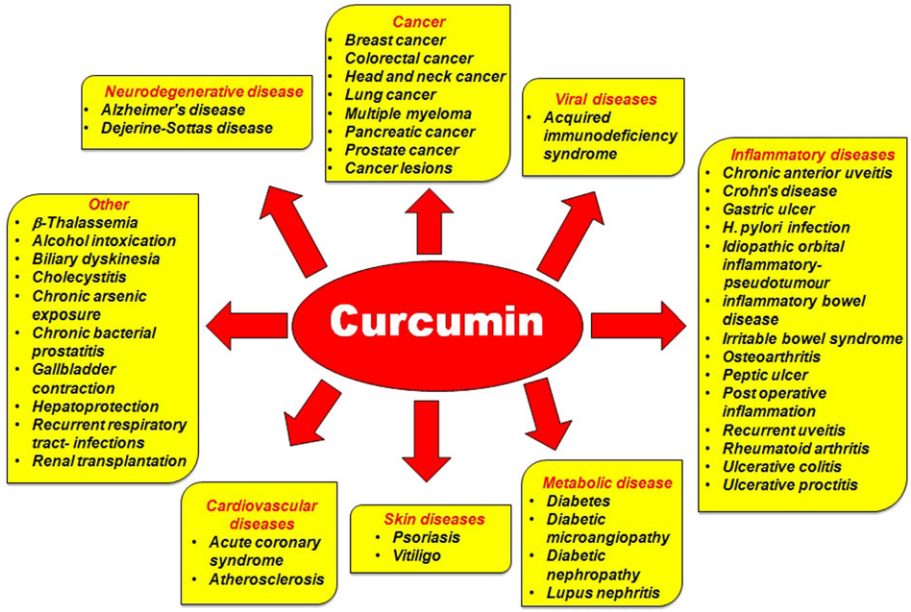

Figure 2
Activity of curcumin against different human diseases based on clinical findings.

ineffective at producing a clinically significant interaction involving CYP3A, CYP2C9 or the paracetamol conjugation enzymes (Volak *et al.,* 2013). Also in another clinical trial, oral curcumin administration was linked with poor bioavailability and was shown not to increase haemoxygenase 1 (HO-1) in peripheral blood mononuclear cells (Klickovic *et al.,* 2014).

Curcumin for cancer

Cancer is one of the prime health concerns today, affecting people of all ages worldwide. The first clinical trial on curcumin was done by Kuttan and colleagues in 1987 by enrolling 62 patients with external cancerous lesions to investigate its potential against cancer. An ethanolic extract of turmeric and an ointment of curcumin caused significant symptomatic relief in these patients along with a reduction in itching and smell. In 70% of the patients, dry lesions were observed and in a few cases, a reduction in lesion size and pain was observed (Kuttan *et al.*, 1987). Henceforth, numerous clinical trials have been carried out using curcumin and its ability to affect multiple targets has enabled it to exert notable activities against different cancer types in human clinical trials (Gupta *et al.*, 2012).

Cervical cancer. Cervical cancer is the second most common form of malignancy in women worldwide. Curcumin exhibits potent effects against this cancer *in vitro, in vivo* and in clinical settings. From an initial study, a dose of 500–12 000 mg·day^{-1} of curcumin was found to be safe, well tolerated and have chemopreventive properties against cervical cancer (Cheng *et al.*, 2001). In another study, when HPV-positive cervical neoplasia patients were treated with Basant polyherbal vaginal cream (containing extracts of curcumin, reetha, amla and *Aloe vera*), HPV clearance rate was found to be significantly high with no adverse side effects (Basu *et al.*, 2013). These studies showed curcumin to be a safe and efficacious compound for the prevention and treatment of cervical cancer.

Colon cancer. Colon cancer ranks third among the most commonly occurring cancers in the world. Despite significant advances in cancer therapy, mortality from colon cancer persists at the same level, highlighting the necessity of improved therapies (Nautiyal *et al.*, 2011). The efficacy of oral curcumin (2 g or 4 g daily for 30 days) in the prevention of colorectal neoplasia was evaluated in a nonrandomized, open-label clinical trial enrolling 44 patients. The results showed a marked reduction in ACF number with 4 g dose of curcumin, which was possibly associated with its increased bioavailabity (fivefold) in plasma (Carroll *et al.*, 2011). A dose-response study was designed to investigate the pharmacology of curcumin in humans with doses ranging from 0.45–3.6 g·day^{-1} up to 4 months. A dose of 3.6 g curcumin per day caused 62 and 57% decrease in inducible PGE_2 production in blood samples taken 1 h after dosing on days 1 and 29, respectively with no dose limiting toxicities (Sharma *et al.*, 2004). Similarly in another pilot dose-response study with curcuma extract in advanced colorectal cancer, the production of basal and LPS-mediated PGE_2 was significantly reduced in a dose-dependent manner (Plummer *et al.*, 2001). Administration of curcumin caused a reduction in M(1)G levels in malignant colorectal tissue, whereas COX-2 protein levels in malignant colorectal tissue remained unaltered (Garcea *et al.*, 2005). Furthermore, curcumin treatment has a significant impact on improving the general health of colorectal cancer patients by enhancing expression of p53 molecules in tumour cells and consequently promoting the apoptosis of tumour cells (He *et al.*, 2011). In colorectal mucosa, pharmacologically active

Table 1

Curcumin clinical trials in patients with various chronic diseases

Disease	Curcumin dose	Pts (#)	Clinical outcome	References
Safety and tolerability				
Healthy volunteers	2 g[b,d]	10	Safe and highly bioavailable	Shoba *et al.*, 1998
	20 mg[d]	12	Safe and induced gall-bladder contraction	Rasyid and Lelo, 1999
	20, 40, 80 mg[d]	12	Safe and increased gall-bladder contraction	Rasyid *et al.*, 2002
	0.5 g; 2 days[c]	10	Safe and no effect on iron absorption	Tuntipopipat *et al.*, 2006
	500–12 000 mg[d]	24	Safe and well tolerated	Lao *et al.*, 2006
	300 mg·day^{-1}; 6 days[b]	12	Safe	Juan *et al.*, 2007
	10 and 12 g[d]	12	Safe and improved absorption	Vareed *et al.*, 2008
	500 mg[b,c,d]	8	Safe and activated bowel motility	Shimouchi *et al.*, 2009
	150 mg·day^{-1}; 2 weeks[b]	11	Safe and well tolerated	Dominiak *et al.*, 2010
	0.5–6 g·day^{-1}; 7 days	24	Safe and decreased lipid levels	Pungcharoenkul and Thongnopnua, 2011
	30 mg[a,d]	14	Safe and bioavailable	Sasaki *et al.*, 2011
	3 × 209–376 mg·day^{-1}[a]	9	Safe and improved absorption	Cuomo *et al.*, 2011
	80 mg·day^{-1}; 4 weeks	38	Safe and have multiple health benefits	DiSilvestro *et al.*, 2012
	150 mg·day^{-1}; 8 weeks	45	Safe and improved BP and heart rate	Sugawara *et al.*, 2012
	1 g[d]	10	Safe and bioavailable	Vitaglione *et al.*, 2012
	2 g[b,d]	8	Safe and bioavailable	Kusuhara *et al.*, 2012
	4 × 4 g; 2 days[b]	8	Safe and highly bioavailable	Volak *et al.*, 2013
	376 mg[a,d]	15	Safe and bioavailable	Jager *et al.*, 2014
	12 g[a,d]	10	Safe and well tolerated	Klickovic *et al.*, 2014
Cancer				
BPH	1 g·day^{-1}; 24 weeks[b]	61	Reduced signs and symptoms	Ledda *et al.*, 2012
Breast	6 g·day^{-1}; 7 days[b]	14	Safe and well tolerated	Bayet-Robert *et al.*, 2010
Cancerous lesions	Ointment	62	Reduced lesion size and pain	Kuttan *et al.*, 1987
	0.5–1.2 g·day^{-1}; 3 months	25	Well tolerated and efficacious	Cheng *et al.*, 2001
Cervical	500 mg·day^{-1}; 30 days	280	Increased HPV clearance rate	Basu *et al.*, 2013
CML	3 × 5 g; 6 weeks[c]	50	Reduced nitric oxide levels	Ghalaut *et al.*, 2012
Colorectal	220 mg·day^{-1}; 29 days[a]	15	Inhibited basal and LPS-induced PGE_2	Plummer *et al.*, 2001
	2.2 g·day^{-1}[c]; 4 months	15	Well tolerated	Sharma *et al.*, 2001
	0.45, 3.6 g·day^{-1}; 4 months	15	Well tolerated and efficacious	Sharma *et al.*, 2004
	0.45, 1.8, 3.6 mg·day^{-1}; 7 days	12	Inhibited inflammation and DNA damage	Garcea *et al.*, 2005
	1.08 g·day^{-1}; 10–30 days	26	Improved the general health	He *et al.*, 2011
	2 or 4 g·day^{-1}; 30 days	44	40% reduction in ACF number	Carroll *et al.*, 2011
	2.35 g·day^{-1}; 14 days	26	High levels of curcumin were recovered	Irving *et al.*, 2013
HNSCC	2 g[d]	39	Decreased IKKβ kinase activity in saliva	Kim *et al.*, 2011
Pancreatic	8 g·day^{-1}; 8 weeks	25	Safe, well tolerated and efficacious	Dhillon *et al.*, 2008
	8 g·day^{-1}; 4 weeks[b]	17	Showed partial response and stable disease	Epelbaum *et al.*, 2010
	8 g·day^{-1}; 14 days every 3 weeks[b]	21	Safe and well tolerated	Kanai *et al.*, 2011
	0.2–0.4 g·day^{-1}; 9 months	16	Safe and well tolerated	Kanai *et al.*, 2013
Prostate	100 mg·day^{-1}; 6 months[b]	85	Reduced serum PSA levels	Ide *et al.*, 2010
	3 g·day^{-1}; 3 months	40	No significant effect	Hejazi *et al.*, 2016

(continues)

Table 1 (Continued)

Disease	Curcumin dose	Pts (#)	Clinical outcome	References
Solid tumours	3 × 100 mg·day^{-1};4 months[a]	160	Decreased side effects of chemotherapy	Belcaro *et al.*, 2014
	180 mg·day^{-1}; 8 weeks	80	Improved quality of life	Panahi *et al.*, 2014c
Cardiovascular disease				
ACS	15–60 mg·day^{-1}; 2 years	75	Reduced total and LDL cholesterol	Alwi *et al.*, 2008
AMI	4 g·day^{-1}; 7 days	121	Inhibited MI associated with CABG	Wongcharoen *et al.*, 2012
CVH	180 g[c,d]	14	Improves postprandial endothelial function	Nakayama *et al.*, 2014
Dyslipidemia	1 g·day^{-1}; 30 days	30	Decreased triglycerides level	Mohammadi *et al.*, 2013
Metabolic and CVH	0.9 g·day^{-1}; 24 weeks[b]	56	No effect	Soare *et al.*, 2014
MS	1890 mg·day^{-1}; 12 weeks	65	Lowered lipid level	Yang *et al.*, 2014
	1000 mg·day^{-1}; 8 weeks[b]	100	Effective as adjunctive therapy	Panahi *et al.*, 2014a
Inflammatory diseases				
Bronchial asthma	500 mg·day^{-1}; 30 days	77	Decreased airway obstruction	Abidi *et al.*, 2014
CKD	2 × 824 mg·day^{-1}; 8 weeks[b]	16	Safe and well tolerated	Moreillon *et al.*, 2013
Crohn's disease	1.1 and 1.6 g·day^{-1}; 1 month	5	Efficacious	Holt *et al.*, 2005
FAP	3 × 480 mg·day^{-1}; 6 months[b]	5	Decreased number and size of adenomas	Cruz-Correa *et al.*, 2006
Gastritis	3 × 700 mg·day^{-1}; 4 weeks[c]	36	No significant effect	Koosirirat *et al.*, 2010
Gingivitis	Mouthwash	30	Effective in mechanical periodontal therapy	Muglikar *et al.*, 2013
H. pylori infection	2 × 30 mg·day^{-1}; 7 days	25	Improved dyspeptic symptoms	Di Mario *et al.*, 2007
IBD	1–4 g·day^{-1}; 3 weeks	11	Significant decrease in relapse	Suskind *et al.*, 2013
Nephritis	500 mg·day^{-1}; 3 months	24	Decreased proteinuria, haematuria and BP	Khajehdehi *et al.*, 2012
OLP	2000 mg·day^{-1}; 7 weeks	100	Safe and well-tolerated	Chainani-Wu *et al.*, 2007
	6000 mg·day^{-1}	20	Safe, well-tolerated and efficacious	Chainani-Wu *et al.*, 2012b
	2.137 g·day^{-1}; 30 months	53	Efficacious	Chainani-Wu *et al.*, 2012a
Oral mucositis	2 × 10 drops per day[a]; 21 days	7	Well-tolerated and efficacious	Elad *et al.*, 2013
	With honey[b,c]	60	Inhibited oral mucositis	Francis and Williams, 2014
Osteoarthritis	1 g·day^{-1}[a]	100	Safe and efficacious	Belcaro *et al.*, 2010a
	200 mg[a]	50	Efficacious	Belcaro *et al.*, 2010b
	1000 mg·day^{-1}; 3 months	44	Served as adjuvant therapy	Pinsornsak and Niempoog, 2012
	1500 mg·day^{-1}; 4 weeks	185	As effective as ibuprofen	Kuptniratsaikul *et al.*, 2014
	1500 mg·day^{-1}; 3 weeks	40	Safe and efficacious	Panahi *et al.*, 2014b
	180 mg·day^{-1}; 8 weeks[a]	45	Efficacious	Nakagawa *et al.*, 2014
	2 × 126 mg·day^{-1}; 3 months	22	Significant improvement	Henrotin *et al.*, 2014
Pancreatitis	0.5 g·day^{-1}; 6 weeks[b]	20	Reduced MDA and increased GSH	Durgaprasad *et al.*, 2005
Peptic ulcer	3 g·day^{-1}; 4–12 weeks	45	Alleviated abdominal pain and discomfort	Prucksunand *et al.*, 2001
Periodontitis	2% gel[c]	37	Effective in scaling and root planing	Behal *et al.*, 2011
	1%·week^{-1}; 3 weeks[a]	23	Mild to moderate beneficiary effect	Gottumukkala *et al.*, 2013
	1%; 1, 3 and 6 months[a]	20	Inhibited growth of oral bacteria	Bhatia *et al.*, 2014
	50 mg·cm^{-2}; 6 months[a]	60	Reduced plaque and gingival index scores	Gottumukkala *et al.*, 2014
Plaque	2 × 0.1%; 21 days[c]	100	Prevented plaque and gingivitis	Waghmare *et al.*, 2011
Prostatitis	200 mg·day^{-1}; 14 days[b]	284	Improved efficacy of prulifloxacin	Cai *et al.*, 2009

(continues)

Table 1 (Continued)

Disease	Curcumin dose	Pts (#)	Clinical outcome	References
Pulmonary complication	500 mg; 4 weeks	89	Safe, well-tolerated and efficacious	Panahi *et al.*, 2015b
Rheumatoid arthritis	1.2 g·day^{-1}; 2 weeks	18	Reduced stiffness and joint swelling	Deodhar *et al.*, 1980
	2 × 500 mg·day^{-1}; 8 weeks[b]	45	Reduced DAS and ACR scores	Chandran and Goel, 2012
Ulcerative colitis	2 g·day^{-1}; 6 months	45	Prevented disease relapse	Hanai *et al.*, 2006
	0.5 g·day^{-1}; 1 year	1	Efficacious	Lahiff and Moss, 2011
	140 mg·day^{-1}; 8 weeks[a,b]	45	Safe and efficacious	Singla *et al.*, 2014
	3 g·day^{-1}; 1 month[b]	50	Effective, no adverse effects	Lang *et al.*, 2015
Ulcerative proctitis	1.1 g and 1.65 g·day^{-1}; 1 month	5	Efficacious	Holt *et al.*, 2005
Uveitis	1.125 g·day^{-1}; 12 weeks	53	Efficacy equal to corticosteroid therapy	Lal *et al.*, 1999
	2 × 0.6 g·day^{-1}; 12–18 months	106	Well tolerated and reduced eye discomfort	Allegri *et al.*, 2010
Metabolic disease				
Diabetes	5 g·day^{-1}; 3 months	1	Decreased fasting blood sugar level	Srinivasan, 1972
	600 mg·day^{-1}; 8 weeks	72	Inhibited cytokines and oxidative stress	Usharani *et al.*, 2008
	3 × 500 mg·day^{-1}; 2 months[c]	40	Attenuated proteinuria, TGFβ and IL-8	Khajehdehi *et al.*, 2011
	1.5 g·day^{-1}; 3, 6 and 9 months	240	Safe, well tolerated and efficacious	Chuengsamarn *et al.*, 2012
	300 mg·day^{-1}; 3 months	100	Effective, decreased serum A-FABP level	Na *et al.*, 2014
	2 × 750 mg·day^{-1}; 6 months	240	Lowered the atherogenic risks	Chuengsamarn *et al.*, 2014
	500 mg·day^{-1}; 15–30 days	–	Reduced albumin excretion, activated Nrf2	Yang *et al.*, 2015
	1 g·day^{-1}; 4 weeks[a]	25	Decreased oedema score, improved response	Appendino *et al.*, 2011
	500 mg·day^{-1}; 4 weeks[a]	38	Efficacious	Steigerwalt *et al.*, 2012
Obesity	1 g·day^{-1}; 30 days	30	Decreased oxidative stress	Sahebkar *et al.*, 2013
	1 g·day^{-1}; 4 weeks	30	Improved immune response	Ganjali *et al.*, 2014
	1 g·day^{-1}; 30 days	30	Reduced anxiety	Esmaily *et al.*, 2015
Neurological disease				
Alzheimer's disease	2 and 4 g·day^{-1}; 24 weeks	33	Patients' response yet to be published	Ringman *et al.*, 2005
	1 and 4 g·day^{-1}; 6 months	34	Safe and increased vitamin E level	Baum *et al.*, 2008
Depression	500 mg·day^{-1}; 5 weeks	40	Reduced symptoms	Bergman *et al.*, 2013
	1 g·day^{-1}; 8 weeks	56	Reduced depression	Lopresti *et al.*, 2014
	1000 mg·day^{-1}; 6 weeks	60	Safe and efficacious	Sanmukhani *et al.*, 2014
	10–1000 mg·day^{-1}; 6 weeks[b]	111	Safe and efficacious	Panahi *et al.*, 2015a
	2 × 0.5 g·day^{-1}; 8 weeks	50	Reduced IDS-SR30 score	Lopresti *et al.*, 2015
	2 × 1 g·day^{-1}; 6 weeks	108	Reduced depression	Yu *et al.*, 2015
Skin diseases				
Psoriasis	2 × 1%·day^{-1}; 4 weeks	40	Suppressed PhK activity	Heng *et al.*, 2000
	4.5 g·day^{-1}; 16 weeks[a]	12	Showed response rate 16.7%	Kurd *et al.*, 2008
	2 g·day^{-1}; 12 weeks	63	Effective and decreased serum IL-22 levels	Antiga *et al.*, 2015
Radiation dermatitis	6 g·day^{-1} throughout RT	30	Reduced severity of radiation	Ryan *et al.*, 2013
Vitiligo	2× cream per day; 12 weeks	10	Improved degree of repigmentation	Asawanonda and Klahan, 2010

(continues)

Table 1 (Continued)

Disease	Curcumin dose	Pts (#)	Clinical outcome	References
Infectious diseases				
HIV	2.5 g·day^{-1}; 56 days	40	Well tolerated	James, 1996
Tuberculosis	6 g·day^{-1}; 2–4 months[a]	578	Prevented hepatotoxicity	Adhvaryu *et al.*, 2008
Others				
Arsenic carcinogenicity	2 × 500 mg·day^{-1}; 3 months[b]	286	Reduced DNA damage	Biswas *et al.*, 2010
Cholecystectomy	500 mg every 6 h	50	Improved post-operative pain	Agarwal *et al.*, 2011
CRT	480 mg·day^{-1}; 1 month[b]	43	Improved graft function, reduced rejection	Shoskes *et al.*, 2005
Déjérine-Sottas	50–75 mg·kg^{-1}·day^{-1}; 12 months	1	Improved patient's quality of life	Burns *et al.*, 2009
MGUS and SMM	2 × 2 g·day^{-1}; 3 months	36	Slowed the disease process	Golombick *et al.*, 2012
MGUS	2 × 2 g·day^{-1}; 3 months	26	Reduced paraprotein levels	Golombick *et al.*, 2009
Oxidative stress	90 mg[d]	10	Reduced oxidative stress	Takahashi *et al.*, 2014
PMS	2 capsules·day^{-1}; 7 days	70	Attenuated severity of PMS symptoms	Khayat *et al.*, 2015
Pruritus	1 g·day^{-1}; 4 weeks	96	Safe, effective and anti-inflammatory	Panahi *et al.*, 2012a
Salivary pathogens	1.5 g·L^{-1}	13	Not effective	Araujo *et al.*, 2012
Thalassemia	3 × 500 mg·day^{-1}; 12 months	21	Ameliorated oxidative damage	Kalpravidh *et al.*, 2010
VEF	150 mg·day^{-1}; 8 weeks	32	Improved endothelial function	Akazawa *et al.*, 2012

[a]Curcumin formulation.
[b]Combination.
[c]Turmeric.
[d]Administered once.
AC, arsenic carcinogenicity; ACS, acute coronary syndrome; ACR, American College of Rheumatology; AMI, acute myocardial infarction; BPH, benign prostatic hyperplasia; CABG, coronary artery bypass graft; CBP, chronic bacterial prostatitis; CDAI, clinical disease activity index; CKD, chronic kidney disease; CML, chronic myeloid leukaemia; CP, chronic periodontitis; CRT, cadaveric renal transplantation; CVH, cardiovascular health; DM, diabetic microangiopathy; DR, diabetic retinopathy; DAS, disease activity score; FAP, familial adenomatous polyposis; GSH, glutathione; HC, hepatocellular carcinoma; HM, haematological malignancies; HNSCC, head and neck squamous cell carcinoma; IBD, inflammatory bowel disease; LN, lupus nephritis; MI, myocardial infarction; MDA, malonaldialdehyde; MDD, major depressive disorder; MGUS, monoclonal gammopathy of undetermined significance; MS, metabolic syndrome; OLP, oral lichen planus; PSA, prostate-specific antigen; PMS, premenstrual syndrome; SMM, smoldering multiple myeloma; T2D, type 2 diabetes; THC, tetrahydrocurcuminoid; UC, ulcerative colitis; VEF, vascular endothelial function.

concentrations of curcumin were achieved after administration of curcumin C3 complex (Irving *et al.*, 2013).

Head and neck cancer. Curcumin has also been found to have potential against head and neck cancer, which generally arises in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx. An investigation was carried out by Kim *et al.* to determine the potential anti-inflammatory effect of curcumin in HNSCC patients. Curcumin was found to suppress inflammatory cytokines such as IL-6, IL-8, granulocyte macrophage colony stimulating factor and TNF-α as well as IKKβ kinase in the saliva of patients. They also suggested that IKKβ kinase could be a plausible biomarker for the detection of the effect of curcumin in head and neck cancer as curcumin inhibited IKKβ kinase activity in the saliva of HNSCC patients, and this effect was strongly correlated with the reduced expression of a number of cytokines (Kim *et al.*, 2011).

Pancreatic cancer. Pancreatic cancer is one of the most lethal human cancers and the conventional treatment approaches have had little impact on the course of this aggressive neoplasm (Li *et al.*, 2004). However, new therapeutic strategies based on curcumin seem to hold great promise. Studies have shown that oral curcumin is safe and well-tolerated, and despite its limited absorption has clinical biological effects in pancreatic cancer patients. Its intake causes the down-regulation of NF-κB, COX-2 and phosphorylated STAT3 in peripheral blood mononuclear cells from patients with pancreatic cancer (Dhillon *et al.*, 2008). However, a study conducted by Epelbaum *et al.* to investigate the activity and feasibility of gemcitabine in combination with curcumin in advanced pancreatic cancer patients, suggested that the dose of 8 g curcumin per day is inadvisable and can be reduced by combining it with systemic gemcitabine (Epelbaum *et al.*, 2010). Furthermore, the safety and feasibility of combination therapy using curcumin and gemcitabine was evaluated in a different

Table 2

Systematic review/meta-analyses based on clinical trials of curcumin for human data

Disease	Publications analysed	Outcome	References
Skin health	PubMed and Embase till Aug 2015	Benefits skin health	Vaughn *et al.*, 2016
Depressive disorder	Literature until Aug 2015	Reduces depressive symptoms	Al-Karawi *et al.*, 2016
Circulating TNF-α	PubMed-Medline, Scopus, Web of Science, Google Scholar till Sep 2015	Lowers circulating TNF-α	Sahebkar *et al.*, 2016
Painful conditions	Literature till Sep 2014	Safe and effective	Sahebkar and Henrotin, 2016
Musculoskeletal pain	CINAHL, Embase, CENTRAL, PubMed, Scopus, PsycINFO, Clinicaltrials.gov, unpublished studies	Analysis not completed	Gaffey *et al.*, 2015
IBD	Cochrane Library, Pubmed/Medline, PsychINFO, Scopus through Mar 2014	Effective	Langhorst *et al.*, 2015
Dementia	Medline, Embase, Cochrane till Jul 2013	Safe (Short term use)	Brondino *et al.*, 2014
Diabetes	Medline database in 2013	Effective	Zhang *et al.*, 2013
Blood lipid levels	PubMed-Medline, Scopus, Ovid-AMED, Clinical trial registry, Cochrane through Sep 2012	No effect	Sahebkar, 2014a
Malignant disorders	PubMed, Google J-Gate	–	Ara *et al.*, 2016
Analgesic efficacy and safety	Scopus and Medline till Sep 2014	Safe and effective	Sahebkar and Henrotin, 2016
Circulating CRP levels	PubMed/Medline and Scopus	Reduces circulating CRP levels	Sahebkar, 2014b

CENTRA, Cochrane Central Register of Controlled Trials; CRP, c-reactive protein; IBD, inflammatory bowel disease

study; this contradicted the previous report and suggested 8 g oral curcumin daily combined with gemcitabine-based chemotherapy is extremely safe and practicable enough for pancreatic cancer patients (Kanai *et al.*, 2011). Another group explored the safety of repeated administration of Theracurmin® in those pancreatic or biliary tract cancer patients who failed to respond to standard chemotherapy. Theracurmin® was administered orally, with standard gemcitabine-based chemotherapy, starting with a dose containing 200 mg of curcumin (Level 1) and then increasing the dose to 400 mg of curcumin (Level 2). With this regime, peak plasma curcumin levels at Level 1 was found to be 324 ng·mL^{-1} and, at Level 2, 440 ng·mL^{-1}. No adverse side reactions were observed and three patients continued the treatment for nine months (Kanai *et al.*, 2013).

Other cancers. Curcumin exhibited potential against various other cancers as well in clinical settings. In an attempt to evaluate the clinical efficacy of curcuminoid therapy, a bioavailable-boosted formulation was given to patients with solid tumours of different cancers such as colorectal, gastric, breast, sarcoma, lymphoma, prostate, bladder, oesophagus, ovary, testicles and hepatocellular carcinoma. It was observed that its supplementation suppressed systemic inflammation and significantly improved the quality of life of these patients (Panahi *et al.*, 2014c). In a phase I clinical trial of curcumin in patients with high-risk or pre-malignant lesions of bladder cancer, oral leucoplakia, intestinal metaplasia of the stomach, uterine cervical intraepithelial neoplasm and Bowen's disease, the curcumin treatment was found to improve the histology of precancerous lesions (Cheng *et al.*, 2001). In another study, a lecithinized delivery system of curcumin (Meriva®, Indena S.p.A. - Viale Ortles, Milano, Italy) was shown to alleviate the adverse side effects associated with the chemo- and radiotherapy of different tumours, such as colon, liver, kidney, lung and stomach (Belcaro *et al.*, 2014). Another clinical trial found that a dose of 6 g·day^{-1} of curcumin for seven consecutive days in every 3 weeks in combination with a standard dose of docetaxel was safe, tolerable and highly effective against breast cancer (Bayet-Robert *et al.*, 2010). The administration of curcumin to paediatric patients with relapsed brain tumours undergoing chemotherapy increased their response compared with the institutional controls (Wolff *et al.*, 2012). Curcumin was also shown to possess a potent chemosensitizing effect in a study conducted with 50 chronic myeloid leukaemia patients, where the patients receiving both imatinib and curcumin showed better prognosis with reduced nitric oxide levels than the patients receiving imatinib alone (Ghalaut *et al.*, 2012).

Curcumin for cardiovascular diseases

Cardiovascular diseases, which include acute coronary syndrome, acute myocardial infarction and dyslipidaemia, are the number one cause of mortality worldwide. There are many drugs approved for the treatment of this disease but they are not devoid of severe side effects. Therefore, the effect of curcumin has been studied in patients with this disease.

Acute coronary syndrome. Acute coronary syndrome (ACS) is used to define any group of clinical symptoms compatible with acute myocardial ischaemia (Kumar and Cannon,

2009). In a randomized controlled trial with 75 ACS patients, curcumin was evaluated for its effects on lipid levels. Curcumin was administered to the patients at increasing doses three times a day (low dose 15 mg, moderate dose 30 mg and high dose 60 mg). The findings revealed that curcumin effectively reduced the total cholesterol and low-density lipoprotein cholesterol levels in the patients at low doses when compared with the higher doses (Alwi *et al.*, 2008).

Acute myocardial infarction. Curcuminoid was found to reduce the myocardial infarction associated with coronary artery bypass grafting (CABG) significantly. Wongcharoen *et al.* evaluated the effects of curcuminoids on the frequency of acute myocardial infarction after CABG. A total of 121 patients were enrolled for this trial. The curcuminoid group exhibited lower levels of post-operative C-reactive protein (CRP), malondialdehyde and N-terminal pro-B-type natriuretic peptide levels. These antioxidant and anti-inflammatory effects might contribute to the cardioprotective effects of the curcuminoids (Wongcharoen *et al.*, 2012).

Dyslipidaemia. Dyslipidaemia is a well-established modifiable cardiovascular risk factor. Treatment of this disease is usual for the prevention of cardiovascular diseases (Cicero and Colletti, 2015). The hypolipidaemic activity of curcumin was examined in a randomized, double-blind, placebo-controlled, crossover trial. Supplementation of curcuminoid resulted in a decrease in the concentrations of serum triglycerides without causing any marked impact on the lipid profile, body mass index and body fat (Mohammadi *et al.*, 2013).

Metabolic and cardiovascular health. Although dietary supplements have extensive health benefits, Soare *et al.* observed that a combination of dietary supplements had no cardiovascular or metabolic effects in non-obese relatively healthy individuals. In their study, 24 weeks of dietary supplementation did not influence arterial stiffness or endothelial function, or alter body fat measurements, blood pressure, plasma lipids, glucose, insulin, insulin-like growth factor-1 (IGF1) and markers of inflammation and oxidative stress in non-obese individuals (Soare *et al.*, 2014). In contrast, it has been found that the consumption of curry spices rich in antioxidative compounds like curcumin and eugenol, improves postprandial endothelial function in healthy male subjects, which is beneficial for cardiovascular health. The participants who ate curry had an increased flow-mediated vasodilatation response. Moreover, the presence of spices in the curry did not significantly change the systemic and forearm haemodynamics, or any biochemical parameters (Nakayama *et al.*, 2014).

Regular consumption of curcumin is probably an alternative way of modifying cholesterol-related parameters, as evidenced by a study that measured the effect of curcumin extract on weight, glucose and lipid profiles in patients with metabolic syndrome. At 12 weeks after intake of the curcumin extract, there was an elevation in the high-density lipoprotein cholesterol level, whereas the level of low-density lipoprotein cholesterol was decreased significantly (Yang *et al.*, 2014). In another study conducted with 32 participants, curcumin was shown to increase the vascular endothelial function in postmenopausal women, which in turn decreases the risk of cardiovascular diseases (Akazawa *et al.*, 2012).

Curcumin for inflammatory diseases

The effect of curcumin on different inflammatory diseases in humans, such as bronchial asthma, uveitis, periodontitis and inflammatory bowel diseases, has also been studied in detail.

Biliary diseases. The first clinical trial of curcumin in human diseases was done by Oppenheimer in 1937 to examine the effects of 'curcumen' or 'curcunat' (contains 0.1 to 0.25 g sodium curcumin and 0.1 g calcium cholate) on human biliary diseases. Healthy persons were subjected to an i.v. injection of 5% sodium curcumin solution, which resulted in rapid emptying of the gallbladder. Notably, one patient showed a complete cure throughout a long period of observation (Oppenheimer, 1937). In another study, Cholagogum F Nattermann (dried extracts from *Schöllkraut* and *Curcuma*) treatment caused an effective reduction in biliary dyskinesia (Niederau and Gopfert, 1999).

Bronchial asthma. Curcumin has also found to be highly effective against bronchial asthma. Abidi *et al.* (2014) investigated the effectiveness of curcumin as an add-on therapy in patients with bronchial asthma. Administration of curcumin capsules improved the mean forced expiratory volume 1 s (FEV1) values, which signifies an improvement in the airway obstruction. Moreover, improved haematological parameters were also obtained (Abidi *et al.*, 2014).

Chronic anterior uveitis. Uveitis is a major cause of vision loss worldwide. Chronic anterior uveitis (CAU) includes a heterogeneous group of diseases, of which some are idiopathic in origin (McCluskey *et al.*, 2000). As curcumin has shown to be effective as a treatment of diverse inflammatory conditions, a few clinical trials were attempted to evaluate its efficacy against CAU of different aetiologies. The oral administration of curcumin to CAU patients improved their health and a follow-up after 3 years indicated a 55% recurrence rate (Lal *et al.*, 1999). Another group investigated the efficacy of oral phospholipidic curcumin on recurrent CAU of different aetiologies. The findings claimed that phospholipidic curcumin reduced the symptoms and signs of eye discomfort efficiently after a few weeks treatment in the majority of the patients (Allegri *et al.*, 2010).

Chronic cutaneous complications. Chronic cutaneous complications are one of the major and frequent complaints of patients exposed to sulphur mustard (SM). A trial conducted by Panahi *et al.* investigated the effect of curcumin on serum inflammatory biomarkers such as IL-8 and hs-CRP and their association with the severity of a chronic cutaneous complication called pruritus. The results implied that curcumin is highly effective at lessening the inflammation in patients with chronic SM-induced cutaneous complications, which might account for its

ability to ameliorate pruritus and improve the quality of life of these patients (Panahi *et al.*, 2012b).

Chronic periodontitis. Curcumin, being a well-known anti-inflammatory agent, can be used to develop an effective preventive and treatment approach for chronic periodontitis. A comparative study was conducted to measure the therapeutic efficacy of chlorhexidine (CHX) chips and indigenous curcumin-based collagen as adjuncts to scaling and root planing in the management of chronic periodontitis through nonsurgical procedures. At the end of a 6 month study period, a decrease in plaque and gingival index scores and improved microbiological parameters, probing pocket depth and clinical attachment levels were observed in both CHX chips and curcumin-based collagen-treated patients (Gottumukkala *et al.*, 2014), indicating their beneficial therapeutic effects in the nonsurgical treatment of periodontal disease. Another study carried out by the same group of investigators indicated that 1% curcumin irrigation when used as an adjunct to scaling and root planing had a mild to moderate beneficiary effect (Gottumukkala *et al.*, 2013). In addition, 1% curcumin solution was found to cause a better resolution of inflammatory symptoms, in cases of chronic periodontitis (Suhag *et al.*, 2007). Thus, based on the results of other experiments, a local drug-delivery system comprising 2% whole turmeric gel, which exerts high activity, can be used as an adjunct to scaling and root planing in the treatment of periodontal pockets (Behal *et al.*, 2011).

Gingivitis. Gingivitis is one of the most common inflammatory periodontal diseases that affect more than 80% of the world's population (Pulikkotil and Nath, 2015). Curcumin therapy holds high potential as a treatment of gingivitis. As an anti-inflammatory, curcumin mouthwash was found to be almost as good as CHX and hence it may act as an efficacious adjunct to mechanical periodontal therapy (Muglikar *et al.*, 2013). Similarly, the anti-inflammatory potential of topical curcumin was found to be comparable with that of CHX-MTZ and higher than CHX in affecting the levels of IL-1β and CCL28 (Pulikkotil and Nath, 2015). Besides curcumin, in another clinical study turmeric mouthwash was found to be useful as an adjunct to mechanical plaque control methods in the prevention of plaque and gingivitis (Waghmare *et al.*, 2011).

Oral mucositis. Oral mucositis is a commonly occurring problem in cancer therapy. Several *in vivo* studies have shown that curcumin can avert oral mucositis. In clinical settings as well, a pilot study was undertaken to measure the tolerability and efficacy of a curcumin mouthwash against oral mucositis in paediatric patients receiving doxorubicin-based chemotherapy. Curcumin mouthwash resulted in decreased inflammatory scores, and the study documented no adverse reactions in the patients (Elad *et al.*, 2013).

Oral lichen planus (OLP). Oral lichen planus (OLP) is a chronic, mucocutaneous, immunological disease. Curcuminoids were assessed for their efficacy against OLP and found to be well tolerated (Chainani-Wu *et al.*, 2007). Another study performed by the same group suggested curcuminoids at doses of 6000 mg·day^{-1} in three divided doses to be well tolerated and might be of use in regulating the signs and symptoms of OLP (Chainani-Wu *et al.*, 2012b). Furthermore, in another controlled trial conducted with 53 patients, administration of 6000 mg·day^{-1} curcuminoids reduced the symptoms of OLP in 60% of the patients (Chainani-Wu *et al.*, 2012a).

Chronic pulmonary complications. Pulmonary complications are major and frequent chronic problems of SM intoxication. Curcuminoids were found to suppress systemic inflammation in patients with chronic pulmonary complications induced by SM. This anti-inflammatory effect of curcuminoids was found be mediated through the modulation of inflammatory mediators such as IL-6, IL-8, TNF-α, TGFβ, substance P, hs-CRP, CGRP and MCP-1. Curcuminoids were also found to be safe and well tolerated throughout the trial (Panahi *et al.*, 2015b).

Chronic kidney disease. Chronic kidney disease (CKD) is characterized by reduced kidney function, enhanced inflammation and decreased antioxidants. To evaluate the effect of curcumin against CKD in humans, a study was conducted with 16 patients. A herbal supplement composed of *C. longa* and *Boswellia serrata* or placebo was given to non-dialysis CKD patients and plasma levels of IL-6, TNF-α, glutathione peroxidase and serum CRP were measured. Curcumin was found to be safe and well tolerated and helped to reduce the levels of the inflammatory cytokine IL-6 (Moreillon *et al.*, 2013).

Gastritis. Gastritis is caused by the production of an array of inflammatory cytokines induced by *Helicobacter pylori* infection in the stomach. A study conducted among *H. pylori*-infected gastritis patients by Koosirirat and colleagues evaluated the effect of curcumin on the production of IL-8, IL-1β, TNF-α and COX-2 in gastric mucosa. However, curcumin was ineffective at decreasing the production of these cytokines, which indicates it has a limited effect on *H. pylori*-induced inflammatory cytokine production. Nevertheless, other studies have reported that the symptoms of these patients with gastritis were ameliorated by the curcumin treatment (Koosirirat *et al.*, 2010).

Inflammatory bowel disease. Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis (UC), is a type of chronic and relapsing disorder characterized by inflammation of the gastrointestinal tract (Aguas *et al.*, 2016). Although, mortality due to IBD is not very high, it still presents a major healthcare burden. It damages the patient's quality of life to a considerable extent due to its onset in early adulthood and chronicity (Simian *et al.*, 2016). It enhances the risk of colorectal cancer and possibly is also associated with leukaemia and lymphoma (Wheat *et al.*, 2016).

Considering the well-established anti-inflammatory potential of curcumin, a pilot study was conducted to obtain a probable dosage of curcumin for children suffering from IBD. Curcumin was well tolerated, but a consistent increase in gassiness was reported in some patients. However, other

patients showed an improvement in the symptoms of the disease (Suskind *et al.*, 2013).

Crohn's disease. Crohn's disease is an immune-mediated IBD, which has become increasingly prevalent throughout the past decade (Lauro *et al.*, 2016; Manuc *et al.*, 2016). A pilot study was conducted with Crohn's disease to determine the effect of curcumin, as an addition to the existing treatments, in decreasing inflammation. This was done by reducing the doses of the other concomitant anti-inflammatory agents. Out of five patients, four showed lower Crohn's Disease Activity Index scores and sedimentation rates (Holt *et al.*, 2005), indicating that curcumin has potential at ameliorating inflammatory Crohn's disease.

Ulcerative colitis (UC). UC is a commonly occurring inflammatory disease and the usefulness of curcumin in the experimental models of UC has been well demonstrated. Its efficacy was investigated in a pilot study where it was evident that use of NCB-02 (a standardized curcumin preparation) as an enema caused greater improvements in disease activity in distal UC patients (Singla *et al.*, 2014). In another trial, curcumin improved both the clinical activity index and endoscopic index and in turn suppressed the morbidity linked with UC. Therefore, curcumin could be an important, safe and effective alternative treatment for maintaining remission in quiescent UC patients (Hanai *et al.*, 2006; Lang *et al.*, 2015).

Osteoarthritis (OA). The management of osteoarthritis remains a challenge and hence a safe and efficient treatment modality is much in demand. Several *in vitro* studies have demonstrated the beneficial effects of curcumin on cartilage in OA. Hence, a handful of clinical trials were undertaken (Henrotin *et al.*, 2014). Panahi *et al.* showed that treatment with curcuminoids (1500 mg·day^{-1} in three divided doses) of OA patients resulted in a reduction in pain and physical function scores but not the stiffness score OA index. Thus, curcuminoids present a safe and highly efficacious treatment choice for OA (Panahi *et al.*, 2014b). Another study also reported the efficacy of curcumin in the treatment of knee OA patients as evinced through the decrease of a cartilage specific biomarker, Coll2-1 (Henrotin *et al.*, 2014). In addition, adjuvant therapy of curcumin with diclofenac has exhibited advantageous outcome in the treatment of primary knee OA (Pinsornsak and Niempoog, 2012). In addition, turmeric extract has also shown to be safe and effective in reducing the pain and improving the function of OA patients. In a study conducted with 367 patients, administration of *Curcuma domestica* extracts (1500 mg·day^{-1} for 4 weeks) resulted in improved osteoarthritis index, and its efficacy was found to be quite comparable with that of ibuprofen (Kuptniratsaikul *et al.*, 2014).

To improve the efficacy of curcumin, different formulations have been used for the treatment of OA patients. Theracurmin® (manufactured by Theravalues Corporation, Kioicho, Tokyo, Japan) was used by the Nakagawa and group to evaluate its improved efficacy in the treatment of patients with knee OA. Theracurmin was shown to be effective against knee OA by lowering the knee pain visual analogue scale without causing any major toxic effects (Nakagawa *et al.*, 2014). Another formulation Meriva, a complex of curcumin with soy phosphatidylcholine, has been found to be highly effective in the clinicomanagement of OA. The report also suggested the enhanced stability and improved absorption of curcumin taken in this form, as well as improvements in the clinical and biochemical end points in OA patients (Belcaro *et al.*, 2010b; 2014).

Peptic ulcer. Peptic ulcer is a multifactorial disease, the complications of which remain a major challenge (Farzaei *et al.*, 2015). There is much evidence suggesting that curcumin could play a pivotal role in the management of such ulcers. Henceforth, a phase II clinical trial to measure the effect of turmeric on the healing of peptic ulcers was performed. A few patients showed a complete absence of ulcers after the 8 weeks of treatment, whereas others did not have ulcers after 12 weeks (Prucksunand *et al.*, 2001), indicating its great efficacy against this disease.

Rheumatoid arthritis (RA). Curcumin has displayed potent antiarthritic effects. A pilot clinical study investigated the safety and efficacy of curcumin in active rheumatoid arthritis patients and it showed an improvement in overall DAS (disease activity score) and ACR (American College of Rheumatology) scores. The safety and superiority of curcumin treatment was well evidenced (Chandran and Goel, 2012). Moreover, the curcumin treatment was also found to reduce the stiffness and swelling in the joints of patients with RA (Hanai *et al.,* 2006).

Curcumin for metabolic disease

Curcumin have also been shown to be very effective in the management of different metabolic diseases such as diabetes and obesity.

Diabetes. Diabetes is a cluster of metabolic diseases associated with high blood sugar levels. Several pilot studies have been carried out in human participants with curcumin to measure its effect on diabetes and associated metabolic conditions. The first study of this kind showed that curcumin could effectively lower the blood sugar levels in diabetic patients. Treatment with turmeric powder resulted in a decrease in fasting blood sugar from 1400 to 700 mg·L^{-1} in a patient suffering from diabetes for 16 years (Srinivasan, 1972). The intake of curcuminoids exerted a favourable effect on endothelial dysfunction along with a reduction in cytokines and markers of oxidative stress (Usharani *et al.*, 2008). Another trial advocated curcumin's potential in delaying the development of type 2 diabetes mellitus. It ameliorated beta cell functions, elevated HOMA-β and reduced C-peptide levels (Chuengsamarn *et al.*, 2012). The same group also reported that the intake of curcumin could reduce atherogenic risks and amend the metabolic profiles of high-risk populations (Chuengsamarn *et al.*, 2014). Similarly, in overweight/obese type 2 diabetic patients, curcuminoids lower blood glucose levels (Na *et al.*, 2014). Furthermore, Meriva was shown to be effective in the management of diabetic microangiopathy and retinopathy (Appendino *et al.*, 2011; Steigerwalt *et al.*, 2012). In a recent study, it was found that curcumin treatment improved the

skeletal muscle atrophy in type 1 diabetic mice through inhibition of protein ubiquitination, inflammatory cytokines and oxidative stress (Ono *et al.*, 2015). Another initial study indicated that a novel, chemically-modified curcumin was able to normalize wound-healing in diabetes I-induced rats by reducing the excessive collagenase-2 as well as MMP-13/collagenase-3 (Zhang *et al.*, 2016).

Obesity. Obesity is a global health problem and is a condition where the excess fat accumulates and exerts a negative impact on health (Ganjali *et al.*, 2014). Curcumin has proven its effectiveness in obese patients too. It reduces the symptoms of anxiety and depression associated with obesity (Esmaily *et al.*, 2015). Curcumin modulates circulating levels of IL-1β, IL-4 and VEGF, thus exhibiting an immunomodulatory effect and also reduces oxidative stress in obese patients (Sahebkar *et al.*, 2013; Ganjali *et al.*, 2014).

Curcumin for neurological disease

The effect of curcumin was also studied in neurological disorders such as Alzheimer's disease and depression in humans.

Alzheimer's disease. Alzheimer's disease is a progressive neurodegenerative disorder, usually affecting people older than 65 years. A randomized, double-blind, placebo-controlled study enrolled 34 patients with Alzheimer's disease and randomly administered curcumin at two different doses (1 or 4 g) or placebo (4 g). The curcumin treatment resulted in elevated levels of vitamin E without causing any adverse reactions through the antioxidant effects of curcuma (Baum *et al.*, 2008; Gupta *et al.*, 2013b).

Depression. Depression is a disorder in which many dysregulated pathways have been identified. As curcumin is known to target many pathways, its effect on depression has also been studied and it was observed that treatment with curcumin altered the biomarkers of depression and also improved the mood of the patients (Lopresti *et al.*, 2014; Lopresti *et al.*, 2015). A study conducted by Sanmukhani *et al.* confirmed curcumin to be effective and safe for the treatment of patients with major depressive disorder without concurrent suicidal ideation or other psychotic disorders (Sanmukhani *et al.*, 2014). In another randomized, double-blind, placebo-controlled study, it was observed that 4 to 8 weeks of treatment with curcumin was effective at improving several mood-related symptoms in these patients (Lopresti *et al.*, 2014). Subsequently, the same group demonstrated that curcumin supplementation affected several biomarkers such as thromboxane B2, substance P, aldosterone, cortisol, endothelin-1 and leptin, which might be responsible for its antidepressant effect (Lopresti *et al.*, 2015).

Curcumin for skin diseases

Curcumin has also been shown to be very effective against various skin diseases such as psoriasis and vitiligo.

Psoriasis. Psoriasis is an autoimmune disorder characterized by patches of abnormal skin. In a clinical trial, curcumin was found to exhibit an antipsoriatic effect by altering PhK activity (Heng *et al.*, 2000). Recently, in a randomized, double-blind, placebo-controlled clinical trial, patients treated with the curcumin formulation, Meriva, showed reduced disease conditions. It also increased the anti-psoriatic effects of topical steroids in these patients when treated in combination. Thus, it was highly effective as an adjuvant therapy against psoriasis vulgaris and, notably, caused a reduction in serum levels of IL-22 (Antiga *et al.*, 2015). Moreover, the safety and efficacy of curcumin was documented in a phase II, open-label, Simon's two-stage trial where the plaque psoriasis patients received 4.5 g of oral curcuminoid C3 complex daily. The intention-to-treat analysis response rate was found to be 16.7%, and none of the participants had to withdraw from the study due to associated adverse events (Kurd *et al.*, 2008).

Dermatitis. A randomized, double-blind, placebo-controlled clinical trial has been conducted to investigate curcumin's potential at reducing the severity of radiation-associated dermatitis in 30 breast cancer patients. A decrease in the severity of radiation dermatitis was observed in those patients receiving 6 $g \cdot day^{-1}$ curcumin p.o. during their radiotherapy sessions (Ryan *et al.*, 2013).

Vitiligo. Vitiligo is a chronic skin condition characterized by loss of pigmentation of the skin. The beneficial effect of curcumin on vitiligo has been demonstrated by Asawanonda and Klahan (2010); treatment with narrow band UVB plus topical tetrahydrocurcuminoid cream was found to be effective and well tolerated (Asawanonda and Klahan, 2010).

Curcumin for infectious diseases

Curcumin has also been shown to be effective in the treatment of various infectious diseases in humans.

Acquired immunodeficiency syndrome. Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), which interferes with and weakens the immune system. A clinical trial from New England evaluated the effectiveness of curcumin as an antiviral agent in 40 AIDS patients. The patients were allotted to either a high dose group (2.5 $g \cdot day^{-1}$) or a low-dose group in a random fashion for the treatment of 8 weeks. Though statistically insignificant, a mild increase in CD4 cells was observed in the high-dose group and a consistent decrease in the low-dose group. However, no evidence was obtained related to a decrease in viral load (James, 1996).

Curcumin for liver diseases. Curcumin exhibits effects against different liver diseases such as hepatitis B, hepatitis C, alcoholic liver disease, non-alcoholic fatty liver disease, drug-induced hepatotoxicity, liver cancer, biliary cirrhosis and primary sclerosing cholangitis. The antioxidant and inhibitory effects of curcumin on NF-κB play a vital role in its effect against a diverse range of hepatic diseases (Nanji *et al.*, 2003, Rivera-Espinoza and Muriel, 2009, Nabavi *et al.*, 2014). Curcumin was shown to reduce the liver damage in several animal models of liver injury (Bruck *et al.*, 2007). The herbal formulation comprising of *C. longa* and *Tinospora*

Table 3

Ongoing clinical trials of curcumin for various diseases in humans

Disease	Dose	Pts	Phase	Affiliation	Start date
Safety and tolerability					
Healthy individuals	2, 4 g[b]	12	I	Gary N Asher; UNC-CH USA	Mar 2011
	500 mg	23	0	Jan Frank; UHOH, Germany	Oct 2011
	2790 mg·day^{-1}; 18 months	132	II	Gary Small; UC, LA	Mar 2012
	80 mg[a]	23	0	Jan Frank; UHOH, Germany	Nov 2012
	NA[a]	12	I	Tetyana Pelipyagina; KGK Synergize	Apr 2015
Cancer					
ADH	50 and 100 mg; 3 months	30	–	Lisa Yee; OSU, USA	June 2013
Breast cancer	500 mg	2	II	Andrew Mille; Emory University, USA	May 2015
	Curcumin gel; 4–6 h[a]	180	II	Gary Morrow, URCC NCORP	Oct 2015
Cancer	200 mg·day^{-1}; 28 days	28	I	David Hong; MDACC USA	Oct 2011
	100–300 mg·m2^{-1}; 8 weeks[a]	28	I/II	Richard Greil; Internistische Onkologie	Mar 2014
	NA[b]	40	I	Aminah Jatoi; Mayo Clinic	Mar 2016
CIN	1000 mg·day^{-1}; 12 weeks	14	0	Carolyn Matthews; Texas Oncology	Mar 2016
Colon cancer	NA[b]	100	III	Arie Figer; TASMC, Israel	Mar 2006
	4 g·day^{-1}; 30 days[a]	40	I	Gary Asher; UNC-CH, USA	Nov 2010
	NA; 7 days[b]	35	I	Donald Miller; JGBCC, USA	Jan 2011
	2–4 g·day^{-1}; 6years[b]	51	I/II	William Steward; UHL, UK	Feb 2012
	1–4 g·day^{-1}; 4 days[b]	20	I	Gary Asher; UNC-CH, USA	Jun 2013
	0.5,1 g·day^{-1}; 28 days[a,b]	100	II	Andrea DeCensi; Ente Ospedaliero Ospedali Galliera	Mar 2014
	100 mg·day^{-1}[b]	44	II	Jeong-Heum Baek; Gachon University	May 2015
	1000 mg·day^{-1}; 2 weeks[b]	14	0	John Preskitt; Texas Oncology, PA	Mar 2016
EC	2 g·day^{-1}; 2 weeks[a]	10	II	Frederic Amant; UZ, Belgium	Oct 2013
Glioblastoma	NA	15	0	Stephan Duetzmann; Goethe University Germany	Oct 2012
H&NC	8 g·day^{-1}; 21–28 days	33	0	Cherie-Ann Nathan; LSUHSC, USA	Jun 2010
Lymphoma	NA[b]	35	II	Paolo Caimi Case; CCC, USA	Sep 2014
Osteosarcoma	Curcumin powder	24	I/II	Manish Agarwal; TMH, India	May 2008
NSCLC	80 mg·day^{-1}; 8 weeks[a,b]	20	I	Victor Cohen; LDI, Canada	Aug 2015
Pancreatic cancer	NA[b]	–	III	Arber Nadir; TAU, Israel	Jun 2005
Prostate cancer	NA[b]	100	II	Centre Jean Perrin	Mar 2014
	120 mg·day^{-1}; 3 days[a,b]	64	II	Abolfazl Razzaghdoust; SBUMS, Iran	Mar 2016
Rectal cancer	8 g·day^{-1}[b]	45	II	Sunil Krishnan; MDACC, USA	Aug 2008
Cardiovascular disease					
CVD	NA[a]	21	–	Anwar Tandar; University of Utah,USA	Jun 2013
MS	240 mg·day^{-1}; 6 weeks	42	II	Jan Frank; UHOH, Germany	Jul 2013
Inflammatory diseases					
RA	1–2 × 4 cap·day^{-1}; 2 weeks	40	0	Dinesh Khanna;UC, USA	Jan 2010
	2 and 4 g·day^{-1}; 1 month[a]	45	I	Janet Funk; UA, USA	Nov 2015
Crohn's disease	3 g·day^{-1}; 6 months[b]	122	III	Gilles Bommelaer; UCF, France	Dec 2014
FAP	2 × 3 pills·day^{-1}; 12 months	50	–	Cruz-Correa; UPR, Puerto Rico	Nov 2007
	NA; 12 months	50	II	Francis Giardiello; NCI, USA	Oct 2010
Bowel syndrome	Coltect; 4 weeks[a]	40	II	Timna Naftali; TAU, Isreal	Apr 2011
CP	2 times; 4 weeks	100	IV	Agarwal; TKDC, India	Jan 2014
Mucositis	0.33–3 g·day^{-1}; 4–6 weeks	38	I and II	Dhimant Patel; ABMC, USA	Feb 2015
OSMF	Curcumin gel	30	II	SVSIDS; India	Dec 2013
Orthodontis	Mouthwash[b]	24	I	Vitor H Panhóca; USP, Brazil	Jan 2014

(continues)

Table 3 (Continued)

Disease	Dose	Pts	Phase	Affiliation	Start date
Osteoarthritis	2 × 3 caps ·day^{-1}; 3 months[b]	22	0	Caroline Castermans; CHL, Belgium	Mar 2012
UC	2 × 2 tab ·day^{-1}; 2 months	30	–	Iris Dotan; TASMC, Israel	Nov 2008
	Curcumin capsules	60	III	Amit Assa; SCMCI, Israel	Sep 2016
	50–100 mg; 2 weeks[b]	50	III	Rupa Banerjee; AIG, India	Feb 2016
Metabolic disease					
Diabetes	2 cap·day^{-1}; 6 months	70	–	Alan Chous; Chous Eye Care Associates, USA	May 2012
	500 mg	50	II/III	NNFTRI, Iran	Jul 2015
Neurological disease					
Alzheimer's disease	2 or 3 g·day^{-1}	26	II	Fali Poncha ; JHRC, India	Oct 2009
	800 mg·day^{-1} ; 6 months[b]	80	II	Sally Frautschy; VAORD, USA	Jan 2014
Schizophrenia	720 mg·day^{-1}	36	I/II	Michael Davis; VAGLAHS, USA	Jul 2014
	3 g·day^{-1}; 6 months	40	IV	Vladimir Lerner; BMHC, Isreal	Jan 2015
	1200 mg·day^{-1}; 8 weeks	40	II	Cenk Tek; Yale University, USA	Jan 2016
Skin disease					
Psoriasis	E2 per day; 28 days[a]	21	I	Elorac, Inc. USA	Sep 2014
Other					
AAA	2 g·day^{-1}; 2 days	3500	II	Amit Garg; LHRI, Canada	Nov 2011
ADPKD	25 mg·kg^{-1}·day^{-1}; 1 year	68	IV	Kristen Nowak; CU, USA	Nov 2015
Bipolar disorder	0.5–2 g·day^{-1}; 3–8 weeks	30	II	Benjamin Goldstein; SHSC, Canada	Sep 2013
Erectile dysfunction	12 g·day^{-1}; 8 weeks[a]	44	IV	Hyun Jun Park; PNUH, South Korea	Feb 2012
ESRD	3 cap·day^{-1}; 8 weeks	48	I/II	SUMS, Iran	Apr 2011
Fibromyalgia	5 weeks[a]	40	–	Grégoire Cozon; HCL, France	Nov 2011
H. Pylori infection	NA[b]	150	–	Gingold Rachel; RMC, Israel	Jan 2014
Hyper prolactinoma	NA	30	I	Mashhad University of Medical Sciences	July 2011
Inflammation	2 capsules[b]	22	–	Charles Couillard; LU, Canada	Oct 2013
Kidney allografts	2 mL of 12 mg·mL^{-1}[a,b]	20	I	Kaija Salmela; HUCH, Finland	Jan 2011
Kidney disease	90 mg·day^{-1}; 6 months	750	III	Matthew Weir; LHRI, Canada	Sep 2015
Migraine	4 g·day^{-1}; 2 months	80	IV	TUMS, Iran	Sep 2015
Multiple sclerosis	1 g·day^{-1}	2780	II	Merck KGaA; Germany	Apr 2012
NAFLD	NA[a]	150	–	Giovanni de Gaetano; Neuromed IRCCS	May 2015
Prostatectomy	1 g·day^{-1}; 6 months	600	II	Yair Lotan; UTSW, USA	May 2014
Proteinuria	NA	120	III	Magdalena Madero; Inst Nacional de Cardiología	Feb 2013
Vascular ageing	500–2000 g·day^{-1}	118	–	Douglas Seals; CU, USA	Jun 2013
Vascular reactivity	–	21	I/II	Jean-René LUSSON; UCF, USA	Feb 2012
Vascular stiffness	200 mg·day^{-1} ; 7 days	40	I	Jamie Burr; UPEI, Canada	Nov 2014

[a]Curcumin formulation.
[b]Combination.
AAA, abdominal aortic aneurysm; ACF, aberrant crypt foci; ADH, atypical ductal hyperplasia; ADPKD, autosomal dominant polycystic kidney disease; CIN, cervical intraepithelial neoplasia; CP, chronic periodontitis; CVD, cardiovascular disease; EC, endometrial carcinoma; ESRD, end-stage kidney disease; FAP, familial adenomatous polyposis; H&NC, head and neck cancer; MDS, myelodysplastic syndrome; MS, metabolic syndrome; NA, not available; NAFLD, non-alcoholic fatty liver disease; NSCLC, non-small cell lung cancer; OLP, oral lichen planus; OSMF, oral submucous fibrosis; RA, rheumatoid arthritis; T2D, type 2 diabetes; UC, ulcerative colitis.

cordifolia was found to prevent anti-tuberculosis treatment-induced hepatotoxicity significantly without causing any toxic effects (Adhvaryu *et al.*, 2008).

Other diseases. The multitargeting potential of curcumin is extended to many other diseases as well like arsenic carcinogenicity and dyspepsia. Curcumin with its intrinsic antioxidant properties could limit the toxic effects associated with arsenic (Biswas *et al.*, 2010). It also inhibits exercise-induced oxidative stress in humans and reduces the severity of premenstrual syndrome in women by modulating the levels of neurotransmitters and anti-inflammatory biomolecules (Takahashi *et al.*, 2014; Khayat *et al.*, 2015). Administration of curcuminoids to

β-thalassemia/Hb E patients reduces oxidative damage (Kalpravidh *et al.*, 2010). Furthermore, curcumin increased the quality of life in a 15-year-old Caucasian girl with Déjérine–Sottas (Burns *et al.*, 2009). It also improves the post-operative outcomes of patients who have undergone laparoscopic cholecystectomy (Agarwal *et al.*, 2011). A randomized controlled trial demonstrated that curcumin, due to its anti-inflammatory effects, can combat pruritus and improve the quality of life of these patients (Panahi *et al.*, 2012a). Moreover, oral administration of curcumin suppresses the symptoms of lupus nephritis – inflammation of the kidney (Khajehdehi *et al.*, 2012), and significantly reduces the paraprotein (a monoclonal protein) levels in the blood of patients with monoclonal gammopathy of undetermined significance (MGUS) (Golombick *et al.*, 2009). In another study, curcumin slowed the disease progression of patients with MGUS and smouldering multiple myeloma (Golombick *et al.*, 2012).

Synergy of curcumin with other nutraceuticals in the clinic

To attain an improved therapy with better efficacy and less toxicity, the effects of curcumin when used in combination with other safe agents have been investigated. Several clinical trials have attempted to explore the feasibility and tolerability of the combination of curcumin with various nutraceuticals. For example, oral curcumin with piperine can reverse lipid peroxidation efficiently in patients with tropical pancreatitis (Durgaprasad *et al.*, 2005). Cruz-Correa's group have evaluated the effect of a combination therapy of curcumin and quercetin to reduce adenomas in patients with familial adenomatous polyposis. The combined treatment caused a decrease in the number and size from baseline of polyps with negligible adverse reactions and no laboratory abnormalities (Cruz-Correa *et al.*, 2006). Rafailov and group conducted a phase I trial to evaluate the effect of a herbal preparation containing curcumin, known as 'Zyflamend', against prostatic intraepithelial neoplasia (PIN). The biopsy revealed benign prostatic hyperplasia alone at the end of 6-months, and after 18 months, the biopsy was negative for cancer and PIN (Rafailov *et al.*, 2007; Sung *et al.*, 2012). The application of Indian turmeric with honey is highly effective as a complementary therapy for oral mucositis (Francis and Williams, 2014). Moreover, Oxy-Q bioflavonoid therapy with curcumin and quercetin improves the early graft function in dialysis-dependent cadaveric kidney recipients (Shoskes *et al.*, 2005). Likewise, in a cohort of 311 patients, Cinarepa, a mixture of various phytochemicals, including curcumin, chlorogenic acid, inulin and rosemary bud essential oil, was shown to suppress the symptoms of functional dyspepsia significantly (Sannia, 2010).

Curcumin has not only been combined with other natural compounds but also with different therapeutic drugs. In a prospective randomized study, the therapeutic effect of quercitin and curcumin (FlogMEV) in combination with prulifloxacin was assessed in chronic bacterial prostitis patients, and FlogMEV was found to improve the clinical efficacy of prulifloxacin (Cai *et al.*, 2009). The efficacy of another 7-day non-antibiotic therapy, comprising curcumin, lactoferrin, N-acetylcysteine and pantoprazole, at eradicating *H. pylori* infection and reducing gastric inflammation has also been determined. However, this therapy was not particularly effective (Di Mario *et al.*, 2007). Nevertheless, curcumin has been found to have high potential against different diseases either alone or in combination with other agents. In addition, there are more than 100 ongoing clinical trials of curcumin (Table 3); the findings of these clinical trials can be anticipated to be of immense help in providing a better understanding of curcumin's potential and its future prospects in the clinicomanagement of various human diseases.

Conclusions

There is an abundance of preclinical and clinical evidence indicating that curcumin has potential as a therapy for a wide variety of chronic diseases including cancer, cardiovascular, inflammatory, metabolic, neurological and skin diseases, and various infectious diseases. Unlike most pharmaceutical drugs, curcumin modulates multiple targets that affect different diseases. Safety, efficacy and affordability are some of the added advantages exhibited by this compound. There are also increasing lines of evidence suggesting it has a potent chemosensitizing effect in various cancers. Nevertheless, a few studies have reported that curcumin can function as an antagonistic as well. However, its therapeutic efficacy is hindered to a certain extent by its low bioavailability. Therefore, various strategies are being implemented, which include the development of curcumin analogues and formulations such as adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes, to improve its bioavailability. In addition, several other approaches have been employed to enhance its bioavailability, which include altering the route of administering curcumin and obstructing the metabolic pathways via co-treatment with other agents. Therefore, more detailed and well-controlled clinical trials are inevitable to evaluate the efficacy of these new formulations as compared with the parental compound. Thus, the results of these further investigations are likely to increase the bioavailability, therapeutic importance and application of curcumin and make this agent a cutting edge therapeutic strategy for the prevention and treatment of a variety of chronic diseases.

Author contributions

B.B.A. and A.K. contributed to the study design and writing. D.B., G.P., J.M. and N.K.R. performed bibliographic search and artwork. S.P. contributed to proofreading and writing.

Conflict of interest

The authors declare no conflicts of interest.

References

Abidi A, Gupta S, Agarwal M, Bhalla HL, 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.

Adhvaryu MR, Reddy N, Vakharia BC (2008). Prevention of hepatotoxicity due to anti tuberculosis treatment: a novel integrative approach. World J Gastroenterol 14: 4753–4762.

Agarwal KA, Tripathi CD, Agarwal BB, Saluja S (2011). Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study. Surg Endosc 25: 3805–3810.

Aggarwal BB, Sung B (2009). Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci 30: 85–94.

Aggarwal BB, Kunnumakkara AB, Harikumar KB, Tharakan ST, Sung B, Anand P (2008). Potential of spice-derived phytochemicals for cancer prevention. Planta Med 74: 1560–1569.

Aggarwal BB, Gupta SC, Sung B (2013a). Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 169: 1672–1692.

Aggarwal BB, Yuan W, Li S, Gupta SC (2013b). Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: identification of novel components of turmeric. Mol Nutr Food Res 57: 1529–1542.

Aggarwal BB, Deb L, Prasad S (2015). Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. Molecules 20: 185–205.

Aguas M, Hoyo JD, Faubel R, Nos P (2016). Use of telemedicine in inflammatory bowel disease: a real monitoring option? Expert Rev Gastroenterol Hepatol 10: 879–881.

Akazawa N, Choi Y, Miyaki A, Tanabe Y, Sugawara J, Ajisaka R *et al.* (2012). Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. Nutr Res 32: 795–799.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015a). The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 172: 6024–6109.

Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015b). The Concise Guide to PHARMACOLOGY 2015/16: G protein-coupled receptors. Br J Pharmacol 172: 5744–5869.

Alexander SPH, Cidlowski JA, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015c). The Concise Guide to PHARMACOLOGY 2015/16: Nuclear hormone receptors. Br J Pharmacol 172: 5956–5978.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015d). The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 172: 5729–5143.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015e). The Concise Guide to PHARMACOLOGY 2015/16: Catalytic receptors. Br J Pharmacol 172: 5979–6023.

Al-Karawi D, Al Mamoori DA, Tayyar Y (2016). The role of curcumin administration in patients with major depressive disorder: mini meta-analysis of clinical trials. Phytother Res 30: 175–183.

Allegri P, Mastromarino A, Neri P (2010). Management of chronic anterior uveitis relapses: efficacy of oral phospholipidic curcumin treatment. Long-term follow-up. Clin Ophthalmol 4: 1201–1206.

Alwi I, Santoso T, Suyono S, Sutrisna B, Suyatna FD, Kresno SB *et al.* (2008). The effect of curcumin on lipid level in patients with acute coronary syndrome. Acta Med Indones 40: 201–210.

Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007). Bioavailability of curcumin: problems and promises. Mol Pharm 4: 807–818.

Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB (2008). Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer Lett 267: 133–164.

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: 283634.

Appendino G, Belcaro G, Cornelli U, Luzzi R, Togni S, Dugall M *et al.* (2011). Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. Panminerva Med 53: 43–49.

Ara SA, Mudda JA, Lingappa A, Rao P (2016). Research on curcumin: a meta-analysis of potentially malignant disorders. J Cancer Res Ther 12: 175–181.

Araujo NC, Fontana CR, Gerbi ME, Bagnato VS (2012). Overall-mouth disinfection by photodynamic therapy using curcumin. Photomed Laser Surg 30: 96–101.

Asawanonda P, Klahan SO (2010). Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study. Photomed Laser Surg 28: 679–684.

Basu P, Dutta S, Begum R, Mittal S, Dutta PD, Bharti AC *et al.* (2013). Clearance of cervical human papillomavirus infection by topical application of curcumin and curcumin containing polyherbal cream: a phase II randomized controlled study. Asian Pac J Cancer Prev 14: 5753–5759.

Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J *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.

Bayet-Robert M, Kwiatkowski F, Leheurteur M, Gachon F, Planchat E, Abrial C *et al.* (2010). Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer Biol Ther 9: 8–14.

Behal R, Mali AM, Gilda SS, Paradkar AR (2011). Evaluation of local drug-delivery system containing 2% whole turmeric gel used as an adjunct to scaling and root planing in chronic periodontitis: a clinical and microbiological study. J Indian Soc Periodontol 15: 35–38.

Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG *et al.* (2010a). Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Altern Med Rev 15: 337–344.

Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG *et al.* (2010b). Product-evaluation registry of Meriva(R), a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. Panminerva Med 52: 55–62.

Belcaro G, Hosoi M, Pellegrini L, Appendino G, Ippolito E, Ricci A *et al.* (2014). A controlled study of a lecithinized delivery system of curcumin (Meriva(R)) to alleviate the adverse effects of cancer treatment. Phytother Res 28: 444–450.

Bergman J, Miodownik C, Bersudsky Y, Sokolik S, Lerner PP, Kreinin A *et al.* (2013). Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. Clin Neuropharmacol 36: 73–77.

Bharti AC, Takada Y, Aggarwal BB (2004). Curcumin (diferuloylmethane) inhibits receptor activator of NF-kappa B ligand-induced NF-kappa B activation in osteoclast precursors and suppresses osteoclastogenesis. J Immunol 172: 5940–5947.

Bhatia M, Urolagin SS, Pentyala KB, Urolagin SB, K BM, Bhoi S (2014). Novel therapeutic approach for the treatment of periodontitis by curcumin. J Clin Diagn Res 8: ZC65–ZC69.

Biswas J, Sinha D, Mukherjee S, Roy S, Siddiqi M, Roy M (2010). Curcumin protects DNA damage in a chronically arsenic-exposed population of West Bengal. Hum Exp Toxicol 29: 513–524.

Bordoloi D, Roy NK, Monisha J, Padmavathi G, Kunnumakkara AB (2016). Multi-targeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far. Recent Pat Anticancer Drug Discov 11: 67–97.

Boyanapalli SS, Tony Kong AN (2015). "Curcumin, the king of spices": epigenetic regulatory mechanisms in the prevention of cancer, neurological, and inflammatory diseases. Curr Pharmacol Rep 1: 129–139.

Brondino N, Re S, Boldrini A, Cuccomarino A, Lanati N, Barale F *et al.* (2014). Curcumin as a therapeutic agent in dementia: a mini systematic review of human studies. ScientificWorldJournal 2014: 174282.

Bruck R, Ashkenazi M, Weiss S, Goldiner I, Shapiro H, Aeed H *et al.* (2007). Prevention of liver cirrhosis in rats by curcumin. Liver Int 27: 373–383.

Burns J, Joseph PD, Rose KJ, Ryan MM, Ouvrier RA (2009). Effect of oral curcumin on Dejerine–Sottas disease. Pediatr Neurol 41: 305–308.

Cai T, Mazzoli S, Bechi A, Addonisio P, Mondaini N, Pagliai RC *et al.* (2009). *Serenoa repens* associated with *Urtica dioica* (ProstaMEV) and curcumin and quercitin (FlogMEV) extracts are able to improve the efficacy of prulifloxacin in bacterial prostatitis patients: results from a prospective randomised study. Int J Antimicrob Agents 33: 549–553.

Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L *et al.* (2011). Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res (Phila) 4: 354–364.

Chainani-Wu N, Silverman S Jr, Reingold A, Bostrom A, Mc Culloch C, Lozada-Nur F *et al.* (2007). A randomized, placebo-controlled, double-blind clinical trial of curcuminoids in oral lichen planus. Phytomedicine 14: 437–446.

Chainani-Wu N, Collins K, Silverman S Jr (2012a). Use of curcuminoids in a cohort of patients with oral lichen planus, an autoimmune disease. Phytomedicine 19: 418–423.

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

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.

Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS *et al.* (2001). Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 21: 2895–2900.

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

Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S (2014). Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. J Nutr Biochem 25: 144–150.

Cicero AF, Colletti A (2015). Combinations of phytomedicines with different lipid lowering activity for dyslipidemia management: the available clinical data. Phytomedicine 23: 1113–1118.

Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD *et al.* (2006). Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol 4: 1035–1038.

Cuomo J, Appendino G, Dern AS, Schneider E, McKinnon TP, Brown MJ *et al.* (2011). Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. J Nat Prod 74: 664–669.

Davis JM, Murphy EA, Carmichael MD, Zielinski MR, Groschwitz CM, Brown AS *et al.* (2007). Curcumin effects on inflammation and performance recovery following eccentric exercise-induced muscle damage. Am J Physiol Regul Integr Comp Physiol 292: R2168–R2173.

Deodhar SD, Sethi R, Srimal RC (1980). Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). Indian J Med Res 71: 632–634.

Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL *et al.* (2008). Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res 14: 4491–4499.

Di Mario F, Cavallaro LG, Nouvenne A, Stefani N, Cavestro GM, Iori V *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.

DiSilvestro RA, Joseph E, Zhao S, Bomser J (2012). Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J 11: 79.

Dominiak K, McKinney J, Heilbrun LK, Sarkar FH (2010). Critical need for clinical trials: an example of a pilot human intervention trial of a mixture of natural agents protecting lymphocytes against TNF-alpha induced activation of NF-kappaB. Pharm Res 27: 1061–1065.

Durgaprasad S, Pai CG, Vasanthkumar AJF, Namitha S (2005). A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. Indian J Med Res 122: 315–318.

Elad S, Meidan I, Sellam G, Simaan S, Zeevi I, Waldman E *et al.* (2013). Topical curcumin for the prevention of oral mucositis in pediatric patients: case series. Altern Ther Health Med 19: 21–24.

Epelbaum R, Schaffer M, Vizel B, Badmaev V, Bar-Sela G (2010). Curcumin and gemcitabine in patients with advanced pancreatic cancer. Nutr Cancer 62: 1137–1141.

Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G *et al.* (2015). An investigation of the effects of curcumin on anxiety and depression in obese individuals: a randomized controlled trial. Chin J Integr Med 21: 332–338.

Farzaei MH, Abdollahi M, Rahimi R (2015). Role of dietary polyphenols in the management of peptic ulcer. World J Gastroenterol 21: 6499–6517.

Francis M, Williams S (2014). Effectiveness of indian turmeric powder with honey as complementary therapy on oral mucositis : a nursing perspective among cancer patients in Mysore. Nurs J India 105: 258–260.

Gaffey A, Campbell J, Porritt K, Slater H (2015). The effects of curcumin on musculoskeletal pain: a systematic review protocol. JBI Database System Rev Implement Rep 13: 59–73.

Ganjali S, Sahebkar A, Mahdipour E, Jamialahmadi K, Torabi S, Akhlaghi S *et al.* (2014). Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. ScientificWorldJournal 2014: 898361.

Garcea G, Berry DP, Jones DJ, Singh R, Dennison AR, Farmer PB *et al.* (2005). Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev 14: 120–125.

Ghalaut VS, Sangwan L, Dahiya K, Ghalaut PS, Dhankhar R, Saharan R (2012). Effect of imatinib therapy with and without turmeric powder on nitric oxide levels in chronic myeloid leukemia. J Oncol Pharm Pract 18: 186–190.

Goel A, Aggarwal BB (2010). Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. Nutr Cancer 62: 919–930.

Goel A, Kunnumakkara AB, Aggarwal BB (2008). Curcumin as "curecumin": from kitchen to clinic. Biochem Pharmacol 75: 787–809.

Golombick T, Diamond TH, Badmaev V, Manoharan A, Ramakrishna R (2009). The potential role of curcumin in patients with monoclonal gammopathy of undefined significance – its effect on paraproteinemia and the urinary N-telopeptide of type I collagen bone turnover marker. Clin Cancer Res 15: 5917–5922.

Golombick T, Diamond TH, Manoharan A, Ramakrishna R (2012). Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4 g study and an open-label 8 g extension study. Am J Hematol 87: 455–460.

Gottumukkala SN, Koneru S, Mannem S, Mandalapu N (2013). Effectiveness of sub gingival irrigation of an indigenous 1% curcumin solution on clinical and microbiological parameters in chronic periodontitis patients: a pilot randomized clinical trial. Contemp Clin Dent 4: 186–191.

Gottumukkala SN, Sudarshan S, Mantena SR (2014). Comparative evaluation of the efficacy of two controlled release devices: chlorhexidine chips and indigenous curcumin based collagen as local drug delivery systems. Contemp Clin Dent 5: 175–181.

Gupta SC, Kim JH, Prasad S, Aggarwal BB (2010). Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. Cancer Metastasis Rev 29: 405–434.

Gupta SC, Kim JH, Kannappan R, Reuter S, Dougherty PM, Aggarwal BB (2011a). Role of nuclear factor kappaB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. Exp Biol Med (Maywood) 236: 658–671.

Gupta SC, Prasad S, Kim JH, Patchva S, Webb LJ, Priyadarsini IK *et al.* (2011b). Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 28: 1937–1955.

Gupta SC, Patchva S, Koh W, Aggarwal BB (2012). Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol 39: 283–299.

Gupta SC, Kismali G, Aggarwal BB (2013a). Curcumin, a component of turmeric: from farm to pharmacy. Biofactors 39: 2–13.

Gupta SC, Patchva S, Aggarwal BB (2013b). Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 15: 195–218.

Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB (2013c). Multitargeting by turmeric, the golden spice: from kitchen to clinic. Mol Nutr Food Res 57: 1510–1528.

Gupta SC, Tyagi AK, Deshmukh-Taskar P, Hinojosa M, Prasad S, Aggarwal BB (2014). Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols. Arch Biochem Biophys 559: 91–99.

Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A *et al.* (2006). Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 4: 1502–1506.

Hasima N, Aggarwal BB (2012). Cancer-linked targets modulated by curcumin. Int J Biochem Mol Biol 3: 328–351.

Hasima N, Aggarwal BB (2014). Targeting proteasomal pathways by dietary curcumin for cancer prevention and treatment. Curr Med Chem 21: 1583–1594.

He ZY, Shi CB, Wen H, Li FL, Wang BL, Wang J (2011). Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest 29: 208–213.

Hejazi J, Rastmanesh R, Taleban FA, Molana SH, Hejazi E, Ehtejab G *et al.* (2016). Effect of curcumin supplementation during radiotherapy on oxidative status of patients with prostate cancer: a double blinded, randomized, placebo-controlled study. Nutr Cancer 68: 77–85.

Heng MC, Song MK, Harker J, Heng MK (2000). Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br J Dermatol 143: 937–949.

Henrotin Y, Gharbi M, Dierckxsens Y, Priem F, Marty M, Seidel L *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.

Holt PR, Katz S, Kirshoff R (2005). Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci 50: 2191–2193.

Ide H, Tokiwa S, Sakamaki K, Nishio K, Isotani S, Muto S *et al.* (2010). Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen. Prostate 70: 1127–1133.

Irving GR, Howells LM, Sale S, Kralj-Hans I, Atkin WS, Clark SK *et al.* (2013). Prolonged biologically active colonic tissue levels of curcumin achieved after oral administration – a clinical pilot study including assessment of patient acceptability. Cancer Prev Res (Phila) 6: 119–128.

Jager R, Lowery RP, Calvanese AV, Joy JM, Purpura M, Wilson JM (2014). Comparative absorption of curcumin formulations. Nutr J 13: 11.

James JS (1996). Curcumin: clinical trial finds no antiviral effect. AIDS Treat News : 1–2.

Juan H, Terhaag B, Cong Z, Bi-Kui Z, Rong-Hua Z, Feng W*et al.* (2007). Unexpected effect of concomitantly administered curcumin on the pharmacokinetics of talinolol in healthy Chinese volunteers. Eur J Clin Pharmacol 63: 663–668.

Kalpravidh RW, Siritanaratkul N, Insain P, Charoensakdi R, Panichkul N, Hatairaktham S *et al.* (2010). Improvement in oxidative stress and antioxidant parameters in beta-thalassemia/Hb E patients treated with curcuminoids. Clin Biochem 43: 424–429.

Kanai M, Yoshimura K, Asada M, Imaizumi A, Suzuki C, Matsumoto S *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.

Kanai M, Otsuka Y, Otsuka K, Sato M, Nishimura T, Mori Y *et al.* (2013). A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin) in cancer patients. Cancer Chemother Pharmacol 71: 1521–1530.

Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, Nasab MH *et al.* (2011). Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-beta 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.

Khajehdehi P, Zanjaninejad B, Aflaki E, Nazarinia M, Azad F, Malekmakan L *et al.* (2012). Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. J Ren Nutr 22: 50–57.

Khayat S, Fanaei H, Kheirkhah M, Moghadam ZB, Kasaeian A, Javadimehr M (2015). Curcumin attenuates severity of premenstrual syndrome symptoms: a randomized, double-blind, placebo-controlled trial. Complement Ther Med 23: 318–324.

Kim SG, Veena MS, Basak SK, Han E, Tajima T, Gjertson DW *et al.* (2011). Curcumin treatment suppresses IKKbeta kinase activity of salivary cells of patients with head and neck cancer: a pilot study. Clin Cancer Res 17: 5953–5961.

Klickovic U, Doberer D, Gouya G, Aschauer S, Weisshaar S, Storka A *et al.* (2014). Human pharmacokinetics of high dose oral curcumin and its effect on heme oxygenase-1 expression in healthy male subjects. Biomed Res Int 2014: 458592.

Kocaadam B, Şanlier N (2015). Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. Crit Rev Food Sci Nutr 3: 0.

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.

Kumar A, Cannon CP (2009). Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc 84: 917–938.

Kunnumakkara AB, Anand P, Aggarwal BB (2008). Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 269: 199–225.

Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P, Chootip C *et al.* (2014). Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clin Interv Aging 9: 451–458.

Kurd SK, Smith N, VanVoorhees A, Troxel AB, Badmaev V, Seykora JT *et al.* (2008). Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: a prospective clinical trial. J Am Acad Dermatol 58: 625–631.

Kusuhara H, Furuie H, Inano A, Sunagawa A, Yamada S, Wu C *et al.* (2012). Pharmacokinetic interaction study of sulphasalazine in healthy subjects and the impact of curcumin as an in vivo inhibitor of BCRP. Br J Pharmacol 166: 1793–1803.

Kuttan R, Sudheeran PC, Josph CD (1987). Turmeric and curcumin as topical agents in cancer therapy. Tumori 73: 29–31.

Lahiff C, Moss AC (2011). Curcumin for clinical and endoscopic remission in ulcerative colitis. Inflamm Bowel Dis 17: E66.

Lal B, Kapoor AK, Asthana OP, Agrawal PK, Prasad R, Kumar P *et al.* (1999). Efficacy of curcumin in the management of chronic anterior uveitis. Phytother Res 13: 318–322.

Lang A, Salomon N, Wu JC, Kopylov U, Lahat A, Har-Noy O *et al.* (2015). Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. Clin Gastroenterol Hepatol 13: 1444–1449 e1441.

Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ *et al.* (2015). Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis 9: 86–106.

Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM *et al.* (2006). Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 6: 10.

Lauro ML, Burch JM, Grimes CL (2016). The effect of NOD2 on the microbiota in Crohn's disease. Curr Opin Biotechnol 40: 97–102.

Ledda A, Belcaro G, Dugall M, Luzzi R, Scoccianti M, Togni S *et al.* (2012). Meriva(R), a lecithinized curcumin delivery system, in the control of benign prostatic hyperplasia: a pilot, product evaluation registry study. Panminerva Med 54: 17–22.

Li D, Xie K, Wolff R, Abbruzzese JL (2004). Pancreatic cancer. Lancet 363: 1049–1057.

Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD (2014). Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. J Affect Disord 167: 368–375.

Lopresti AL, Maes M, Meddens MJ, Maker GL, Arnoldussen E, Drummond PD (2015). Curcumin and major depression: a randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change. Eur Neuropsychopharmacol 25: 38–50.

Manuc TE, Manuc MM, Diculescu MM (2016). Recent insights into the molecular pathogenesis of Crohn's disease: a review of emerging therapeutic targets. Clin Exp Gastroenterol 9: 59–70.

McCluskey PJ, Towler HM, Lightman S (2000). Management of chronic uveitis. BMJ 320: 555–558.

Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M *et al.* (2013). Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytother Res 27: 374–379.

Moreillon JJ, Bowden RG, Deike E, Griggs J, Wilson R, Shelmadine B *et al.* (2013). The use of an anti-inflammatory supplement in patients with chronic kidney disease. J Complement Integr Med 10. pii: /j/jcim.2013.10.issue-1/jcim-2012-0011/jcim-2012-0011.xml.

Muglikar S, Patil KC, Shivswami S, Hegde R (2013). Efficacy of curcumin in the treatment of chronic gingivitis: a pilot study. Oral Health Prev Dent 11: 81–86.

Na LX, Yan BL, Jiang S, Cui HL, Li Y, Sun CH (2014). Curcuminoids target decreasing serum adipocyte-fatty acid binding protein levels in their glucose-lowering effect in patients with type 2 diabetes. Biomed Environ Sci 27: 902–906.

Nabavi SF, Daglia M, Moghaddam AH, Habtemariam S, Nabavi SM (2014). Curcumin and liver disease: from chemistry to medicine. Compr Rev Food Sci Food Saf 13: 62–77.

Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, Aggarwal BB (2010). Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. Biochem Pharmacol 80: 1833–1843.

Nakagawa Y, Mukai S, Yamada S, Matsuoka M, Tarumi E, Hashimoto T*et al.* (2014). Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. J Orthop Sci 19: 933–939.

Nakayama H, Tsuge N, Sawada H, Masamura N, Yamada S, Satomi S *et al.* (2014). A single consumption of curry improved postprandial endothelial function in healthy male subjects: a randomized, controlled crossover trial. Nutr J 13: 67.

Nanji AA, Jokelainen K, Tipoe GL, Rahemtulla A, Thomas P, Dannenberg AJ (2003). Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes. Am J Physiol Gastrointest Liver Physiol 284: G321–G327.

Nautiyal J, Banerjee S, Kanwar SS, Yu Y, Patel BB, Sarkar FH *et al.* (2011). Curcumin enhances dasatinib-induced inhibition of growth and transformation of colon cancer cells. Int J Cancer 128: 951–961.

Niederau C, Gopfert E (1999). The effect of chelidonium- and turmeric root extract on upper abdominal pain due to functional disorders of the biliary system. Results from a placebo-controlled double-blind study. Med Klin (Munich) 94: 425–430.

Ono T, Takada S, Kinugawa S, Tsutsui H (2015). Curcumin ameliorates skeletal muscle atrophy in type 1 diabetic mice by inhibiting protein ubiquitination. Exp Physiol 100: 1052–1063.

Oppenheimer A (1937). Turmeric (curcumin) in biliary diseases. Lancet 229: 619–621.

Panahi Y, Sahebkar A, Amiri M, Davoudi SM, Beiraghdar F, Hoseininejad SL *et al.* (2012a). Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. Br J Nutr 108: 1272–1279.

Panahi Y, Sahebkar A, Parvin S, Saadat A (2012b). A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Ann Clin Biochem 49: 580–588.

Panahi Y, Khalili N, Hosseini MS, Abbasinazari M, Sahebkar A (2014a). Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. Complement Ther Med 22: 851–857.

Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A (2014b). Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytother Res 28: 1625–1631.

Panahi Y, Saadat A, Beiraghdar F, Sahebkar A (2014c). Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. Phytother Res 28: 1461–1467.

Panahi Y, Badeli R, Karami GR, Sahebkar A (2015a). Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytother Res 29: 17–21.

Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A (2015b). Short-term curcuminoid supplementation for chronic pulmonary complications due to sulfur mustard intoxication: positive results of a randomized double-blind placebo-controlled trial. Drug Res (Stuttg) 65: 567–573.

Pinsornsak P, Niempoog S (2012). The efficacy of *Curcuma longa* L. extract as an adjuvant therapy in primary knee osteoarthritis: a randomized control trial. J Med Assoc Thai 95 (Suppl 1): S51–S58.

Plummer SM, Hill KA, Festing MF, Steward WP, Gescher AJ, Sharma RA (2001). Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. Cancer Epidemiol Biomarkers Prev 10: 1295–1299.

Prasad S, Gupta SC, Tyagi AK, Aggarwal BB (2014a). Curcumin, a component of golden spice: from bedside to bench and back. Biotechnol Adv 32: 1053–1064.

Prasad S, Tyagi AK, Aggarwal BB (2014b). Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat 46: 2–18.

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.

Pulikkotil SJ, Nath S (2015). Effects of curcumin on crevicular levels of IL-1beta and CCL28 in experimental gingivitis. Aust Dent J 60: 317–327.

Pungcharoenkul K, Thongnopnua P (2011). Effect of different curcuminoid supplement dosages on total in vivo antioxidant capacity and cholesterol levels of healthy human subjects. Phytother Res 25: 1721–1726.

Rafailov S, Cammack S, Stone BA, Katz AE (2007). The role of Zyflamend, an herbal anti-inflammatory, as a potential chemopreventive agent against prostate cancer: a case report. Integr Cancer Ther 6: 74–76.

Rainey N, Motte L, Aggarwal BB, Petit PX (2015). Curcumin hormesis mediates a cross-talk between autophagy and cell death. Cell Death Dis 6: e2003.

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.

Rasyid A, Rahman AR, Jaalam K, Lelo A (2002). Effect of different curcumin dosages on human gall bladder. Asia Pac J Clin Nutr 11: 314–318.

Ravindran J, Prasad S, Aggarwal BB (2009). Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J 11: 495–510.

Reddy S, Aggarwal BB (1994). Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase. FEBS Lett 341: 19–22.

Remely M, Lovrecic L, de la Garza AL, Migliore L, Peterlin B, Milagro FI *et al.* (2015). Therapeutic perspectives of epigenetically active nutrients. Br J Pharmacol 172: 2756–2768.

Reuter S, Gupta SC, Park B, Goel A, Aggarwal BB (2011). Epigenetic changes induced by curcumin and other natural compounds. Genes Nutr 6: 93–108.

Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL (2005). A Potential role of the curry spice curcumin in Alzheimer's disease. Current Alzheimer Research 2: 131–136.

Rivera-Espinoza Y, Muriel P (2009). Pharmacological actions of curcumin in liver diseases or damage. Liver Int 29: 1457–1466.

Ryan JL, Heckler CE, Ling M, Katz A, Williams JP, Pentland AP *et al.* (2013). Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. Radiat Res 180: 34–43.

Sahebkar A (2014a). A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. Clin Nutr 33: 406–414.

Sahebkar A (2014b). Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res 28: 633–642.

Sahebkar A, Henrotin Y (2016). Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and meta-analysis of randomized controlled trials. Pain Med 17: 1192–1202.

Sahebkar A, Mohammadi A, Atabati A, Rahiman S, Tavallaie S, Iranshahi M *et al.* (2013). Curcuminoids modulate pro-oxidant-antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. Phytother Res 27: 1883–1888.

Sahebkar A, Cicero AF, Simental-Mendía LE, Aggarwal BB, Gupta SC (2016). Curcumin downregulates human tumor necrosis factor-α levels: a systematic review and meta-analysis ofrandomized controlled trials. Pharmacol Res 107: 234–242.

Sahu PK, Sahu PK, Sahu PL, Agarwal DD (2016). Structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives. Bioorg Med Chem Lett 26: 1342–1347.

Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B *et al.* (2014). Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytother Res 28: 579–585.

Sannia A (2010). Phytotherapy with a mixture of dry extracts with hepato-protective effects containing artichoke leaves in the management of functional dyspepsia symptoms. Minerva Gastroenterol Dietol 56: 93–99.

Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T*et al.* (2011). Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull 34: 660–665.

Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM *et al.* (2001). Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res 7: 1894–1900.

Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR *et al.* (2004). Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 10: 6847–6854.

Shimouchi A, Nose K, Takaoka M, Hayashi H, Kondo T (2009). Effect of dietary turmeric on breath hydrogen. Dig Dis Sci 54: 1725–1729.

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 64: 353–356.

Shoskes D, Lapierre C, Cruz-Correa M, Muruve N, Rosario R, Fromkin B *et al.* (2005). Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo controlled trial. Transplantation 80: 1556–1559.

Simian D, Fluxá D, Flores L, Lubascher J, Ibáñez P, Figueroa C *et al.* (2016). Inflammatory bowel disease: a descriptive study of 716 local Chilean patients. World J Gastroenterol 22: 5267–5275.

Singla V, Pratap Mouli V, Garg SK, Rai T, Choudhury BN, Verma P *et al.* (2014). Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis – a randomized, placebo-controlled, pilot study. J Crohns Colitis 8: 208–214.

Soare A, Weiss EP, Holloszy JO, Fontana L (2014). Multiple dietary supplements do not affect metabolic and cardio-vascular health. Aging (Albany NY) 6: 149–157.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP *et al.* (2016). The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res 44: D1054–D1068.

Srinivasan M (1972). Effect of curcumin on blood sugar as seen in a diabetic subject. Indian J Med Sci 26: 269–270.

Steigerwalt R, Nebbioso M, Appendino G, Belcaro G, Ciammaichella G, Cornelli U *et al.* (2012). Meriva(R), a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. Panminerva Med 54: 11–16.

Sugawara J, Akazawa N, Miyaki A, Choi Y, Tanabe Y, Imai T*et al.* (2012). Effect of endurance exercise training and curcumin intake on central arterial hemodynamics in postmenopausal women: pilot study. Am J Hypertens 25: 651–656.

Suhag A, Dixit J, Dhan P (2007). Role of curcumin as a subgingival irrigant: a pilot study. PERIO: Periodontal Pract Today 2: 115–121.

Sung B, Prasad S, Yadav VR, Aggarwal BB (2012). Cancer cell signaling pathways targeted by spice-derived nutraceuticals. Nutr Cancer 64: 173–197.

Suskind DL, Wahbeh G, Burpee T, Cohen M, Christie D, Weber W (2013). Tolerability of curcumin in pediatric inflammatory bowel disease: a forced-dose titration study. J Pediatr Gastroenterol Nutr 56: 277–279.

Takahashi M, Suzuki K, Kim HK, Otsuka Y, Imaizumi A, Miyashita M *et al.* (2014). Effects of curcumin supplementation on exercise-induced oxidative stress in humans. Int J Sports Med 35: 469–475.

Tuntipopipat S, Judprasong K, Zeder C, Wasantwisut E, Winichagoon P, Charoenkiatkul S *et al.* (2006). Chili, but not turmeric, inhibits iron absorption in young women from an iron-fortified composite meal. J Nutr 136: 2970–2974.

Tuorkey MJ (2014). Curcumin a potent cancer preventive agent: mechanisms of cancer cell killing. Interv Med Appl Sci 6: 139–146.

Tyagi AK, Prasad S, Yuan W, Li S, Aggarwal BB (2015). Identification of a novel compound (beta-sesquiphellandrene) from turmeric (*Curcuma longa*) with anticancer potential: comparison with curcumin. Invest New Drugs 33: 1175–1186.

Usharani P, Mateen AA, Naidu MU, Raju YS, Chandra N (2008). Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. Drugs R D 9: 243–250.

Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, Djuric Z *et al.* (2008). Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev 17: 1411–1417.

Vaughn AR, Branum A, Sivamani RK. Effects of turmeric (*Curcuma longa*) on skin health: a systematic review of the clinical evidence. Phytother Res 2016. doi: 10.1002/ptr.5640. [Epub ahead of print] Review. PubMed PMID: 27213821.

Vitaglione P, Barone Lumaga R, Ferracane R, Radetsky I, Mennella I, Schettino R *et al.* (2012). Curcumin bioavailability from enriched bread: the effect of microencapsulated ingredients. J Agric Food Chem 60: 3357–3366.

Volak LP, Hanley MJ, Masse G, Hazarika S, Harmatz JS, Badmaev V *et al.* (2013). Effect of a herbal extract containing curcumin and piperine on midazolam, flurbiprofen and paracetamol (acetaminophen) pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 75: 450–462.

Waghmare PF, Chaudhari AU, Karhadkar VM, Jamkhande AS (2011). Comparative evaluation of turmeric and chlorhexidine gluconate

mouthwash in prevention of plaque formation and gingivitis: a clinical and microbiological study. J Contemp Dent Pract 12: 221–224.

Wheat CL, Clark-Snustad K, Devine B, Grembowski D, Thornton TA, Ko CW (2016). Worldwide incidence of colorectal cancer, leukemia, and lymphoma in inflammatory bowel disease: an updated systematic review and meta-analysis. Gastroenterol Res Pract 2016 .1632439

Wolff JE, Brown RE, Buryanek J, Pfister S, Vats TS, Rytting ME (2012). Preliminary experience with personalized and targeted therapy for pediatric brain tumors. Pediatr Blood Cancer 59: 27–33.

Wongcharoen W, Jai-Aue S, Phrommintikul A, Nawarawong W, Woragidpoonpol S, Tepsuwan T*et al.* (2012). Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. Am J Cardiol 110: 40–44.

Yadav VR, Aggarwal BB (2011). Curcumin: a component of the golden spice, targets multiple angiogenic pathways. Cancer Biol Ther 11: 236–241.

Yang YS, Su YF, Yang HW, Lee YH, Chou JI, Ueng KC (2014). Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. Phytother Res 28: 1770–1777.

Yang H, Xu W, Zhou Z, Liu J, Li X, Chen L *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.

Yu JJ, Pei LB, Zhang Y, Wen ZY, Yang JL (2015). Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychopharmacol 35: 406–410.

Zhang DW, Fu M, Gao SH, Liu JL (2013). Curcumin and diabetes: a systematic review. Evid Based Complement Alternat Med 2013: 636053.

Zhang Y, McClain SA, Lee HM, Elburki MS, Yu H, Gu Y*et al.* (2016). A novel chemically modified curcumin "normalizes" wound-healing in rats with experimentally induced type I diabetes: initial studies. J Diabetes Res 2016: 5782904.